ABSTRACTS

POSTER PRESENTATIONS

Poster Session I

BIOLOGICAL STUDIES

ABSTRACTS - Fourth International Conference on Malignant Lymphoma, Lugano

P 1

GROWTH MODULATION OF TWO LYMPHOMA CELL LINES BY A NOVEL CALCITRIOL ANALOGUE MC903. Hickish T[1], Soukop M[2], Millar BC[1], Purvies H[1], McElwain TJ[1], Cunningham D[1]. [1]Royal Marsden Hospital, Sutton, Surrey; [2]Glasgow Royal Infirmary, Scotland.

After apparently successful induction chemotherapy almost all patients with low grade non-Hodgkins lymphoma relapse, therefore there is a requirement to develop novel treatments for application to the maintenance phase. In this regard we have previously shown that alfacalcidol (which is metabolised to calcitriol) can produce tumour regression in 30% of patients with low grade non-Hodgkins lymphoma. The dose limiting toxicity of alfacalcidol is hypercalcaemia but the analogue MC903 has similar anti-proliferative effects to calcitriol but 100 times less of an effect on mineral metabolism. We have studied the growth modulating effect of calcitriol and MC903 (Leo laboratories) on two diffuse histocytic cell lines SU-DHL8 and SU-DHL4*. The latter has a t(14;18) characteristic of 80% of follicular small cleaved cell lymphoma. Toxicity was measured using the incorporation of ^{3}HThymidine and by the growth of colonies in soft agar. Results are shown below.

	Controls		Calcitriol		MC903			Surviving fraction		
Cpm Min^{-1}	Mean	SD	Mean	SD	Mean	SD		10^{-6}	10^{-7}	10^{-8} Molar
SU-DHL4	22079	4564	706	346	112	46	MC903	.46	.50	.53
SU-DHL8	3815	1218	229	134	202	103	Calcitriol	.48	.52	.54

These data show MC903 and calcitriol produce a similar reduction in the thymidine uptake suggesting an antiproliferative effect on both cell lines. The clonogenic assay shows an antiproliferative effect that is similar for the two drugs on the clonogicity of SU-DHL4 cells. These data suggest MC903 may be an effective antiproliferative agent in lymphoma and indicate a role for a calcitriol analogue in the maintenance phase of low grade lymphoma.
*kindly provided by A Epstein

P 2

MALIGNANT HISTIOCYTOSIS MAY DERIVE FROM AN NK-COMMITTED PROGENITOR.
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Malignant histiocytosis (MH) is a rapidly progressive hematological disease sharing several clinical and pathological features with monocytic cytotypes (FAB M4,M5) of acute myeloid leukemias (AML). The cellular origin of MH remains however controversial in that the presence of both T lymphoid (CD2,CD4,CD1a) and myelomonocytic (CD13, CD33, CD14, ANAE activity, lysozyme production) markers have been reported to be expressed by MH cells. We observed four MH cases which were extensively analyzed by combining immunophenotyping and gene rearrangement studies. Our results show that MH cells from all patients displayed NK-related surface markers along with a restricted number of T cells antigens, while myelomonocytic antigens were heterogeneously expressed. In particular several monoclonal antibodies (MoAbs) recognizing NK-related antigens clustered into the new CD56 group (N-CAM) were strongly reactive with bone marrow and peripheral blood MH cells which also expressed CD16 antigens. Other two NK-associated surface molecules recognized by anti CD59 and anti CD53 MoAbs were also detected on malignant histiocytes cells. MH cells were moreover strongly reactive with anti CD4 MoAbs and, in three out of four cases, CD2 antigens were also detected. Malignant cells did not react with other T cell antigens and lacked CD30 expression ruling out an alternative diagnosis of Ki-1 lymphoma. Myelomonocytic antigens (CD13, C33, CD14) were in general absent or weakly expressed by MH cells with the exception of CD36 molecules. All MH samples were finally strongly reactive with anti-HLA-DR MoAbs, presented ANAE activity, lysozyme secretion and lacked any B cell-associated antigen. Malignant histiocytes from all patients displayed a germ line configuration of T cell receptor genes (TCRβ,TCRγ) and JH region of immunoglobulin genes (see Table). Finally, one case studied showed a spontaneous cytotoxic activity against K562 cells (15% of specific lysis) not increased by IL-2.

				CD		CD				CD					
CASE	TCRβ	TCRγ	JH	2	4	3	30	13	14	33	36	16	56	59	53	NSE	LYS
1 MH	G	G	G	+	+	-	-	-	-	-	+	+	+	+	+	+	+
2 MH	G	G	G	-	+	-	-	-	-	+	+	-	+	+	+	+	+
3 MH	G	G	G	+	+	-	-	-	+	-	+	+	+	+	+	+	+
4 MH	G	G	G	+	+	-	-	+	-	-	+	+	+	+	+	+	+

G, germline configuration. R, rearranged configuration. NA, not available. NSE, non-specific esterase. LYS, lysozime activity.

Our data suggest that MH could arise from an unfrequent subpopulation of lymphohemopoietic precursors capable of differentiation toward both the NK and the monocytic lineage or might represent the neoplastic counterpart of a rare NK precursors subset with unique biological features. Supported by the A.I.R.C.*Fellow of the A.I.R.C.

P 3

ANAPLASTIC LARGE CELL LYMPHOMA: A HISTOLOGICAL AND IMMUNOLOGICAL STUDY OF 72 CASES V. de Montpreville, P. Gaulard, M-F. d'Agay, G. Delsol, J. Diebold and the GELA executive committee. Histopathology Departments of CHU Henri Mondor, Créteil; Hôpital St Louis and Hôtel Dieu, Paris; CHU Toulouse Purpan, Toulouse.

Among the first 1000 patients included in the GELA treatment protocol for aggressive lymphomas, 78 cases were classified initially as anaplastic large cell lymphomas, 72 of which were confirmed on review by a panel of 5 haematopathologists. These cases were further subclassified into the following categories: "common" (30 cases); giant cell-rich (3 cases); Hodgkin's-related (9 cases); atypical (18 cases); and large cell lymphoma with a significant anaplastic component (12 cases). Immunohistological studies were performed on paraffin sections using antibodies against CD antigens (CD3, 15, 20, 30, 45 and 68) and other markers (UCHL1,MB2, LN1, LN2, EMA, BNH9). In addition 34 cases were studied in frozen section. Most cases were positive for CD30 (Ki-1) and CD45 (68 and 63 cases respectively), whereas CD15 was found in only 30% of cases (20/67). 28 cases (29%) were considered to be of T cell origin, and 23 (32%) as B cell neoplasms. 21 cases (29%) could not be identified as being of T or B cell origin, including 2 cases in which antigens associated with both T and B cells were co-expressed. T cell neoplasms were commonest among the "common" type, and those of B cell origin among the large cell group with an anaplastic component. Hodgkin's-related cases were mostly of "null" phenotype. No cases was considered to be of true histiocytic origin, although staining for CD68 (antibody KP1) disclosed numerous reactive histiocytes, often showing erythrophagocytosis. Antibody BNH9 (against the H and Y blood group antigen) was found in 14/62 cases (23%), 12 of which were of common or giant cell type.

These results emphasise the heterogeneity of anaplastic large cell lymphoma. Since all patients had been treated according to standardised regimes as part of the GELA treatment trial, and then followed up regularly, the prognostic significance of the different histological and phenotypic features could be evaluated. The results of this correlative review will be presented.

P 4

Angiodestructive Lymphoma (ADL): A novel subtype with unfavorable prognosis. J ITAMI, M ITAMI, J TAMARU, T ARUGA, A MIKATA, N ARIMIZU. Department of Radiology and Pathology, Chiba University Hospital, 280 Chiba, JAPAN.

ADL is clinically discovered mainly as midline lethal granuloma of the upper respiratory tract. To study the clinicopathologic feature of ADL, retrospective study was undertaken.
[MATERIAL and METHOD] By reviewing the pathology slides of head and neck lymphomas treated in our Department from 1975 through 1989, 8 cases of lymphoma with prominent angiodestruction were found. The formalin-fixed paraffin-embedded materials were studied with monoclonal antibodies (MT-1, MB-1, L-26, UCHL-1). The male : female ratio was 6 : 2 with a mean age of 60. Clinically 6 cases had only localized involvement (Ann-Arbor CS I) and remaining two more advanced disease (One CS II and another one CS IV). Seven out of the 8 had involvement of nasal cavity and remaining one had cheek involvement. Six patients with CS I and II were treated by involved field RT with/without simultaneous mild chemotherapy. CS IV patient was treated with CHOP. Remaining one with CS I is now under treatment.
[RESULT] Immunohistochemical study showed that all but one had T-cell phenotype. Remaining one had B-cell marker. According to WF, DL was the most predominant subtype. All cases belonged to grade 2 or 3 by Jaffe's criteria. It is notable that in 5 cases repeated biopsy more than twice was necessary to reach the diagnosis. Two cases had long standing history allergic rhinitis. Out of 7 patients who completed treatment, only one remained disease free after 3 year-follow-up, while remaining 6 all succumbed to fatal recurrence. Local recurrence in the nasal cavity was always accompanied by widespread disease primarily in the lungs, spleen and skin. A patient treated by CHOP was totally refractory to it.
[DISCUSSION] Although some literature has suggested that RT is curative in MLR, our results revealed that ADL of grade 2 or 3, which seems to comprise most of the MLR, is not amenable to RT even when limited to the primary site. For improvement of prognosis of these patients, aggressive approach employing intensive chemotherapy will be warranted.

P 5 CLINICAL COURSE OF ANGIOIMMUNOBLASTIC LYMPHADENOPATHY UNDER A STANDARDIZED TREATMENT - RESULTS OF A PROSPECTIVE MULTICENTER TRIAL.

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Angioimmunoblastic lymphadenopathy (AILD) is a rare lymphoproliferative disorder recently classified as a subentity of peripheral T-cell lymphomas of low grade malignancy.The finding of clonal chromosome abnormalities (+3,+5) and of rearrangements of T-cell receptor genes in most of the cases proves the concept of its clonal origin. Retrospective data demonstrate the usually aggressive course of AILD, although spontaneous remissions were reported occasionally. There is little information about the value of cytoreductive treatments. Therefore, a prospective study was designed to define the responsiveness of AILD to a standardized therapy. The protocol consisted of an initial treatment with prednisone (Pred) 2 mg/kg for 2 - 4 weeks. Pts achieving a complete remission (CR) did not receive further therapy. Pts failing to respond or relapsing after achievement of CR or presenting already initially with life threatening tumor progression then received COP-BLAM/IMVP-16 (CHT). 53 pts were evaluable. Their median age was 64 (range 25-88) years. Thirtyfour of 53 (64%) pts received primary Pred (A), 21/51 (40%) secondary CHT (B) and 19/53 (36%) primary CHT (C). Response rates were 29% CR in A, 57% CR in B and 37% CR in C with a median first CR duration of 4.5 months (mo) in A, 3.5 mo in B and 8.5 mo in C. The relapse rate was high in A (8/10) and lower in B (2/12) and C (3/7). In lifetable analysis the median survival was 15 mo for pts with primary CHT and 10 mo for pts with Pred +/- CHT (n.s.). The probability of survival at 2 years was 48% for both treatment groups. The probability of eventfree survival at 2 years was only 20%. These results emphasize the aggressive clinical course in most of the patients. However, further data are required for a precise evaluation of this T-cell lymphoma including the definition of prognostic subgroups and their appropriate treatment.

P 6 BIVARIATE FLOW CYTOMETRIC MEASUREMENT OF DNA CONTENT AND CELL-SURFACE IMMUNOFLUORESCENCE: A NEW APPROACH FOR STUDYING CELL PROLIFERATION IN NON-HODGKIN'S LYMPHOMA.

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Several studies have shown that S-phase DNA content (S-DNA), an indicator of cell proliferation, is of prognostic relevance in Non-Hodgkin's Lymphoma (NHL). However, controversies still exist. Due to admixture of non-tumor cells (up to 60%) as well as ploidy heterogeneity, a reliable analysis of S-DNA in tumor cells may be jeopardized. Therefore, we measured S-DNA of distinct subpopulations defined by cell-surface immunofluorescence.

