T 57 Pathobiology of Relapsing Lymphomas: The Possible Role of Immunophenotypes, Virus Association, and the Expression of Drug Resistance P-glycoprotein

Ih-Jen Su and Ann-Lii Cheng Departments of Pathology and Clinical Oncology, National Taiwan University Hospital and College of Medicine, Taipei, Taiwan

In order to investigate the possible underlying mechanism of the tumor relapsing in malignant lymphomas, freshly frozen tissue specimens from 27 patients with relapsing or resistant lymphomas were studied for the histologic progression, the immunophenotypic features, the association with human oncogenic viruses (EBV and HTLV-1), and the expression of multidrug resistance gene P-glycoprotein by immunohistochemistry and Southern blot hybridization methods. Histologic progression was found in 4 cases, evolving either from a mixed cell pattern to a homogeneous large cell/immunoblastic type in 2 cases of peripheral T cell lymphomas, or from a follicular pattern to a predominantly diffuse histology in 2 cases of B cell lymphomas. No significant change of immunophenotype was demonstrated except for a higher percentage of Ki-67 expression in 5 cases of recurrent tumors. The expression of P-glycoprotein were found in 13 (48%) of the cases; T cell phenotype in 9 and B phenotype in 4. Prechemotherapy tumor tissues were available for studies in 11 cases, of which only 2 (18.2%) expressed mdr-1. Nine of the 10 cases of virus (EBV in 7 and HTLV-1 in 3) had detectable expression of P-glycoprotein in the relapsing tumors; 8 of them had T cell immunophenotype. The survival-after-recurrence curves significantly favored the mdr-1 (-) recurrent lymphomas, and also for B cell lymphomas. We conclude that different mechanisms may be responsible for the relapsing or the resistance to treatment in lymphomas with different immunophenotypes or the histology subtypes. The virus association may play a significant role in the subsequent development of drug resistance, particularly in T cell lymphoma. Further studies based on larger series of cases may be needed to clarify our current observation.

T 58 Clinicopathologic Spectrum of Epstein-Barr Virus-Associated Cutaneous T Cell Lymphoma

Ih-Jen Su Department of Pathology, National Taiwan Univ. Hospital and College of Medicine, Taipei, Taiwan

The cutaneous T cell lymphoma (CTCL) has been recently shown to be associated with Epstein-Barr virus (EBV). In this study, 14 cases of EBV-associated T cell lymphoma presenting primarily or secondarily with cutaneous lesions were investigated for the clinical manifestations, histopathologic and immunophenotypic features and the prognosis. Southern blot and in situ hybridization were performed to demonstrate the EBV genomes. The cutaneous lesions varied from ulcerations, panniculitis to violaceous papules or tumors. Three clinicopathologic subgroups were recognized: (A) cutaneous angiocentric T cell lymphoma, 7 cases, 2 with NK activity, presenting with chronic ulcers or panniculitis. The local phase is indolent, but disseminated in 3-5 years with a rapid terminal phase, (B) T large cell lymphoma with hemophagocytosis, 5 cases, presenting with fever, multiple violaceous papules or nodules. Frequent association with hepatosplenomegaly, jaundice, and pancytopenia, rapidly terminating within 2 months due to systemic hemophagocytic syndrome, mimicking malignant histiocytosis, (C) classical cases of CTCL, 2 cases, but with relatively aggressive course. The median survival for the whole series was 8 months only. Clonotypic proliferation of EBV genomes were demonstrated in all cases. In situ EBER hybridization revealed nuclear localization of EBV granules in the atypical large lymphoid cells which expressed T cell antigens. In conclusion, we have reported the clinicopathologic observations on 14 cases of EBV-associated cutaneous T cell lymphoma. To recognize these patients will be important for proper management of the patients.

T 59 ASSOCIATION OF JAPANESE POST-PYOTHORAX LYMPHOMAS WITH THE EPSTEIN-BARR VIRUS INFECTION.

Sasajima, Y., Yamabe, H., Kobashi, Y., Hirai, K. and Mori, S. . Department of Pathology, Institute of Medical Science, University of Tokyo. 4-6, Shirokanedai, Minato-Ku, Tokyo 108, Japan

BACKGROUND Non-Hodgkin's malignant lymphoma (ML) rarely affects pleural cavity, while most of such pleural MLs develop in patients with long-standing tuberculous pyothorax. Over 50 cases of such post-pyothorax lymphomas were reported in Japan. They were preferentially of high grade morpthology, in B cell lineage, and with rather rapid course. Peculiarly, no cases have been described in Western countries (Iuchi et al. Jpn J Clin Oncol 19: 249, 1989; Aozasa et al. Jpn J Clin Oncol 21: 417, 1991). The pathogenesis of these MLs remain unknown.

EXPERIMENTAL DESIGN With an assumption, based on our personal experience that these MLs may be related to Epstein-Barr virus (EBV) infection, we studied the expression of two representative EB-viral proteins, EBNA2 and LMP1, on unfixed-frozen tissues of 4 cases of post-pyothorax lymphoma. Fifty randomly selected B-MLs and five EBV-bearing lymphoblastic proliferations produced in SCID mice by the transplantation of EBV-positive human B lymphocytes (SCID EBV+ tumor) were used as controls. The labeled avidin-biotin method was introduced for the immunohistological demonstration of these viral proteins.

RESULTS EBNA2 was demonstrated heavily in neoplastic cells of all 4 post-pyothorax lymphomas. LMP was also demonstrated in all cases, while their staining intensity as well as the number of stained cells were far much less than the SCID-EBV+ tumors. None of the 50 control B-MLs were stained with anti-EBNA2 nor anti-LMP1 antibodies.

CONCLUSION Definite association of EBV infection with post-pyothorax ML was shown. The significance of weaker expression of LMP1 in post-pyothorax MLs than SCID EBV+ tumors waits for further molecular studies.

T 60 EPSTEIN-BARR VIRUS INFECTION: ETIOLOGICAL VERSUS COINCIDENTAL EVENT IN MALIGNANT LYMPHOMAS.

P. Lardelli [1]*, R. Cisterna [1], I Anton [1], R. Garcia del Moral [2]. 1 Department of Microbiology and Immunology, School of Medicine, University of the Basque Country, Bilbao. 2 Department of Pathology, School of Medicine of Granada 18012, Spain.

A causal relationship has been documented for Epstein-Barr virus (EBV) in some types of malignant lymphoma, i. e. X-linked lymphoproliferative disease and Burkitt's lymphoma. However, this association is less evident in other types of lymphoma, such as Hodkin's disease (HD). Moreover, in this latter condition it is difficult to distinguish an etiologic versus a coincidental role for EBV. In situ hybridization enables to identify the type and number of cells which harbor EBV genome, thus contributing to assess those cases in which EBV may have an active etiological role. We have analyzed the presence of EBV DNA in 20 cases of Hodgkin's disease and in 13 non-Hodgkin's lymphomas, by in situ hybridization on sections of conventionally processed tissue. A non-radioisotopic labeled probe (cloned Bam HI W segment) was used. Viral DNA was detected in four HD cases (20%); in two of these, the signal was localized in Reed-Sternberg cells and in surrounding lymphocytes. In the other two cases, EBV DNA was observed only in some of the admixed lymphocytes. In addition, EBV DNA was demonstrated in two cases of non-Hodgkin's lymphomas (15%). In one of these, a small non-cleaved lymphocytic lymphoma, Burkitt's type, positivity was found in almost every tumor cell. In the other case, EBV-positive cells were seen in low proportions, scattered throughout the lesion. We conclude that EBV may be related to the development of the lymphomas in only half of the EBV positive-HD cases and in one of the non-Hodgkin's cases, corresponding the remaining ones to latent infection.

T 61 EXPRESSION OF THE EPSTEIN BARR VIRUS ENCODED LATENT MEMBRANE PROTEIN IN HODGKIN'S DISEASE OCCURING IN CHILDHOOD.

M. Kalmanti, P. Kanavaros, A. Sakalidou, M. Tzardi, E. Kazlaris. Department of Pediatric Hematology-Oncology and Pathology, University Hospital of Heraklion, University of Crete, Greece.

Paraffin sections from 21 cases of Hodgkin's disease(HD), 28 cases of non - Hodgkin's Lymphomas (NHL) and 34 cases of non-specific reactive lymphadenitides occuring in childhood ware examined for the presence of the Epstein-Barr Virus(EBV)-encoded Latent Membrane Protein (LMP) using a double layer immunohistochemical method.

LMP was detected in 12/21 (57%) cases of HD but not in NHL or reactive lymph nodes. LMP reactivity was restricted to Reed Sternberg and Hodgkin's(HRS) cells in 4 of 9 (45%) cases of nodular sclerosis (NS), 6 of 9 (66%) cases of mixed cellularity (MC) and 2 of 2 (100%) cases of lymphocyte deplation (LD) while it was undetectable in the one case of lymphocyte predominance (LD) subtype.
These results provide further evidence for an association between EBV and Hodgkin s disease, and they show that LMP expression occurs more frequently in the clinically more aggressive subtypes of HD. Furthermore, in view of the in vitro transforming potenrial of the LMP protein, the exclusive immunolocalization of LMP in HRS cells, suggests that EBV may be involved in the pathogenesis of a proportion of cases of HD.

T 62 EBV POSITIVITY IN HODGKIN'S DISEASE: RELATIONSHIP TO CLINICAL AND PROGNOSTIC PARAMETERS.

Anne Lennard[1], Ruth Jarrett[2], Alison Armstrong[2], Stephen Proctor[1], Brian Angus[3], F E Alexander[4], Departments of [1]Haematology, [3]Pathology, Royal Victoria Infirmary, Newcastle upon Tyne, NE1 4LP, [2]LRF Virus Centre, Department of Veterinary Pathology, University of Glasgow, Bearsden Road, Bearsden, Glasgow, G61 1QH, [4]University of Southampton, Graham Road, Southampton, SO9 4PE, UK

Evidence is accumulating that the EB virus is frequently involved in the pathogenesis of Hodgkin's disease. In this study we have investigated the incidence of EBV positivity in a cohort of patients and correlated the results with clinical and prognostic parameters. Sections from paraffin-embedded biopsies from 60 Hodgkin's disease patients diagnosed and treated in the same institute were screened for the presence of EBV-encoded latent membrane protein-1 (LMP-1) and nuclear RNA (EBER) using immunohistochemical and *in situ* hybridization techniques. Overall 35% of cases were EBV +ve.

EBV positive and negative cases were compared with regard to age, sex, Ann Arbor stage, site of presentation of disease, histopathological subtype, prognostic index and clinical outcome of disease. Median follow-up of patients is 88 months (range 3-170).

As in previous studies EBV positivity correlated with age being high in young (<15) and older(>50) age groups, but low in the young adult group with nodular sclerosing disease. EBV positivity was not found to correlate with any of the other clinical parameters measured.

Our results suggest that EBV positivity is not a useful prognostic marker for patients with Hodgkin's disease.

T 63 DETECTION OF EPSTEIN-BARR VIRUS DNA IN HODGKIN- AND REED-STERNBERG- CELLS BY SINGLE CELL PCR.

J. Roth, H. Daus, A. Gause, L. Trümper and M. Pfreundschuh. Dep. Internal Medicine I, University of Saarland, D-6650 Homburg/Saar, Germany

The Epstein-Barr virus (EBV) can be detected in a majority of cases in Hodgkin's lymphoma using the highly sensitive polymerase chain reaction (PCR). However, the rate of EBV-DNA detection by *in situ* hybridisation, which allows allocation of EBV to a defined cell population, is consistently lower. In an attempt to combine high sensitivity with specificity in localizing the PCR-products to Hodgkin- and Reed- Sternberg- (H&RS)- cells, we isolated single H&RS- cells from biopsy tissue by micromanipulation and amplified EBV-sequences by single-cell PCR. EBV was found in all H&RS-cells from 4 of 6 patients, whereas other cells in the biopsy tissue involved by EBV-positive H&RS-cells were negative. This indicates, that EBV may be of etiologic relevance in a majority but not all cases of Hodgkin's disease.

T 64 HODGKIN'S DISEASE: A TUMOR OF UNBALANCED CYTOKINE PRODUCTION?

H.J. Gruß, M.A. Brach, and F. Herrmann. Dept. of Oncology and Applied Molecular Biology, Free University of Berlin, UKRV, Robert-Roessle Clinic, and Max-Delbrück-Center for Molecular Medicine, Berlin-Buch, Germany

We show by Northern Blot analysis and ELISA protein assay, that cultured Hodgkin and Reed-Sternberg (H-RS) cells (cell lines HDLM-2 and KM-H2) produce a variety of different cytokines either constitutively or upon induction such as Interleukin (IL)-1 alpha, IL-3, IL-5, IL-6, IL-8, IL-9, Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF), Macrophage (M)-CSF, Tumor Necrosis Factor (TNF)-alpha, TNF-beta, Leukemia Inhibitory Factor (LIF) and Transforming Growth Factor (TGF)-beta. Transcripts and the corresponding proteins for Granulocyte (G)-CSF, IL-1-beta, IL-2, IL-4, IL-7, IL-10, and the MCAF/JE were not detectable in cytoplasmic RNA and culture supernatants obtained from both lines. In addition, IL-2 receptors (R) p55, and M-CSF R (c-fms) genes were expressed by both lines, while HDLM-2 but not KM-H2 cells displayed IL-6 R p80 chain and IL-2R p75 chain transcripts. The pattern of transcription factors (AP 1, NF kappaB and NFAT 1) isolated from nuclear extracts of HD cell lines resembled that of activated T cells. HDLM-2 and KM-H2 cells constitutively displayed NFAT1 binding previously described to be T cell specific. In addition, UV-crosslinking experiments showed that NF kappaB binding proteins with 85, 75, and 50-55 kD in size were present in T cell and both HD lines, while monocytes and B cells exhibited the 50-55 kD and 75 kD protein complex only. Taken together, our results suggest that HD may be a tumor of unbalanced cytokine production. Cytokines produced by H-RS cells may either interact with their neighboring tissues and may thus be responsible for some of the clinical or histopathological features characteristic of HD or may be used as autocrine growth factors. First results suggest that IL-9 may be a candidate molecule in this regard by acting as an autostimulatory growth factor for H-RS cells.

T 65 ASSESSMENT OF PLOIDY AND S-PHASE FRACTION IN RELAPSED PATIENTS WITH HODGKIN'S DISEASE BY FLOW CYTOMETRIC ANALYSIS

P.C. Pasman, F.L.G. Erdkamp, W.P.M. Breed, W.C. Janssen, J.J. Hoffmann, H.C. Schouten. Departments of Internal Medicine, Maasland Hospital Sittard, Catharina Hospital Eindhoven and University Hospital Maastricht. PO Box 5800, 6202 AZ Maastricht.

In relapsed patients with Non-Hodgkin's lymphoma the S-Phase fraction (SPF) in tumor cells has been reported to be higher compared to the SPF at diagnosis. To assess whether in Hodgkin's disease the same observation can be made, this study was performed. Therefore, of 9 patients with Hodgkin's disease paraffinised lymph-nodes, obtained at diagnosis and at relapse, were examined by flow cytometric analysis. DNA-content and SPF were determined. At diagnosis three patients were diploid and 6 aneuploid, with a DNA-index ranging from 0.8 to 1.5. Median SPF at diagnosis was 6%. At relapse two of three diploid samples remained diploid; of the 6 samples, aneuploid at diagnosis, three cases became diploid at relapse. Three patients had multiple relapses. One patient, diploid at diagnosis, was aneuploid at first relapse, and diploid at second relapse. Two patients aneuploid at diagnosis, had several relapses: one remained diploid at all three relapses, the other was aneuploid at first relapse and diploid at second relapse. The SPF increased in three patients (median 5%), and decreased slightly in three other patients (median 0.9%). In one patient with multiple relapses, the SPF increased first (2.6%), and at a subsequent relapse decreased (7.4%). In conclusion, based on this small population sample, no correlation was found between flow cytometric parameters at time of diagnosis and at relapse. The data suggest that previous cytotoxic therapy does not preferentially select a diploid or aneuploid malignant population.

T 66 THE PROGNOSTIC VALUE OF PAS REACTION OF CIRCULATING LYMPHOCYTES IN PATIENTS WITH HODGKIN'S LYMPHOMA

M. Petrović, G. Janković, Institute of Hematology, University Clinical Center, Koste Todorovića 2, Belgrade, Yugoslavia

PAS reaction of circulating lymphocytes was studied in 36 patients with Hodgkin's disease (HD) treated between 1982-1984 and followed up through 1990. Ten healthy volunteers served as controls. The HD group consisted of 25 men and 11 women, mean age 37,7 yrs (range 19-61) with the following distribution of clinical stages: CS I:4/36 (19.9%), CS II:11/36 (30.5%), CS III:13/36 (36.1%) and CS IV:7/36 (19.5%). Majority of patients had a mixed cellular type:20/36 (55.5%) while lymphocyte depletion type was the least common: 1/36 (2.8%). Nodular sclerosis was present in 11/36 pts (30.5%) and lymphocyte predomination in 4/36 pts (11.1%).

The aim of the study was to establish a possible difference in PAS positive lymphocytes values between HD patients and controls. We also wanted to indentify possible prognostic significance of the difference. Finally, we wanted to determine whether PAS reaction of circulating lymphocytes depends on the clinical stage and pathohistologic type of HD.

PAS reaction of circulating lymphocytes showed significantly higher rate of PAS positive lymphocytes in HD patients than in controls (C) ($p < 0.01$).

Study of PAS lymphocyte reaction in HD patients showed significantly higher rate of PAS positive circulating lymphocytes in patients with complete remission and five yrs disease free survival (DFS) than in those with early relapse or those who died without entering remission ($p < 0.001$).

Analysis of survival curve showed the rate of five yrs survival to be significantly higher in patients with higher PAS lymphocyte positivity irrespectively of their CS or pathohistological type of disease. Two factor variance analysis showed PAS positivity of circulating lymphocytes of HD patients to be prognostic factor independent of clinical stage or pathohistologic type of the disease.

T 67 ABSOLUTE LYMPHOCYTE COUNT AS AN INDEPENDENT AND T-LYMPHOCYTE COUNT AS A CLINICAL STAGE AND PATHOHISTOLOGIC TYPE-DEPENDENT PROGNOSTIC FACTORS IN HODGKIN'S DISEASE.

Snežana Janković*, Milica Marinković** and Milan Petrović*
* Institute of Haematology,University Clinical Center,Belgrade
** Institute of Oncology/Radiology, Belgrade, Yugoslavia

Total lymphocyte count in the peripheral blood is often decreased in Hodgkin's disease (HD) suggesting poor prognosis. However, it is still unresolved whether lymphocytopenia is a result of underproduction, overutilization or redistribution of lymphocytes.On the other hand T lymphocyte predominance in lymph node in cases with mixed cell type, indicating a progressive disease (Poppema,1970), may be a counterpart of lymphocytopenia in patients with poor prognosis. At the same time it may suggest, at least in some types of disease, the redistribution of T lymphocytes.

In this study we estimated the absolute count of total and T lymphocytes(ERFC) counts in order to see whether T lymphocyte count was behaving in the same way as total lymphocyte count in predicting the course of disease. We followed each consecutive patient from the presentation to following 9 yrs. A group con sisted of 25 males and 11 females, median age 37.7 yrs (range:19-61 yrs) with clinical stage (CS) I(4/36,13.9%), CS II(11/36,30.5%), CS III (13/36, 36.1%), and CS IV (7/36, 19.5%). 20/36 (55.5%) of the patients had a mixed cell pattern of HD, nodular sclerosis (11/36, 30.5%), lymphocyte predomination (4/36, 11.1%) and lymphocyte depletion 1/36 (2.8%) of the patients.

The results showed that an increased absolute count of total and T lymphocytes at the presentation had been indicative of the patients evolving to a complete remission. Two-way factorial analysis showed that the high total lymphocyte count in pšeripheral blood was factor independent of level of clinical stage and pathohistologic type of HD. The increased level of T lymphocytes was associated with clinical stage and pathohistologic type with favorable prognosis.

Our study suggests that the changes in peripheral blood lymphocyte count in our patients, could be associated with redistribution at least of some lymphocyte subpopulations.

T 68 P-GLYCOPROTEIN EXPRESSION IN HODGKIN'S DISEASE

P.C. Pasman, F.L. Erdkamp, L. Vrints, W.P. Breed, J.W. Arends, H.C. Schouten. University Hospital Maastricht, Departments of Internal Medicine and Pathology, Catharina Hospital Eindhoven, Maasland Hospital Sittard and University Hospital Maastricht, P.O. Box 5800, 6202 AZ Maastricht, The Netherlands.

Multidrug resistance is defined as non- or low-response of a patient with cancer to treatment with various chemotherapeutic agents, and associated with relapsing disease. Patients with Hodgkin's disease usually respond very well to the initial chemotherapy, although in about 30% of the patients a relapse occurs. P-glycoprotein (P-gp) is a transmembrane protein associated with multidrug resistance. Its function is extruding large lipophilic molecules, like certain cytotoxic drugs, out of the cell. This study was performed to assess whether P-gp plays an important role in Hodgkin's disease. Fifteen deep frozen lymph nodes from 10 newly diagnosed and 3 relapsed patients were used for the immunohistochemistry. Sections were stained with an antibody, C219, directed against P-gp. Of the 10 newly diagnosed patients with Hodgkin's disease 3 were positive for P-gp expression. Of the three relapsed patients P-gp expression was seen in only one patient at the time of relapse. Of these 3 patients one patient had three relapses. All three lymph node samples were negative. In positive samples, mainly the membranes of cells with a large nucleus stained positive, which may correlate with the Hodgkin and Reed-Sternberg cell population. The data indicate that P-gp is present in Hodgkin's disease in roughly the same percentage (33%) in both initial and relapse material. In view of this finding and because of the negativity for P-gp in sections of relapsed Hodgkin, we conclude that P-gp is not likely to be the only mechanism for relapsing Hodgkin's disease.

T 69 IN VITRO STUDIES OF CELL-MEDIATED IMMUNITY IN HODGKIN'S DISEASE (HD).

E.Di-Biagio, J.Desenne, M.Sánchez-B., R.Suárez-Ch., R. Somoza and G.Acquatella. National Center for Oncology-Hematology, and Lymphoma Clinics, Caracas University Hospital, Caracas, Venezuela.

We have been interested in the immunological abnormalities which are present in patients with HD, especially those related to eosinophil (Eos) and IgE production, and its regulation by T lymphocytes. 18 untreated HD patients (11 male, 7 female, mean age 28.7+/-17.6 years) and 16 healthy age- and sex-matched controls were studied. Absolute Eos counts, T cell subpopulations, serum IgE, DTH skin tests, were investigated, and in vitro IL-2, GM-CSF, Gamma-Interferon (IFN), and sCD23 secretion by PHA-stimulated PBL were determined.

A decreased cellular immunity in HD patients, when compared to controls, was evidenced by a reduced ^{3}HT incorporation (HD 27451+/-3769 cpm, Controls 42123+/-2999 cpm; p=.003), IL-2 (HD 1797+/-259 pg/ml, Controls 2892+/-293 pg/ml; p=.008), and GM-CSF production (HD 120+/-17 pg/ml, Controls 184.8+/-18.8 pg/ml; p=.01); IFN production was also lower in HD patients (216+/-55 pg/ml) than in Controls (491+/-165 pg/ml) but this difference was not statistically significant.

We also found increased Eos counts in HD (HD 444.3+/-119 cells/ cu mm, Controls 180.1+/-35 cells/cu mm; p=.04). 5 patients had significant eosinophilia (> 500/cu mm), none of the control individuals had eosinophilia. Serum IgE was elevated in HD patients (481.1+/-131 KU/l) compared to controls (192+/-78 KU/l), but this difference was not statistically significant.

In vitro production of soluble low-affinity IgE receptor (sCD23) in HD was lower than in controls (HD 42.2+/-7 U/ml, controls 89+/-16 u/ml p=.01). There were no differences between HD patients with increased Eos counts (> 500 cells/cu mm) in serum IgE levels, CD3, CD4, CD8 T cell counts, IL-2 and IFN production when compared to HD patients without eosinophilia. However, GM-CSF production was decreased in HD patients with eosinophilia (p=.04).

Partially supported by FUNDACION VENEZOLANA DE INMUNOLOGIA (FUNVENIN)

T 70 CORRELATION BETWEEN SOLUBLE IL-2 RECEPTOR(SIL-2R)AND NEOPTERIN SERUM LEVELS IN HODGKIN'S DISEASE (HD).

P.Lissoni,S.Barni, M.Cazzaniga,A.Ardizzoia,F.Rovelli,G.Tancini.Division of Oncological Radiotherapy,Ospedale San Gerardo,Monza,Italy.

The nature of Reed-Stenberg(RS-cell,which represents the classical neoplastic cell in HD,is still unclear.Either T or B lymphocytes have been considered to be the source of RS cells.Moreover,recently it has been proposed that RS cell may be a macrophagic cell, and this hypothesis is also supported by the evidence of high levels of neopterin,which is a specific macrophage marker,in patients(pts)with HD. Neopterin levels have been shown to be correlated to the stage of disease,and to be associated with a poor prognosis.Another unfavourable marker in HD is represented by SIL-2R,mainly released from T lymphocytes following a macrophage stimulation. Therefore,SIL-2R would reflect the macrophage activity,rather than the activation of lymphocytes per se.At present,no study has been carried out to evaluate which correlation may exist between neopterin and SIL-2R in HD. To investigate this biological question,we have measured serum levels of SIL-2R and neopterin in 20 pts with HD and in 58 healthy subjects,as controls. Mean levels of SIL-2R and of neopterin were significantly higher in pts than in controls. Moreover, mean serum levels of SIL-2R and of neopterin were significantly higher in pts at clinical stage III-IV (n=9) than in pts at clinical stage I-II(n=11). Finally, a positive correlation was seen between SIL-2R and neopterin serum concentrations. These preliminary results would suggest that the increased release of SIL-2R in HD is related to an increased macrophage activation,as documented by the enhanced secretion of the specific macrophage marker,neopterin. Since the elevated levels of SIL-2R may allow a decreased bioavailability of IL-2, we could hypothesize that the immunosuppression,which characterizes pts with HD, is at least in part a consequence of an enhanced activation of macrophages,which have been proven to inhibit IL-2-dependent immune functions.

T 71 PROGNOSTIC ROLE OF SERUM FERRITIN AND CA-125 IN HODGKIN'S DISEASE.

R.Abdyldaev, O.Modnikov, S.Dyikanbaeva. Kirghiz Research Institute of Oncology & Radiology, 720064 Bishkek, Kyrghyzstan

The detection of adjunctive clinico-laboratory factors permitting to prognosticate a clinical course and efficacy of the cytostatic therapy in Hodgkin's disease (HD) is of a great significance. Parodoxically, but just in HD only some separate prognostic laboratory assays have been revealed. To determine additional laboratory assays for the prognostication of the course of the disease and the effectiveness of the combined-modality treatment with chemotherapy and radiation, the serum concentrations of ferritin and CA-125 have been measured in 61 HD patients in the dynamics (before, during and after treatment).

	Before treatment	After the 1st stage of treatment	After completion
Serum ferritin ng/ml	201.3±20.2	269.9±22.6	155.7±12.6
CA-125 E/ml	29.3± 9.0	24.0± 9.7	4.2±1.2

Thus, the serum concentrations of ferritin and CA-125 may be prognostic factors (P<0.05) in HD patients. The decrease in their concentrations to the normal level is an adjunctive criterion that confirms the attainment of the complete clinical remission.

T 72 PROGNOSTIC VALUE OF SERUM C REACTIVE PROTEIN (CRP) LEVELS IN PATIENTS WITH HODGKIN'S DISEASE.

Gregg AR[1], Sweetenham JW[1], Stevenson FK[2], Mead GM, Whitehouse JMA[1]. [1]CRC Wessex Medical Oncology Unit, [2]Tenovus Research Laboratory, University of Southampton, Southampton General Hospital, Tremona Road, Southampton SO9 4XY, UK.

Elevated serum CRP levels have been reported previously in patients (pts) with Hodgkin's disease (HD). We have conducted a study on pts presenting to this Unit to assess its prognostic value.

From September 1984 to March 1992, 207 pts with HD presented to this Unit. Serum samples taken at presentation, and stored at -20°C were available for 86 pts.

These 86 pts were comparable to the entire group with respect to age, sex, stage and other major prognostic factors. CRP levels were measured by 2-site ELISA.

Case records were reviewed, and univariate and multivariate analysis was performed. Factors included in analysis: age, sex, Ann Arbor Stage, B symptoms, bulk, mediastinum +, serum albumin, alkaline phosphatase, lactate dehydrogenase, haemoglobin, erythrocyte sedimentation rate (ESR), total lymphocyte count. End points were overall survival (OS) and failure free survival (FFS).

Pt characteristics: n = 86; median age = 32 (range 15 - 86); male = 53; stages: I - 27, II - 35, III - 16, IV - 8, B symptoms - 31; > 10cm bulk - 6.

Results: median CRP = 28mg/l (range 1-268, NR - <20). Univariate analysis: serum CRP is significant adverse prognostic factor: 4 yr FFS = 90% for CRP <20mg/l, 60% for CRP > 20mg/l (P=0.012).

Using Cox regression model, CRP had no prognostic significance in multivariate analysis.

T 73 STAGING LAPAROTOMY IN SUPRADIAPHRAGMATIC HODGKIN'S DISEASE.

M. Vovk, M. Jenko, J. Petrič et al.
Institute of Oncology, 61105 Ljubljana, Slovenia

The results of 95 staging laparotomies for Hodgkin's disease with supradiaphragmatic presentation, performed at our Institute from 1974-1989, are presented in a retrospective analysis. Subdiaphragmatic involvement was found in 34% of cases; 88% of these had upper abdominal involvement (PS III 1), most frequently in the spleen (84%), and in 31% of cases the spleen was the only localization. Male sex and age >40 years (LRA) were the only independent significant predictors for positive surgical staging in CS I-II. On the basis of these observations, low-risk (<15%), intermediate-risk (16-50%) and high-risk (>50%) groups for predicting positive laparotomy can be defined. These observations can form the basis for the selection of patients for staging laparotomy, and for treatment planning. No statistically significant differences in survival and relapse free survival could be established between the group with (95 patients) and without (124 patients) laparotomy.

T 74 Hodgkin's Disease in older patients.

A.F. Abrahamsen*, E.Hannesdal*, J.F.Abrahamsen*, S.Hansen**,S.Kvaløy*, *Dept. of Oncology, The Norwegian Radium Hospital, Montebello, 0310 Oslo, Norway, **The Cancer Registry of Norway.

During 1974 - 1985, 1087 patients had the first diagnosis of Hodgkin's Disease in Norway. 36% were >60 years old. 60% of these died during the first year after diagnosis, and only 12% were alive after 5 years.

753 of the national material were referred to the Norwegian Radium Hospital, 172 patients to other cancer hospitals, and 162 patients were not referred for staging and treatment. Most of these were older patients.

In a hospital study of the 753 patients referred to our hospital, 25% were >60 years old. 40% of these died during the first year after diagnosis. Only 20% were alive after 5 years, against 86% in age of 15 - 40 years. Older patients had an increased number of bad prognosis histology, more advanced disease, often inadequate treatment and severe complications. 80% of the older patients who died during the first year had still Hodgkin's disease. About one-third died of Hodgkin's Disease, one-third of complications to treatment, and one-third of other diseases.

It is concluded that Hodgkin's disease in older patients have a bad prognosis, partly because of more severe disease, and partly from severe complications and inadequate treatment. Older patients present different therapeutic problems from younger patients. More clinical studies are needed to evaluate the best treatment strategies for older patients.

T 75 LATE RELAPSE IN HODGKIN'S DISEASE: REPORT OF SIX CASES AND A REVIEW OF THE LITERATURE.

G. Lugassy, Y. Ilan, S. Gillis, A. Polliack.
Lymphoma Unit, Departments of Hematology, Hadassah University Hospital and Hebrew University Hadassah Medical School, Jerusalem, Israel, and Hematology Service, Barzilai Hospital, Ashkelon, Israel.

During the past 15 years the treatment of Hodgkin's disease (HD) with chemo/radiotherapy has been shown to appreciably improve the long-term prognosis of patients, even those with more advanced disease. In the past it was accepted that the probability of primary relapse 5 years after achieving complete remission (CR) was small and a 5-year disease-free period was sufficient to be considered as a cure. During the past 15 years, however, more data has been published relating to late relapses in these patients after an initial "cure" has been achived. This report briefly examined our own experience with six patients initially "cured" who relapsed 5 to 11 years after achieving CR and also reviews recent literature on the subect. Three of the six patients had pulmonary involvement on relapse 8, 8 and 11 years after initial remission. In two of these cases the lung involvement was the only extranodal site of disease at the time or relapse while in the third it was part of disseminated disease. The remaining cses had nodal relapse. The phenomenon of late relapse has thus become a more important tissue in the management of patients with HD.

T 76 HODGKIN'S DISEASE - RECURRENCES AFTER PRIMARY ADVANCED STAGES

For the German Hodgkin's disease study group.
R.Fuchs, M.Löffler, M.Pfreundschuh, G.Dölken, H.Gerhartz, U.Hagen-Aukamp, E.Hiller, S. Petsch, K.-H.Pflüger, U.Rühl, K.Smith, J.Teichmann, V.Diehl

In a multicentre study on the treatment of Hodgkin's disease(HD3 recruitment 1984 - 1988) 88 out of 297 patients with primary advanced stages IIIB/IV failed to respond to alternating COPP/ABVD chemotherapy ± radiotherapy. The treatment failures may be broken down as follows: tumor progression under current therapy (PD) 23/88, partial remission at the end of treatment (PR) 28/88, early nodal recurrence 13/88, late nodal recurrence 15/88, extranodal recurrence 7/88, unclear localisation 1/88. Thirty-six months after noting failure of treatment, 45% of all patients were still alive. The prognosis was poorest in the case of primary PD. Only 1/23 of these patients experienced lasting complete remission due to salvage treatment (cCR). Eleven patients with an exclusively nodal recurrence reached a cCR on treatment with radiation alone, and may be considered as a low-risk recurrence group. For a high-risk recurrence group (n = 57), indication for high-dose chemotherapy with subsequent autologous bone marrow transplantation (HDC/ABMT)whould have been recognized on the basis of modern eligibility criteria. The survival probability of these HDC/ABMT candidates, who only received conventional salvage treatment, was 38% after 30 months (95% confidence limit, 22% to 54%). These data would not appear to be appreciably poorer than those reported in the literature for comparable patients receiving HDC/ABMT. Only a randomized comparison would be capable of showing whether HDC/ABMT is superior to high-dose conventional chemotherapy with haematopoietic growth factors. The German Hodgkin's disease study group has now activated such an appropriate trial (HDR1 protocol).

T 77 RECURRENCE OF HODGKIN'S DISEASE. HISTOPATHOLOGIC FINDINGS.

A. Poletti, M. Sorarù*, L. Salvagno*, N. Pennelli, M. Fiorentino*
Inst. of Pathological Anatomy and Oncology*, 35128 Padua, Italy

Histopathologic findings of 20 cases od Hodgkin's disease (HD) (age range from 16 yrs to 80 yrs) relapsed after more than 1 year from the end of therapy (range 1-11 yrs, mean 4.6 yrs) were analyzed. Subtypes included 3 lymphocyte predominance (LP), 10 nodular sclerosis (NS) and 7 mixed cellularity (MC). Our study was aimed to evaluate possible cytologic and histologic pattern modifications occuring during clinical course of HD. LP cases (relapsed after 3, 5, and 6 yrs) did not show relevant variations between initial and relapse pattern, although the latter showed an increase in the number of L&H cells associated with scattered typical Reed-Sternberg cells in two cases. MC cases (relapsed after a mean of 7 yrs, range 1-10 yrs) did not present relevant modifications except for a single case that shifted to a NS-like pattern including the presence of lacunar cells. MC pattern persisted with a concomitant increase of broad band fibrosis in 5 MC cases. Typical Reed-Sternberg cells were also increased in 3 MC cases, with focal features of lymphocyte-depleted HD. As to NS cases (relapse after a mean of 4.8 yrs, range 2-11 yrs), although NS pattern remained unchanged, a significant increase of fibrosis occurred in 6 cases. Reed-Sternberg cells increased in 2 cases. Three NS cases had multiple relapses (2 repalses in two pts, after 6 and 8 yrs and 5 and 10 yrs respectively; 3 relapses in one pt after 4, 6, and 7 yrs). The relapse pattern showed significant increase of Reed-Sternberg cells in 2 pts and increased fibrosis only in the remaining patient. Our data seem to suggest that variation of the primary histologic pattern is a rare event in HD whereas an increased amount (12/20) of fibrosis was a common finding. An increased number of Reed-Sternberg cells is relatively frequent (7/20). Immunophenotype counterpart of HD pattern variation observed in the present series remain to be investigated.

T 78 VBM CHEMOTHERAPY AND LIMITED IRRADIATION: AN EFFECTIVE COMBINATION IN NON LAPAROTOMY STAGED PATIENTS WITH FAVORABLE HODGKIN'S DISEASE (HD).

M. Vespignani*, R.B. Guglielmi*, E. Bonoldi^, G. Capnist*, R. Raimondi*, T. Chisesi*. Department of *Hematology, °Radiotherapy, ^Pathology, S. Bortolo Hospital, 36100 Vicenza, Italy.

Aim. To test in a single institution feasibility, tolerance and efficacy of VBM chemotherapy (CT) plus limited radiotherapy (RT) in clinically staged (CS) patients with favorable HD.
Materials and methods. Since 1990 20 patients with HD have been treated with vinblastine, bleomycin, methotrexate (VBM) regimen for 6 cycles and involved field RT. There were 13 males and 7 females, with a median age of 35 yrs (range 19-61). Histologic subtypes were LP (8 cases) NS (9 cases) MC (3 cases). At diagnosis all patients presented with CS I-II, asymptomatic, non bulky disease, with <=3 nodal regions, low ESR value (median 12 mm, range 2-35). Mediastinum was involved in 8 patients. Only one patient presented with infradiaphragmatic CS I HD. In 3 patients RT was administered before CT, in 6 patients all CT was given before RT and in the remaining patients CT and RT were alternated (2 VBM + RT + 4 VBM). RT dose ranged between 36 and 40 Gy.
Results. Of 17 evaluable patients, 16 achieved CR. One patient who developped signs of active disease shortly after diagnosis, had progressive disease under VBM and was rescued with MOPP/ABVD. One patient demonstrating persistent disease after 6 VBM obtained CR after RT only. With a median follow-up of 18 months (range 5-30), no CR's has relapsed so far. Treatment was generally very well tollerated: myalgias were the main acute toxicity of VBM. Hematologic toxicity was slight or absent never accounting for any dose intensity reduction. No major pulmonary toxicity had been recorded in patients who received mediastinal irradiation followed by CT, providing the bleomycin dose to be reduced after RT. All female patients retained normal menstrual cycles during and after therapy. Four male patients tested mantained a normal semen analysis after the completion of therapy.
Conclusion. Our preliminary results confirm that VBM plus limited RT could represent a viable and safe alternative to standard RT also in non laparotomy staged patients with favorable HD. However longer follow-up is needed to assess long-term results. Moreover we suggest that some note of caution should be placed regarding the efficacy of VBM regimen in active disease, better reserving this approach for carefully selected patients with early-stage HD without adverse prognostic factors.

T 79 ETOPOSIDE AND EPIRUBICIN CONTAINING CHEMOTHERAPY (CT) PLUS IRRADIATION (RT) IN THE TREATMENT OF EARLY STAGES OF HODGKIN'S DISEASE (HD)

P. S. Mitrou*, T. Klippstein, G. Lautenschläger, K.L. Burkhardt

ABVD seems to be at least as effective as MOPP in the treatment of HD with minimal risks of male sterilization and secondary AML when compared to MOPP. In an attempt to reduce toxicity the ABVD regimen was modified by replacing DTIC with etoposide, vinblastine with vincristine to avoid serious myelotoxicity and adriamycin with epirubicin to reduce the risk of cardiotoxicity. The efficacy and toxicity of the combination was investigated in in 65 consecutive patients with HD entered between 1986 and 1991 in a mulicenter study.
Patients: Fifty-five previously untreated patients (pts) with stages I-IIA,B and unfavourable prognostic factors, mainly mediastinal bulky disease or IIIA,B and 6 pts relapsing following RT in irradiated sites are so far evaluable. The median age of the 38 male and 23 female pts was 30 yrs (17-58 yrs.). Nodular sclerosis (40/61) and mixed cellularity (17/61) were the predominating histologies. 70% of the pts had stage I-IIA,B disease with one or more unfavourable factors and 43% B-Symptoms.
Treatment: The regimen consisted of Epirubicin (E) 30 mg/m², Bleomycin (B) 8 mg/m², Vincristine (O) 1,4 mg/m² i.v. d 1+8, Etoposide (E) 100 mg/m² i.v. d 1-4 and Prednisone (P) 40 mg/m² p.o. d 1-8 (EBOEP). Prednisone was administered in cycles 1+4 and bleomycin in cycles 1 to 4. CT was repeated every 3 weeks for 4 cycles followed by EF RT with 30 Gy. Additional 10 Gy were applicated at bulky disease sites. Patients with stage III disease received two additional courses of CT after RT
Results: All patients entered CR after CT+RT. Restaging following 4 courses of CT revealed a PR in 14 pts. Eleven of them had bulky disease, particularly in the mediastinum. The overall and event free survival rate at 5 years in 92% and 80.5%, respectively. Three out of 6 pretreated an 4 out of 55 previously untreated pts. relapsed. Six of them had lymph node relapses and 1 disease dissemination with liver involvement. Two pts. died of disorders unrelated to HD and treatment. An additional death was treatment related.
Toxicity: Acute toxicity was low. Grade 3/4 toxicity was noted in 16% for WBC, 3% for platelets and 1% for haemoglobin of CT courses. Prevailing acute toxicity leading to dose reduction was peripheral neuropathy/obstipation. Grade 3 lung toxicity occured in one patient. Epirubicin, bleomycin and VP16 have been administered at the calculated doses in >90% of all courses. Dose attenuation for vincristine was necessary in 11.5% of all cycles. Spermatogenesis was preserved in male patients receiving 4-6 cycles of CT. Cardiac and lung function testing 1-3 yrs. after treatment did not reveal chronic toxicity. Thus, EBOEP seems to be an effective regimen with acceptable toxicity, which can be introduced in the treatment of more advanced stages of HD. To further reduced toxicity and explore the efficacy of a two-drug regimen in the early stages I-IIA,B with prognostic unfavourable factors it seems reasonable to with draw bleomycin and vincristine from the combination.0

T 80 PRELIMINARY RESULTS OF EBV REGIMEN PLUS RADIOTHERAPY (RT) IN 22 CHILDREN WITH HODGKIN'S DISEASE (HD).

C. de Insausti, M. Martinez-Siso, G.de Acquatella, M. Cova, C. Barroeta, L. Briceño, E. Sahmkow, A. Rosas-Uribe, E. Casale, M. Parodi.
Cooperative Group HUC,Hospital de Niños,Faculty of Medicine,UCV Caracas,Min-SAS, BADAN and FARMITALIA DE VENEZUELA.