Cell suspensions of lymph node biopsies were labeled with unconjugated monoclonal antibodies against T-cells (CD2; CD3; CD4; CD7 and CD8), B-cells (CD9; CD10; CD19; CD20; CD22), and monocytes (CD14). A FITC-conjugated antibody was used as second label. Cellular DNA was proportionally stained for 24 h on ice with propidium iodide in hypotonic citrate. Cells were analysed on a single-laser flow cytometer. The percentages immunofluorescent cells were essentially unaltered after DNA staining.

Of the 14 NHL investigated so far, 5 were low grade (LG), 4 intermediate grade (IG) and 5 high grade (HG) NHL. Eleven were of B-cell and 3 (all HG) were of T-cell (CD7+) phenotype. Considerable admixture of T-cells (CD2+) were seen in the B-cell NHL (mean: 19.1 %) and of B-cells (CD19+ or CD20+) and mature T-cells (CD3+) in the T-cell NHL (mean: 11.3% and 19.3%, respectively).

DNA aneuploidy was observed in 1/5 LG, 4/4 IG and 2/5 HG NHL, all B-cell NHL. In all but one of these cases, analysis of S-DNA in the overall cell-population was not feasible because of overlapping aneuploid and diploid DNA histograms. However, the most predominant B-cell populations (CD19+, CD20+ or CD22+) were almost completely aneuploid whereas only 2-5 % aneuploid cells were seen in the CD2+ cells. This enabled calculations of S-DNA in the subpopulations.

In all of the 5 LG NHL of B-cell phenotype, S-DNA of both T-cells (CD2+) and the most predominant B-cell populations were <2.1%. In the IG and HG NHL of B-cell phenotype, a low S-DNA was measured in the T-cells (CD2+; mean: 4.0%) whereas a remarkably higher S-DNA was found in the most predominant B-cells (mean: 19.3%). In contrast, the 3 HG NHL of T-cell phenotype, showed a relatively high S-DNA of the CD7+ cells (mean: 11.2%), whereas in the B-cells (CD20+) and mature T-cells (CD3+) a low S-DNA was measured (mean: 1.3% and 1.2%, respectively).

This method is promising for studying proliferation activity in NHL, especially in cases of heterogeneous composition due to aneuploidism and admixture of non-tumor cells.

P 7 Histomorphologic and immunophenotypic spectrum of primary gastrointestinal B cell lymphomas.

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In order to compare primary gastrointestinal B cell lymphomas histomorphologically and immunophenotypically with orthologous steps of B cell differentiation within the mucosa-associated lymphoid tissue (MALT) of the gastrointestinal tract, a comprehensive panel of well characterized leucocyte differentiation antigens was composed. It comprised immunoglobulin constituents, CD5, CD10, CD11c, CD23, CD24, CD30, CDw32, CD38, CD39, CDw75, CD76, and L26 antigen. Taken together, these antigens yield characteristic immunoprofiles for the following B cell compartments of the MALT, *per se* closely linked to cytologically distinct B cell phenotypes: mantle zone (MZ), extrafollicular compartment (EF), follicle center (FC), and plasma cell compartment (PC). An unselected series of 27 MALT B lymphomas (14 of low and 13 of high grade malignancy) was first classified histologically in routine preparations and subsequently characterized immunohistochemically using fresh frozen tissue, monoclonal antibodies against the antigen panel listed above and an indirect immunoperoxidase method. The final classification considered both, morphology and immunoprofile of tumor cells. Seven tumors were "typical" in both respects : one closely corresponded to MZ, three to EF, two to FC and one to PC; they all belonged to the subcategory of low grade malignancy. Two further tumors showed two morphologically distinct subpopulations and also were bi-phenotypically on the antigen level. The remaining 18 cases were characterized as "atypical" because of anaplastic cytology and/or abnormal co-expression and/or loss of antigens. A hybrid EF/FC phenotype was most frequently observed together with centrocyte-like or centrocytic anaplastic cytology of tumor cells. We conclude that MALT B cell neoplasia comprises a broad spectrum of histo- and immunophenotypes ranging from well differentiated forms closely mimicking normal B cell development to highly abnormal tumors which cannot be subclassified.

P 8 IMMUNOPHENOTYPIC CHARACTERIZATION OF SPORADIC BURKITT'S LYMPHOMA CELLS AND THEIR NORMAL COUNTERPART. A. Aiello, D. Delia, E. Fontanella and R. Giardini. Istituto Nazionale Tumori', Milano, Italia

We have investigated the immunologic features of 40 pediatric and 4 adult sporadic Burkitt's lymphoma (BL) to assess the degree of phenotypic heterogeneity and to determine which markers are of diagnostic relevance for differential diagnosis with other germinal centre (GC) derived B-cell malignancies. The majority of cases was positive for CD19 (100%), CD20 (92%), CD37 (83%) and HLA-DR (97%) pan-B markers, in accordance with the B-cell derivation of this tumour; the B-cell restricted markers CD21, CD22 and FMC7 reacted with a variable percentage of cases (28%, 66% and 75%, respectively). Of the mantle zone B-cell specific MAbs, CD1c was always negative, whereas CD23 and 2-7 were positive with one and two cases, respectively, providing useful information for differential diagnosis with other B-NHL. CD39, an antigen up-regulated after lymphoblastoid progression of BL cells "in vitro", was weakly reactive with two specimens, one of which was CD23+. The GC specific MAbs CD10 and CD77 (BLA) displayed an heterogeneous pattern of reactivity; in fact, we identified 4 subgroups CD10+/CD77+ (44%), CD10+/CD77- (15%), CD10-/CD77+ (36%) and CD10-/CD77- (5%). Furthermore, we studied the presence of LFA-1 (CD11a and CD18 MAbs) and ICAM-1 (CD54) adhesion molecules, shown to be associated with distinct clinical behaviour. Four subgroups were identified which differentially express LFA-1 and ICAM-1 molecules; in 5 of 6 negative cases the tumour cells were localized in the ascitic fluid and peripheral blood, suggesting that the absence of lymphocyte adhesion molecules may facilitate tumour dissemination. We also investigated whether the lack of these antigens in BL reflected an ontogenic derivation from a normal LFA-1 negative cell. Analysis of the putative normal BL cell counterpart, identified with the CD77 marker from normal lymphoid tissues, showed that 95% of CD77+ B-cells were constitutively CD11a+/CD18+, suggesting that, very likely, BL cells undergo specific downregulation of adhesion molecules during neoplastic transformation.

P 9 HISTOLOGICAL AND IMMUNOLOGICAL STUDY OF 1200 CASES OF AGGRESSIVE LYMPHOMAS INCLUDED IN THE GELA PROTOCOL. MF D'AGAY, P GAULARD, F BERGER, E LEPAGE, A BOSLY, B COIFFIER, C GISSELBRECHT, F REYES, H TILLY, D MASON, J DIEBOLD

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The first 1200 cases included in the GELA multicentre aggressive lymphoma treatment trial were reviewed by at least 3 hematopathologists and 1106 cases were intermediate or high grade lymphomas according to the Working Formulation (WF). The 94 remaining cases were confirmed as been low grade lymphomas (75 cases), Hodgkin's disease (10 cases), carcinoma (6 cases) a non-tumoral (3 cases). The 1106 cases comprised follicular large cell (5,2%), diffuse small cleaved (2,35%), diffuse mixed (10,5%), diffuse large cell non-cleaved (55%), immunoblastic (7,8%), lymphoblastic (3%), Burkitt's (2,6%), an anaplastic (8,4%) ; 2.8% could not be classified according to the WF and 2% were technically unsatisfacory. An immunohistological study was performed in all cases on paraffin sections, using B cell (L26, MB2, LN1) and T cell (UCHL1, CD3) markers. In addition, 395 cases (35.5%) were studied on frozen sections. 770 cases (70%) were classified as B cell lymphomas and 155 (14%) as T cell lymphomas; 181 cases (16%) could not be assigned to a B or T lineage. This phenotypic study allowed a more precise subclassification, especially of mixed and large cell groups, according to the Kiel updated classification. In the diffuse mixed type, 40% were of B cell origin (centroblastic-centrocytic, 11%; polymorphous lympho-plasmacytic 29%), 51% were of T cell origin (Lennert's lymphoma, 12%; T zone, 11%; LAI-like, 18%; others, 10%), and 9% were phenotypically unclassifiable. In the diffuse large cell group, 78% were of B cell type (centroblastic 65%; immunoblastic, 9%; anaplastic, 4%), 8% of T cell type (pleomorphic, 4,5% and anaplastic, 3,5%), and 14% were uncertain phenotype. The majority of cases which could not be classified according to the WF were of T cell lineage. It will be possible in the future to assess the pronostic value of this immunohistological study since all patients had been entered in the same prospective treatment trial of the GELA protocol.

P 10 A DIRECT COMPARISON OF PERIPHERAL T-CELL LYMPHOMAS WITH THEIR B-CELL, COUNTERPARTS. R. Liang[1], D. Todd[1], D. Choy[2], T.K. Chan[1], E. Chiu[1], F. Ho[3]. University Departments of Medicine[1] and Pathology[3], and the Institute of Radiotherapy and Oncology[2], Queen Mary Hospital, Hong Kong

The effect of immunophenotype on the clinical characteristics and prognosis of 144 patients with non-Hodgkin's lymphomas was determined. Well-described entities such as mycosis fungoides, lymphoblastic lymphomas and follicular lymphomas were excluded. There were 42 cases of T-cell and 102 B-cell lymphomas. B symptoms were more commonly present in patients with T-cell lymphomas (52% versus 30%, p=0.05) and more patients with B-cell lymphomas had bulky disease (25% versus 7%, p=0.04). T-immunophenotype was associated with significantly higher incidences of liver (48% versus 24%), spleen (48% versus 20%), marrow (43% versus 18%), nose (29% versus 5%) and skin (29% versus 5%) involvements. Gastrointestinal involvement was however more common in B-cell lymphoma (26% versus 0%). Comparable chemotherapeutic regimes were used for patients with either B or T immunophenotype. Doxorubicin-containing regimes were used in 119 patients (CHOP 23, BACOP 47, m-BACOD 49). Other less intensive regimens (COPP or CVP) were used in 22 patients. Three patients received no chemotherapy. The immunophenotype did not appear to affect their complete remission rate, relapse rate, disease-free survival and overall survival.

P 11 IMMUNOPHENOTYPIC CHARACTERIZATION OF PRIMARY GASTRIC LYMPHOMAS USING PARAFFIN-EMBEDDED ENDOSCOPIC BIOPSY SPECIMENS.

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We reviewed the endoscopic biopsy samples of 15 cases of primary gastric lymphomas subsequently confirmed on gastrectomy specimens. All were of non-Hodgkin type and were classified using the Working Formulation: 11 were of high-grade morphology, while 4 of low-grade, 2 of these latter featuring plasmacytoid differentiation. A full immunological work-up of formalin-fixed and paraffin-embedded biopsy tissue specimens was undertaken. A panel of both monoclonal and polyclonal antibodies effective on routinely processed paraffin sections was used: LC, L26, 4KB5, UCHL1, Ber-H2, M1, MAC 387, IgM, kappa, lambda, lysozyme and low-molecular-weight cytokeratin. All tumours were of B-cell follicular-center origin, being positive with either L26 and/or 4KB5. No cases of T-cell or histiocytic lymphoma were present. A T lymphoid reaction was found inside the lymphomas in 8 cases. Light chain restriction of kappa type was demonstrated in only 4 cases, 2 of which were the lymphomas with plasmacytoid differentiation. Antibody to cytokeratin highlighted the lymphoepithelial lesions found with variable frequency in several cases.
This study emphasizes the usefulness of a panel of antibodies reactive in paraffine-embedded tissue which allowed immunophenotypic characterization even of small routinely processed biopsy specimens obtained from gastroscopic procedures.

P 12 SELECTIVE ELIMINATION OF TdT-POSITIVE NEOPLASTIC CELLS. R. McCaffrey, K.Bulger, R. Duff, H.Safran. Boston University Medical Center, Boston, MA.

We have previously reported that the chain-terminating nucleoside analogue 2',3'-dideoxyadenosine (ddA) is specifically cytotoxic for TdT-positive (TdT(+)) cells, especially in the copresence of the adenosine deaminase (ADA) inhibitor coformycin (CF). The central role of TdT in mediating the ddA/CF cytotoxicity was established with a murine pre-B cell line made TdT(+) by infection with TdT cDNA retroviral vector: significant cytotoxicity was seen in the TdT(+) daughter line but not in the TdT-negative (TdT(-)) parental line. These data suggested the potential clinical utility of ddA/CF in TdT-positive neoplastic diseases. However, because the concentration of ddA required for killing TdT(+) cells ex vivo (250 μM for 48-72hrs.) probably exceeds what is clinically achievable, we sought a more potent ddA derivative. Since substitution of chlorine in the 2-position renders adenosine and deoxyadenosine resistant to deamination by ADA, we reasoned that 2-chloro-ddA would show similar ADA resistance, without loss of specific TdT substrate recognition properties, and thus be a more active TdT-specific cytotoxic agent. We now report that ADA doses not recognize 2-chloro-ddA (K_m > 500 μM), whereas TdT continues to recognize 2-chloro-ddATP as efficiently as ddATP (K_i < 2 μM). After a continuous 72 hour exposure to 2-chloro-ddA, at 5-10μM, 3 TdT-positive cell lines were killed (60-85% trypan staining), while 3 TdT-negative cell lines were unaffected under similar conditions. When given IP to Balb-C mice at 25mg/kg/d for 3 days, 2-chloro-ddA caused a transient depletion of TdT-positive thymic lymphocytes (maximal at day 6, with recovery on day 10). As with the parent ddA compound, we speculate that cell death in TdT(+) cells results from TdT-mediated 2-Cl-ddAMP chain-terminating end-additions, which ultimately produce DNA fragmentation. The efficacy of 2-chloro-ddA in a TdT-positive murine disease model is now being studied.

P 13 INDUCTION OF IL2 RECEPTORS ON FRESH LEUKEMIA/LYMPHOMA CELLS.

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High-affinity, p55/p70 IL2 receptors are constitutively expressed in several forms of leukemia/lymphoma. To take therapeutic advantage of a novel hybrid toxin, in which IL2 is linked to diphtheria toxin, we have asked whether leukemia/lymphoma cells which do not constitutively express IL2R can be induced to an IL2R-positive state, thus rendering them susceptible to killing by the IL2/diphtheria toxin. This hybrid toxin was assembled from an IL2 cDNA fused to a truncated diphtheria toxin gene, and expressed in E. coli. It specifically intoxicates leukemia cells and cell lines expressing high-affinity IL2R (ATL cells; Hut-102 cells; C91/PL cells; $IC_{50} < 1 \times 10^{-10}$M); but not cells expressing p55 alone (MT-1 cells) or p70 alone (YT-2C2 cells)($IC_{50} > 1 \times 10^{-7}$M). To date we have studied high-affinity IL2R-negative leukemia/lymphoma cells from 38 patients (32 CLL; 3 CML; 2 AML; 2 ALL), using as IL2R inducing agents Bryostatin-1, PHA, α-IFN, and IL3. IL2R status post-induction was defined by the acquisition of CD25 reactivity, Scatchard analysis of IL2 binding, or sensitivity to IL2/diphtheria toxin. IL-3 and α-IFN had no demonstrable IL2R inducing activity with any sample. PHA induced IL2R on 70% of the Cll samples; Bryostatin I induced IL2R on 36% of the CLL samples. These data document that some leukemias/lymphoma cells can be converted ex vivo from an IL2R-negative, hybrid toxin insensitive state, to an IL2R-positive, toxin sensitive state. In vivo modulation of IL2R status could render these forms of leukemia/lymphoma sensitive to the clinical administration of IL2/diphtheria toxin as novel therapy for IL2R-positive leukemia/lymphoma.

P 14 ICAM-1 (CD54) AND LFA-1 (CD11a) EXPRESSION IN NEWLY DIAGNOSED, UNTREATED B-CLL IS NOT CORRELATED WITH CLINICAL STAGE.

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ICAM-1 and LFA-1 are complementary cell adhesion molecules expressed in variable amounts by leukocytes. High ICAM-1 expression has been found in non-Hodgkin lymphomas with "bulky disease". In B-CLL the propensity for formation of lymphomas is reflected by the clinical stage. We have estimated ICAM-1 and LFA-1 by two color quatitative flow cytometry in 62 patients with untreated B-CLL at the time of diagnosis. ICAM-1 and LFA-1 were measured after labelling with the corresponding monoclonal antibodies and FITC labelled rabbit anti-mouse Ig. After blocking excess binding sites of the rabbit antibody with normal mouse serum, B-cells were identified by staining with a mixture of phycoerythrin (PE) labelled CD19 and CD20 antibodies. The cells were analysed in a FACScan flow cytometer using a forward versus side scatter gate for lymphocytes and a PE fluorescence gate for positively stained B-cells. A standard calibration diagram was generated by flow cytometry of FITC labelled beads (Flow Cytometry Standards Corporation). The number of FITC molecules bound per cell was translated to protein molecules per cell after determination of conversion factors for ICAM-1 and LFA-1 antibodies with Simply Cellular Microbeads™ (Flow Cytometry Standards Corporation). The results expressed as molecules per cell x 10^{-3} are shown in Table 1.

Clinical stage (Binet)	No. of pts.	ICAM-1 mean	ICAM-1 range	LFA-1 mean	LFA-1 range	ICAM-1 + LFA-1 mean	ICAM-1 + LFA-1 range
A	31	7.9	0-24	11	0-64	19	0-81
B	25	9.8	0-24	7.8	0-35	18	0-53
C	6	12	0-19	2.3	0-14	14	0-27

No difference in the expression of ICAM-1 and LFA-1 was found between patients with no or limited nodal involvement (stage A) and patients with more extensive nodal disease (stage B). The possible correlation of simultaneously high expression of ICAM-1 and LFA-1 with nodal disease was studied by comparing the sum of ICAM-1 and LFA-1 molecules in stage A and B. No difference was found. LFA-1 expression seemed to be low in stage C, but the number of patients is small.

P 15 SOLUBLE INTERLEUKIN 2 RECEPTOR (CD25) MEASUREMENT IN SERA OF ADULT PATIENTS WITH HAEMATOLOGICAL MALIGNANCIES.

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Interleukin 2 (IL-2) exerts its biological activity through a specific membrane receptor. Using specific monoclonal antibodies directed against the IL-2 receptor, a soluble form of this receptor has been recognized in the serum. This soluble part of the human IL-2 receptor (s-IL2R) is released by T and B lymphocytes and plays a role in lymphoid cell growth regulation. We have measured s-IL2R by ELISA (Eurogenetics, Tessenderlo, Belgium) in the serum of 105 patients with hematological malignancies including multiple myeloma, Hodgkin's disease (HD), non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL) and hairy cell leukemia (HCL).

	N	Mean	Median	S.D.	Min	Max	p§
Normals	40	173	109	168	10	780	
Myeloma	8	267	267	128	105	452	0.032
HD	14	519	343	524	110	2140	0.0004
B-NHL	26	953	477	983	171	3910	0.00001
T-NHL	8	1218	581	1186	10	3210	0.0032
CLL	44	1299	945	1127	187	5180	0.00001
HCL	5	17938	2490	23736	760	54000	0.0003

§ Mann-Whitney U test.

s-IL2R levels are particularly elevated in advanced stage NHL and CLL. When NHL were analysed according to the Working Formulation, no significant difference were observed between low, intermediate and high grades. In HD, s-IL2R level increases primarily in patients with constitutional symptoms ($P < 0.0003$). Out of 9 patients with HD and 11 patients with NHL in complete remission, respectively 9 and 7 patients had a normal s-IL2R value suggesting that s-IL2R could be helpful in the monitoring of these patients. In B-CLL soluble IgE-binding factor recently identified as CD23, is significantly (3 to 500 times) increased and correlated with the stage of the disease. A good correlation ($R=0.610$) between soluble CD25 and CD23 in the serum of patients with B-CLL was demonstrated. The interest of both receptors in lymphoproliferative diseases will be discussed.

P 16 INTERACTIONS BETWEEN MEMBRANE-BOUND INTERLEUKIN-2-RECEPTOR (IL-2R), SOLUBLE IL-2R AND NATURAL KILLER CELL-ACTIVITY IN CUTANEOUS T-CELL LYMPHOMA PATIENTS.

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Recently, a soluble form of the p55 protein of the interleukin-2 receptor in normal serum has been reported. High levels of this molecule have been demonstrated in various pathologic (neoplastic and non-neoplastic) conditions. We analysed the sIL-2R, membrane bound IL-2R expression (TAC, CD 25) and natural killer cell-(NK-)activity in cutaneous T-cell lymphoma (CTCL) patients. 9 patients with histologically proven CTCL were investigated. Snap frozen skin biopsies from 7 patients with low-grade and 2 patients with high-grade peripheral T-cell lymphoma were analysed with a panel of monoclonal antibodies including CD 3, 4, 8, 25 using APAAP-technique. Peripheral blood mononuclear cells (PMC) were isolated by Ficoll-Hypaque centrifugation and stained for CD 3, 4, 8, 25 using direct and indirect immunoflourescence and FACS analysis. NK-activity was determined in a four hour ^{51}chromium release assay using the NK-sensitive erythroblastoma cell line K 562 as targets. Soluble interleukin-2-receptors (sIL-2R) in the serum were determined by ELISA technique.

All low-grade cutaneous lymphomas were CD3, 4, 8 positive. Additionally CD 25 was expressed in 2 cases. 2 high-grade pleomorphic lymphomas were strongly stained positive for CD3, 4, 8, 25. A high percentage of TAC-positive lymphocytes in immunohistology or FACS did not correlate with high sIL-2R levels. Regarding on sIL-2R and NK-activity, there was an association between sIL-2R and NK-activity. Five patients had highly elevated sIL-2R levels ($x=4216\pm3788$ minimal=1320, maximal=10700 U/ml) and average NK-activity was $5.4\pm1.1\%$. specific release. These patients had a progressive disease. Four patients had sIL2R in the normal range or slightly elevated ($x=414\pm88$ minimal=330, maximal=538) and the average NK-activity was $15.5\pm12\%$ specific release. The clinical situation in these patients was stable.

We suggest an inhibiting influence of sIL-2R on NK-activity. Recently, it has been demonstrated, that sIL-2R binds IL-2 effeciously. It was speculated, that this 55kD protein might be a physiologic inhibitor for IL-2 which protects immune system from overstimulation. We conclude, that high sIL-2R and reduced NK-activity are unfavorable prognostic factors in CTCL patients. Because of the missing correlation between membrane-bound and soluble TAC-protein we propose a defect in the TAC anchor mechanism in some malignant T-cell clones.

P 17 IL-2 and interferon-γ production in follicular lymphomas.

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Using in situ hybridization with specific RNA radiolabeled probes we analyzed the production of interleukin-2 (IL-2) and interferon-gamma (IFN-γ) in 21 follicular malignant lymphomas (FL). Lymphokine synthetizing-cells were demonstrated in all the 21 FL tested. These cells were present in the interfollicular and follicular areas. Enumeration of lymphokine synthetizing-cells allowed us to demonstrate an heterogeneous production of IL-2 producing-cells, 2 cases out of the 21 FL exhibiting a dramatically higher density of such cells (855 and 570 IL-2 producing-cells / cm2) when compared with the 19 remaining cases (mean = 92+15 IL-2 producing-cells / cm2). Such an heterogeneity was not evidenced for IFN-γ producing-cells (mean = 77+8 IFN-γ producing-cells / cm2). The IL-2 / IFN-γ producing-cells ratio was as a mean 2.69+0.84, emphasizing a preferential induction of IL-2. When analyzed the fine distribution of lymphokine producing-cells we found that IL-2 and IFN-γ producing-cells were preferentially located into the follicular areas. As a mean the follicular / interfollicular ratio was 1.82+0.16 and 1.92+0.19 for IL-2 and IFN-γ producing-cells, respectively.

We herein show that T-cell activation defined by lymphokine production are present in FL lymph nodes, in direct contact with malignant cells. This lymphokine production may play an important role in tumor growth control which is the result of interaction between tumor cells and host derived immune reaction.