Twenty four children with HD with a mean age of 8 (range 2 to 14) years, male/female ratio 17/7, were followed for a mean of 38 (range 16 to 56) months(m.). Distribution of cases according to histology were: L.P. 1 (4%), N.S. 11 (45%), M.C. 11 (45%), and L.D. 1 (4%). Staging laparotomy(similar to adults) was performed in 11 pts. on clinical stages IA and IIA, each one had 4 biopsies of the spleen. No splenectomy was performed. Clinical stages advanced in 3 out 11 (27%). Final stages were: IA=2 (8%), II=10 (42%), and III=12 (50%).
Rates of 4 high risk factors were: bulky disease (nodes >5 cm) in 14/24 (58%), stage III in 12/24 (50%), B symptoms in 8/24 (33%), and M.M. >30% of chest diameter in 6/24 (25%). Two patients were lost to follow-up after one year. Analysis was performed in the rest (22). Treatment consisted of EBV regimen (epirubicin 30mg/m², bleomycin 10 mg/m², vinblastin 6 mg/m²) on days 1 and 15 of each m.The number of cicles were:4 for stages I or II, 6 for stage IIIA, and 8 for stage IIIB. RT (2500 cGy) to affected areas were given in the middle of the course of chemotherapy.
Complete remision (C.R.) was obtained in 16/22 (73%). Early relapse ocurred in 3/16 (18%): 2 in the area of initial bulky disease and responded to MOPP obtaining (C.R.), and 1 with generalized relapse did not responded to MOPP and died. Six of 22 (27%) had partial remission, (P.R.)were given MOPP. Five of them obtained (C.R.), and the other died of progressive disease.
At 3 and 4 years follow-up total survival rate was 85%, failure-free survival was 70%,and disease-free survival was 82%.Because of the high rate of early relapse and P.R.We increased the epirubicin dose to 60mg% in each cicle in another group of patients, since January 1991 until today. Ten additional pts. given this new regimen have been followed for a mean of 12 m.with a range 4-24 without relapse.
We conclude that epirubicin at a dose of 30 mg/m² on EBV regimen is insufficient to provide prolonged remission in children having HD.

T 81 A WEEKLY "INTENSIVE" CHEMOTHERAPY REGIMEN FOR HODGKIN'S DISEASE - ChlOPhEPP-B.

Child J A, Barnard D L, Norfolk D R, Parapia L, Parker D, Simmons A V, Smith G M. For the Yorkshire Regional Lymphoma Group; co-ordinating centre: Yorkshire Regional Cancer Organisation, Leeds, U.K.

Twenty-five patients with either previously untreated advanced Hodgkin's disease (HD) or with relapsed disease were treated with an intensive weekly chemotherapy regimen ChlOPhEPP-B which comprises: epirubicin (Pharmorubicin) 50mg/m² i.v. day 1, chlorambucil 20mg/m² p.o. days 1-3; vincristine 1.4mg/m² i.v. day 8, prednisolone 60mg/m² p.o. days 8-12; etoposide 100mg/m² i.v. day 15, etoposide 50mg t.d.s. days 16 and 17, procarbazine 100mg/m² p.o. days 15 and 16 (escalating to 3 days if possible); vincristine 1.4mg/m² i.v. day 22, bleomycin 10mg/m² i.v. day 22, prednisolone 60mg/m² p.o. days 22-26. The regimen repeats from day 29 in four week modules to a minimum of 12 weeks with at least one module being given post CR. Of the previously untreated patients (n=14), 12(86%) showed a complete response (CR); in the previously treated patients (n=11), CR was achieved in 5(46%). Nausea and vomiting was experienced by the majority of patients, 21 out of 25 (84%), but was usually mild and of WHO grade 3/4 in only 5 patients (20%). Neurotoxicity due to vincristine was the next most commonly reported side effect, occurring in 14 patients (56%) and requiring dose reduction in 8 (33%). Neutropenia leading to treatment delay and/or dose reduction was recorded in 11 patients (44%); but severe neutropenia (WHO grade 4, neutrophils less than 0.5x 10^9/l) was documented in only 6 patients (24%), for a cumulative total of 9 out of 379 treatment weeks (1.8% of the total treatment time). Dose reductions for neutropenia were applied in relation to 11 of the 379 weekly treatment points (2.9%). Delays in treatment, for any reason, averaged 3.65 weeks per patient. The study confirmed the feasibility of a more intensive weekly multidrug schedule comparable to similar regimens adopted in treating high grade non-Hodgkin's lymphoma. This approach may be particularly applicable in the treatment of advanced, poor prognosis HD and as a prelude to additional intensive "consolidation" therapy with autologous bone marrow or peripheral blood stem cell support.

T 82 Mitoxantrone, Vinblastine and CCNU: A Highly Active Regimen in Poor Prognosis Hodgkin's Disease (HD).

Janice P. Dutcher, Peter H. Wiernik. Albert Einstein Cancer Center, Montefiore Medical Center, Bronx, NY; USA.

22 relapsed/recurrent patients (pts) (13 male/9 female, median age 36 yrs, range 19-71) and 12 poor prognosis previously untreated pts (6 male/6 female, median age 30 yrs, range 20-57) with HD were treated with a regimen piloted by us in ECOG (90% response rate, median response duration 12 months, range 2+ - 48 months). The regimen consists of cycles of mitoxantrone 8mg/m²/day IV x 3 days, vinblastine (V) 8mg/m²/day IV day 1 and 22, CCNU 100 mg/m²/day, orally day 1. Cycles were scheduled to be repeated every 6 weeks. The 22 previously treated pts were stage IIB (5 pts), IIBE (1 pt), IIIB (4 pts), IVA (1 pt) and IVB (11 pts). 3/22 had prior RT only, 7 had 1 prior chemotherapy regimen +/- RT, 12 had multiple prior regimens and 11 had prior doxorubicin. 21/22 pts achieved PR or CR with this regimen (95% response rate). There were 12 PR's with a median duration of 5.5+ months, range 2+ - 14 months with 5 pts continuing therapy. There were 9 CR's, with a median duration of 18+ months, range 2 - 53+ months, with 4 ongoing at 3+, 18+, 24+ and 53+ months. Three of the CR's had had prior doxorubicin. The de novo treatment pts were poor prognosis, with bulky disease, stages IIA bulky (1 pt), IIBE (3 pts), IIIA, (3 pts), IIIB (1 pt), IVA (1 pt) and IVB (3 pts). 11/12 (92%) have achieved CR, with a median duration of 30+ months (range 4+ - 50+ months). The PR in a stage IVB pt lasted 11 months. Toxicity from this regimen has been primarily prolonged pancytopenia. This was more pronounced in the previously treated pts (all missed midcycle V doses) and in pts with marrow involvement. One pt with stage IVB HD, whose marrow was replaced with Reed-Sternberg cells prior to this regimen, but who achieved a CR, has developed secondary leukemia at 24+ months. She remains free of HD. None of the other pts has developed another neoplasm. The results with this regimen in poor prognosis HD appear to be excellent, and compare favorably with other approaches. This regimen deserves further evaluation.

T 83 MOPP/EBVD COMBINATION CHEMOTHERAPY +/- RT FOR ADVANCED HODGKIN'S DISEASE.

G.Abate, S.Tafuto, G.Scoppa, G.Marcacci, V.M.Monda, P.Fimiani, G.Corazzelli, E.Gallì, L.Zuccarino, M.di Lanno
Div. Ematologia Onc. - Ist.Naz.Tumori - Napoli, Italy

Twenty-four patients affected by advanced Hodgkin's disease (M/F=15/9; Stage II bulky and/or B=9; Stage III=9; Stage IV=6; PL=5; SN=11; CM=8; median age=28 years, range 17-69) were enrolled to monthly receive MOPP/EBVD combination chemotherapy, up to 8 cycles : HN_2 6 mg/m² i.v. day 1, VCR 1.4 mg/m² i.v. day 1, PCZ 100 mg/m² p.o. days 1-7, PDN 40 mg/m² p.o. days 1-14; VLB 6 mg/m² i.v. day 8, EDX 30 mg/m² i.v. day 8, BLM 10 mg/m² i.v. day 8, DTIC 375 mg/m² i.v. day 8.

They were given a median (range,4-8) of 8 cycles. Additional local radiotherapy (35 Gy in 18 fractions) was delivered to eleven patients with bulky mediastinum (M/T>0.33). Twenty-three (96%) patients attained a CR and one had progressive disease.

After a follow-up ranging from 10 to 55 months (median,24) the actuarial OS and FFP were 82% and 79% respectively. After 4-48 months (median,17) the projected DFS was 72%. Two patients died at 10 and 34 months, and two patients relapsed at 5 and 36 months.

Grade 1-3 alopecia (92%), vomiting (62%) and leukopenia (58%) were the most frequent side effects. Other toxicities included grade 1-2 infection (46%) and paresthesias (25%).

The median "average dose density" actually delivered was 0.86 for HN_2-PCZ and 0.83 for EDX-VLB. The median "average dose intensity" actually delivered in the first four cycles was 0.99 for HN_2-PCZ and 0.97 for EDX-VLB.

MOPP/EBVD +/- RT program for advanced Hodgkin's disease allows adequate doses of cytotoxic drugs to be delivered. Moreover it enables to reach high CR, OS, FFP and DFS rates, with a moderate acute toxicity.

T 84 The effect of ChlVPP versus alternating, ChlVPP/ABOD in Stage III and IV Hodgkin's Disease:A randomized National Study.

H.Holte*,K.Lote**,R.Telhaug***, E.Wist****, S. Kvaløy*,O,Nome*,R.Følling Elgjo*, A.F.Abrahamsen*.*The Norwegian Radium Hospital,**Haukeland University Hospital ***University Hospital in Trondheim, ****University Hospital in Tromsø.

100 patients with Stage III and Stage IV Hodgkin's disease were randomized to 8 courses of ChlVPP or 8 courses of alternating ChlVPP/ABOD. Remission rate was 90% in each group. CR after ChlVPP was 80% against 76% after alternating treatment. Severe toxicity was the same in both groups.

Dose intensity,prognostic factors, relapse-free and actuarial survival will be presented.

T 85 COMBINED THERAPY (CMT) IN BULKY MEDIASTINAL HODGKIN'S DISEASE (HD).

M. De Lena, P. Ditonno, V. Lorusso, A. Timurian, G. Colucci, E. Maiello, A. Pellecchia, M. Brandi, F. Berardi, F. Marzullo.
Oncology Institute, Via Amendola 209, 70126 Bari, Italy.

From July 1981 to June 1989, 23 stage IIA-IIIB previously untreated (2 minimally pretreated) HD patients (pts) with "bulky" mediastinal involvement (max. mediastinal diameter/max. T5-T6 thoracic diameter $\geq$ 0.33) were included in a prospective study. Chemotherapy (CHT) including at least 6 alternating cycles of ABVD/MOPP was administered until reaching maximum clinical remission. Within 30 days after the last CHT course, radiation therapy (RT) was initiated: standard mantle and lomboaortic fields (including spleen pedicle) in stage I/II and total nodal irradiation in stage III. The dose administered was 36 Gy on involved and 30 Gy on the extended fields. Initial staging workup included complete physical examination, routine blood chemistry and serum copper, standard chest X-ray with whole lung tomography or chest CT scan, bipedal lymphography, bilateral posterior iliac crest bone marrow needle biopsy, laparoscopy with multiple liver and spleen biopsies. Staging workup was repeated at the end of CHT if clinical complete remission (CCR) was achieved. Moreover, an EKG, an echocardiogram, lung perfusion scintiscan and spirometry were performed at the beginning of CHT, at complete remission (CR) and when clinically indicated thereafter. Gonadal function toxicity was evaluated after RT according to information provided by the pts. Median age was 28 years (range 16-46); 18 pts had a nodular sclerosis histology; lung hilum was involved in 6. CR was achieved in 22/23 pts (95.6%) after a mean of 8.3 courses (range: 6-12). The median follow-up was 78 months with 19/23 pts still alive and free of disease; actuarial 10 year overall survival is 83% with 91% disease free survival for CRs. Two pts relapsed 8 and 9 months after CR and one refractory were treated with CEP without achieving CR. One 26 yr. woman with a severe bone marrow failure at the end of RT, died with no evidence of HD. Clinically evident acute or chronic heart or lung toxicity was not observed in the 22 CR pts. Permanent gonadal toxicity was observed in 7/14 women and in 4/5 males. In conclusion, we believe that CMT is, actually, the choice treatment for bulky mediastinal HD; and that irreversible gonadal toxicity should be avoided by semen cryopreservation in males. Nevertheless, in our opinion, the use of MOPP and RT should be reduced in future trials particulary in the youngest pts in order to avoid long term toxicity.

T 86 ROLE OF DRUG DOSE INTENSITY AND OF ADJUVANT RADIATION IN ADVANCED HODGKIN'S DISEASE TREATED WITH ALTERNATING CHEMOTHERAPY REGIMENS.

A. Levis, L. Depaoli, U. Ricardi, U. Monetti, M. Bertini, L. Orsucci, U. Vitolo, A. Gallamini, P. Gavarotti, A. Novarino, D. Rota Scalabrini and L. Resegotti. Piemonte Hodgkin's Disease Register (PHDR) c/o Div. of Hematology, Ospedale Molinette, Torino - Italy.

From 1982 to 1991, 159 patients with advanced Hodgkin's disease (HD) were treated with an alternating chemotherapy plan. Subdivision of patients by stage was: IIB 54, IIIB 23, IV 82. The alternating MOPP-ABVD regimen (MMAA) and the hybrid 1/2MOPP-1/2ABVD (MAMA) were used till 1985 and since 1986 respectively. All patients were treated with at least 6 courses. Radiotherapy (Rt) was planned as limited to the sites of previous bulky disease. No prognostic differences were seen between MMAA and MAMA treatment and all patients were evaluated together for the study. Actual and relative dose intensities of each drug, at 3 and 6 courses of chemotherapy, were calculated according to the Hryniuk and Bush method . Rt fields were sometimes increased and patients were retrospectively subdivided, according to the Rt actually done in 3 groups: no Rt 94 pts, limited field Rt 40 pts, extended fields Rt (mantle or subtotal nodal irradiation) 25 pts.
In univariate analysis, among traditional prognostic features, only stage significantly affected ($p<0.05$) both overall survival (OS) and freedom from failure (FFF) curves. When treatment related variables were considered, an early response to chemotherapy (ERC) and a more extensive Rt significantly predicted a better OS and FFF ($p<0.01$), while none of the drug dose intensity variables had prognostic influence. In multivariate analysis Rt grouping was the main prognostic feature for both OS and FFF. When stage and ERC were forced into the Cox regression model and Rt grouping was tested, the last retained its independent prognostic value ($p<0.01$). Of the 20 nodal relapses, only 2 patients (10%) relapsed within irradiated sites.
Our data show that adjuvant Rt has a favourable impact on clinical outcome of patients with advanced HD treated with alternated chemotherapy regimens. On the contrary it was impossible to demonstrate any prognostic influence of drug dose intensity variables.

T 87 PRELIMINARY RESULTS OF AN ALTERNATING CHEMOTHERAPY REGIMEN (ChlVP/CEB) FOR ELDERLY PATIENTS AFFECTED BY HODGKIN'S DISEASE.

B. Botto, A. Levis, L. Depaoli, M. Bertini, L. Mairone, L. Orsucci, U. Vitolo, P. Gavarotti, A. Salomone, G. Buchi and L. Resegotti. Piemonte Hodgkin's Disease Register (PHDR) c/o Div. of Hematology, Ospedale Molinette, Torino - Italy.

As a consequence of the bimodal age-specific distribution, the number of elderly patients affected by Hodgkin's disease (HD) is low and there are so far little data on treatment strategies tailored on advanced age. From January 1990 19 patients over 65 years (median age 71; range 66-80) were treated according to an alternating chemotherapy regimen tailored on elderly people. The chemotherapy regimen was as follows: chlorambucil 6 mg/sqm on days 1 to 7, vinblastine 6 mg/sqm on day 1, procarbazine 100 mg/sqm on days 1 to 7, prednisone 30 mg/sqm on days 1 to 7, cyclophosphamide 500 mg/sqm on day 15, etoposide 70 mg/sqm on day 15 and bleomycin 10 mg/sqm on day 15. Chemotherapy courses were planned every 4 weeks. Four patients in stage IA and IIA were treated with 3 courses of ChlVP/CEB followed by involved field radiotherapy. The 15 patients with more advanced stage (4 in stage IIB, 7 in stage IIIB and 4 in stage IV) were planned to receive 6 courses of chemotherapy, with radiotherapy limited to bulky areas. Haematopoietic growth factors were not emploied. The method of Hryniuk and Bush was used to calculate the relative dose intensities of each drug at 3 and 6 courses, as well as their arithmetic means (RDI3 and RDI6).
Results of ChlVP/CEB in terms of dose intensity and toxicity, as compared to our hystorical data on 65 elderly pts. treated beetween 1982 and 1989 are as follows:

	Previous analysis (1982-89)	ChlVP/CEB (1990-91)	p value
RDI3	68%	80%	0.04
RDI6	58%	76%	0.02
Toxic deaths	17%	5%	n.s.

ChlVP/CEB is a regimen well tollerated in elderly people and the use of growth factors could further improve results. So far 80% of patients treated with ChlVP/CEB entered CR and freedom from failure curve is projected to 54%. These preliminar data are better than our hystorical control, but a longer follow up and a larger number of patients is needed to draw definite conclusions.

T 88 CYTOSINE ARABINOSIDE(A), CIS-PLATINUM(P), AND ETOPOSIDE(E) FOR THE TREATMENT OF PATIENTS WITH RELAPSED HODGKIN'S DISEASE(HD): A PEDIATRIC ONCOLOGY GROUP (POG) STUDY.

R. Wimmer, M. Weiner, C. Schwartz, and B. Leventhal for the POG, St. Louis, MO, USA.

Salvage therapy for patients with HD who relapsed after exposure to both standard combination chemotherapy regimens (MOPP and ABVD, or their equivalents) is variable at present. Preliminary data (Proc AM So Clin Oncol 6:191, 1987) suggested that multiple sequenced pulses of an APE chemotherapy regimen might offer such patients an effective alternative. From April, 1988, to September, 1992, the POG conducted a study (#8827) utilizing APE infusions in relapsed HD patients who had received MOPP and ABVD, and were beyond consideration that radiotherapy alone might be curative. Study objectives were to estimate disease response to APE and to measure toxicity. All patients had measurable disease at study entry. APE is administered as: A-375 mg/sqM IV bolus followed by 375 mg/sqM as a 3 hour continuous infusion, P-15 mg/sqM at one hour into the A infusion, and E-20 mg/sqM at the end of the A infusion. A single monthly APE cycle gives 4 doses of this sequence every 12 hours. The study suggested 8 monthly cycles if a complete remission was obtained.

Of 29 currently evaluable study entrants, 12 (41%) achieved a complete remission, 7 (24%) a partial remission, 5 (17%) obtained a mixed response, and 5 (17%) had progressive disease. Significant toxicity was limited to hematologic parameters, with 56% of patients experiencing neutropenia less than 500/cu mm and 36% thrombocytopenia less than 25,000/cu mm. Only 2 episodes of bacterial sepsis, one of which was central line related, were seen. Transfusions of red blood cells or platelets were infrequent. Emesis was well controlled with standard agents.

Thus, APE has been documented to have activity in a group of heavily pre-treated HD patients with very tolerable side effects. Its role as induction therapy for relapsed patients prior to bone marrow transplant, or as initial therapy for early stage HD remains to be evaluated.

T 89 M-CAVE-CEC: AN EFFECTIVE SALVAGE CHEMOTHERAPEUTIC REGIMEN FOR EARLY RELAPSED OR PROGRESSIVE HODGKIN'S DISEASE FOLLOWING INITIAL CHEMOTHERAPY.

G. Vreugdenhil, M. Jongen, R.M.A. Kurstjens *, B.E. de Pauw, J.M.M. Raemaekers. Dept. Hematology, University Hospital Nijmegen and * Dept. Internal Medicine, Groot Zieken Gasthuis, Den Bosch, The Netherlands

Failure or early relapse of Hodgkin's disease (HD) following MOPP-like chemotherapy is associated with a poor outcome. Non-cross resistent salvage regimens, such as ABVD, resulted in 5-year survival rates of 10-20 %. We studied M-CAVe-CEC as an alternating salvage chemotherapeutic regimen in early relapsed or progressive Hodgkin's disease after MOPP containing initial treatment schedules.

Patients and methods. Sixteen patients (early relapse: n=9; primary refractory: n=7) were studied. Their mean age was 33 ± 11 years (12 males and 4 females). Thirteen (81 %) had nodular sclerosing and 3 (19 %) had mixed cellularity histologic subtype. Their clinical stage (CS) at diagnosis was IIA (n=4; 25 %), IIB (n=3; 19 %), IIIB (n=5; 31 %) and IVB (n=4; 25 %). Initial treatment consisted of MOPP in 3 (19 %), MOPP and radiotherapy in 10 (62 %) and MOPP/ABV in 3 (19 %) patients. After relapse or progression had been established, they started bi-monthly courses with M-CAVe-CEC (Methotrexate 30 mg/m2 IV; day 1. Cyclophosphamide 300 mg/m2, Adriamycine 40 mg/m and Vinblastine 6 mg/m2 IV; day 1/15. CCNU 100 mg/m2 orally day 28. Chlorambucil 8 mg/m2 and Etoposide 100 mg/m2 orally day 29-33 until a total of 4 courses).

Results. When M-CAVe-CEC was commenced, 4 patients (25 %) were in CS IIA, 2 (13 %) in IIB, 1 (6 %) in IIIA, 4 (25 %) in IIIB and 5 (31 %) in IVB. Seven (44 %) patients achieved a complete remission (CR). Of these patients 4 (56 %) were in CS IIA, 1 (18 %) in IIB, 1 (18 %) in IIIA and 1 (18 %) in IVB. Four (24 %) patients achieved a partial remission (PR), of whom 1 (25 %) was in CS IIIA, 1 (25 %) in IIIB and 2 (50 %) in IVB. Five (31 %) had a failure, of whom 1 (20 %) was in CS IIB, 2 (40 %) in IIIB and 2 (40 %) in IVB. In the 7 CR patients 1 relapsed after 59 months and subsequently achieved a third CR and 1 developed a secondary acute leukemia after 36 months and died. Serum lactate dehydrogenase (LDH) was lower in patients achieving CR as compared to those who did not (197 ± 39 vs 336 ± 80 U/l; $p<0.05$). Time between diagnosis and progression or relapse did not influence CR rate. The actuarial overall survival was 54 % and 38 % at 2 and 5 years respectively. The actuarial progression free survival was 34 % at 2 and 5 years. Dose reductions were necessary in 62 % during the first part of courses (M-CAVe) given and in 49 % during the second part of the courses (CEC) delivered, usually due to granulocytopenia.

Conclusions. M-CAVe-CEC constitutes an effective non-cross resistant alternating salvage chemotherapeutic regimen for early relapsed or progressive HD previously treated with MOPP containing regimens. The majority of responses were obtained in patients with a limited stage of disease and low serum LDH at time of relapse or progression and start of treatment. Bone marow toxicity was considerable, leading to frequent dose reductions. Possibly, the use of hematopoietic growth factors may further increase the therapeutic potential of this regimen in a larger phase II study.