**GELF: Groupe d'Etude des Lymphomes Folliculaires.

P 18 CYTOKINE PRODUCTION AND ENDOTHELIAL CELL ACTIVATION IN LYMPH NODES INVOLVED BY REACTIVE LYMPHADENITIS, HODGKIN'S DISEASE, AND NON-HODGKIN'S LYMPHOMA.

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Cryostat sections of 58 lymph nodes were immunostained to investigate the distribution of cells containing IL-1 alpha (Vmp18), IL-1 beta (Vhp20 and BRhC3), or TNF alpha (B154.7). Furthermore, the presence of cytokines was correlated with the expression of activation antigens (ELAM-1 and HLA-DR) by vascular endothelial cells. Endothelial leukocyte adhesion molecule (ELAM)-1 was recognized with two recently developed mAbs (5D11 and 29F2). Cells containing IL-1 and/or TNF alpha were mostly detected in those pathological conditions characterized by reactive or neoplastic expansion of the lymph node paracortex (21 cases of Hodgkin's disease, 4 non-Hodgkin's lymphoma T cell type, and 5 diffuse reactive lymphadenitis). IL-1 alpha was detected in scattered macrophages, interdigitating reticulum cells (IDRCs), endothelial cells and in neoplastic Hodgkin's cells. IL-1 beta was mainly observed in macrophages. TNF alpha was present in macrophages and in Hodgkin's cells. ELAM-1 was expressed by high endothelial venules (HEVs) in 17/21 cases of Hodgkin's disease, in 2/4 T cell NHLs and in 5/5 diffuse lymphadenitis. HEVs were stained for HLA-DR in 13/21 cases of Hodgkin's disease, in 4/4 T cell NHL and in 3/5 diffuse lymphadenitis. HEVs might be double negative, double positive for ELAM-1/HLA-DR, or single positive for either antigen. Moreover, cells containing IL-1/TNF alpha were often detected in close spatial relation with ELAM-1+ HEVs. In pathological conditions characterized by reactive or neoplastic B cell proliferations (12 cases of reactive lymphadenitis with follicular hyperplasia and 16 B cell NHLs) cells containing IL-1/TNF were extremely rare. A few ELAM-1+ HEVs were observed in 2/12 follicular lymphadenitis and in 1/16 B cell NHLs. HLA-DR+ HEVs were more numerous and were detected in 6/12 follicular lymphadenitis, and in 8/16 B cell NHLs. Our results suggest that tissue reactions involving B cell or T cell areas are regulated by different cytokine networks. Furthermore they provide circumstantial evidence that IL-1/TNF production may be responsible for HEVs activation during immune responses involving the T cell area.

P 19 INTERLEUKINE 2 (IL2) IN LYMPHOMAS. A PHASE II MULTICENTRIC STUDY.

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Responses have been observed in lymphomas after IL-2 infusion with or without lymphokine activated killer cells (LAK). In order to better evaluate the activity of r-IL2 a phase II study has been started in non-Hodgkin's lymphomas (NHL) and Hodgkin's disease. Three type of lymphomas were included. 1°) low grade NHL in progression after chemotherapy including an anthracycline. 2°) aggressive NHL refractory to initial treatment or refractory to salvage therapy. 3°) Hodgkin's disease relapsing after autologous bone marrow transplantation (ABMT) or refractory to therapy. r-IL2 (Roussel UCLAF 49637) was administered by continous infusion 20 MU/m^2, for three cycles of 5 days, 4 days and 3 days at 9 days interval. 33 patients have been included, mean age 44 years, 11 low grade NHL, 15 high grade NHL and 7 Hodgkin's desease. In 12/89, 21 pts are evaluable for response. 26 pts received during their first cycle 100 % of the dose. 2 CR lasting 3-6 months were observed in aggressive lymphomas over 9 pts evaluable. 2 dissociated responses over 9 pts were observed in low grade lymphoma including one mycosis fungoïde. No response has been observed among 3 Hodgkin's lymphoma. Severe toxicity in 6 pts led to interruption of treatment : cardiac 2 pts, neurological 2 pts, hypoxia 2 pts. 2 pts died of progressive disease. 1 pt refused to pursue treatment. r.IL2 shows some signs of activity in heavily pretreated lymphomas. More patients will be included in the study to better determine response rate among the different subtypes of lymphoma and updated results presented.

P 20 A CYTOGENETIC/HISTOLOGICAL STUDY IN NON HODGKIN'S LYMPHOMA WITH PARTICULAR REFERENCE TO t (14,18).

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Concurrent histological and cytogenetic examination has been performed on 64 lymph node biopsy specimens collected between January 1981 and January 1989. The trypsin-Giemsa banding technique was employed after short term cell culture and cytogenetic abnormalities were recorded when found in at least 20 cells. Review of paraffin embedded H and E sections supplemented as necessary by special stains and immunohistochemistry was also carried out and classification made according to the Keil system. 25 of 64 (39%) cases had cb/cc follicular (F) or follicular and diffuse (FD) histology and 10 (16%) were cb/cc diffuse. 29 of 64 (45%) were other forms of NHL (immunoblastic 9, centroblastic 8, ML unclassified 5, centrocytic 4, lymphocytic 3). 22 of 64 (34%) cases had t (14,18) and of these, 15 had a concurrent cb/cc(F) histology and 2 were cb/cc (FD). Of the remaining 5 cases, 3 had a cb/cc(F) or (FD) pattern on a previous biopsy. 8 of 25 (31%) pts had (F) or (FD) histology but no t (14,18) and a further 3 pts without the translocation had a (F) or (FD) pattern on previous biopsy. Overall, 20 of 22 (91%) cases with t (14,18) had a (F) or (FD) histological pattern at some stage in their history.

Details of time to first recurrence, number of relapses and overall survival were available for 17 of 20 (F) or (FD) pts with t (14,18) and 10 of 11 (F) or (FD) pts without the cytogenetic marker. With a median follow up of 56 mths, 6 of 17 pts with t (14,18) have died (3 from follicular NHL, 2 from diffuse NHL and 1 from AML) against 5 of 10 pts where t (14,18) was absent (2 from follicular NHL and 3 from diffuse NHL). This is a significant difference between the 2 groups for deaths from NHL (p=0.02) but relapse free survival is the same for both groups (p=0.23). From this small study we conclude that in (F) or (FD) non Hodgkin's lymphoma, the presence of t (14,18) is associated with a significantly better prognosis than where t (14,18) is absent. Larger studies are required to confirm these findings.

P 21

Lymphoproliferative disorders associated with secondary (2ndary) immunodeficiency (ID): Clinicopathologic characteristics and cytogenetic associations. O.I. Olopade, J. Anastasi, T. Heffron, J. Emmond, M.M. Le Beau, R.A. Larson, J.E. Ultmann. University of Chicago, Chicago, IL 60637, USA.

An increased incidence of non-Hodgkins lymphoma (NHL) is well recognized in primary as well as 2ndary ID states. The precise nature and mechanism for initiation and progression of these tumors is unknown. We undertook a retrospective study of 15 patients (pts) with 2ndary ID and NHL who were seen and treated at the University of Chicago between 1983 and 1989, to determine if there were distinguishing features among one group (gp) of pts with post-transplant lymphoproliferative disorders (PTLD) (9pts) and a second gp of pts with 2ndary ID due to other causes (4 pts who received chemotherapy (CT) or radiation therapy (RT) for Hodgkins disease (HD) or for breast cancer (1 pt), and 1 pt with HIV-associated NHL). In the PTLD gp, there were 6 males (M) and 3 females (F), aged 1-62 yrs (median 41 yrs). All the pts had received cyclosporin; median time to development of NHL was 7 mos and all but one had NHL in extranodal sites (3 pts in the allograft, 2 pts in the nasopharynx, 1 pt in the gastrointestinal tract, 1 pt in the brain and 1 pt in the abdominal wall). Pathologic diagnoses in this gp included 5 pts with immunoblastic lymphoma (IL), 3 pts with diffuse large cell lymphoma, 1 pt with small non-cleaved lymphoma, and 1 pt with polymorphic lymphoid proliferation. Immunoglobulin gene rearrangements were observed in 3 of 4 pts in which the tests were performed. Cytogenetic analysis was performed on 3 pts. Trisomy 11 was observed in 2 pts; the third pt had a normal karyotype. Including these cases, trisomy 11 has now been observed in 4 of 5 pts with PTLD for which cytogenetic data are available. Three of the pts are alive and free of disease following reduction of cyclosporin; the remaining 6 pts died of other complications. In the second gp, there were 3 M and 3 F; aged 22-52 years (median 37yrs); median time to development of NHL was 9 years. The 4 post-HD pts had received both CT and RT and were previously treated for recurrent HD. All the pts in this gp presented with stage IV disease. Pathologic diagnoses included 3 pts with small non-cleaved lymphoma, 2 pts with IL and 1 pt with lymphoblastic lymphoma. Cytogenetic analyses of 3 post-HD pts revealed abnormal karyotypes with multiple abnormalities; only 1 pt had a lymphoid specific abnormality involving 14q32. The pt with HIV-associated NHL had a t(8;14)(q24;q32). None of these pts achieved a complete remission following treatment. Thus, based on our findings and the literature, PTLD tend to be heterogenous, have a short latency period, progress from a polymorphic lymphoid proliferation to aggressive NHL, may spontaneously regress and are associated with trisomy 11. NHL following other 2ndary ID states tend to have a longer latency period, present with high grade histology, and behave aggressively. This suggests that the mechanism for disease progression may differ in the two subgroups.

P 22

ONCOGENE REARRANGEMENTS IN CHRONIC LYMPHOCYTIC LEUKEMIA. S. Raghoebier, J.C. Kluin-Nelemans, A. Gillis, G.J.B. van Ommen, G.J. den Ottolander, D. de Jong, Ph.M. Kluin. Laboratory of Pathology, University of Leiden, The Netherlands.

Without help of lymph node histology, distinction between chronic lymphocytic leukemia (CLL) and leukemic non-Hodgkin's lymphomas (NHL) may be difficult. We investigated whether Southern blot analysis of peripheral blood lymphocytes for chromosomal translocations may be of help. The translocation t(11;14)(q13;q32) involves a rearrangement of the BCL-1 locus. This locus is infrequently involved in CLL, NHL and multiple myeloma. The BCL-2 gene is involved in the t(14;18)(q32;q21), and is characteristic of follicular lymphoma and a minor part of diffuse large cell lymphomas. The c-MYC oncogene is frequently rearranged in Burkitt's lymphomas. Immunoglobulin (Ig) gene, BCL-1, BCL-2 and c-MYC rearrangements were studied in 54 blood, 3 bone marrow and 2 lymph node samples obtained from 49 patients with B-CLL. All but 2 leukemias were CD5 positive. All cases showed Ig-heavy chain gene rearrangements. Eight cases had 3 or more rearranged JH bands, indicating oligoclonality or the occurrence of additional alterations within the IgH genes. No c-MYC rearrangements were found. One CD5 negative case had a BCL-1 rearrangement with an unusual translocation breakpoint, reciprocally involving 2 different JH-genes and 2 different parts of the BCL-1 locus. During follow-up this patient developed prolymphocytic transformation. The other CD5 negative case showed comigration of strong rearranged BCL-2 and JH bands, indicating a t(14;18) in the tumor cells. Interestingly, 2 CD5 positive cases with multiple rearranged JH bands of different intensity, had a very weak rearranged BCL-2 band, suggesting either a partial deletion of the involved allele, or more probably, the occurrence of an independent B-cell clone with a t(14;18) additional to the CLL. In conclusion, the concurrence of rearrangements of BCL-1 and BCL-2 with the absence of CD5 expression further suggests that these particular leukemias represent leukemic NHL instead of B-CLL.

P 23

ACTIVATION OF CELLULAR ONCOGENES IN HUMAN LYMPHOMA. H. Tesch, M. Jücker, A. Roebroek, W. van de Ven and V. Diehl. I. Med. Klinik, Universität Köln, F.R.G. and Dept. of Biochemistry, University of Nijmegen, NL

Cellular oncogenes are activated in tumor cells by various mechanisms. We investigated the role of cellular oncogenes in human lymphoma. Northern blot experiments indicate that several genes ie. c-met, c-fes, c-fgr, c-myb and lck are differentially expressed in the lymphoma cells. Aberrant, short transcripts of the c-fes gene were detected in about 50% of the Burkitt's lymphoma and Hodgkin's disease derived cell lines. cDNA cloning and S1 nuclease experiments revealed that the short transcripts use cryptic promotors, start within exon 16 of the c-fes gene and bear the protein kinase domain. There is no evidence for structural alteration of c-fes in the lines which express the aberrant transcripts which may indicate a novel mechanism for oncogene activation in human lymphoma cells.