T 90 CONVENTIONAL CHEMOTHERAPY IN RESISTANT AND RELAPSED HODGKIN'S DISEASE.

M.Herold,U.Börner, G.Anger Department of Internal Medicine,Medical Academy, O - 5010 Erfurt,Germany

The treatment of patients with Hodgkin's disease in advanced stages who do not respond to standard treatment programs or relapse early is still an unsolved problem, the same is true however for those patients who experience multiple relapses.

Starting 1982 we treated 50 heavily pretreated patients with a combination of CCNU 60 mg/m^2 p.o. day 1, Leukeran 12 mg/m^2 p.o. day 1 - 5, Methotrexate 5 mg/m^2 p.o. day 1 - 5 and prednisolon 50 mg p.o. day 1 - 5; given every 4 weeks. Complete remission reached 12/50 (24 %) pts., 7/50 (14 %) had a partial remission and 31/50(62%) did not respond. At present 5/12 complete responders are still in CR. For CR-patients after 5 years RFS-rate is 39 % and survival-rate 57 % (median 29 and 59 + months respectively). For all patients median survival is 18 months, being a survival-rate of 25 % after 5 years of observation (Kaplan-Meier-estimations).

Toxicity was moderate, mucositis being the main problem (48 %, WHO-grade 1 - 3).

The results achieved are well comparable to those of other authors reported recently. The advantages of the program are p.o.-administration and a relatively low toxicity.

Summerizing the results from the literature and the own experiences standard-dose third-line programs are not the solution of salvage treatment in Hodgkin's disease.

T 91 ETOPOSIDE, IFOSFAMIDE, AND CISPLATINUM (VIP REGIMEN) IN RELAPSE AND/OR REFRACTORY HODGKIN'S DISEASE (HD).

V.Ribrag, P. Brault, J.H. Bourhis, J.N. Munck, S. Jimenez, A. Ibrahim, J.L. Pico, M. Hayat.
Institut Gustave Roussy, rue Camille Desmoulins - 94805 Villejuif, France.

From January 1989 to January 1993, 24 patients (pts) with refractory (8 pts) or relapsed (16 pts) HD were included in this prospective study. Sex ratio (M/W): 16/18, median age: 29 (16-57), histology: nodular sclerosis: 17, mixed cellularity: 5, lymphocyte depletion: 2. Previous treatment: chemotherapy + radiotherapy: 17, chemotherapy alone: 7 (6 pts primary refractory, 1 pt stage IV at presentation). At the time of VIP regimen, 3 had bulky disease, 15 had stage IV disease (including 9 bone marrow and/or bone involvment) and 11 pts had a relapse within previously irradiated fields. Among the relapse pts, 11 relapsed less than 12 months after completion of first line therapy, 3 had previously obtained a first CR of more than 12 months but were in second or in third relapse, 2 pts had a first CR of more than 12 months but had previously received MOPP/ABVD as chemotherapy. VIP regimen stands as follows: VP16: 75 mg/m²/day(d) d1-5, Ifosfamide: 1.2 g/m²/d d1-5 , Cisplatinum: 20 mg/m²/d d1-5, one course every 4 weeks. If pts had a chemosensitive disease, high dose chemotherapy followed by autologous bone marrow transplantation (ABMT) were proposed. When ABMT was not feasable, and pts were chemosensitive 6 courses of VIP were given. 89 courses of VIP have been performed. No toxic death was observed. 60 % of pts had grade IV granulocytopenia and 20 % were associated with grade II infection. 22/24 pts had mesurable disease, 2 pts had only bone marrow involvment. After 2 courses of VIP, 21/24 pts (87%) of pts were considered as chemosensitive. 13 of these pts went on to ABMT (2 pts refused, 3 had major organ failure and 3 had previous extensive radiotherapy including pelvic site + chemotherapy). 7/13 (53%) pts treated with high dose chemotherapy and ABMT are alive in CR with a mean follow-up of 20 months. 4/8 pts who did not went on to high dose chemotherapy with ABMT but who were responders to VIP therapy are alive without progressive disease with a follow-up of 12, 24, 26 and 27 months. Conclusion: VIP regimen followed bv intensification with ABMT seems to be an attractive salvage therapy in heavily pretreated Hodgkin's disease and may benefit from the adjunction of hematopoietic growth factors.

T 92 AUTOLOGOUS BONE MARROW TRANSPLANT (AUTO BMT) FOR HODGKIN DISEASE (HD) : REPORT ON 42 PATIENTS FROM A SINGLE INSTITUTION

J. Camerlo, D. Blaise, P. Viens, R. Bouabdallah, A.M. Stoppa, L. Xerri, A.P. Blanc, J.A. Gastaut, Y. Carcassonne and D. Maraninchi, Institut J. Paoli-Calmettes - Marseille, FRANCE.

Patients with refractory and relapsed HD has poor outcome with conventional chemotherapy. These patients seems to benefit from intensive chemotherapy followed by auto BMT.

From 1982 to 1992, we transplanted 42 pts (median age = 32 (16 - 58) ; M/F = 20/22 ; stages at dianosis II : n = 4 ; III : n = 19 ; IV : n = 19).

Thirty six patients were transplanted after relapse (complete remission (CR) : CR2 = 9 ; CR3 = 7 ; CR4 = 1 ; Sensitive Relapse (SR) = 8 ; Refractory Relapse (RR) = 11).

Four patients were transplanted as they did not reach CR1 (Initial Partial Response (IPR) = 3, Initial Refractory Disease (IRD) = 1). Two pts were transplanted in CR1. Median time between diagnosis and auto BMT is 45 months (10-20). Three pts had toxic death (CR3 = 2 ; RR = 1). The 3,5 years probability of relapse, survivol and DFS are :

	N	RELAPSE	SURVIVAL	DFS
OVERALL	42	48 %	71 %	48 %
CR + IPR	22	28 %*	91 %	65 %*
IRD + SR + RR	20	69 %*	48 %	29 %*

* $p < 0.01$

The data support that outcome of poor risk patients benefits from auto-BMT and that this benefit is increased when auto BMT is performed early.
However longer follow up is requested.

T 93 Autologous Blood Stem Cell Transplantation (ABSCT) for Hodgkin's Disease in Sensitive Relapse - The Heidelbeg Experience.

R. Haas, R. Ehrhardt, H. Goldschmidt, B. Witt, W. Hunstein. Dept. of Internal Medicine V, University of Heidelberg, Germany

High-dose therapy followed by autografting with bone marrow or peripheral blood stem cells (PBSC) offers a treatment modality for patients (pts.) with relapsed Hodgkin's disease. Since 3/1986, we autografted 40 pts. with Hodgkin's disease in chemosensitive relapse. PBSC were used because the bone marrow was hypocellular or fibrotic due to previous radio- and/or chemotherapy and therefore not suitable for harvest (Körbling et al., J. Clin. Oncol. 1990, 8; 978-985). With the availability of hematopoietic growth factors, blood stem cell collection could be improved by increasing the number of circulating hematopoietic progenitors. Our experience encompasses the use of GM-CSF administered during steady-state hematopoiesis (Haas et al., Exp. Hematol. 1990, 18; 94-98) as well as following cytotoxic chemotherapy (Haas et al., Bone Marrow Transplantation 1992, 9; 459-465).
We have now evaluated the effect of G-CSF (5ug/kg/day, s.c.; Neupogen, Amgen) on the quantitiy and composition of PBSC when administered 24 hours following Dexa-BEAM in a group of 10 pts. Following autografting with the G-CSF-exposed PBSC, all pts. achieved complete trilineage engraftment with a pattern of hematological recovery predictable by the quantity of CD34+ cells infused. In a prospective randomized study we currently compare the PBSC mobilizing capacity of GM-CSF versus G-CSF.
The clinical results of this single institution can be summarized as follows: of the 40 pts. autografted, 28 were male and 12 female with a median age of 30 years (range 19- 51). At the time of ABSCT, 24 pts. were in complete remission (CR) and 16 pts. in partial remission (PR). It is worth noting that the pretransplant conditioning regimen always consisted of CBV (cyclophosphamide, BCNU, etoposide). Until now, 22 pts. (55%) have an event-free survival (EFS) with a median follow-up of 22.5 months (range 2-72). Five pts. (12.5%) who had extensive pretreatment (median of 18 courses with 2 - 6 different regimens) died of transplantation-related complications and 13 pts. (33%) relapsed after a median time of 5 months (range 1-38). Analyzing factors predictive for treatment failure, we found that the remission status prior to transplantation and the amount of previous chemotherapy are of major importance. For pts. autografted in CR the EFS is 67% compared with 38% for pts. transplanted in PR. Therefore, transplantation-related toxicity can only be lowered and the overall treatment results improved when patients at "high risk" are identified earlier during the course of their disease. The collection of sufficient quantities of blood stem cells may then allow "double-grafting" in pts. achieving PR after salvage therapy.

T 94 HIGH DOSE CHEMOTHERAPY (HD-CT) FOLLOWED BY AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) FOR POOR PROGNOSIS STAGE IV HODGKIN'S DISEASE (HD) IN FIRST COMPLETE (CR1) OR GOOD PARTIAL RESPONSE (PR1).

J. Fleury[1], M. Legros[1], P. Colombat[2], H. Curé[1], P. Condat[1], E. Bélembaogo[1], B. Choufi[1], I. Van Praagh[1], P. Chollet[1], C. Linassier[2], D. Blaise[3], P. Viens[3], D. Maraninchi[3], J.P. Lamagnère[2], R. Plagne[1]. [1]Centre Jean Perrin, 63011 Clermont-Ferrand Cedex 1, [2]C.H.R.U. Bretonneau, 37044 Tours, [3]Institut Paoli-Calmettes, 13273 Marseille, France.

From March 1986 to October 1992, 29 stage IV patients (12 females, 17 males) with HD received HD-CT with ASCT in CR1 (n = 14) or in good PR1 (n = 15) (≥ 75 % reduction mass) after conventional chemotherapy.
The aim of the study was to evaluate the toxicity and the relative effectiveness of high dose consolidation therapy on survival. All patients (median age, 29 ; 18-55) had initially at least 2 of the following poor prognosis factors (median 3 PPF) :
systemic symptoms (n = 25), bulky disease (n = 18), ≥ 2 extranodal sites (n = 13), bone marrow involvement (n = 7), lymphocyte count ≤ 1.10^9/l (n = 8), erythrocyte sedimentation rate ≥ 50 mm (n = 22).
Median time between diagnosis and ASCT was 9 months (5-15). Conditioning regimens were CBV (n = 11) (Cytoxan 140 mg/kg b.w., BCNU 350 mg/m², VP16 600 mg/m²), CBV plus mediastinum irradiation (n = 7) (26 Grays over 10 days with 20 fractions just before CBV), BEAM (n = 11) (BCNU 450 mg/m², VP16 1 g/m², Aracytin 1 g/m², Melphalan 140 mg/m²) followed by bone marrow rescue (n = 23) or peripheral stem cell reinfusion (n = 3). Nine patients received a total (n = 8) or subtotal (n = 1) lymphoid irradiation after transplantation. Median time to engraftment was 16 days (10-30) for neutrophils ≥ 0.5 x 10^9/l and 18 days (6-120) for platelets ≥ 50 x 10^9/l. Toxicity was mild except for one early toxic death from pulmonary 8 infection. Thirteen of 15 in good PR1 achieved CR since 1 died early of toxicity and 1 stayed in PR. Of the 27 patients who were in CR after ASCT, 5 relapsed (3, 4, 4, 18, 36 months). Of the 5 patients (3 CR1, 2 PR1), 1 died of progressive disease and 4 achieved objective response after salvage treatment (3 CR2, 1 PR3). The overall survival and disease-free survival (Kaplan-Meier) for all patients are projected to be 93 % and 75 % at 3 years respectively with a median follow-up of 30 months (3-75). A randomized study evaluating high dose consolidation for stade IV Hodgkin's disease with PPF should be considered.

T 95 AUTOLOGOUS BONE MARROW TRANSPLANTATION IN RELAPSED PATIENTS WITH HODGKIN'S DISEASE CHEMOSENSITIVE TO ACOPE TREATMENT.

A.A.Fauser, G. Köchling, B.Euchenhofer, J. Finke, G. Dölken. Department of Hematology/Oncology, Bone Marrow Transplant Program, Albert-Ludwigs-Universtität, Freiburg, Germany

Short term remissions after appropriate chemotherapy, i.e. MOPP/ABVD, and radiotherapy is a poor prognostic feature in patients with Hodgkin's disease. Autologous bone marrow transplantation (ABMT) might be considered as a treatment modality in order to improve survival. Between May 1990 and July 1992 7 patients with Hodgkin's disease in second or subsequent relapse were treated with ACOPE (Adriamycine 40 mg/m², Cyclophosphamide 800 mg/m² day 1,2, Vincristin 1.4 mg/m² day 1,8, Prednisone 80 mg/m² day 1-10, VP 16 100 mg/m² day 1,2) (two to three cycles) in order to assess the chemosensitivity. Patients were considered as responders by the following criteria: achieving a complete remission after two to three cycles of ACOPE; partial remission, i.e. reduction of the tumor mass or lymph nodes by more than 50 % of the original size. Patients fullfilling these criteria received CBV (BCNU 0,6 g/m² day 1, Cyclophosphamide 1,8 g/m² day 1-4, VP 16 2 x 0,4 g/m² day 2-4) chemotherapy followed by ABMT. At present time, 6 out of 7 patients are disease-free (follow-up time median 19 month). Our result suggested that ACOPE followed by ABMT, after CBV-therapy, might be an appropriate treatment in chemosensitive patients with Hodgkin's disease in second or subsequent relapse.

T 96 HEMATOPOIETIC RECONSTITUTION AFTER AUTOLOGOUS PERIPHERAL BLOOD (PB) AND BONE MARROW (BM) PROGENITOR CELLS TRANSPLANTATION (PCT) IN LYMPHOMAS.

G Milone, J Martinez Rolón, E Diaz Cantón, I Fernandez, C Corrado, P Desmery, A Roncoroni, S Pavlovsky. FUNDALEU, Bs As, Argentina.

Since August 1991 to January 1993, 29 lymphomas (6 Hodgkin's disease and 23 Non Hodgkin's lymphomas), median age 32 (8-56), 18 females and 11 males, were treated with autologous PB and BMPCT. None of the patients (pts) had previous pelvic irradiation neither BM infiltration at time of mobilization. Six pts were in 1st, 10 in 2nd and 1 in 3rd complete remission, and 12 pts in partial remission. PC were mobilized with chemotherapy: ESHAP (17 pts), CAVPE (5 pts), high dose cyclophosphamide (CFM) (3 pts) or other (4 pts), followed by G-CSF 5 mcg/kg/d sc. When pts reached a WBC count ≥ 20.000/mm³, platelet ≥ 50.000/mm³ and CD34+ >1% in peripheral cells, PC were collected with 2 leukapheresis, on the 3rd day harvested the BM. All pts received the same ablative treatment with BCNU 300mg/m² IV day -6, VP16 2.400mg/m² in 34 h infusion days -5 and -4, CFM 60 mg/kg/d IV days -3 and -2 plus MESNA. Pts remains in rooms with HEPA filter, and received since day +1 G-CSF 5 mcg/kg/d sc. BM and PBPC were infused on days 0 and +1 respectively. The median of mononuclear cell infused were $7.7/10^8$/kg (2.3-25.4) of BM and $15.9/10^8$/kg (2.3-49.5) of PB. The median number of CD34+ cells infused was in BM $17.6/10^6$/kg (2.2-100.0) and in PB $41.1/10^6$/kg (2.9-148.5). The median time to achieve ≥1000/mm³ neutrophils was 12 days (7-18), and 17.5 days (8-45) to platelets ≥50.000/mm³. Time to platelet and red blood cell transfusion independence was 11 (2-36) and 10 (3-20) days respectively. Median number of platelet and RBC units transfused was 4 (0-22) and 4 (0-14) respectively. Duration of hospitalization was 22 days (17-27). Twenty three pts had fever, with a median duration of 3 days (1-11) and were treated with antibiotics, 7 received amphotericine due to none resolve fever episodes; 9 pts had confirmed bacterial infection (3 bacteriemies) and none fungemia were found. No treatment related deaths occurred. Three pts died of progressive disease after PCT, 4 pts are alive with active disease and 22 remain disease free from 1 to 15 months.
Conclusion: PCT with mobilized PC from BM and PB in patients with lymphoma resulted in accelerated hematopoietic recovery without mortality. It is too early to comment about freedom from disease progression in this group of patients.

T 97 DOUBLE ABMT IN REFRACTORY HODGKIN DISEASE,AND IL2'GRAFT VERSUS TUMOR EFFECT.M.R.Sajeva,M.M.Greco,A.Morelli,M.Carotenuto,N.Di-Renzo,P.Scalzulli,N.Cascavilla,S.Ladogana,M.A.Falcone,C.Bodenizza.

Sequential autologous bone marrow transplantation(ABMT)is a not common procedure for refractory/resistant Hodgkin disease(MH), although long term free survival are described;recent in vivo and in vitro studies, suggest that IL2 administration following allogenic bone marrow transplantation may enhance the antileukemic potential of the allograft.Moreover the absence of graft-versus tumor effect in ABMT, seems to be a major reason for higher relapse rates. In view of these considerations, two patients with refractory MH underwent double ABMT with the use of IL2 during the second.EDX, BCNU,ETOPOSIDE, were used like first conditioning regimen(CVB), where BUSULPHANO(3.5mg./Kg),ETOPOSIDE(20/mg/Kg)and MELPHALAN (120 mg./m^2) like second.IL2 was start at the first day of the second regimen and was administrated for 6 days in the first patient at the total dose of 26M and than discontinuated for toxicity(fever grade IV WHO). A cutaneous and mucous graft versus host disease (GVHD) grade I-II, histologically proven, developed at +17d, and is occasionally present at +7 months, in absence of clinically and strumentally showed disease.In the second patient IL2 was administrated for 8 days at the dose of 3M/day, during the second conditioning regimen, but any evidence of GVHD appeared, this patient died at +20d for pneumonia.
More experiences are need to prove the thrue effect of a autologous GVHD, and the value of IL2.

T 98 BODY WEIGHT, OBESITY AND DOSE; EFFECTS ON OUTCOME IN HODGKIN'S DISEASE (HD) TREATED WITH MVPP CHEMOTHERAPY. J.A. Radford[1], W.D.J. Ryder[2], M. Ranson[1], D.P. Deakin[3], P.M. Wilkinson[4] and D. Crowther[1]. [1]CRC Department of Medical Oncology and Departments of [2]Medical Statistics, [3]Radiotherapy, and [4]Clinical Pharmacology, Christie Hospital, Manchester, M20 9BX.

Outcome (measured in terms of progression-free survival, PFS) has been studied in 259 pts (170 male, 89 female) treated with fixed dose MVPP (mustine and vinblastine both 10mg i.v. Days 1 and 8; procarbazine 150mg p.o. daily and prednisolone 50mg daily, both for 14 days every 6 weeks) for HD. Median age at presentation was 29 years and 85% had stage III or IV. A median of 7 cycles of MVPP (no drug substitution) were delivered and remission status at completion was CR, 61%; CR(u), 8%; PR, 13%; NC or PD, 11.5%; died during treatment, 6.5%. With a median follow-up for survivors of 7 years, actuarial survival and PFS at 10 years is 60% and 70% respectively.

In univariate analysis, pts with a body weight (BW) of <70kg at presentation had significantly better PFS than those >70kg (80% vs 57% at 10 years) raising the possibility of a dose effect (more mgs drug per kg of BW for lighter pts). This view is supported by Cox multivariate analysis where a model comprising stage, a dose descriptor Z, and sex, best described the data; for pts of the same stage and sex a 50% reduction in Z was found to double the relative risk of progression after the first year. Further analysis shows that weight may be a surrogate for obesity (body mass index, BMI >25) with a model comprising stage and either BW or BMI best describing incidence of progression after the first year. If so, the much poorer PFS in heavier (and more obese) pts might be explained on the basis of a larger volume of distribution and a consequent reduction in drug levels at the tumour surface.

Confirmatory pharmacokinetic studies are required. It would also be of interest to examine the effect of obesity on PFS in pts treated with drug doses calculated on a BW basis and this is planned.

T 99 LATE SEQUELAE FOLLOWING COMBINED MODALITY THERAPY FOR PEDIATRIC HODGKIN'S DISEASE.I.Golubicic,Z.Milosevic,Z.Barjaktarevic,V.Sobic.Institute of Oncology and Radiology,11ooo Belgrade,Yugoslavia

Recent advances in treatment of pediatric cancer have resulted in an increased survival and possible cure for many malignant diseases,such as Hodgkin's disease.Because the majority of children survive long enough to face the risk of development late treatment-related complications,attention has been drawn to minimize these adverse effects.
The aims of our study were: 1.assessment of musculoskeletal deformities,2.evaluation of thyroid function and 3.definition of dependence on side-effects to the radiotherapy parameters (irradiation technique and given doses).The study included 85 long-term survivors treated with radiotherapy for pediatric Hodgkin's disease (mean age at diagnosis 11years,range 3-18yrs.) and being off tretment 2-12years (Me=5yrs.).All children also received chemotherapy (MOPP and/or ABVD).Various megavoltage technique were used according to clinical stages.The majority of children were irradiated with "mantle field" and TD 25-35Gy (range 2o-45Gy).Chest and neck deformities were discovered in 22pts.Mild or moderate degree of impairments were documented in 17pts. and severe in 5pts.Ten children received radiotherapy under 11years,all under 14years old.The mean dose applied in all pts. was>3oGy.Evaluation of thyroid gland function showed compensated hypothyroidism in 2o.o5% and no one case of overt dysfunction (mean basal TSH= 7.78mU/1).Elevated Tg were detected in 23.o7% (mean Tg=8o.o6nmol/1).In 3pts. increased TSH velues were transient,as well as Tg velue in one case.TSH was normal in all pts. receiving low dose neak irradiation.Two second tumors were diagnosed.Both of them developed within radiation portals after "mantle"technique and were histologically benign:adenoma of thyroid gland and osteohondroma of right scapula(latent periods 1o and 4yrs.)
It can be concluded that irradiation in combined modality therapy had no prominent effects on quality of life in pts.treated for pediatric Hodgkin's disease.A few severe musculoskeletal deformities due to large-volume and high dose radiotherapy were noticed.Risk for thyroid dysfunction seems to be associated with high dose neak irradiation.