P 24

Evaluation of translocation t(14;18) by polymerase chain reaction and conventional Southern analysis of DNA from 29 cytogenetically positive patients. J.Klefström, P.Peltomäki, M.Kaartinen, M.Solin, K.Franssila and S.Knuutila. Depts. of Med.Genetics, Bact.&Immunol.and Rad.Therapy, University of Helsinki, Haartmaninkatu 3, 00290 Helsinki, Finland.

DNA from 29 Finnish patients with t(14;18) in their lymph node cells was studied by means of the polymerase chain reaction (28 patients) and/or Southern blot analysis (17 patients). DNA from 16 of these patients was studied both by PCR and Southern analysis. PCR amplification was carried out using the Taq-polymerase (Cetus) and two different primers to the 3' end of the Bcl-2 gene region on chromosome 18. JH-universal primer (3'ACCTGAGGAGACGGTGAC'5) was used for heavy chain-joining segments of the immunoglobulin coding region on chromosome 14. These regions are known to be the major reciprocal junctional regions in the translocation t(14;18). Four of the presumed rearrangement bands (positive cases) were confirmed with a radioactive labeled Bcl-2 specific probe. In Southern analysis of DNA, the restriction fragments were blotted from agarose gel on to nylon filters, and probed with a Bcl-2 major breakpoint probe, which is a 3.5 kb EcoRI/HindIII fragment complementary to the Bcl-2 gene. In our case Southern blot revealed only major breakpoint region (MBR) rearrangements. PCR analysis showed a total of 16 rearranged DNA-fragments from the 28 patients studied (57%). In Southern analysis only 6 of the 17 patients studied (35%) were positive with the MBR probe; nevertheless, 10 of the 11 Southern-negative patients were also PCR-negative. This means that PCR and Southern blot results were equal except in one case. In this case PCR was positive, whereas Southern blot negative.

Our results suggest that up to 57% of t(14;18) rearrangements in the MBR can be detected by PCR with previously described techniques. In the above study, PCR proved to be at least as reliable as Southern analysis of DNA in MBR rearrangement detection. According to other studies (Bo-Yee Ngan & al., Blood 73,1989:1759),up to 25% of breakpoints do not fall within the MBR region but occur at a second, distant site on chromosome 18. At this minor clustering region (MCR) breakpoints cluster tightly within a 500 bp segment. In our on-going study, MCR breakpoints will be evaluated by PCR by combining a MCR specific primer with the JH-universal primer. The vast majority of reported breakpoints can then be detected using only three oligonucleotide primers, because the MCR primer and the MBR primer can both be combined with the JH-universal primer. Distinguishing rearrangement bands from occasional irrelevant bands is not always unambiguous. Probing PCR-amplified DNA-fragments with both chromosome 14 and 18 specific radioactive labelled oligonucleotides may be useful method to exclude such irrelevant bands. We are currently conducting studies using this technique.

P 25 B-CELL CHRONIC LYMPHOCYTIC LEUKAEMIA WITH CLONAL T-CELL RECEPTOR β GENE REARRANGEMENTS: POSSIBLE ASSOCIATION TO DELETIONS OF THE LONG ARM OF CHROMOSOME 6.

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Clonal rearrangements of the T-cell receptor (TcR) genes are regular findings in T-lymphoproliferative malignancies, but are found also in some cases of non-T-cell acute leukaemias and blastic lymphomas, and rarely in B-cell chronic lymphocytic leukaemia (CLL). The TcRβ is located on chromosome 7 band q34. We have here studied the frequency of clonal TcRβ gene rearrangements in B-cell CLL, and compared the immune phenotype, cytogenetic findings, and clinical course of TcRβ+ and TcRβ- B-CLL cases.

Fourty-eight patients with B-CLL were studied. The clonal B-cell proliferation was always documented by cell surface markers (SmIg+, CD19+, CD20+) and by clonal immunoglobulin JH gene rearrangements. DNA was extracted from isolated leukemic cells, and digested with the restriction enzymes *Hin*dIII and *Bam*HI. Cleaved DNA was separated by electrophoresis in an agarose gel, and then transferred to a nylon filter by Southern blotting. Filters were hybridized with ^{32}P-labelled probes identifying JH and TcRβ gene segments. Clonal TcRβ rearrangements were found in five patients (10%). The SmIg phenotype of these cases were μδκ, μδκ, μδλ, γκ, and γλ, respectively. One patient had a Rai stage 0 disease without disease progression for 4 years. One patient with stage I developed a prolymphocytic transformation within 9 months from diagnosis. One patient with stage IV died from carcinoma developing 6 months from diagnosis. Two patients with stage II died from progressive CLL 6 and 10 years from diagnosis, respectively. Chromosome analysis showed that 3 of the 5 patients had deletions of the long arm of chromosome 6. These specific karyotypes were 46,XX,del(6)(q15), 46,XX,del(6)(q23), and 47,XX,+12,del(6)(q24),del(15)(q23),t(2;14)(p22;q32),t(1;18)(p35;q21). Two TcRβ+ patients had no clonal chromosome abnormality. No TcRβ- patient had 6q-, and the overall frequency of 6q- in B-CLL is 4%.

Thus, about 10% of B-CLL seem to be TcRβ+. No common immune phenotype or clinical features were identified, but there was a high incidence of 6q- chromosome deletions in TcRβ+ patients as compared to TcRβ- patients.

P 26 EXPRESSION OF c-myc P62 PROTEIN IN NON-HODGKIN'S LYMPHOMAS. ITS RELATION TO HISTOLOGIC SUBTYPE, CLINICAL STAGE AND RESPONSE TO THERAPY.

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The expression of c-myc oncogene in the lymphoid tissue of 181 patients of non-Hodgkin's lymphomas (NHL) was studied using the specific monoclonal antibody c-myc 1-9E10 and the 3 step streptavidin-biotin immunoperoxidase method in paraffin sections. The staining pattern was mainly nuclear but cytoplasmic reaction was also occassionally observed. The percentage of positive lymphoma cells per total cell population was estimated and all cases were classified into four groups: 0-15%, 16-30%, 31-45% and >45% positive cells. In twelve reactive lymph nodes studied, mainly germinal center cells were stained with a percentage of positive cells less than 15%. The distribution of positivity in relation to the histologic subtype using the Working Formulation was as follows:

Grade of Malignancy	No of Cases	Percentage of positive cells			
		<15%	16-30%	31-45%	>46%
Low	66	51	8	5	2
Intermediate	84	24	20	29	11
High	31	5	1	10	15

As it is clearly evident from this table fifty-six per cent of our cases had more than 15% positive cells and the percentage of positive cells was greater in the high grade than in the intermediate and low grade NHL. This correlation proved to be statistically very significant ($p<0.001$). When our results were compared with the clinical stage, response to therapy and freedom from relapse of our patients, we observed that: there was a correlation between c-myc protein expression and the clinical stage ($p<0.01$), response to therapy and relapse rate of our patients ($p<0.05$). We concluded from our study that the expression of c-myc p62 protein in NHL may predict their prognosis.

P 27 NON-IPSID ENTEROMESENTHERIAL LYMPHOMAS IN SERBIA: CLINICAL AND IMMUNOCHEMICAL FEATURES IN 2o PATIENTS

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Non IPSID enteromesentherial lymphomas are characterised by the absence of alpha-chains in the biological fluids and are usually supposed to be more or less confined to the tumor site.

During the period 1984-1988 the authors have observed 2o patients with non IPSID lymphomas, 11 males amd 9 females, all patients originating from Serbia. In 11 patients first symptoms were abdominal colics requiring laparotomy, in 3 patients ileus, in 1 dysphagia and in 5 perforation with peritonitis. Resection of involved part of the intestine was performed in 17 patients, 9 of them had on histological examination lymphoma tissue on apparently healthy resection line, or lymphoma affection of other parts of the GI tract on laparotomy.

According to Working formulation, 3 had low grade, 3 intermediate and 14 had high grade histology. Affection of extra-GI lymphoid structures was found in 1o/15 patients, of the nasopharynx in 8/15, of the bone marrow in 2/15, and in extrahematopoietic tissues in 5/15 patients where it was looked for. According to the 1982 Crowther classification, 55% of patients were in stage IV, 35% in stage III and 1o% in stage II.

On serum/urine immunochemical analysis, two patients had monoclonal immunoglobulins (IgG lambda and IgA kappa respectively) and 1 had free gamma chains in urine. Increased levels of circulating immunocomplexes were detected in all patients, and 6 had polyclonal hypergammaglobullinaemia.

19 patients were treated with chemotherapy alone, 13 with agressive alternating regimens and 6 with CHOP-type schedules. 1o/2o patients are alive and in complete remission for over 3 years (7/11 of stage IV and 3/9 with stages II/III, 8/14 with high grade and 2/6 with low/intermediate grade histology).

Our findings suggest that GI tract lymphoma infiltration of the non IPSID lymphomas may be more extensive than expected from literature data. Surgical procedures have diagnostic, tumor bulk reducing and perforation/haemorrhage -preventing function. As nearly all patients are Ann Arbor clinical stage IV, Crowther classification does not affect the potentially curative therapeutic approach, which seems to be chemotherapy.

P 28 BURKITT'S LYMPHOMA: A TWENTY YEAR RETROSPECTIVE SURVEY (IN KENYA)

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A retrospective survey of Burkitt's Lymphoma (BL) as reported in the Kenya Cancer Registry was carried out covering the years 1968 to 1987 inclusive. There was a total of 786 cases, 491 of whom were males and 289 females, giving a male to female ratio of 1.7:1. Six cases had sexual identity not determined. 382 out of 786 cases (48.6%) were reported from the Lake Victoria region which is a hot, wet woodland and savannah country with high rates of malaria transmission. 242 out of 786 cases (30.8%) came from cold wet woodland and savannah country which is to the central and north-eastern part of the country with low rates of malaria transmission. The median age was 6.5 years.

The face was the commonest site of involvement in the hot, wet savannah and woodland areas while the abdomen was more commonly involved in the cold, wet highland savannah and woodland areas. Over the years there were no significant migratory trends in areas of occurrence, sites involved, sex or median age. The rate of diagnosis of BL was highest in late sixties to early seventies, gradually dropping to lowest in 1981 after which it started rising gradually to mid eighties.

It appears that the environmental factors associated with the development of BL in Kenya have not changed over the last 20 years. It also appears that the tumour pattern seen in the western hotter part of the country is more akin to the so called African type of BL while the non-African tumour type is found in the colder mountain regions.

P 29 CLINICAL AND PATHOLOGICAL FEATURES OF EXTRANODAL NON-HODGKIN'S LYMPHOMAS.

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ABSTRACT

The clinicopathological features of 463 consecutive and unselected cases of extranodal non-Hodgkin's lymphoma (NHL) were studied.
The case material was gathered prospectively in a regional Danish multicenter study, Lyfo-1, conducted between 1983 and 1988. The extranodal cases represented 37% of all cases of NHL (n=1257) registered in the study. They had a mean age of 61,6 years (range 6-94 years) and 53% of them were women. The most frequent site of involvement was the gastrointestinal tract with a total of 139 cases (30%), 87 (19%) localized to the stomach and 52 (11%) to the gut. A strong female predominance was found for thyroid lymphomas(female:-male ratio = 7,3) and salivary gland lymphomas (female:male ratio = 2,5). Lymphomas of the gut and lungs were more common in male patients (male:female ratios respectively 2,4 and 2,3). Stage 1 and stage 4 were the most frequent clinical stages. Most cases of localized disease occurred in salivary gland lymphomas (71%). High-grade histology was the most common, in particular the large cell, diffuse type found in 23% of the cases.

P 30 USE OF TRANSESOPHAGEAL ECHOCARDIOGRAPHY IN THE STAGING AND FOLLOW-UP OF MEDIASTINAL LYMPHOMAS.