T 100 LATE PULMONARY AND CARDIOVASCULAR COMPLICATIONS OF THERAPY IN HODGKIN'S DISEASE. E. Dan, R. Or, C. Putterman, A. Polliack. Lymphoma-Leukemia Unit, Department of Hematology, Hadassah University, Jerusalem, Israel.

With the advent of modern therapeutic approaches, even patients with advanced Hodgkin's disease have high cure rates today. Therefore, more attention is gradually being focused upon the late complications of chemotherapy and irradiation, appearing long after the patient is in remission and thought to be cured. In this report, we review the incidence and presentation of some of the cardiovascular and pulmonary complications which may appear later in the course of the disease. Cardiovascular mishaps include pericardial manifestations, conduction abnormalities, cardiomyopathy, and premature coronary artery disease. Pulmonary complications discussed are lung fibrosis, spontaneous pneumothorax, pumonary veno-occlusive disease, and hyperlucent lung. Three instructive cases from our recent experience, are presented here. One fatal case was due to cardiac failure because of radiation-induced pericarditis and coronary artery disease. Another patient with an almost fatal complication required lung transplantation because of severe bilaterial radiation fibrosis of the lung and pulmonary veno-occlusive disease. The third instance was also life-threatening in nature, with radiation-induced arterial changes in the major arteries of the chest and neck, resulting in recurrent cerebral and ophthalmic thrombo-embolic disease. It is suggested that potentially severe cardiopulmonary complications be considered during the planning of the initial and subsequent management of patients with Hodgkin's disease, particularly in an era employing autologous and allogeneic bone marrow transplantation as part of therapy in selected cases.

T 101 ADRENERGIC MODULATION OF HEMOPOIESIS AFTER SYNGENEIC BMT AND IN NORMAL MICE.

G.J.M. Maestroni, A. Conti, E. Pedrinis. Lab for Experimental Pathology, Istituto Cantonale di Patologia, 6604 Locarno, Switzerland.

Autologous or syngeneic and allogeneic bone marrow transplantation (BMT) are increasingly used in the therapy of lymphohemopoietic and solid malignancies and in genetic or acquired hemopoietic diseases. Besides tumor eradication, the success of such procedures depends also on the rate and completeness of reconstitution of hemopoietic and immune functions after lethal irradiation and BMT. We demonstrated that lympho-hemopoietic reconstitution in mice is under an adrenergic control (1). Chemical sympathectomy by 6-OH-dopamine (6-OHDA) increased significantly the number of peripheral blood leukocytes after syngeneic BMT. The α-1 adrenergic antagonist prazosin but not the β-blocker propranolol mimicked and extended the effect of 6-OHDA inducing a rapid and significant increase also of platelets, granulocyte-macrophage colony forming units (GM-CFU) in the bone marrow and mononucleated spleen cells (1). The prazosin-induced increase in platelets concentration was counteracted by the contemporary administration of propranolol. Moreover, prazosin treatment inhibited T lymphocytes reconstitution as it was apparent by FACS analysis of spleen and thymus cells. The mechanisms of such interesting effects seem to depend on the presence of adrenergic receptors on bone marrow cells. In fact, addition of noradrenaline (NA) in the GM-CFU assay resulted in an inhibition of GM colonies. This inhibition was counteracted by adrenergic antagonists in the following order of potency: prazosin > phentolamine > yohimbine, which is typical for α1-adrenergic receptors. The presence of α1-adrenergic receptors was further confirmed by the effect of agonists such as the α1-agonist methoxamine and the α2-agonist clonidine. However, the dose-response curve of the antagonists was biphasic suggesting the involvement of other types of adrenergic receptors. In fact, blockade of β-adrenoceptors by propranolol turned the biphasic inhibition shown by α-adrenergic antagonists in a single-phase curve. In addition, we found a specific ^{3}H-prazosin binding in membranes from bone marrow cells. In conclusion, we claim that the sympathetic nervous system participate in the physiological regulation of hemopoiesis via specific adrenergic receptors on bone marrow cells. This finding opens interesting new possibilities in the management of BMT as well as in the study and perhaps therapy of immunological and hemopoietic disorders.

1. Maestroni, G.J.M., Conti, A., E. Pedrinis. 1992. Blood, 80: 1178-1182.

T 102 MANTLE ZONE LYMPHOMA (MZL).A CLINICAL STUDY OF 26 CASES.

A.Colombo,G.Castelli,G.Pagnucco,L.Vanelli,C.Bernasconi.
Chair of Haematology,Policlinico San Matteo,27100 Pavia.

Intermediate lymphocytic lymphoma /lymphocytic lymphoma of intermediate differentiation (ILL/IDL)is considered to be a subtype of non-Hodgkin Lymphoma with cytological features of small lymphocytic lymphoma and of small cleaved cell lymphoma;the nodular variant is mantle zone lymphoma (MZL).Recent immunological and molecular studies of ILL/IDL have suggested that ILL/IDL is distinct from B-cell lymphomas of follicular center cell.ILL/IDL has not,however, been identified as a specific category in the Working Formulation classification;cytologically and phenotypically most cases are equivalent to centrocytic lyphoma in the Kiel scheme.
In this study we analyzed retrospectively the clinical and pathological features of 26 patients with MZL treated in the Haematology Division of Policlinico San Matteo of Pavia between 1979 and 1991.The clinical and/or pathological staging was determined by Ann Arbor criteria.All the histological criteria of MZL are present in the reviewed nodes and parenchymal biopsies.
A total of 26 patients was examined.The median age at the onset of the disease was 57,6 years,with a range of 30-81 years.Fourteen patients were female and twelve male.
All the patients in our series presented with advanced disease.Twenty-two patients (84,6%) were in III-IV stage but had minimal parenchymal organ dysfunction. The percentage of patiens presenting superficial nodes enlargement was 86,4; 3,8% had mediastinal and 26,9 % abdominal node involvement.Splenomegaly occurred in 60,2% of cases ,hepatomegaly in the 19,2%.The commonest extranodal involvement were skin(15,3 %),Waldeyer (11,3%)and enteric apparatus(0,70%).The hemoglobin level ranged from 8,7-14,8 with a median of 12,50 g/dl.
The total leukocyte count ranged from 2.9-150 x10^{3} WBC/mmc ,with a median of 15,2x10^{3}/mmc.Only the 11,2% of patients presented a peripheral blood lymphocytosis.Two patients were considered to be leukemic at initial diagnosis.Platelets ranged from 70-380 x10^{3}/mmc.Bone marrow specimens were positive for lymphoma in 62,2% of cases.Surface analysis performed in six bone marrow and three peripheral blood samples,revealed a monoclonal B-lymphoproliferative disease,CD5 positive and CD10 negative.In only one case was found a lymphoproliferative T-cell subset.
All patients received therapy:3 monotherapy(chlorambucil or cyclophosphamide), 21 polichemiotherapy(CHOP,CVP) and 2 radio-chemotherapy combination.We have confirmed a low frequency of complete remission(3 patients); the median survival for the entire population was 38 months.Twelve of 26 patients were alive at the end of the study, ,9 with active disease and 3 in C.R.,with a median follow-up of 31 months.Fourteen patients died of lymphoma progression. The low C.R.rate after therapy,notwithstanding the indolent nature of this disseminated disease in its initial phase,indicates the difficulty of devising a therapy that really modifies survival .The clinical presentation and course of the patients observed in our study suggests that MZL is a relatively low grade lymphoma.Additional clinical and biological studies are needed,however,for further characterization of this entity.

T 103 A HIGHLY DISSEMINATIVE MANTLE CELL LYMPHOMA PRESENTING WITH DIFFUSE SKIN INVOLVEMENT EXPRESSES A VERY UNUSUAL ADHESION RECEPTOR PROFILE . *A case report.*

K. Fischer, Ch. Degenhart, W. Hunstein, and P. Möller
Dept. Internal Medicine, Division of Hematology, and Institute of Pathology, University of Heidelberg, Heidelberg, Germany

A 66 years old male with a leukemic non-Hodgkin´s lymphoma presented with generalized lymph node swelling and diffuse nodular infiltration of the skin. He died shortly afterwards despite of aggreessive treatment. Histology of a lymph node showed a high grade malignant B-cell lymphoma. The lymphoma cells were described as centrocytic. Proliferation rate (Ki-67) was 70 %. The tumor cells expressed the following immunophenotype: IgM+; IgD+; kappa +; lambda-; CD10 weakly +; CD20+; CD21+; CD22+; CD23+; CD38 weakly +; CD39+. This immunoprofile is largely corresponding to the mantle zone B cell. In addition, the stem cell antigen CD34 was expressed. The final diagnose was *leukemic mantle cell lymphoma, CD34+*.
It has recently been demonstrated that leukemic B cell neoplasias differ in several aspects from a-leukemic and locally growing ones. This could be traced down to differences in the adhesion receptor profile expressed on the neoplastic cells. The adhesion receptor profile of this lymphoma was as follows: β1-integrins (VLA): α1+; α2+; α3+; α4+; α5+; α6-. LFA-1 (CD11a/CD18)+; ICAM-1 (CD54) +; CD44+; LECAM-1+. We have shown that the leukemic phenotype of a B-cell lymphoma might crucially depend on the expression of VLA-5 (*Möller et al., Leukemia 6: 256-264; 1992*). In this study mantle cell lymphomas - presenting as nodal lymphomas - were α3+; α4+ but lacked α1; α2 and expressed α5 in only 1/4 cases. Among 100 cases of B-cell leukemias/lymphomas α1 expression was exceptionally rare (1 case of CLL) and α2 was restricted to a subset of CLL. The pattern of CD44 and LECAM-1 expression corresponds to that found in nodal mantel cell lymphomas (*Möller et al., Virchows Arch A Pathol Anat 421: 305-313; 1992*). LFA-1 and ICAM-1 are more often expressed in lymphomas presenting as locally growing tumor (*c.f. Möller et al., Am J Pathol 141: 729-741; 1992*); nevertheless, these molecules were present on the tumor cells of this case. In conclusion, this unusual, highly disseminative B cell lymphoma expressed a very unusual adhesion receptor profile, indicating that these molecules are crucially modulating the biology of neoplastic B-lymphocytes.

T 104 PRIMARY CUTANEOUS LARGE CELL LYMPHOMAS OTHER THAN MYCOSIS FUNGOIDES.A CLINICAL FOLLOW-UP STUDY OF 54 CASES.

P. Joly, H. Tilly, E. Esteve, E. Vasseur, M. Leibovitch, J. Wechsler, E. Thomine, A. de Muret, L. Vaillant, F. Dreyfus, C. Haioun, J. Revuz, J.P. Escande, G. Lorette, Ph. Lauret, M. Bagot.
Groupe Français d'Etude des lymphomes cutanés.

Cutaneous lymphomas other than Mycosis Fungoides (MF) represent a rare and heterogeneous group of lymphomas. Large cell lymphomas are the most common histopathologic subtype. The clinical, immunohistological characteristics and follow-up data of 54 well-documented cases of primary cutaneous large cell lymphomas other than MF, presenting with exclusive cutaneous lesions (stage IE) were reviewed. 46 patients presented with unique or localized skin lesions and 8 patients had multiple tumors involving non contiguous anatomic sites at presentation. 51 tumors were classified as Intermediate Grade Lymphoma : diffuse large cell lymphoma (36 ; 67%), diffuse mixed small and large cell lymphoma (15 ; 28%). 2 patients had immunoblastic lymphoma and 1 patient had an anaplastic large cell lymphoma. A B-cell phenotype was most often expressed (45 ; 75%). T-cell lymphomas (9 ; 25%) were most likely to be disseminated (4 of 8 : 50%). Clinical course was closely dependant upon clinical presentation (disseminated or localized lesions), seric LDH levels and to a lesser degree : T or B phenotype. 8 patients with disseminated cutaneous lesions were treated with multiagent chemotherapy. 7 of 8 died after a mean time of 11.5 months. Among the 46 patients with localized skin lesions, 4 refused to be treated, 25 were treated with radiotherapy alone, 8 patients with surgical excision and 9 with an initial polychemotherapy. 16 of 32 patients treated by radiotherapy or surgical excision relapsed within two years post treatment . 13 of 16 (80%) relapsed outside the initial site involved. 7 patients died after the relapse suggesting that local treatment alone is not adequate for these patients. 8 of 9 patients with localized skin lesions treated with an initial polychemotherapy, achieved complete remission and are alive at the time of the study (median follow-up : 55.4 months).

T 105 LYMPHOMA OF MUCOSA-ASSOCIATED LYMPHOID TISSUE (MALT) INVOLVING 3 DIFFERENTS ORGANS IN A SAME PATIENT.

F. Viseu, L. Rodriguez, I. Costa, C. Lopes.
Clínica Oncológica V - Instituto Português de Oncologia Centro do Porto

L.L. is a 59 years old male with mucosa-associated lymphoid tissue (MALT) lymphoma involving the lungs, stomach and parotid glands, at different times, during a period of 9 years of disease development.

We emphasize the occurrence of two relapses in the organs initially involved (lung and stomach) and invasion to the parotid glands 8 years after the diagnosis.

We confirm the indolent condition of this type of lymphoma wich appears to be the most relevant clinical feature.

T 106 Immunoproliferative Small Intestinal Disease (I.P.S.I.D) in Algerians.

F. Asselah, H. Asselah, Pathology Department University Hospital of Bab El-Oued, Algiers; Department of Internal Medecine and GastroEnterology University Hospital of Bologhine, Algiers, Algeria.

A clinicopathological study based on our experience of 120 patients with IPSID during these last two decades is presented. All these patients were Algerians of the same ethnic origin. The mean age was 23,8 years and the sex ratio 1.9:1. The median duration of symptoms prior to diagnosis was 26.5 months. Most patients presented with malabsorption associated chronic diarrhea and weight loss.
Two groups of patients were individualized from the presence or not of the immunological protein abnormality detected in the sera by rocket immunoselection electrophoresis and the positivity or negativity of representative intestinal and mesenteric lymph node tissue for the presence of intra cellular abnormal Ig A using an immunoperoxydase method. Alpha chain disease represents in this study 56.2% of IPSID.
The Clinicopathological comparative study between these two groups - IPSID with or without alpha chain disease - did not show any statistical significant difference.
In this series, IPSID was diagnosed in two sets of siblings pointing to a possible genetic factor.
A well documented histopathology study completed by an immunohistochemical study was done in most cases.
The types of lymphoma were given according to the Kiel classification. A higher proportion of high malignant lymphoma (62.2 %) was found on staging laparotomy specimen compared to those on duodenal biopsies (15.7 %) suggesting that duodenal biopsies are not quite representative of the type of lymphoma in IPSID.

The response to treatment according to the histological grading is discussed as only 46.4% achieved a complete remission under a C.H.O.P regimen and/or radiotherapy. Prospective randomized clinical trials based on a accurate histological grading and staging could appreciate the merits of different treatment programs. The application of modern technologies renewed hope of establishing the etiopathogenesis of the disease.

T 107

IMMUNOPROLIFERATIVE SMALL INTESTINAL DISEASE: THE GROOTE SCHUUR HOSPITAL EXPERIENCE

C. Johnson[1*], G. Adams[2], S. Price[3], D. Dent[4], P. Jacobs[5] and I. Marks[2].
Departments of [1]Radiation Oncology, [2]Gastroenterology, [3]Surgery, [4]Histopathology and [5]Haematology, Groote Schuur Hospital and University of Cape Town, Observatory 7925, South Africa.

Immunoproliferative Small Intestinal Disease (IPSID) is a spectrum of disease with both clinical and pathological features. The first cases were originally called "Mediterranean Lymphoma", and in 1977 the WHO developed the term IPSID. The first cases in South Africa were reported in 1971 from our centre.

This is a review of 44 patients followed through our combined IPSID clinic from 1964-1992. Where possible all pathology specimens have been reviewed and immunohistochemistry is available on 38 patients.

We have divided the patients into the following groups 1) Plasma Cell Infiltrate (PCI) - associated with specific disease 2) PCI - non-specific 3) Low Grade Mucosal Associated Lymphoid Tissue (MALT) lymphoma 4) Monocytoid B Cell Non-Hodgkin Lymphoma 5) High Grade MALT Lymphoma and 6) Immunoblastic Lymphoma.

2 cases of low grade MALT Lymphoma are described who developed Immunoblastic Lymphoma years later as well as 3 cases of IPSID developing in black patients.

Clinical and pathological features of the different groups are described. Investigation, management and outcome in each category will be presented.

T 108 Immunoproliferative small intestinal disease (IPSID) in an African woman living in Europe for 18 years

J.Zahner, T.Kirchner, C.Aul, W.Schneider, Heinrich-Heine-Universität 4000 Düsseldorf, Germany

Immunoproliferative small intestinal disease (IPSID) is a rare entity almost exclusively seen in Asia and Africa. Most oftenly people from low social classes from the age of 10 to 30 years are involved. Recurrent intestinal parasitic infections, which are endemic in 3rd world countries and which almost regularily coincide with IPSID, are supposed to be a risk factor for the disease. Characteristically abnormal α-1 heavy chains are found immunohistologically in intestinal biopsies or in serum, urine or jejunal juice (α -1 heavy chain disease). There seems to be a genetic association with several HLA types, such as A9, A19 and B12. In the clinical course of the disease a Mediterranean lymphoma ultimately evolves. Antibiotics have successfully been used in stage A of Galian (tumor restricted to the mucosa). In the more advanced stages chemotherapy and radiation have been tried.

We saw a 27 year old Moroccan woman with a history of chronic diarrhea for 12 years, who lived in Germany for more than 18 years. She complained about progressive diarrhea and weight loss. In the stomach a low grade lymphoma was found without evidence of the α-1 heavy chain. Biopsies of the colon showed immunohistological presence of IPSID with positive reaction for IgA and light chain restriction. Barium study showed involvement of the small bowel. Neither in serum nor in urine or jejunal juice the abnormal α-1 heavy chain could be demonstrated. In the stool we found Salmonella glostrup, Pseudomonas aeroginosa and cysts of Giardia lamblia. HLA typing gave evidence of A9.

The diagnosis of IPSID is supported by the patient's nationality and HLA type, her young age, the histologic findings and the recurrent intestinal infections. This case of a Moroccan woman, living in Germany for over 18 years, points out that there must be a strong genetic influence beside from environmental factors in the development of IPSID.

Dr.Johannes Zahner. Klinik für Hämatologie, Onkologie und Klin. Immunologie, Heinrich-Heine-Universität Moorenstr.5 D-4000 Düsseldorf
I intend to apply for the travelling award, date of birth: 17.1.1961

T 109 ENTEROPATHY ASSOCIATED T-CELL LYMPHOMA WITH MULTIPLE SKIP LESIONS IDENTIFIED A DISTINCT CLINICOPATHOLOGICAL SUBSET OF PRIMARY SMALL BOWEL LYMPHOMA WITH POOR PROGNOSIS.

L.Grogan, D.Devaney, N.Corbally, PA. Dervan, DN. Carney. Depts. of Medical Oncology and Pathology, Mater Misericordiae Hospital & Dept. Pathology, University College Dublin, Dublin, Ireland.

Enteropathy associated T-cell lymphoma of the small bowel has been recognised as a distinct clinicopathological entity with a reported poor outcome. We retrospectively analysed the clinicopathological data on all patients (n=17) treated in our hospital between 1985 and 1991 with newly diagnosed primary small bowel lymphoma to determine the clinicopathological characteristics, response to therapy and survival of these patients. The most common clinical problems at presentation were abdominal pain (16/17) and bowel obstruction (14/17). All the patients had a laparotomy and in the majority (16/17) there was complete resection of macroscopically involved bowel. Patients were staged using standard methods and criteria. Overall 8 patients had a T-cell and 9 had B-cell lymphoma with 1 patient in each group having a history of preexisting coeliac disease. Comparing the 2 groups before treatment, patients with T-cell lymphoma were more likely to have an associated enteropathy 7/8 versus 1/9, multiple skip lesions 6/8 versus 3/9, stage 3 or 4 disease, 3/8 versus 1/9, and bulky disease 3/8 versus 0/9. The median age (49-51) and proportion of patients over 65 years (25-30%) were similar in both groups as were other prognostic characteristics. All patients received at least 3 cycles of standard dose M.B.A.C.O.D. (methotrexate, bleomycin, adriamycin, cyclophosphamide, vincristine and dexamethasone) with the majority receiving 6 cycles. Patients with T-cell lymphoma had an inferior complete response rate 38% versus100% ($p<0.01$), an inferior 2 year disease free survival of 13% versus100% ($p<0.01$), and a significantly shorter overall survival ($p<0.05$), with a median of 12 months (range 3-45) compared to patients with B-cell lymphoma whose median survival was 49+ months (range 15-90+) with no patient relapsing post treatment. Whereas in primary small bowel lymphoma, B-cell phenotype identified a group of patients with an excellent outcome following surgery and standard chemotherapy, T-cell phenotype identifies a distinct clinicopathological subset of patients with an associated enteropathy and multiple skip lesions who in contrast have a very poor prognosis. Further strategies to improve the outcome of patients with T-cell phenotype will require more novel therapies at diagnosis including autologous bone marrow transplantation.

Supported by Cancer Research Advancement Board, Irish Cancer Society.