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The assessment of the infiltration of cardiovascular structures in the staging of mediastinal Hodgkin (HD) and non-HD (NHL) lymphomas may be clinically relevant. Transesophageal echocardiography (TEE) has been used for several years to obtain high quality images of the heart and of the mediastinal vessels. The currently used ultrasonic probes are similar to a small-size gastroscope and allow to obtain both a high resolution two-dimensional image of the mediastinal stru tures and a qualitative and quantitative evaluation of the blood flo within the heart and the mediastinal vessels. We used TEE in the st ging of 21 consecutive patients (pts) with mediastinal lymphoma(8 HD 13 NHL) and in the restaging of 3 additional pts previously treated for HD (2 pts) or NHL (1 pt) with residual or recurrent mediastinal masses. Four pts repeated TEE during the follow-up: overall we performed 30 examinations on 24 pts. The procedure lasted 15 to 45 minutes (mean 35) and was well tolerated by all pts. As compared to co puted tomography (CT), TEE gave additional informations in 13 out of 24 pts. It was useful mainly in assessing the compression or infiltr tion of superior vena cava, of pulmonary veins and of the pulmonary artery or its branches and in detecting or excluding pericardial infiltration. In one pt with HD and with a bulky mediastinal mass that relapsed 7 years after radiotherapy, TEE allowed to detect an intracardiac mass extending into the pulmonary artery and to suggest the presence of a cardiac sarcoma (confirmed by open-chest biopsy). On the other hand, in one case of HD the abnormal mediastinal lymph nodes (<2.5 cm) detected by CT scan, were not identified by TEE. In conclusion, TEE may be useful as a complement to other imaging techniques in the staging and follow-up of mediastinal lymphomas. It appears to be a safe, low-cost procedure that can be performed even bedside and seems to be particularly useful in those pts with hypersensitivity to contrast media. Further studies are necessary in order to define the cost/benefit ratio of TEE in this particular field, and if TEE should be suggested routinely or only in selected cases.

P 31 CT GUIDED BIOPSY IN THE MANAGEMENT OF NON HODGKINS LYMPHOMA (NHL).

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The indications for biopsy in patients with presumed NHL include: establishing a diagnosis, confirmation of relapse, evaluation of suspected transformation to high grade pathology and histological assessment of residual radiological abnormalities after therapy. Correct histological diagnosis carries implicatons for treatment and prognosis and demands adequate tissue specimens. The accuracy of diagnosis may be enhanced by immunocytochemistry, for which fresh tissue may be required. In the absence of peripheral lymphadenopathy, methods of obtaining tissue are required which avoid laparotomy or mediastinotomy.

Twenty six biopsies have been performed under CT(22) or ultrasound(4) guidance in 21 patients, age range 31-86, with known or suspected NHL. Nineteen patients had intraabdominal disease and 1 a mediastinal mass. Tru-cut type cutting needles, 14-18G, were used in conjunction with a hand held biopsy "gun", and an average of 2 passes made.

The procedure, performed under local anaesthesia, was well tolerated. There were no complications. The platelet count and clotting screen were normal in all but 1 patient with a platelet count of $33x10^9/l$, who was successfully biopsied under platelet cover. A primary histological diagnosis was made in 7/7 patient (6 NHL, 1 seminoma). In only 1 of the 6 patients with NHL was laparotomy required to confirm the subtype of lymphoma. Relapse was confirmed in 14/14 biopsies; 6/8 biopsies in patients with previously dianosed follicular lymphoma showed transformation to high grade histology and were treated appropriately. Residual radiological abnormalities were biopsied in 3 cases: 2 patients initially treated for diffuse centroblastic lymphoma were found to have follicular lymphoma and 1 negative result was subsequently confirmed at laparotomy. Two other patients had biopsies to obtain fresh tissue for immunophenotyping.

Guided cutting needle biopsy with the biopsy "gun" was successful in providing diagnostic specimens in all cases. Only twice was laparotomy necessary for further clarification. This technique is therefore of great value in the management of NHL and may avoid the need for more invasive investigations.

P 32 MAGNETIC RESONANCE IMAGING (MRI) FOR PREDICTING PROGNOSTIC GRADE IN NON-HODGKIN LYMHOMAS (NHL).

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The subgrouping between low and high grade NHL is usually easy providing the amount of biopsy material is sufficient and of good quality. It is, however, sometimes difficult to obtain such biopsies, particularly if e.g. only intraabdominal involvement is present. There is in these cases a need for other diagnostic techniques. Besides this, the histopathological subgroup may vary between different lymph nodes/lymph node regions.

Fifty patients with NHL were examined with MRI in order to analyze whether it was possible to distinguish in vivo between the two major prognostic groups low grade and high grade according to the Kiel-classification. Most high grade NHL nodes (15/24, 63%) had an inhomogeneous signal intensity at MRI, in contrast to low grade NHL where it was homogeneous in virtually all patients (18/20, 90%, $p<0.001$). A homogeneous picture was also found in 6 previously low grade NHL which, at the time of examination, had transformed into a high grade NHL. Necrosis, detectable in the histopathological sections, was usually (5/6 cases) associated with an inhomogeneous image. An inhomogeneous image was, however, found in 12/44 cases (27%) without any signs of necrosis in the histopathological sections. Patients with high grade NHL and a homogeneous image tended to have a better survival than those with an inhomogeneous image. It thus appears to be possible to predict prognostic grade in vivo using MRI.

P 33 THE ASSESSMENT OF TREATMENT RESPONSE IN LYMPHOMA BY IN-VIVO IMAGE GUIDED ^{31}P MAGNETIC RESONANCE SPECTROSCOPY.

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In vivo ^{31}P MRS allows the non-invasive assessment of intracellular pH and tumour bioenergetic pathways via the relative levels of high energy substrates phosphoceatine (PCr), adenosine triphosphate (ATP) and inorganic phosphate (Pi). Phospholipid flux through the metabolic intermediaries, the phosphomonoesters (PME) and phosphodiesters (PDE), may be similarly detailed. We have used a 1-dimensional chemical shift imaging (1D-CSI) technique to study the ^{31}P MRS characteristics of non-Hodgkin's lymphoma (NHL), and the alterations in tumour metabolism that are associated with a response to chemotherapy.

Nine patients (age range 32-78, 6 female) with bulky abdominal NHL (3 high, 5 low and 1 intermediate grade) were studied prior to, and then serially (mean no of studies = 5, range 3-10) after commencing chemotherapy. MRS studies were performed on a 1.5 Tesla G.E Signa system using 8 cm surface coils and a 1D-CSI localisation technique[1].

High grade NHL had larger pretreatment Pi resonances in relation to either PME or βATP producing differences in the PME/Pi ($p=0.018$), and Pi/βATP ($p=0.036$) metabolite ratios, when compared to low grade NHL. This probably represents a larger hypoxic cell fraction in high grade NHL due to out growth of tumour blood supply.

Marked changes in tumour metabolism were seen after commencing chemotherapy, and before alterations in tumour size. In high grade NHL tumour deactivation (↓ βATP, ↑ Pi) was seen within 24 hours following combination chemotherapy, while in low grade NHL treated with oral chlorambucil similar changes were detected by days 10 -28. Tumour deactivation was followed by marked increases in PDE consistent with the mobilisation of membrane components and cell lysis. Increases in the PDE/βATP ratio (51-266%) were seen in all tumours after chemotherapy and prior to reductions in tumour size. An alkaline shift in tumour pH was seen in 7 of the tumours after chemotherapy.

These studies illustrate the potential role of ^{31}P MRS in the assessment of treatment response. Increases in the PDE/βATP ratio may be an early metabolic marker of response to chemotherapy in lymphomas.

1. Glazer GM, Smith SR, Chenevert T et al. NMR Biomed 1989;1: 184-189.

P 34 PREDICTING SURVIVAL IN HIGH AND INTERMEDIATE GRADE NON-HODGKIN'S LYMPHOMA (HIGNHL).

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Between 1979 and 1987, 1130 patients with Working Formulation HIGNHL registered with SNLG. Clinical, haematological and pathological data were analysed on 972 adults as prognostic (PROG) factors (treatment variables excluded). Median available follow-up was 47 months. A Cox multivariate analysis was used. 310 patients presenting to Edinburgh were excluded to provide an independent test group. The best PROG model was based (rank order) on: performance status, age, liver involvement (H+) B symptoms, white cell count (WCC) and stage. Best survival was predicted for fit young patients, with stage 1 or 2, no B or H+ and normal WCC. The analysis provided estimates of relative risk for deviations from this best survival status. A simple multivariate PROG index was constructed. Patients were predicted to fall into 3 PROG groups according to their index scores. Tested on the independent Edinburgh subgroup, 39% had good PROG. They had median survival of 65 months, 33% had intermediate PROG, median survival of 19 months, 5-year survival of 20%. 28% had poor PROG, median survival 8 months, 5-year survival <10%. Tested on Edinburgh patients <70, the index provided equally good separation of PROG groups. This simple index allows better prognostication, stratification of future treatment studies, and selection of poor risk patients <70 for aggressive therapy. Patient selection could explain disparities in results of earlier HIGNHL phase II treatment studies.

P 35 PROGNOSTIC FACTORS IN AGGRESSIVE MALIGNANT LYMPHOMAS : VALIDATION OF A PROGNOSTIC INDEX THROUGH LNH 87 PROTOCOL. A GELA STUDY.

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Prognostic model are used to better determine group of patients with different prognosis who are eventually candidate for different therapeutic strategies. Multivariate analysis on LNH 84 lymphoma patients (J.C.O. 08/89) led to a prognostic model including three clinical parameters, tumoral mass > 10 cm, number of extra nodal sites > 2, stage III or IV and one biological parameter, increased LDH level. Partition in three index were established : index 1, no adverse prognostic factors ; Index 2, existence of one or two clinical parameters with normal LDH or increased LDH alone ; Index 3, existence of three clinical parameters with normal LDH or increased LDH with one to three others parameters. For each level, the estimated 3 year overall survival was 88 %, 71 % and 41 %. LNH 84 protocol was a single arm study which yield a 75 % CR rate and a probability of survival of 60 %. The goal of LNH 87 protocol was in patients < 70 y to compare by randomization our previous LNH 84 arm to other chemotherapy regimen in different prognostic subgroups. From 10/87 to 12/89, 1562 aggressive lymphomas have been included in LNH 87 of whom, 1286 were < 70 y. 490 pts are evaluable in the control arm and 498 in the others arms. Mean age 49, 6 y. Histology was according to the working formulation : D 5% ; E 3%, F 16%, G 44%, H 10%, I 4%, J 2%, M 5%, not classified 6 %. Stage: I-IE 11%, II-II E 27%, III 11%, IV 49%. Tumoral mass > 10 cm, 35 %, extranodal sites > 2, 32 %, increase LDH 44%, bone marrow positive 23%, B symptoms 35%. Complete remission rate for the control arm was 72%, overall survival is 60%. Using the prognostic index, partition in three groups was highly significant with a probability of survival at 15 months of 80%, 65%, 35% for each index level ($p < 0.0001$). The same model was used for others arms and allowed a highly significant partition ($p < 0.0001$) in 3 levels. Preliminary results of LNH 87 protocol validate for survival the proposed prognostic index and can be used in other regimens.

P 36 PROGNOSTIC FACTORS OF NON HODGKIN LYMPHOMA WITH PROMINENT SPLENOMEGALY (*LPS*). A STUDY OF 59 PATIENTS (PTS).