T 110 NON MEDIASTINAL T CELL NON HODGKIN'S LYMPHOMA OF CHILDHOOD 1985-91

V Saha, O B Eden, I M Hann, R Carter, on behalf of the United Kingdom Children's Cancer Study Group

A minority (15%) of children with T Cell NHL have primary non mediastinal disease. We report the presentation and therapy response of 36 children with non mediastinal T cell NHL treated between 1985 and 1991 in 21 UKCCSG centres. Sexes were equally distributed, and the mean age at presentation was 108 months (range 23-196). Twenty-two (61%) presented with either isolated or diffuse lymphadenopathy; 5 (14%) with primary skin involvement; 3 (8%) with abdominal tumours; 2 (5.5%) with bone lesions and one each with maxillary sinus, parotid, thyroid and lung primaries. Breakdown by Modified Murphy Staging was Stage I = 8; II = 9; III = 10; IV = 9, without predilection for sex or age. Histopathology was of lymphoblastic lymphoma in 19 (53%) and large cell anaplastic lymphomas (LCAL) in 16 (44%). Of those with LCAL, 10 were Ki-1 positive (Stage I = 1, II = 2, III = 6, IV = 1). Histopathology was inconclusive in one child. There was no clear pattern of abnormal karyotyping. 27 children were treated on intensive lymphoblastic leukaemic schedules (8503, 9004) and 8 on regimens incorporating cyclophosphamide designed for localised NHL or advanced B cell disease (8501, 9002, Macho). 24/27 on leukaemic therapy and 7/8 on "cyclo" schedules achieved complete remission. One central nervous system and 2 bone marrow relapses have occurred on the leukaemic schedules (all Stage IV disease). Overall all Stage I and II patients are alive; 8/10 with Stage III but only 4/9 with Stage IV at a median follow up of 31 months (range 12-88 months). Of the Ki-1 positive children, induction failure occurred in one Stage III patient, the rest remain in clinical remission. Short course intensive chemotherapy would appear to be adequate for all but Stage IV disease which requires new, intensive and innovative therapy.

T 111 PRIMARY EXTRANODAL NON-HODGKIN'S LYMPHOMA.

T. Economopoulos, N. Stathakis, N. Asprou, J. Dervenoulas, E. Papageorgiou, K. Xanthaki, S. Raptis.

Second Department of Internal Medicine - Propaedeutic, Athens University, Evangelismos Hospital, Athens, Greece.

Among 318 cases of non-Hodgkin's lymphoma (NHL) treated in our unit, 145 (45.6%) had primary extranodal NHL (PE-NHL). The stomach was the most common site (42.1%), followed by the PE-NHL of the head and neck region. Histologically aggressive histologies (65.5% intermadiate and 20.7% high grade) predominated. 89.6% of the cases were localized (stage I_E, 51% and stage II, 38.6%) but 29% had B symptoms. CR was achieved in 82.1% of the cases. 5-years disease free survival and overall survival were both 65%. Factors that influence prognosis were stage and high grade histology. Among various primary sites the Waldeyer's ring, small intestine and testes had the worse prognosis. Compared to nodal NHL, the PE-NHL were more frequently localized, belonged more often to aggressive histologies and had more often distal extranodal relapses. CR rates and disease free and overall survival were significantly better for PE-NHL. The survival rates, however, listed according to stage and histology for nodal and PE-NHL were not different.
We conclude that although PE-NHL differed from nodal NHL in several respects, prognosis is mainly a factor of stage and histology rather than of the primary localization per se.

T 112 NON-HODGKIN'S LYMPHOMA FOLLOWING BREAST CARCINOMA : high rate of therapeutic response and long term favourable prognosis.

J. Dumont, P. Charpy-Validire, S. Fraslin, P. Validire and M. Laurent. Haematology Unit and Histopathology Laboratory, Institut Curie, 26 rue d'Ulm - 75005 Paris

The occurence of myeloid leukaemias after the treatment of breast carcinoma is usually considered as therapy-related and associated with a very unfavourable prognosis. The occurrence of lymphoid malignancies is less frequent and their long term prognosis is still not clear. 16 patients were observed at the Curie Institute with such an association, and the clinical, pathological, and therapeutic data were analysed following the treatment of both malignancies.
12 patients (Age 28-74) were first treated for a breast carcinoma and then developed a non-Hodgkin's lymphoma (NHL) after a mean time of 98 months. The breast carcinoma had been apparently cured by surgery (3 cases), surgery and radiotherapy (4 cases), radiotherapy and chemotherapy (3 cases) or hormonothrapy (2 cases). NHL were predominantly of low-grade histological type, following the Working Formulation : A : 3, B : 4, D : 1, E : 1, and G : 3 cases. There were 5 localized and 7 disseminated stages. Treatment was given according to the usual protocols of corresponding stages and histology of NHL. All the patients experienced at least one complete and durable remission, there were 2 relapses with a second complete remission, all the patients are presently alive.
In 2 other cases, the NHL was observed respectively 11 and 35 months before the clinical appearance of the breast carcinoma. In both cases a complete therapeutic result was obtained for each tumour with a long-term follow-up. In 2 other supplementary cases, both tumours were discovered within the same short period of time (less than 6 months). 1 of these patients is apparently cured for more than 5 years. The second commited suicide.
Non-Hodgkin's lymphomas associated with breast carcinoma :
1 - are relatively frequent
2 - are most often B low grade or intermediate malignancy (all stages)
3 - are not apparently related to the first therapy received by the patient,
4 - do not share the unfavourable prognosis of myeloid malignancies usually observed in the groups of breast carcinoma patients.

T 113 TESTICULAR LYMPHOMAS: A POPULATION-BASED STUDY

M.B. Moeller[1], F. d'Amore[1] B.E. Christensen[1], on behalf of the Danish Lymphoma Study Group, LYFO
[1] Dept. of Haematology, Odense University Hospital, 5000 Odense C, Denmark

Population-based data on testicular non-Hodgkin's lymphomas (TL) are rare. Most series have been collected over extensive time spans, resulting in considerable heterogeneity of the study material. The present series represents all the newly diagnosed cases of TL from a Danish population-based NHL registry (LYFO) in the period 1983-1992. Of 2687 registered patients, 39 (1.4%) had testicular involvement at the time of diagnosis. This corresponded to an age-standardised (European population) incidence of $0.26/10^5$/year. The median age of TL patients was 67 years (range 10-86 years). Twenty-two cases had localised (stage I_E) and 17 disseminated (stage IV) disease. At presentation, the most common symptom was a painless, enlarged testis. Histologically, all cases were diffuse with the majority (65%) being of centroblastic type. The majority of patients (27 out of 39) were immunophenotyped. Of those, 11% were of T- and 89% of B-phenotype. The largest diameter of affected testicles ranged from 3-9cm (median: 6.8cm). Vascular invasion was found in 10 (30%) of 33 orchiectomised patients; in 22 (67%) epididymis and/or spermatic cord invasion was found. At the time of diagnosis only 2 patients had bilateral testicular involvement. Orchiectomy was performed in 21 out of 22 TL patients with localised disease (1 received radiotherapy). In 13 of these cases surgery was supplemented by chemotherapy (CT), whereas 9 only received regional treatment (orchiectomy and/or radiotherapy). The relapse rate in the former group was 23%, in the latter 56%. Relapse-free survival was 27.5 and 18.8 months, respectively. Cases with stage I_E disease, where microscopic invasion of the epididymis and/or spermatic cord was found, had a relapse rate of 42% vs 25% for stage I_E cases without this feature. Among patients with disseminated disease, 9 received combination chemotherapy. Six (67%) achieved CR or PR and 5 relapsed with a median relapse-free survival of 11 months (range: 2-35 months). The most common sites of relapse/disease progression were CNS (5 cases), retroperitoneum (4), skin (3), and kidneys (2). One patient relapsed in the contralateral testis. Overall 5-year survival was 17%, belonging to the lowest values among extranodal sites. Adverse prognostic factors (univariate) were: stage IV, B-symptoms and s-LDH elevation. Age (all cases) and local vascular invasion (localised cases) did not have prognostic influence.

T 114 LYMPHOMA OF THE VAGINA: CASE REPORT.

V.Ferrari,F.Lonardi,G.Pavanato,A.Jirillo,G.Bonciarelli,M.Balli. Division of Radiotherapy/Oncology, ULSS 28, 37045 Legnago (Vr), Italy.

Extranodal malignant lymphomas involve the female genital tract in 30% of cases and more of 90% are non-Hodgkin lymphomas. The vagina is an uncommon site of disease (6-7% of all genital localizations), so we report a case of vaginal lymphoma we observed in a 55 yrs old female in our Center in November 1991. The patient 8 years erlier underwent total hysterectomy and bilateral salpingo-oophorectomy owing to multiple uterine fibromas. The examination of the vagina by colposcopy showed a 5 cm diameter circular bleeding ulcered lesion located in the upper third of the organ. Multiple biopsies were performed and revealed a centrocytic-follicular malignant lymphoma whose grading was "F" according to the Working Formulation. Immunophenotyping confirmed the B-cell proliferation. Staging showed the involvement of the para-aortic and common iliac lymphonodes. Although it remains uncertain whether lymphomas of the female genital tract by itself carries a poorer prognosis than the nodal lymphomas of comparable stage, we decided an aggressive therapeutic approach. Chemotherapy was started according to the ProMACE/CytaBOM schedule; a total of 6 cycles were administered and 100% of the planned dose was delivered. CT scan and colposcopy after 3 cycles showed partial remission of the disease; local complete pathologic remission (vaginal random biopsies were performed) was obtained after 6 cycles. Treatment was completed with "involved fields" radiation therapy: it consisted of 3600 cGy to the para-aortic area and the whole pelvis through anterior-posterior opposite fields plus 1000 cGy moving technique boost to the vagina and the cervical stump, given with standard fractionation. Hematologic toxicity was not observed during chemotherapy. Grade II leukopenia emerged during irradiation but treatment was never held. Grade III hair loss and grade II stomatitis were seen as far as hematologic toxicity is concerned. Actually the patient is in complete clinical remission and the follow-up is on-going.

T 115 PRIMARY LYMPHOMA OF THE PAROTID GLAND.

G. Lugassy, Y. Katz, R. Or, A. Polliack, Hematology Unit, Barzilai Hospital, Ashkelon, and Lymphoma-Leukemia Unit, Department of Hematology, Hadassah University Hospital, Jerusalem, Israel.

Primary extranodal lymphoma of the salivary gland is an extremely rare disease. In this report we describe 12 cases of primary lymphoma of the parotid gland seen at a single center and review the relevant literature. The 12 cases were treated in different departments and did not receive a uniform therapeutic approach. All 3 patients with Hodgkin's disease are still alive and two are in complete remission after initial radiotherapy. One of these cases developed stage 4 disease and had to receive combination chemotherapy subsequently. Of the 9 non-Hodgkin's lymphoma (NHL) patients, 4 had low grade NHL, and 4 intermediate or high grade NHL. Of these 2 died with disseminated disease. However, 6 are still alive and well from 1 to 5 years after therapy. These cases were treated with surgery alone, radiotherapy alone or combination chemotherapy with an anthracycline-bearing regimen. Consequently, we are unable to draw any conclusions relating the success of therapy in these cases, nor can we suggest therapeutic guidelines on the basis of this study alone. The treatment of parotid lymphoma was reviewed in the light of the available literature. In most cases of parotid lymphoma, symptoms related to an enlarging mass in the parotid region, are evident. In the light of the above data, we suggest that, despite its rarity, lymphoma of the salivary gland should always be considered in the differential diagnosis of a parotid mass. No correlation between lymphoma and Sjogren's syndrome was noted in the present study.

T 116 NON-HODGKIN LYMPHOMA OF THE THYROID GLAND: CLINICAL FEATURES AND TREATMENT RESULTS

G. Petrič-Grabnar, M. Bizjak Schwarzbartl, J.Jančar, M. Auersperg, A. Vodnik-Cerar, M. Vovk, M. Jenko. Institute of Oncology, Ljubljana, Slovenia

The purpose of this study was to evaluate clinical features and treatment results of 15 patients with non-Hodgkin lymphoma (NHL) of the thyroid, seen at the Institute of Oncology, Ljubljana, between 1980 and 1990. There were 14 females and 1 male, age range 46 - 86 years (mean 72 years). A short history of less than 3 months of neck tumor (13 pts), and symptoms of local compression (12 pts) was the typical clinical picture. Twelve pts had disease limited to the thyroid, or also to the cervical lymph nodes (7 pts IEA, 5 pts IIEA). The other 3 had more advanced disease: 1 mediastinal and paraaortic lymph node involvement (III EA). another bone marrow infiltration, and the third subcutaneous and cutaneous involvement (IV EA).Diagnosis was confirmed by histology in 6 pts, and by fine-needle biopsy of large tumor masses in 9 pts. According to Kiel classification, 4 were centroblastic, 2 immunoblastic, whereas the rest were unclassified. Only 3 pts were suitable for surgery; 2 had lobectomies with removal of the isthmus; the third had a total thyreoidectomy. All three had postoperative radiotherapy (RT), the third one followed by ChT. Of the remaining pts 2 had only RT, 2 only ChT,and 7 had both. One patient refused treatment. ChT was mostly CHOP (6 cycles), given at 14-21 day intervals; RT field was the neck and upper mediastinum, target dose (TD) 14-42 Gys. Complete tumor regression was noted in all pts. Eight have been without evidence of disease for 55 to 144 months (mean 82 months). In one pt with lobectomy and postop. RT dissemination into the lungs and abdomen was evidenced 6 months after primary treatment; she died 13 months after diagnosis, despite ChT. Of the other 5 deceased patients, 2 died because of myocardiac infarction, 3 because of old age and related undefined reasons, all without evidence of the disease. Our data indicate that NHL of the thyroid occurs in older patients, and more frequently with a larger primary tumor than other extranodal NHL. Combined therapy with ChT and low-dose RT (20-30 Gy) may offer a good chance of survival.

T 117 PRIMARY CARDIAC LYMPHOMA.

M. Morret-Rauis, P. Gurnet, B. Abramovich et al. Department of Internal Medicine, Hôpital Universitaire Brugmann, Brussels, Belgium

We report the case of a 62 years old man who was admitted for weight loss, atypical retrosternal pain and dyspnea.
Further evaluation revealed massive involvement of the right ventricular wall, the tricuspid valve and the right atrium by a diffuse large cell lymphoma. Staging failed to show any other involved site.
Multiagent chemotherapy (ProMACE-CYTABOM) was induced in september 92. G-CSF was added to prevent neutropenia.
After 5 cycles of this treatment, the patient is now in quasi complete remission.
The only complication under treatment was a pneumonia, evolving to "BOOP" (bronchiolitis obliterans organizing pneumonia) which is well controlled by low doses of Methylprednisolone.

T 118 NON HODGKIN LYMPHOMAS OF THE TONSIL - REPORT OF 15 CASES

Vera Šobić, Svetislav Jelić, Olivera Frim, Vladimir Kovčin, Vesna Stanković

Institut za onkologiju i radiologiju, Belgrade, Pasterova 14, Yugoslavia

During the period 1987 - 1992. in our institution we have observed 15 patients with Non-Hodgkin lymphoma localized to 1 tonsil. 10 out of them also an enlarged ipsilateral angular lymph node, while in 5 patients the lymphoma was localized only to the tonsil, without signs of lymphoma in other lymphonodal or extranodal territories. The histological types were immunoblastic 6/15, centroblastic 5/15, centrocytic 2/15, lymphoplasmocytic 1/15 and T-epitheloid 1/15. In all patients the diagnosis of lymphoma was made on tonsillar material following tonsillectomy. In all 10 patients in which following tonsillectomy, a residual angular lymph node was present the following adjuvant treatment was applied: 5/10 patients loco regional radiotherapy, 3/10 patients chemotherapy, 2/10 patients 2-3 cycles of chemotherapy followed by loco regional radiotherapy.

Initially in all patients treated by any adjuvant approach, the local control of lymphoma was achieved.

5 patients who had lymphoma localized only to the tonsil were subjected only to close follow up with no adjuvant treatment following tonsillectomy.

The free interval in the group treated with loco regional radiotherapy was 9 - 31 months. None of the patients relapsed with lymphoma. One patient subsequently developed a squammous cell carcinoma of the orbit after 31 months.

The free interval in the group treated with chemotherapy only was 3 - 5 months. One patient relapsed with subcutaneous deposits of lymphoma after 5 months, the other 2 patients were lost from follow up.

The free interval in the group treated with chemotherapy followed by loco regional radiotherapy is at the moment 22 + months for one patient, while the other one relapsed following 32 months with gastric lymphoma with no local relapse.

The free interval in the group with no adjuvant treatment following radical tonsillectomy is at the moment 9 - 27 months mean 18 months. At the moment none of these patients relapsed or developed lymphoma in other sites. It is of interest to note that this group comprised 1 centroblastic, 2 immunoblastic, 1 T-epitheloid and 1 lymphoplasmocytic lymphoma.

Our findings justify the loco regional adjuvant radiotherapy for patients with tonsilar lymphoma with the adjacent angular lymph node. Patients with lymphoma localized to the tonsil only, after radical tonsillectomy, apparently do not need any immediate adjuvant approach.

T 119 SYNCHRONOUS AND METACHRONOUS LYMPHOMA AND RENAL CARCINOMA. REPORT OF EIGHT CASES.

A.Romanelli, L.Tedeschi, G.Dallavalle, D.Tabiadon, G.Luporini. Division of Medical Oncology, S.Carlo Borromeo Hospital, 20153 Milan, Italy.

Since 1980 in our Institution we observed six cases of lymphomas (five non Hodgkin's lymphomas (NHL) and one Hodgkin's disease) associated with synchronous primary renal carcinoma (ca) and two cases of NHL that developed metachronous renal ca. In all six cases of synchronous tumors, renal carcinoma was asymptomatic and discovered during staging procedures for lymphoma (four cases on computed tomographic scans of abdomen and two during exploratory laparatomy). Two patients (pts) with NHL developed renal ca after 100 and 38 months respectevely from achieved complete remission for lymphoma; in the first case metachronous renal tumor was discovered on ultrasound scan of abdomen performed during the usual follow-up; in the second case hematuria and flank pain were the presenting patterns of renal ca. These two pts underwent nefrectomy and actually are alive and without evidence of recurrence of the two tumors.

4 pts with synchronous lymphoma and renal ca were treated firstly for lymphoma (1 RT, 2 CT, 1 CT + RT) achieving complete remission (CR) and then underwent nefrectomy: all are alive and without evidence of either lymphoma or renal ca. Two pts did not perform nefrectomy because of their bad phvsical conditions; the first one, male, with cerebral NHL,is alive at three months with progressive lymphoma after brain RT; the second one,female , low-grade NHL was missed to follow-up. The incidence of multiple primaries in the literature has resulted of 2.7% to 6.8% (O'Boyle et al Am. J. Med. 87;1989). Apart from some autopsy data we found very little information on pts with both lymphomas and renal ca. and the most of few reports are about association of colon and renal ca.; in our Institution during last two decades we observed only a case of colon and metachronous renal ca. The increasingly common use of CT scanning in this last decade may account for finding of a relatively high incidence of synchronous lymphoma and renal ca., when it is still asymptomatic. This can make problems of differential diagnosis and, in the case of synchronous tumors potentially curable, the necessity to state the prior treatment.

T 120 NON-HODGKIN'S LYMPHOMA OF WALDEYER'S RING : LONG-TERM RESULTS AFTER RADIATION THERAPY.

N. Masaki, Y. Matayoshi and H. Ikeda. Department of Radiation Oncology,The Center for Adult Diseases, Osaka. 1-3-3, Nakamichi, Higashinari-ku, Osaka, Japan 537 and Department of Radiology, Osaka University Hospital*, 1-1-50 Fukushima, Osaka Japan 553

From 1971 through 1987, 118 out of 277 (43%) patients with stage IA and IIA aggressive non-Hodgkin's lymphoma presented in Osaka University Hospital with involvement of Waldeyer's ring. Staging evaluation included history and physical examination, chest x-ray, abdominal CT-scan (or lymphangiography) and bone marrow biopsy. The median age was 52 years (range 7 - 77). 57 were males and 61 females. Clinical stage IA disease was diagnosed in 37 of the 118 patients (31%) and stage IIA in 81 (69%). Bulky disease (> 5 cm) was present in 51 patients (43%). Histological subgroups (all diffuse) were mixed 15, large 81, immunoblastic 7, large cell otherwise unclassified 15. Treatment modalities consisted of extended field radiotherapy alone in 64 patients (22 of the 37 stage IA and 42 of the 81 stage IIA patients), whereas combined chemotherapy (1-2 courses of CHOP-like regimen) and radiotherapy was instituted in 54 patients (including 37 bulky disease).

After a observation period of 5 - 20 years, 58 (49%) of the patients had died: 45 of lymphoma and 13 of unrelated causes. Of 45 relapses, 8(18%) were locoregional relapses, 14(31%) GI tract and 17(38%) lymphatic sites. Five year relapse free survival, overall survival and disease specific survival, respectively, were all patients; 63%, 71% and 73 %; stage IA: 70 %, 86% and 86 %: stage IIA: 60 %, 64% and 68%.

In the group of 64 patients who had received radiotherapy alone, 5 year relapse free survival and overall survival, respectively, were 64% and 73% (stage IA: 86% and 86%; stage IIA: 52% and 67%), whereas in 54 patients of chemoradiotherapy, 5 year relapse free survival and overall survival, respectively, were 61% and 67% (stage IA: 67% and 80%); stage IIA: 59% and 62%). Adjuvant chemotherapy has not shown any improvement in relapse free survival nor overall survival.

In 21 stage IA patients with small tumors (< 5 cm), 5 year relapse free and overall survival, respectively, were 81% and 91%, whereas 16 patients with bulky mass (> 5 cm), those were 63% and 81%. Patients with small tumors seemed to fare better than those with bulky mass. However, in stage IIA patients tumor size did not seem to be a prognostic factor.

T 121 STAGE II MALIGNANT LYMPHOMA OF WALDEYER'S RING: LONG-TERM FOLLOW-UP AND PROGNOSTIC FACTORS FOR PATIENTS TREATED WITH CHEMOTHERAPY ALONE.