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We retrospectively studied with Log Rank and Cox analysis (SAS software, VAX n°6210 computer) the prognostic factors for survival in 59 pts with *LPS*, without peripheral lymphadenopathy and leukemic involvement, diagnosed between Jan 1974 and Feb 1989, (median age 65, range 34-81; M/F=0.55). The last 46 pts were negative for HIV. Using the Working Formulation, histologic subtypes were: A: 32 pts, B and C: 11 pts, Intermediate lymphocytic lymphoma: 2 pts, E: 1 pt, F: 4 pts, G: 5 pts, H: 4 pts. Immunophenotype was B in 88% and T in 12% of cases. 47 pts had one or more cytopenia, 16 pts had B symptoms. 40 pts underwent splenectomy (*spl*) before chemotherapy (CT) (group 1); 19 pts did not (group 2). Staging (ANN-ARBOR) was: in group 1: stage I: 3 pts, IE: 1 pt, stage II: 4 pts, IIE: 2 pts, stage IV: 30 pts (with liver involvement in 6 pts, bone marrow in 8 pts, both in 16 pts); in group 2: stage IIE: 2 pts (diagnosis obtained with lymph node biopsy guided by CT-scan), stage IV: 17 pts, all with bone marrow involvement. Bone marrow involvement was more frequent in group 2 ($p=0.04$), no other initial parameters differed between the 2 groups. After *spl* there was one postoperative death, 2 other pts died before starting CT, 9 pts were carefully watched, 4 pts received Chlorambucil alone for 1 to 4 years (protocol A), 19 pts 6 to 8 MOPP or COPB cycles (Cyclophosphamide 1 g/m² d1,Vincristine 1.4 mg/m² d1, Bleomycin 10 mg/m² d1, Prednisone 60 mg/m² d1-5), followed by a maintenance with Chlorambucil for 1 to 3 years (protocol B). 5 high or intermediate grade NHL were treated with CHOP courses or LNH84 regimen (a third generation CHOP regimen with increased doses of Adriamycin and Cyclophosphamide). In group 2: Protocol A was performed in 7 pts, protocol B in 6, CHOP in 2, splenic XRT in 1, watchful waiting in 3. The following parameters were analyzed for survival: age, sex, symptoms, spleen size, staging, bone marrow involvement, histology, complete initial blood count, albumin, gammaglobulin and LDH level, splenectomy, further treatment. The same parameters and weight of the spleen and blood count after *spl* were studied in group 1. Median actuarial survival of all the pts was 42 months. In Log Rank analysis, the only factors associated with longer survival duration were: age < 55 ($p=0.03$), male sex ($p=0.04$), albumin > 35g/l ($p=0.03$), initial hemoglobin level > 100g/l ($p=0.01$), *spl* ($p=0.0001$). Histology and further treatment had no prognostic significance. A Cox analysis found the best factors predicting survival duration to be *spl* ($p=0.0001$), initial hemoglobin ($p=0.01$), albumin ($p=0.03$) and age ($p=0.03$); in multivariate analysis the most powerful association was *spl* and albumin ($p= 9.10^{-5}$). In group 1, 33 pts had one or more initial cytopenia, which persisted in 5 of them after *spl*; prognostic factors were initial hemoglobin level ($p=0.04$) and hemoglobin level ($p=0.004$) and platelets ($p=0.02$) after *spl*.

Cytopenias are usual at presentation in *LPS*, and are generally corrected by *spl*. Most *LPS* are low grade non hodgkin's lymphomas. Our findings suggests that *spl* improves survival in *LPS* at least if it is associated with correction of anemia and thrombocytopenia. Initial albumin level is also of important prognostic value.

P 37 AGE AS A PROGNOSTIC FACTOR IN 537 PATIENTS WITH NON-HODGKIN'S LYMPHOMAS ENTERED IN EORTC CLINICAL TRIALS BETWEEN 1975 AND 1986.

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From 1975 to 1986, 563 patients (pts) with non-Hodgkin's lymphomas (NHL) were treated with 3 consecutive prospective randomized trials, comparing different chemotherapeutic and/or radiotherapeutic regimens. In the first study (351 pts) all histologies were included, in the second (42 pts) only follicular growth pattern and in the third study (179 pts) only mixed and diffuse growth patterns were included. Only the 537 pts with age less than 70 were evaluated for this study. Pts were prospectively followed-up, and progressions, relapses, treatment side effects and deaths recorded. Data were up-dated November 1, 1989. The logrank trend was used to compare survival curves between 3 age groups (<50, 50-59 and 60-70 years). There were 230 pts with age less than 50, 148 pts with age 50-59, and 159 pts with age 60 to 70. Females were significantly more present in older group (p0.003). As far as growth pattern, diffuse histology was more represented in older pts but not at a significant level. As far as Working Formulation, intermediate and high grades did not significantly differ in older vs younger pts. Only 9 pts had stage I and II disease, due to entry criteria for these trials. Stage III was more frequent in youngers, whereas stage IV in olders, but not at a significant level. Older pts however had a statistically increased involvement of Waldeyers ring (21% in age group 60-70 vs 11% in age group less than 50, p0.01). Systemic symptoms did not differ between the 3 different age groups. As far as complete response rate obtained with treatments employed, there was no significant difference between the age groups, with 50% CR observed in youngers vs 46% CR in olders. As far as survival, there was a significant lower survival in pts between 60 and 70 of age in comparison with younger pts.

In conclusion, age in pts with NHL included in prospective randomized trials of EORTC Lymphoma Group since 1975 and with an upper age limit of 70 years was significantly associated with survival but not with the achievement of complete response. Age is a prognostic factor that require careful interpretation. Infact, one third of pts with NHLs are older than 70 years of age and were not included in these clinical trials. Therefore conclusions on age as prognostic factor among pts with NHL must always take in consideration this important methological aspect. Nevertheless, from this EORTC study, it appears that survival is lower in pts 60-70 years of age in comparison with younger pts.

P 38 CONFIRMATION OF THE M.D. ANDERSON STAGING CLASSIFICATION (MDASC) FOR INTERMEDIATE GRADE LYMPHOMA (IGL).

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In prior publication, we have identified tumor burden (TB), serum level of lactic dehydrogenase (LDH) and age as the major independent factors for survival in 250 patients with diffuse large cell lymphoma (DLCL) treated with CHOP-Bleo (Blood 74:551-557, 1989). Thus, a prognostic model for staging classification (MDASC) was proposed. In order to validate it, we have applied the same concept to 243 cases of intermediate grade lymphoma (IGL) treated from 1984-1988 which includes 203 patients with DLCL. Treatment for Ann Arbor (AA) stages II-IV consisted of alternated cycles of CHOP-Bleo and CMED (Cytoxan 750 mg/m^2, Mtx 1000 gm/m^2 with Leucovorin rescue, VP-16 100 mg/m^2 x 3d, Dexamethasone 40 mg/d x 4d). Pts with stage I received CHOP-Bleo only. XRT was also given to stage I-III pts. CR was attained in 189 pts (78%). With a median follow-up of 30 mos, overall survival at 5 yrs was 63%. There was no significant difference in the 5 year survivals of patients in AA stages I, II, and III (67%-75%), but stage IV patients fared worse with a 5 year survival of 55%. MDA stage was determined by TB and LDH levels according to published guidelines. Results were as follows:

MDA	DLCL (1974-84)		IGL (1984-88)	
Stage	N	5-Yr Survival	N	5-Yr Survival
A	50	85%	54	88%
B	86	68%	76	74%
C	76	48%	73	60%
D	38	18%	40	38%

We conclude: 1) the proposed system has a better prognostic discrimination than the Ann Arbor Classification System; 2) the currently treated pts show better survival than the older group. Longer follow-up time would be needed for a more definitive conclusion.

P 39 AGRESSIVE NON HODGKIN'S LYMPHOMA (NHL) IN FAILURE AFTER TREATMENT WITH LNH84 PROTOCOL. EVOLUTION AND PROGNOSIS FACTORS IN 208 PATIENTS.

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Seven hundred thirty seven (737) patients with aggressive NHL were treated with LNH84 protocol (Coiffier et al., J. Clin. Oncol., 1989; 7 : 1018). Overall and failure free survivals were estimated at 2 year at 67 % and 56 % respectively.
Out of these patients 208 were studied after failure : 137 were in relapse after complete response (CR) and 71 were in first progression after partial response (PR) (36) or stable disease (35). For these 208 patients, the three-year probability of survival (S) from the failure was 15 % and 3- year probability of failure free survival (FFS) is 8 %.
Treatment was given in 191 patients, with radiotherapy alone in 18 patients.
A second complete remission was obtained in 44 patients (23 %) and a second partial response in 65 pts (34 %). Three-year probability of S and FFS after 2 CR was 51 % and 32 % respectively. Intensive chemotherapy ± radiotherapy followed by bone marrow transplantation (BMT) was performed in 34 patients (1 syngenic, 5 allogenic, 28 autologous). BMT was given either after second CR (14), second PR (11) or failure (9).
Three-year probability of S and FFS after BMT were 30 % and 26 % respectively.
Prognosis factors for S after failure are immunology (T better than B), Working formulation (intermediate/high), stage (A/B), stage (I-II-III/IV) performance status (PS) (O-1/2+), number of extranodal sites (0-1/2+), tumoral mass (10 cm), LDH level, relapse (on or off therapy) . The same prognosis factors are found for FFS but, in addition, BMT is significantly superior to no-BMT.
A multivariate analysis performed in 163 patients by COX model shows that only PS (p = 0.0019) LDH initial level (p = 0.0028) and BMT (p = 0.0009) remain independent prognosis factors. The benefit of BMT persists if we analyse only patients under 60 year-old (p = 0.002) or only CR2 and PR2 patients (p = 0.0294).
In conclusion failure patients after treatment with LNH84 protocol have an extremely poor prognosis. The best way to improve these results is to obtain a second response and to perform IC + BMT.

P 40 PROGNOSTIC VARIABLES IN THE TREATMENT OF NON-HODGKIN'S LYMPHOMA IN ELDERLY PATIENTS.

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Non-Hodgkin's lymphoma (NHL) frequently occurs in patients older than 65 years. Most studies exclude elderly patients, if not by virtue of age, then by virtue of concomitant disease. To assess the long-term outcome of these elderly patients, an analysis of prognostic factors was performed on 277 patients with NHL, 84 of whom were older than 65 years. All patients were seen at a single institution and elderly patients, who might otherwise have been excluded from study analysis, were included. Twenty clinical, radiological and laboratory parameters were studied including variables reported to be important indicators of prognosis in previous series. These variables were subjected to univariate and multivariate analysis.
When the whole group was considered, the factors associated with prolonged survival were a good performance status (PS), age < 65 years and a favourable histology. For patients > 65 years, however, the factors of prognostic importance were female sex, a longer time to dose limiting toxicity ((TDLT), a favourable histology and a good PS. It appears therefore, that elderly patients have similar prognostic variables to the general population, although tolerance of cytostatic drugs is important in patients > 65 years.
Factors associated with a shorter TDLT were a poor PS, a raised LDH, unfavourable histology and treatment with an adriamycin-containing regimen. As TDLT is a measure of both dose intensity and functional reserve, treatment regimens for elderly patients should consist of cytostatics with acceptable toxicity, given in adequate doses. The prognostic significance of chronological age, therefore, incorporates the physiological reserve and immune status of the patients and these should be considered when deciding on patient management.

P 41 IDENTIFICATION OF PROGNOSTIC GROUPS IN ADVANCED STAGE DIFFUSE LARGE CELL LYMPHOMA (DLCL) TREATED WITH MACOPB: A MULTICENTER ITALIAN STUDY. U.Vitolo, M.Bertini, E.Brusamolino, B.Comotti, A.Gallamini, E.Gallo, R.Ghio, A.Levis, G.Luxi, U.Meneghini, L.Orsucci,G.Palestro, C.Tarella, G.Todeschini, P.Viero, T.Barbui, C.Bernasconi, G.Perona, A.Pileri and L.Resegotti. MRSGNHL c/o Div. of Hematology, Molinette Hosp, Torino, Italy.

From June 1986 to March 1989 180 pts with advanced stage DLCL were treated with MACOPB. The median age was 44 yrs (range 15-68). 58% were large cell (G) and 42% immunoblastic type (H). 54% had tumor bulk, 31% E lesions and 59% a LDH >500. 43% were advanced stage II, 24% stage III and 33% stage IV. 10% had Bone Marrow involvement (BM inv). 71% achieved a CR, 12% a PR, 13% a NR while 4% died due to toxicity. With a median follow up of 22 months, 2-yr survival (S) for all 180 pts was 59% and 2-yr disease-free survival (DFS) for the 127 CRs was 70%. Overall toxicity was acceptable with mucositis being the most frequent severe side effect. All pts were evaluated for pre-treatment characteristics predicitive for CR, DFS and S. Factors studied included: age, performance status (PS), stage, B symptoms, tumor bulk, LDH, Histologic subtype (HS), BM inv and tumor burden (TB) assessed as proposed by MDAH. In univariate analysis variables significant for response and survival were: LDH, TB, HS, PS, stage and BM inv. A regression tree model with survival as endpoint was then used to subdivide pts in different risk groups. In this model BM inv emerged as the major predictor of shortened survival (BM+ pts 2-yr S 11%). In BM negative pts LDH (< or >500) was the most important factor for predicting survival. Both in pts with LDH <500 and in those with LDH >500 TB and HS were found to be significant. We used these 4 simple pre-treatment clinical features (BM , LDH , TB and HS) to construct a model with 3 groups at increasing risk for shortened survival:

		CR%	DFS%	S%
A	BM neg, LDH <500 +/- TB high or HS H	84	80	80
B	BM neg, LDH <500 + TB high and HS H or BM neg, LDH >500 +/- TB high or HS H	71	63	55
C	BM pos or LDH >500 + TB high and HS H	23	13	8

This study confirm the effectiviness of MACOPB in DLCL, but poor-risk subsets of pts still exist and they need a different more aggressive therapy.