T.Takagi[1] and K.Sampi[2], [1]Divisions of Hematology-Chemotherapy, [2]Chiba Cancer Center Hospital, Chiba 260 and [2]Hematology Clinic, Saitama Cancer Center, Saitama 362, Japan

Malignant lymphoma arising from Waldeyer's ring (ML-WR) comprises an almost uniform histology of diffuse large-cell type. Stage II ML-WR is treated with initial chemotherapy followed by radiation therapy (combined modality treatment), but the question remains wheather the following radiation therapy is essential. We retorspectively analyzed the results of therapy in 43 patients with stage II ML-WR who were treated with chemotherapy alone between 1984 and 1990 in two institutions; Chiba Cancer Center Hospital and Saitama Cancer Center. Adriamycin-based first-generation chemotherapies (CHOP therapy for 38 patients and MEVP therapy for 5 patients) were used. Complete response (CR) was achieved in 37 (90.2%) of the 41 evaluable patients, but relapse occurred in 9 (24.3.0%). There were two patient groups with different prognoses. Patients with normal LDH levels and tumors smaller than 5 cm in maximal diameter (low-risk group), had a CR rate of 100%; their relapse-free (RF) rate at 5 years was 85.4%. Patients with higher LDH than normal and tumors more than 5 cm in maximal diameter (high-risk group) had lower CR (77.8%) and RF rate (57.1%). The differences of CR and RF rates between these two groups were statistically significant ($p<0.05$). Initial CHOP therapy alone produced excellent relapse-free survival for the low-risk group, but it was sub-optimal for other patients with stage II ML-WR. For improving relapse-free survival in high-risk patients, the combined modality treatment will be required.

T 122 MALT lymphoma of the stomach : is surgical resection necessary ? , M. Ben-Shahar, Y.Ben-Arie , R. Epelbaum, M. Leviov , A.Kuten and N.Haim

Departments of oncology and pathology Rambam medical center , Haifa 35254 , Israel.

MALT lymphoma of the stomach has been recently recognised as a new entity with unique clinico-pathlogical features. Most of the published series dealt with the pathological characteristics and retrospectively analyzed clinical parameters of patients who mostly underwent laparotomy and tumor resection.Since endoscopy became widely available in the last decade, primary lymphoma of the stomach is frequently diagnosed preoperatively. As a result, more cancer centers have adopted the approach of stomach preservation . The gastric lesions of MALT are usually superficial, mostly limited to the mucosa and submucosa and are of low grade malignancy. Thus it seems reasonable that radio±chemotherapy would be sufficient. In the years 1989-1992 , 11 patients (pts) with primary MALT lymphoma of the stomach were consecutively referred to our center. Nine of them were diagnosed by endoscopy and 2 after surgical intervention . All pts underwent routine staging procedures. Ten pts had stage Ie and one IIe. Five pts underwent surgical resection , however in 3 of them post-operative , radiotherapy (2 pts) or chemotherapy (1 pt) , was indicated because the surgical margins were microscopically infiltrated with malignant cells. The 6 non-resected pts were treated as follows : 3 by radiation , 2 by chemotherapy and radiation and one by chemotherapy only. All 10 stage I pts achieved a complete remission confirmed by repeated endoscopies and are currently alive free of symptoms and disease. Follow up duration is 2-44 months (median 24m). The single stage II patient died within 3 months because of rapid transformation to high grade malignancy and dissemination of the disease.
Conclusions: 1. MALT lymphoma of the stomach is usually diagnosed by endoscopy, thus enabling clinicians to properly select treatment modality. 2. The malignant infiltration has frequently no clear margins and sometimes is multifocal. Thus resection might be insufficient. 3. Non-surgical treatment can be curable as well as surgery and should be considered the treatment of choice in limited MALT stomach lymphoma.

T 123 PRIMARY GASTROINTESTINAL NON HODGKIN LYMPHOMA: REPORT OF 24 CASES.

C. Baiocchi, G. Landonio, D. Cattaneo, M. Majno, F. Scanzi, M. Ferrari. Divisione di Oncologia Medica Falck - Ospedale Niguarda Cà Granda - Milano.

Out of 120 patients, 24 presented a gastrointestinal onset (20 gastric and 4 ileum-lymphomas).
12 were males and 12 females. Mean age 58.6 (m: 27-84).
Histology (according WF): 2B, 1C, 1 "malt" (= 4 low grade malignancy - LGM -); 3E, 3F (= 6 intermediate - IGM -); 9G, 2H, 2I, 1K, (= 14 high grade - HGM). 20/24 underwent radical excision. 14/20 patients were also treated with CT and 4/10 with RT.
4/24 patients couldn't have radical excision and they had a short survival, despite palliative CT and RT.
Response to treatment is presented below.

	< 60 y	>60 y	L+IGM	HGM	Total
Number of patients	13	11	10	14	24
Median overall survival (months)	68	18	42	22	32
Survival at 5 years (%)	58	16	52	32	44

Complete remission occurred in 16/24 patients; their median disease free survival over 6 years. We conclude:

- Histology confirmed to be a valid prognostic factor.
- The worse prognosis in older patients could be due to reduced compliance to therapies rather than to histology.
- Radical surgery is still the corner stone of treatment.
- Radical excision can be considered the only treatment in patiens older than 60 years with more favorable histology.

T 124 ROLE OF POSTOPERATIVE RADIOTHERAPY IN THE MANAGEMENT OF PRIMARY GASTRIC NON HODGKIN ' S LYMPHOMAS (G-NHL) : A RETROSPECTIVE STUDY.

L. Cerizza, D. Varinelli, P. Antognoni, V. Vavassori, M. Tordiglione. Division of Radiation Therapy, Regional Hospital of Varese, Italy;

The treatment of primary localized G-NHL is controversial and the role of postoperative radiotherapy, despite its wide application, is still to be clearly defined. We examined retrospectively a series of 27 patients (pts.) with primary G-NHL treated at our Institution from December 1978 to December 1990. There were 12 males and 15 females with a median age of 55 years (range: 26-74). The Musshoff staging system showed 16 pts. in stage I E and 11 in II E (II E1: 7 pts. and II E2: 4 pts.). According to the Working Formulation, there was a prevalence of intermediate grade malignancy (22 pts.) versus low (3 pts.) and high grade (2 pts.). Surgery consisted of subtotal gastric resection in 17 pts. (3 cases with positive margins), and total gastrectomy in 10 pts. Adjuvant chemotherapy (CHOP/CEOP) was also administered to 10 pts., 9 II E and 1 I E for 4-6 cicles.
Postoperative radiotherapy was delivered with 10 MV photons and large fields upper abdominal irradiation, consisting of AP/PA parallel opposed portals, from the diaphragm to L4, with liver and kidneys shields in PA (5 HVL shaped blocks). Daily fractions of 1.5 - 2 Gy were employed, 5 times/week, up to a median total dose of 30 Gy (range: 27-36 Gy) in 21 pts. ; 6 pts. were irradiated only on the surgical bed, with a combination of AP and LL fields, up to a median total dose of 40.5 Gy (range: 39-40.5 Gy).
With a median follow up of 50 months (range: 16-100), the 5-year overall survival (Kaplan-Meier) is 92.4% (93.3% and 90.9% for stage I E and II E respectively). We did not see any recurrence in the abdomen. The 5-year NED survival of the whole series is 89.8% (100% and 68.1% for stage I E and II E respectively, with p = n.s.). Two pts. with stage II E disease developed distant relapses and none of them was salvaged by further chemotherapy. Acute radiotherapy complications consisted of mild (grade 1-2) nausea and vomiting in most patients, one case of grade 1 diarrhoea, one case of grade 3 leucopenia (in a patient pretreated with chemotherapy) and one case of transient ascites. Late sequelae were grade 1 hydronephrosis in one case and dilatative cardiomyopathy in another one who also received chemotherapy. One patient developed a second tumour (thyroid papilliferous adenocarcinoma), 3 years after treatment. Two pts. died of systemic progressive disease and one died for an accident while disease free.
Postoperative irradiation seems an advisable treatment modality for primary G-NHL, due to its good results and the relative lack of toxicity. Notwithstanding this, the optimal management of G-NHL still remains uncertain and multi-institutional prospective randomised studies are strongly warranted.

T 125 PRIMARY GASTRIC NON-HODGKIN LYMPHOMA: RETROSPECTIVE STUDY ON 40 PATIENTS.

L.Orsucci, M.Bertini, U.Vitolo, A.Levis, R.Freilone, D.Novero and L.Resegotti. Division of Haematology, Ospedale Molinette, Torino, Italy.

Involvment of stomach is the most common site of primary extranodal lymphomas. We studied 40 patients (pts)(male 22, female 18) treated between 1971 and 1992. The median age was 53 years (range 28 to 80). The most frequent symptom was epigastric pain (85%). Gastric bleeding was observed in 4 cases. The disease was localized at fundum in 2 pts, gastric body in 20 pts, antrum in 12 pts. The depth of tumor invasion was: superficial in 14 pts, in 23 there was m.mucosae penetration. The lesion size was less then 5 cm. in 19 pts and > 5 cm. in 21 pts. The patients were classified according to the Musshoff staging system: 23 (57%) pts in stage IE, 10 pts (10%) in IIE_1, 6 pts (15%) in IIE_2 and 1 pts in stage IV. According to the Working Formulation 6 pts (15%) had low grade histology, 19 pts (48%) intermediate grade and 15 pts (37%) high grade. 37 pts underwent surgical procedures (33 complete resection of lymphoma and 4 parzial resection) and 3 biopsies only. The treatment consisted in surgery alone in 11, surgery+chemotherapy (CT) in 17 pts, surgery+radioterapy (RT) in 2 pts, surgery+CT+RT in 6 pts, only CT in 1 pts, CT+RT in 1 pts and only RT in 2 pts. Complete remission (CR) was achieved in 39 pts (98%): 2 pts relapsed at 6 and 91 months. Both were treated with surgery plus radioterapy without chemotherapy . One patients showed a local recurrence and the second one a disseminated relapse. Median follow-up is 4 years. The 20-years survival is 83% and the disease free survival (DFS) is 86%. One patient died in CR at 60 months because of rinopharyn carcinoma.
The encouraging results obtained confirme the good prognosis of gastric lymphoma as compared to nodal non-Hodgkin lymphomas. The best treatment for these neoplasms still remains uncertain. Our study suggests that surgery resection plus chemoterapy or radioterapy is a significant determinant for long term survival.

T 126 PRIMARY GASTRIC LYMPHOMAS - NO ADJUVANT TREATMENT FOLLOWING RADICAL SURGERY.

S. Jelić, N. Milanović, V. Jovanović, M. Oprić. Institut za onkologiju i radiologiju, Belgrade, Yugoslavia.

The stomach, differently from other gastrointestinal structures does not contain its own lymphoid apparatus in the mucosa. It has been conceived that primary gastric lymphomas arise from neoplastic transformation of lymphoid cells present in the inflammatory infiltrate in gastric mucosa associated with chronic gastritis. This conception might have a strong impact concerning spontaneous biological evolution of these tumors and the therapeutic approach. During the period 1988-1992, 22 patients with primary gastric lymphoma were observed in our Institution, 8 males and 14 females, median age 54 years (range 23-73). In 20 patients the diagnosis of lymphoma was made postoperatively, by histological examination of the surgical material, and in only 2 patients it was made preoperatively by histological examination of the gastroscopy specimens. In all patients the surgical procedure included total gastrectomy, splenectomy, omentectomy, lymphadenectomy and eventually resection of the distal part of esophagus. By histological analysis of the resected material, lymphoma tissue was found involving the gastric wall in different extent, and no lymphoma was found in perigastric lymph nodes, omentum and spleen. Histological types of lymphoma were: lymphocytic 1/22, lymphoplazmocytoid 5/22, centrocytic 5/22, centroblastic 5/22, immunoblastic 5/22, and lymphoblastic 1/22. In five patients there was definite evidence that the lymphoma was of the MALT type. The staging of lymphoma was thus performed postoperatively in nearly all patients (chest X-rays, abdominal echography or CT, bone marrow punctuie smear, immunochemical analysis of serum and urinary proteins, and other procedures as needed), and none of them had any evidence of lymphoma outside the stomach wall. Following operative procedure an expectative approach was adopted in all patients, with clinical controls only and no adjuvant chemotherapy or radiotherapy. 20 patients have a period of observation longer than 6 months. Their median survival is at the moment 20+ months and the median has not yet been reached. One patient developed 10 months following gastrectomy a carcinoma of the sigmoid colon and was successfully operated upon. In only 2 patients (less than 10%) there was an intra abdominal relapse of lymphoma in the lymph nodes of the porta hepatis, 7 and 8 months respectively following gastrectomy (lymphoplasmocytoid and centroblastic histology, the former MALT type). Both patients achieved a complete response following chemotherapy. For the remaining 18 patients with an observation period over 6 months, the disease free interval following gastrectomy is for 1 patient between 6-11 months, for 11 between 12-23, for 2 between 24-35, for 2 between 36-47 and for 2 between 48-60 months. These findings would imply that for patients with gastric lymphoma involving only the gastric wall, following a radical surgical intervention, no adjuvant treatment (either chemotherapy or radiotherapy) seems indicated.

T 127 PRIMARY GASTRIC NON-HODGKIN LYMPHOMAS. LONG-TERM FOLLOW-UP OF 168 PATIENTS.

L. Salvagno*, M. Sorarù*, C. Puccetti°, M. Busetto§, M. Giusto°, L. Endrizzi^, R. Polico§, D. Nitti*, S.M.L. Aversa*, V. Chiarion Sileni*, A. Montaguti#, A. Poletti*, N. Pennelli*, M.V. Fiorentino*. * Centro Oncologico Regionale, Padova; °Medical Oncology, Belluno; §Radiotherapy, Mestre (VE); ^Medical Oncology, Bassano (VI); #Dpt. Pathology, Dolo (VE), Italy.

168 patients (pts) with primary Gastric non-Hodgkin Lymphomas (G-NHL), treated between 1980 and 1992, are analyzed; the lymphoma was considered Primary G-NHL if the main symptoms are those of a gastric disease. There were 87 males and 81 females; the median age was 62 (range: 16-85). According to the Working Formulation, 68 pts had low grade lymphoma (A->C), 40 intermediate (D->F), 54 G + high grade and 6 could not be classified. According to Musshoff, 89 pts had stage I, 17 II_1, 32 II_2, 12 III, 18 IV (10 for liver, 6 for bone marrow, 2 for pleura).
130 pts underwent subtotal or total gastric resection. Splenic involvement was demontrated in 4 of 34 pts who had splenectomy; in addition, the spleen was involved in 3 further pts.
Among the 106 pts with limited disease (stage I or II_1), 37 of 92 resected pts received further therapy which consisted of chemotherapy (31 pts), radiotherapy (5) or both (1); 9 were not resected; 5 pts received no treatment. The 5-year survival for pts treated with surgery alone was 90% and with surgery plus chemotherapy was 96%. The relevance of adjuvant chemotherapy may consequently be questioned.
The 5-year survival, relating to low / intermediate / high grade of malignancy was 78 / 68 / 45 %; relating to stage I / II_1 / II_2 / III / IV, it was 83 / 93 / 39 / 19 / 25 %.
The 5-year survival of unresected pts was 19%, while it was 44% for pts with residual disease after gastrectomy and 87% for radically resected pts.
Conclusions: A lower 5-year survival was found in pts with advanced disease or high grade lymphoma: aggressive chemotherapy appears advisable in this group of patients.
The spleen appears to be involved only in a small percentage of cases.
Stage I-II_1 pts with no residuum after surgery alone have a 5-year survival comparable to those who received "adjuvant" chemotherapy: a study of prognostic factors is necessary to define which subgroups of pts may benefit by postsurgical therapy.

T 128 NON-HODGKIN'S LYMPHOMA (NHL) OF THE GASTRO-INTESTINAL TRACT; A REVIEW OF 109 CASES TREATED AT A SINGLE CENTRE.

P. Lorigan[1], P. Bishop[2], J.A. Radford[1], D.P. Deakin[3], D. Ryder[4], P.M. Wilkinson[5], M. Harris[2] and D. Crowther[1]
[1]CRC Department of Medical Oncology and Departments of [2]Histopathology, [3]Radiotherapy, [4]Medical Statistics and [5]Clinical Pharmacology, Christie Hospital, Manchester

Since 1975, 109 patients (pts) with NHL of the gastro-intestinal (GI) tract have been treated at this institute. Median age at presentation was 54 years (range 19-77) and 62 were male and 47 female. Most common presenting symptoms were abdominal pain (80%), weight loss (59%), nausea and vomiting (38%), dyspepsia (27%) and altered bowel habit (21%). Abdominal surgery was performed in 100 (92%) patients and for 29 this was an emergency procedure. Resection of the GI tumour took place in 86 (79%) of pts and in 52 (60%) of these resection was complete.

Gastric involvement alone was the most common site of GI disease (35%) with more distal regions of bowel less frequently affected (jejunum alone, 10%; ileum alone, 13%; jejunum and ileum, 10%; ileum and colon, 6%; colon alone, 4%; rectum alone, 1.8%). In 12 (11%) pts the GI tumour was of bulk proportions (largest diameter ≥10cm). Cotswold stage was predominantly II (46 pts, 42.2%) or IV (49 pts, 45%) but 13 (11.9%) pts had stage I and one pt had stage III disease.

Review of histological diagnosis was performed in 105 cases using haematoxylin and eosin stained sections, supplemented where possible by immunohistochemical techniques. Eighty (76%) cases were Kiel high grade, 13 (12%) low grade and 12 (12%) grade undetermined. Thirty-eight (36%) of all cases had centroblastic NHL.

Treatment following surgery was with VAP (until 1987) or VAPEC-B (since 1987) chemotherapy (CT) followed by abdominal radiotherapy. Sixty- two pts have died, either during treatment (n=23), from progressive disease (PD) since completing treatment (n=34), or from unrelated causes (n=5). The 23 deaths during treatment occurred mainly as a result of sepsis (n=12) or PD (n=5), with bowel perforation, haemorrhage from tumour, pulmonary embolism, tumour lysis syndrome, respiratory distress syndrome and haemorrhage from a non-involved region of bowel accounting for the others. With a median follow-up for survivors of 51 months (range 2-166), actuarial survival at 10 years is 38% with pts in whom the tumour involving the stomach or bowel was completely resected faring better than incompletely resected or unresected GI disease (44% vs 32% vs 30%) but these differences are non-significant.

In this series, NHL of the GI tract commonly presented with local symptoms and/or weight loss and was more likely to involve proximal than distal sites. Partial or complete resection of involved bowel was performed in the majority of cases and this probably accounts for the subsequent low incidence of local complications during CT.

T 129 PROGNOSTIC FACTORS FOR SURVIVAL IN 90 PATIENTS WITH PRIMARY GASTRIC NON-HODGKIN LYMPHOMA.

A. Rossi, S. Cortelazzo, P. Viero,^T. Motta, B. Comotti, * A. Perna, T. Barbui. Division of Hematology and ^Pathology, Ospedali Riuniti di Bergamo, and * Istituto 'Mario Negri', Bergamo, Italy.

Primary Gastric non Hodgkin's lymphoma (PGL) is the most frequent extranodal lymphoma accounting for approximately 40% of all extranodal primary non Hodgkin's lymphoma. The role of surgery and other treatment modalities in the management of these patients is still controversial. We have retrospectively examined a cohort of pts with PGL with the aim of identifying patient categories at different prognostic risk .

From 1981 to 1992, 90 cases of PGL, 43 males and 47 females, median age 60 years (range, 16-82) were diagnosed in our Department. Fourteen patients (15%) had systemic symptoms. Sixty four pts were in localized stage (I E, II-1E), while 26 had extensive disease (II-2E- IV E). Bulky disease (i.e. mass $\geq$ 7 cm) was present in 39 patients. Thirty two pts had low grade and 58 intermediate grade lymphoma according to the Working Formulation. Patients were treated with surgery alone (n=26) or associated with chemotherapy (n=39), or chemotherapy alone (n=21). Four pts did not undergo treatment for coesistent medical illness. The overall survival of 90 pts was 68% at 5 year. Seventeen pts (19%) died: 2 of surgery, 9 of chemotherapy-related complications, 4 because of disease progression and 2 of causes not related to disease.

Nine clinico-pathologic parameters at presentation were examined in univariate analysis: age $\leq$ 60 vs > 60 years; sex M vs F; B symptoms ; performance status (ECOG scale) $\leq$ 1 vs >1; stage < II-2E vs $\geq$ II-2E; bulk; low grade versus intermediate grade histology; high levels of LDH; treatment: surgery alone vs chemotherapy alone vs surgery + chemotherapy.

We have identified 5 criteria associated with a poor prognosis in univariate analysis: 1) bulky disease ($p<0.01$); 2) performance status (ECOG scale) >1 ($p<0.01$); 3) high levels of LDH ($p>0.025$); 4) stage $\geq$ II-2E ($p<0.05$); 5) no surgery ($p<0.05$).

Using Cox proportional hazard model, there were three independent risk factors : 1) no surgery ($p=0.0001$); 2) stage $\geq$ I I-2E ($p< 0.006$); 3) Bulky disease ($p= 0.008$).

Thus, surgery had a role for improving survival in PGL, 84% of pts who underwent surgery being alive at 3 years vs 65 % of pts who did not ($p< 0.05$).

T 130 COMPARISON OF TREATMENT STRATEGIES IN 197 GASTRIC LYMPHOMAS: THE DANISH LYFO-EXPERIENCE

H. Brincker[1], F. d'Amore[1], on behalf of the Danish Lymphoma Study Group, LYFO

[1] Dept. of Haematology, Odense University Hospital, 5000 Odense, Denmark

Among 2446 patients with non-Hodgkin's lymphomas, registered prospectively by the Danish population-based LYFO-registry during the 9-year period 1983-91, 197 cases of primary gastric lymphomas occurred (8% of all lymphomas). 106 of the patients (54%) had localized disease with stages I_E (87) and II_{iE} (19). The remaining 91 patients had stages II_{2E} (14), III (4) and IV (67). The stage was unknown in 6 patients.

By univariate analysis a good prognosis was associated with age <74 years, localized disease, absence of nodal involvement, low-grade histology, MALT histology, absence of fever, absence of LDH-elevation, and absence of performance scores 3 and 4. Overall 5-year survival (actuarial) was 44%, and cause-specific 5-year survival 63%. For the stages $I_E + II_{iE}$ overall 5-year survival was 67%, while overall 5-year survival for stages $II_{2E} + III + IV +$ unknown was 14%, demonstrating an excellent separation of good-risk from poor-risk patients by the Musshoff staging system.

Among the 106 patients with localized disease 67 had surgical resection (SURG), 55 chemotherapy (CT), and 51 radiotherapy (XRT), or various combinations thereof. By multivariate analysis the presence of fever, LDH-elevation, or performance scores 3 and 4 had a far more significant influence on survival than any of the treatments or treatment combinations. SURG resulted in hematemesis in 1 patient, and 9 patients had subsequent malabsorption. Non-SURG treatment resulted in hematemesis in 2 patients and gastric perforation in 2 patients (none of these complications were lethal), but no patients had malabsorbtion. Three patients died of complications following SURG, and 2 patients died of complications following CT (1 infection, and 1 cardiomyopathy). There were no deaths following XRT.

In this retrospective analysis of various treatment strategies in localized gastric lymphoma, SURG was followed by more cases of late complications and treatment associated death than XRT without any apparent difference in survival. The addition of CT to SURG or XRT did not result in any obvious additional survival benefit.

T 1

T 131 GASTRIC AND INTESTINAL LYMPHOMAS: POPULATION-BASED DATA FROM A DANISH LYMPHOMA REGISTRY

F. d'Amore[1], H. Brincker[1], K. Grønbæk[1]

For the Danish Lymphoma Study Group, LYFO

[1]Dept. of Haematology, Odense University Hospital, 5000 Odense C, Denmark

Thi
trea
mye.
23-8.
infiltr
remis
give a
attainn
and B
immun
(p=0.00
mucosit
patients
This stu
cell NHL
to a bett
the thera

Over a 9-year period (1983-1991) a population-based non-Hodgkin's lymphoma (NHL) study from Western Denmark registered 2446 newly diagnosed NHL cases. Of these, 306 (12.5%) had a gastrointestinal localisation (175 gastric only, 109 intestinal only, 22 both). The age standardised incidences for gastric and intestinal NHL were 0.71 and $0.48/10^5$/year, respectively. Age-specific incidences showed for both localisations an exponential rise as a function of age. An incidence trend analysis for the period 1983-1991 showed no significant de- or increase for any of the two localisations. The age range of gastrointestinal NHL was 5-94 years (median: 67.5). The age distribution of gastric and intestinal cases did not differ significantly. However, intestinal NHL had more female cases (M/F ratio: 2.0 vs 1.3), were more often disseminated (Musshoff stage II_{2E}-IV), had a higher occurrence of constitutional symptoms and were more frequently of T-cell phenotype (10% vs 2%). Histologically, gastric NHL had a higher proportion of low-grade cases (almost all of MALT type), than intestinal NHL (37% vs 20%), while the reverse was true for intermediate- and high-grade histology. In accordance with the higher occurrence of generalised disease, intestinal cases were more frequently treated with chemotherapy than gastric ones, where surgery and radiotherapy were more commonly adopted. The cause-specific 9-year survival for gastric NHL was 60% (5-year: 63%), for intestinal NHL 47% (5-year: 49%). The Musshoff staging system was an excellent discriminator between truly localized ($I_E + II_{iE}$) and disseminated cases (II_{2E}-IV) for both gastric and intestinal NHL. Interestingly, no significant difference ($p=0.10$) was found between 9-year survival values of surgically vs conservatively staged localized cases. A Cox-regression analysis was performed for both gastric and intestinal NHL. For gastric cases following adverse pretreatment prognostic factors for cause-specific survival were identified: Musshoff stage $\geq II_{2E}$ (RR = 4.8), fever (as the most important among B-symptoms) (RR = 3.4), age > 74 (RR = 1.8). MALT histology was a strongly favourable prognostic factor for gastric lymphomas (RR = 0.5). Adverse pretreatment prognostic factors for intestinal cases were: high (WHO 3-4) performance score (RR = 4.9), age > 59 (RR = 2.8), B-symptoms (RR = 2.7) and Ann Arbor stage $\geq II_E$ (RR = 2.6).

T 132 THE REGISTRY OF THE "GRUPPO VENETO LINFOMI".

R.Polico*, M.Busetto*, L.Salvagno+, F.Gaion#, E.Radin**, V. Chiarion Sileni+, C.Puccetti@, M.Giusto@, P.Manente#, A.Bononi°, A.Scattolin**, M.Antonello*, E.Ferrazzi°, L. Endrizzi++, M.V.Fiorentino+.

* Dept of Radiotherapy, Ospedale di MESTRE (VE)
**Dept of Haematology, Ospedale di MESTRE (VE)
\+ Dept of Medical Oncol, Ospedale di PADOVA
@ Dept of Medical Oncol, Ospedale di BELLUNO
\# Dept of Medical Oncol, Ospedale CASTELFRANCO(TV)
° Dept of Medical Oncol, Ospedale di ROVIGO
++Dept of Medical Oncol, Ospedale di BASSANO (VI)
Italy

Since January, 1991 a new project was developed amongst 6 oncologic centers, including haematology, medical oncology and radiotherapy departments. All the centers being Bassano, Belluno, Castelfranco, Mestre, Padova and Rovigo, are neighbouring and from the same area of the Veneto in North-Eastern Italy and are the referring centers for about 1,120,000 people. The aim was to retrieve all new lymphoma cases and cases diagnosed during previous four years.

The data retrieved consists of patient identification, hystology and extension of the disease, staging, sites of primitive extranodal disease, first line treatment and response, relapse and status.

All patients are followed-up and records regularly updated. By January, 1993 we collected a total of 757 cases, 550 NHL and 207 HDL. 675 patients (89%) are fully evaluable; the remaining are still on treatment. According to the Working Formulation, of 550 NHL, 104 are classifiable of High grade, 224 Intermediate and 191 Low grade. Of 207 HDL patients, 112 are NS, 21 LP, 59 MC and 5 LD. 350 patients are registered as primitive extranodal lymphomas, 306 NHL and 44 HDL: 116 of the gastrointestinal tract (91 gastric), 47 from the ORL district, 49 from the skin, 30 from the lungs, 16 from the breast (1 male).

This data will be useful to see the incidence of lymphomas in our area, as well as the hystology, the site of presentation, their clinical course and outcome. This will improve our knowledge and standards.

T 133 PRIMITIVE BREAST LYMPHOMA. A REPORT OF 15 CASES FROM THE "GRUPPO VENETO LINFOMI".

M.Busetto*, R.Polico*, A.Bianco+, M.Sorarù+, C.Puccetti@, M.Giusto@, F.Gaion#.
* Dept of Radiotherapy, Ospedale di MESTRE (VE)
+ Dept of Medical Oncol, Ospedale di PADOVA
@ Dept of Medical Oncol, Ospedale di BELLUNO
# Dept of Medical Oncol, Ospedale CASTELFRANCO (TV) Italy

The breast is a rare site for primary extranodal lymphoma. 15 cases of malignant lymphoma with primitive localization in the breast were observed by the "Gruppo Veneto Linfomi" (Northern Italy).

The average age was 62.3 (SE 12.6), ranging between 36-79 years of age, 1 patient was male. 7 cases were grouped at stage I, 3 at stage II, 3 at stage III and 2 at stage IV. These last two were referred to the oncologist for the breast nodule, but other visceral localizations in the lungs were found during staging.

According to the Working Formulation, 2 were of High-grade, 9 Intermediate and 3 Low-grade. The male was an Intermediate grade, stage 1E. The only case of Hodgkin's disease was of the Nodular Sclerosis type. None had "B" symptoms. Both the high grade cases were at stage IV and were treated in one case with local RT and CT (Promace-Mopp) with Partial Response. The patient progressed in retroperitoneum 11 months later and died of disease. The other high grade case, aged 74, was treated with CT alone (MVP) but progressed in bone marrow and died of disease 13 months later. Five of the eight patients in Intermediate grade were at stage I and were treated with local RT alone; one more patient at stage I was treated with surgery and local RT. The last three patients, 2 of which were at stage II and one at stage III, were treated with CT alone. All these patients are alive and well. The three cases of low-grade NHL at stage I and II were treated with surgery and CT, but they relapsed 9, 30 and 33 months later on peripheral lymphnodes or skin. Neither of the three present any evidence of disease after 2nd line treatment. The patient with Hodgkin's Disease, stage III, had Partial Response after a full course of MAMA, but progressed on bone marrow 13 months later and died of disease.

The mean follow-up time is 25 months (range 3-89), 12 out of 15 patients are alive and well, nobody has been lost to follow-up, and the overall mean survival time is 72.4 months (SE 10.7).

T 134 RISING INCIDENCE OF NON-HODGKIN'S LYMPHOMA IN WESTERN DENMARK OVER THE LAST TWO DECADES

F. d'Amore[1], L.S. Mortensen[2]
[1] Dept. of Haematology, Odense University Hospital, 5000 Odense C, Denmark
[2] Dept. of Medical Statistics, UNI-C, 8200 Aarhus N, Denmark

Recent reports from the United States, UK, Italy and Sweden have suggested an increase in incidence rates for non-Hodgkin's lymphoma (NHL) within the range of 3-4% yearly. This increase, which is AIDS-unrelated and probably not solely attributable to improved diagnostic practice, seems especially evident in the older age groups (>65).

We analysed the incidence rates (IR) for NHL in Western Denmark over the past two decades (1972-1991). For this purpose data from two registries were used: the Danish Cancer Registry (DCR) covering the period 1972-1988 and a population-based NHL registry from Western Danmark (LYFO) covering the period 1983-1991. A comparison of the number of registered cases in the overlapping period (1983-1988) showed consistently higher figures for LYFO as compared to DCR. This difference ranged from 31.8% in 1983 to 70.9% in 1987 (mean value: 55.4%). According to the DCR, European age-standardised IR for the period 1972-1988 were in the range: 4.1 (1972)-7.0 (1988). A linear regression analysis showed a significant yearly increase of 5.0% ($r=0.754$, $p<0.001$). According to the LYFO registry, the European age-standardised IR for the period 1983-1991 were in the range: 6.66 (1983)-11.03 (1988). A minor flexion was seen for the last 3 yrs (1989: 10.02, 1990: 8.66, 1991: 8.84). In 1991 a cross-check with the DCR covering the period 1983-1988 revealed a 4% fraction of cases, which had escaped LYFO registration. The flexion in LYFO incidence values observed after 1988 may therefore be reduced or even cancelled by a corresponding registry update. Nevertheless, and in spite of the shorter observation period (LYFO 9 yrs vs DCR 17 yrs), a linear regression analysis of the LYFO data showed a marginally significant annual increment of 3.1% ($r=0.592$, $p=0.093$). A third regression analysis was performed for the period 1972-1991 based on pooled DCR and LYFO data. In order to make DCR and LYFO data comparable, each DCR-based IR value for the period prior to the LYFO registry (1972-1982) was increased by 55.36% (see above). The results of this third analysis confirmed those of the two previous ones showing an annual incidence increment of 4.6% ($r=0.764$, $p<0.001$). A further evaluation of incidence trends related to geography, age, histological subtype and anatomic localization is currently in progress.

T 135 Non-Hodgkin's lymphoma (NHL) after Hodgkin's Disease (H.D).

A.F.Abrahamsen, D.K.Blystad, R.Langholm, J.F.Abrahamsen, O.Nome, H. Høst, S. Kvaløy. Dept. of Oncology and Pathology, The Norwegian Radium Hospital, Montebello, 0310 Oslo, Norway.

During 1968 - 1985, 1152 patients started treatment for H.D. in the Norwegian Radium Hospital. 20 patients developed NHL ≥ 1 year after diagnosis of H.D. The time from HD to NHL was 1-22 years, mean 11 years. The risk of NHL was not related to the treatment of H.D. 9 NHL's occurred in mixed cellularity HD, 7 in lymphocytic predominance and only 2 in nodular sclerosis H.D. and 2 in lymphocytic depleated H.D.

NHL were classified according to the Kiel classification. 16 patients had high grade malignant NHL, 4 patients low grade malignant NHL. Most patients had NHL starting as an abdominal mass with extra nodal disease. The relation of histology to immunophenotypic studies will be discussed.

Relapse after treatment of Hodgkin's Disease should be biopsied, especially when the relapse occurs several years after HD, and present with extra nodal abdominal mass.

T 136 IS STAGE I AND II FOLLICULAR LYMPHOMA A LOCALISED DISEASE ? A PCR-STUDY IN t(14;18)-POSITIVE LYMPHOMA.

Caro Lambrechts *, Pauline E. Hupkes *, Lambert.C.J. Dorssers *, Mars B. van 't Veer**; Department of *Molecular Biology and **Haematology, Dr. Daniel den Hoed Cancer Center, Rotterdam, The Netherlands.

Most patients with follicular lymphoma, the most common type of Non-Hodgkin's Lymphoma and in the majority of the cases characterised by the chromosomal translocation (t)(14;18), present with disseminated disease (stage III and IV). After clinical staging, including CT scan and morphological and immunological examination of blood and bone marrow, 10 - 20% of the patients appear to have localised disease (stage I or II). These patients are usually treated with involved field radiotherapy only. Longstanding complete remissions and even cure has been described, suggesting that these patients have really localised disease. We found in 11 patients with follicular lymphoma stage I or II t(14;18)+ cells in the blood and/or bone marrow with the polymerase chain reaction (PCR) at initial staging, during clinical complete remission or both. Out of 8 patients, of whom a lymph node biopsy was available and t(14;18)+, 7 showed t(14;18)+ cells in the blood or bone marrow. At initial staging in 6 patients (4 proven to be t(14;18)+ on the biopsy) t(14;18)+ cells were found in the blood and/or bone marrow. Nine patients (6 proven to be t(14;18)+ on biopsy) in complete remission showed t(14;18)+ cells in the blood or bone marrow at one or more occasions. Of these 9 patients 3 relapsed at 55, 60 and 100 months after therapy, respectively. Six patients are in clinical complete remission with a mean follow-up time of 32 months (range 3-148 months). From these data we conclude: 1. stage I and II t(14;18)+ follicular lymphoma is usually not a localised disease and 2. the presence of t(14;18)+ cells, demonstrated by PCR, in the blood or bone marrow in these patients appears not to be predictive for an impending relapse.

T 137 THE FOLLICULAR NON HODGKIN'S LYMPHOMAS - 2: PATTERNS OF DISSEMINATION.

J W Denham, G Vaughan-Hudson, B Vaughan-Hudson, M H Bennett, A M Jelliffe, W R Pratt, and E E Denham, for the British National Lymphoma Investigation

The records of 398 patients with Follicular Non Hodgkin's Lymphoma followed for a minimum of 12 years, who were entered into the British National Lymphoma Investigation Trials between 1974 and 1980, have been reviewed to determine the patterns of dissemination of this group of disease processes.

The anatomical distribution of disease was found to vary little between subgroups defined by sex and age. However, patients with predominantly small cell histological subtype had higher incidences of marrow involvement and splenomegaly. It was observed that contiguous spread from one lymph group to another could **not** have taken place in at least 25% of patients. Marrow involvement and features such as the presence of splenomegaly and constitutional symptoms were found to increase in incidence in direct relation to increasing number of lymph node regions involved. The presence or absence of marrow involvement was **not** found to influence the deteriorating gradients in relapse free and cause specific survival that were observed to take place with increasing lymph node region involvement. Support for this observation came from a series of Cox proportional hazards regression analyses which suggested that an increasing number of nodal regions involved, the presence of splenomegaly and constitutional symptoms had powerful, independent adverse prognostic significance, but that marrow involvement did **not**.

The findings of this study support the notion that the Follicular Lymphomas are "semi-solid" lymphoid tumours in which advancement of the disease process is characterised by an accumulation of neoplastic lymphocytes throughout the lymphoid system and marrow. This accumulation may be evidenced by an increasing number of nodal groups becoming involved and by an increasing incidence of marrow involvement as time passes after initiation of the disease process.

T 138 PROSPECTIVE STUDY OF A WATCHFUL WAITING POLICY IN LOW TUMOR BURDEN FOLLICULAR LYMPHOMA (FL).

P. Brice, P. Solal-Celigny, B. Coiffier, N. Milpied, C. Haioun, N. Brousse for the groupe d'Etudes des lymphomes folliculaires GELF, hôpital Saint-Louis, Paris, FRANCE

Since January 1987, 157 patients (pts) among 520 pts with FL registred in the GELF protocol were considered as having a low tumor burden when they had none of the following criteria (involvement of 3 or more lymph nodes each with a diameter of at least 3 cm, one site of at least 7 cm, B symptoms, blood lymphoid cells greater than 50.10^9/l, cytopenia or local risk of complication eg. pleural epidural...) Among these pts 49 were **randomly assigned to "watch and wait"**, the remaining pts received interferon therapy (5 MU three times weekly) or prednimustine (200 mg/m² five consecutive days monthly). Pts were designed as progressive with high tumor burden when they had at least one of the previous criteria ; after progression they were treated with chemotherapy (ADR : 25 mg/m², CPM : 600 mg/m², VM 26 60 mg/m² on day 1 and Prednisone).
PATIENTS : 44 pts were evaluable (2 pts excluded for wrong histology and 3 pts with a short follow up). Median age : 52 y (24 to 70 y), male : 24 pts, female : 20 pts, stage III : 14 pts, stage IV : 30 pts (bone marrow involvement in 29 pts), follicular smal cells : 18 pts, follicular mixed : 24 pts, others : 2 pts, abdominal lymph nodes : 26 pts.
RESULTS : the median follow up is at 42 months, 17/44 pts progressed at a median time of 9 months after inclusion (3 to 39 months) ; 2/17 pts had histological conversion in high grade lymphoma. The remaining 27 pts have stable disease without treatment. 14/17 pts with progressive disease are evaluable for therapeutic response, there were 3 failures with 2 deaths from disease at 30 and 42 months after diagnosis, 11/14 pts responded to chemotherapy. Overall survival will be presented and compared to the two other arms with treatment.
CONCLUSION : At a median follow up of 42 months (6 to 72 months) 38 % of pts in a watchful waiting policy progressed, this rate is closed to other series. We will analysed in detail the outcome of early progression.

T 139 INTENSIVE COMBINATION CHEMOTHERAPY FOR DIFFUSE LOW GRADE NON-HODGKIN'S LYMPHOMAS OF B- AND T-CELL LINEAGE.

JS Whelan,[1] JA Radford,[2] AG Stansfeld,[3] M Harris,[4] PWM Johnson,[1] J Matthews,[1] D Deakin,[2] AZS Rohatiner,[1] D Crowther,[2] TA Lister.[1] [1]Imperial Cancer Research Fund Department of Medical Oncology and [3]Department of Pathology, St. Bartholomew's Hospital, London and Cancer Research Campaign Departments of [2]Medical Oncology and [4]Pathology, Christie Hospital, Manchester, U.K.

Thirty eight patients with diffuse low grade non-Hodgkin's lymphoma (NHL) were treated at presentation with VAPEC B, a 12 week programme of alternating myelo- and non-myelosuppressive agents. The mean age was 60 years (range 23-85); 30 patients (78%) had stage IV disease, mostly due to bone marrow infiltration. Thirty seven patients are evaluable for response, in whom complete remission was documented in 7 (19%) and partial remission in a further 18 to give an overall response rate of 67%. Factors which correlated favourably with attainment of remission included histology of lymphoplasmacytoid type (p=0.01) and B-cell immunophenotype (p=0.05). Several factors, notably B-cell immunophenotype (p=0.01) and a pre-treatment albumin level of >33 g/l (p=0.001) were favourably associated with survival. Myelosuppression and mucositis resulting in treatment delay or dose reduction was common. Four patients died during therapy (10%).
This study confirms that low grade T-cell NHL carries a worse prognosis than B-cell NHL. Treatment of diffuse low grade NHL with intensive therapy does not lead to a better complete remission rate than single agent therapy. New approaches to the therapy of this heterogenous group of diseases are therefore required.

T 140 CH2OP VERSUS CHOPBLEO REGIMEN IN LOW-GRADE LYMPHOMA: A MONOCENTRIC RANDOMIZED STUDY.

P. Bourquard[1,3], V. Lavabre-Bertrand[1,3], MC. Picot[2], C. Bonifaci[2], T. Rousset[1], F. Bertheault[1], JM. Karsenti[1], N. Fégueux[1], MP. Cabrol[1], D. Donadio[1], M. Navarro[1]. Service des Maladies du Sang[1], Département de l'Information Médicale[2], CHRU Lapeyronie, 34059 Montpellier cedex, INSERM U291[3] 99 rue Puech Villa 34097 Montpellier cedex, France. Service de Médecine CHG Béziers 34500 Beziers France.

Between 1984 and 1990, patients with low grade lymphoma according to Kiel classification were randomized to receive 4 courses of the CH2OP regimen (Cyclophosphamide(C) 600mg/m² day(d)1, Doxorubicin(D) 50mg/m² d1 and 2, Vincristine(V) 2mg d1 and Prednisolone(P) 1mg/kg d1 to 5) or 8 courses of the CHOPBleo regimen (C 600mg/m² d1, D 50mg/m² d1, V 2mg d1, P 1mg/kg d1 to 5 and Bleomycin(B) 15mg d1) every 4 weeks. Fifty-four patients were included, 51 were evaluable, 22 received the CH2OP regimen and 29 received the CHOPBleo regimen. Both groups were comparable as concerning age (median 57), sex, histologic type, disease stage, B signs, bone marrow involvement.
No statistically significant difference was observed between those groups for objective response rate (reduction of more than 50% of the tumor mass and disappearance of bone marrow involvement) (59% with CH2OP/64% with CHOPBleo), complete remission rate (41%/50%), response duration (median 17 months/29), and overall survival duration (median 70 months/52). Toxicity of both regimens wasn't different as concerning neurological, digestive, cardiovascular, respiratory effects of drugs (2 patients developed cardiac adverse effects in CH2OP arm and 1 in CHOPBleo arm; 3 patients had toxic manifestations of Bleomycin). We compared the number of neutropenia episodes less than 1000/mm³ and less than 500/mm³ per course of chemotherapy for both regimens, and observed a significantly higher frequency of neutropenia (<1000 and <500) with CH2OP (p=0.0011 and 0.0059 respectively) but this wasn't accompanied by a greater incidence of infectious complications or by the necessity of larger interval between courses.
We conclude that reinforcement of the anthracycline dosage for a short induction duration (4 courses) doesn't improve therapeutic beneficial effects when compared to a regimen including a fifth drug (Bleomycin) for a longer induction duration (8 courses), although it induces a greater rate of neutropenia which isn't riskless.