Poster Session II

HODGKIN'S DISEASE

ABSTRACTS - Fourth International Conference on Malignant Lymphoma, Lugano

P 1 HETEROGENEITY IN THE RELATIONSHIP BETWEEN THE HIGH GRADE MALIGNANT LYMPHOMA AND THE CHRONIC LYMPHOCYTIC LEUKEMIA IN PATIENTS WITH RICHTER'S SYNDROME

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Richter's syndrome is defined as large cell malignant non-Hodgkin lymphoma (NHL) supervening in the course of chronic lymphocytic leukemia (CLL). Based on the presence of identical immunoglobulin (Ig) heavy and light chains on the surface of CLL and NHL cells in patients with Richter's syndrome, it was concluded that Richter's syndrome may represent transformation or progression of the CLL clone to the B-NHL clone. However, the presence of identical Ig heavy and light chain is not synonymous with clonality, since most B-CLL and B-NHL carry the μ heavy chain and the statistical likelyhood of two independent B cell clones having the same light chain is more than 50%. Southern blot analysis of the Ig genes is an accurate method to prove or exclude the clonal origin of two B cell populations. We studied three cases of Richter's syndrome by Southern blot analysis.

In our first case of Richter's syndrome with different Ig light chain expression on the CLL cells and centroblastic NHL cells we demonstrated different Ig heavy and Ig light chain gene rearrangements and concluded that in this case the NHL most likely should be considered as a second independent malignancy (Blood 1984;64:571-5).

In our second case of Richter's syndrome the CLL and centroblastic NHL cells were found to express the same μ and κ Ig chains and appeared to have identical Ig heavy chain gene rearrangements. This indicates that the NHL cells in this patient represent a clonal progression of the CLL cells (Leukemia 1989;3:819-24).

In our third case of Richter's syndrome the CLL was followed by an immunoblastic NHL and subsequent acute macroglobulinemia with hyperviscosity syndrome. The CLL, immunoblastic NHL and bone marrow plasma cells expressed the same Ig heavy and Ig light chains (IgM-κ). The Ig heavy chain gene rearrangements of the NHL and bone marrow plasma cells were identical but differed from the CLL cells. Identical results were obtained by Igκ gene analyses. This indicates that the CLL and the immunoblastic NHL with subsequent progression to acute macroglobulinemia represent two independent malignancies.

Our observations indicate that the immunologic and molecular genetic features of Richter's syndrome appear to be more heterogeneous than assumed from the clinical picture. Systematic and prospective studies using the combined morphologic, immunologic and molecular approaches have to elucidate the clinical relevance of this heterogeneity in Richter's syndrome.

P 2 EFFICACY OF LOW-DOSE RECOMBINANT INTERFERON-α IN THE TREATMENT OF HAIRY CELL LEUKEMIA.

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Treatment with recombinant Interferon-α (rIFN-α) has become a standard treatment in hairy cell leukemia (HCL). Both in splenectomized as well as in non-splenectomized patients remission rates up to 90% have been reported, although a complete remission is obtained in only <10% of the patients. The optimal dose regimen has not been identified as yet. We report here the results of a Dutch multicentre study in 40 consecutive patients with HCL, treated in the period 1984-1989 with different doses of rIFN-α. All patients had a histologically confirmed diagnosis of HCL (central review by one of us, M.B.). Twenty-one patients had been treated with splenectomy in the past. None of the patients had received prior Interferon treatment. Treatment indication consisted of one or more of the following criteria: hemoglobin < 7.3 mmol/l, platelets < $70x10^9$/l, granulocytes < $0.5x10^9$/l or symptomatic splenomegaly. The first 19 patients received $5x10^6$ U rIFN-α2c daily s.c. for 12 weeks followed by maintenance treatment with $5x10^6$U twice weekly (group A). The second group of 6 patients received $3x10^6$ U rIFN-α2a thrice weekly s.c. (group B) and the remaining 15 patients received $1.5x10^6$ U rIFN-α2a thrice weekly s.c. (group C). Treatment response criteria were defined as follows: complete remission (CR): normalization of all abnormal parameters including reduction of hairy cells in the bone marrow biopsy to <5%; hematologic remission (HR): as CR but with persistent hairy cells in the bone marrow biopsy >5% and at least 50% reduction in hairy cells in the bone marrow biopsy; minor response (MR): normalization of one of the hematologic parameters. There were 6 female and 34 male patients with a median age of 53 years, not significantly different between the 3 groups of patients. Pancytopenia was present in 11 patients (27%). Seven of these patients were treated in group C with the lowest dose of IFN-α. Two patients experienced early death within one month due to infectious complications (group A, n=1; group B, n=1). After 3 months of treatment, the overall response rate was 90% (CR+HR 28%; MR 62%). The response rate increased to 95% after 6 months of treatment with a remarkable increase of CR+HR to 68%. Response rates did not differ significantly between the 3 treatment regimens: after 6 months CR+HR 78% in group A, 80% in group B and 60% in group C ($p>0.1$). The time to recovery of hemoglobin and platelet counts did not differ significantly between the 3 groups (median values 4 months and 3 weeks respectively). Splenomegaly, if present, resolved within 3 months in all patients. However, recovery of granulocyte counts $>1.5x10^9$/l was delayed in group C as compared to group A: 5 versus 2 months. In spite of the slower recovery of granulocytes, no increased frequency or severity of infectious complications was encountered in group C. Toxicity was substantially reduced in group C, especially chronic fatigue grade I/II occurring in only 27% in group C vs. 61% in group A ($0.05<p<0.1$).
These data highlight the efficacy of rIFN-α in the treatment of HCL even at low dose regimens. At the lower dose regimens, recovery of granulocyte counts is delayed without increased infection rates. The lower dose regimens are substantially better tolerated than the higher dose protocols.

Special acknowledgements to the participating 18 Dutch centers. This study was supported by a grant from Boehringer Ingelheim, The Netherlands (r-IFNα2c) and Hoffman-La Roche, The Netherlands (r-IFNα2a).

P 3 IMMUNOCYTOLOGY OF LYMPH NODE ASPIRATES FROM PATIENTS WITH MALIGNANT LYMPHOMAS.

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Lymph node aspirates from 137 patients with malignant lymphomas were analyzed. Cytological and immunocytological studies were performed on cytospin preparations using the alkaline phosphatase-anti-alkaline phosphatase (APAAP) method with a panel of monoclonal antibodies (CD3, CD4, CD8, CD15, CD19, CD30, CD45, CD71). The cytological diagnosis was confirmed by histological investigation.
62 aspirates from patients with B-non-Hodgkin's lymphoma of low malignancy were investigated. 61 cases were monoclonal with respect to their light chain determinants. 35 aspirates were obtained from patients with B-non-Hodgkin's lymphoma of high malignancy. 34 patients showed light chain restriction and a high (>40%) percentage of $CD71^+$ cells. 18 malignancies were considered to be of T-cell origin. Nine lymph node aspirates from patients with Lennert's lymphoma, angioimmunoblastic type and pleomorphic small cell type were composed predominantly of small to intermediate sized lymphocytes. Nine lymph node aspirates from patients with T-immunoblastic lymphoma, pleomorphic large cell type and large cell anaplastic ($Ki\text{-}1^+$) lymphoma showed marked cytological heterogeneity. Immunocytological investigation is helpful for differentiation from reactive lymphadenopathy and other malignant lymphomas. In 22 cases of Hodgkin's disease there were 17 correct cytologic diagnoses. A significant number of $CD30^+$ $CD15^+$ $CD45^-$ cells having the morphology of Sternberg-Reed cells supports this diagnosis.
Our findings indicate that the immunocytological method is applicable towards improving the cytological diagnosis of malignant lymphomas.

P 4 B-FOLLICULAR STRUCTURES IN HODGKIN'S DISEASE OTHER THAN LYMPHOCYTE PREDOMINANCE, NODULAR TYPE.

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The presence of large networks of follicular dendritic cells in lymphocyte predominance, nodular type (LPN) of Hodgkin's disease (HD) or nodular paragranuloma is well known. This and other findings has led to the hypothesis of B-cell nature of LPN. In the present study a monoclonal antibody detecting follicular dendritic cells in paraffin sections (Ki-B1p) was used to investigate nodular sclerosis (NS, n = 31) and mixed cellularity (MC, n = 16) type of HD. Follicular dendritic cell networks, occupied by Sternberg-Reed and/or lacunar cells, could be demonstrated in approximately 50 % of NS and approximately 18 % of MC cases. They were accompanied by clusters and/or strands of B cells. These findings indicate that a portion of the NS and MC types also comprise a B-cell microenvironment with a close association to the morphologically specific cells of HD.

P 5 HODGKIN-ASSOCIATED SOLUBLE CD30 ANTIGEN (CD30s) IN THE SERA OF PATIENTS WITH HODGKIN'S DISEASE (HD): A PROGNOSTIC FACTOR.

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We detected a 80kd soluble CD30 (CD30s) antigen released into the supernatant of Hodgkin's derived cell lines in vitro by a recently developed ELISA using the two monoclonal antibodies HRS-1 and HRS-2 which were developed by immunization with the Hodgkin's derived cell lines L428 and L540. HRS-1 and HRS-2 detect two different epitopes of the 120 kd membrane-bound CD30 antigen on Hodgkin cells. CD30s was also detected in the serum of 23/100 patients (23%) with newly diagnosed Hodgkin's disease, 8/50 (16%) patients with non-Hodgkin's lymphoma (especially large-cell anaplastic lymphoma), and 8/10 patients (80%) with HTVLV1+ T-ALL. In all cases, CD30s disappeared after successful therapy. No CD30s antigen was detected in 100 other hematological malignancies (ALL, ANLL, CLL, CML, plasmocytoma), 50 solid tumors (breast, lung, ovarian, colorectal, stomach cancers), 50 immunological disorders (SLE, RA), and 100 healthy controls. Of 20 septicemias and 50 viral infections (EBV, CMV, HSV, HIV), only 8/10 with acute infectious mononucleosis (anti-EBV-IgM$^+$) were positive. Thus, CD30s is a valuable and highly specific marker for disease activity in Hodgkin's lymphoma, certain types of NHL and adult T-ALL (HTLV1$^+$). Of 87 pts. with HD evaluable for response, 65 (75%) achieved complete remission (CR). The CR rate was significantly lower ($p<0.001$) for 20 CD30s$^+$ (10/20 = 50%) compared to CD30$^-$ pts. (55/67 = 82%). Progressive disease was more frequent in CD30s$^+$ (6/20 = 30%) than in CD30$^-$ (12/67 = 18%; $p<0.01$). After a median time of observation of 21 months, the curves for freedom from treatment failure (FFTF) of CD30$^+$ and CD30- pts. are significantly different ($p<0.01$). We conclude that the presence of CD30s in the pretreatment serum of pts. with HD has prognostic significance for CR rate and FFTF.

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P 6 A NEUROENDOCRINE APPROACH TO STUDY THE SYSTEMIC SYMPTOMATOLOGY IN HODGKIN'S DISEASE.

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The mechanisms responsible for the systemic symptomatology in Hodgkin's disease (HD) are still unclear.However,since the neurovegetative status is regulated by the hypothalamus,it is probable that the systemic symptoms may depend on an action at hypothalamic sites.Moreover,because of the documented influence of cytokines on hypothalamic neurotransmitter contents (Besedovsky et al.,1981),it is possible to hypothesize that the alteration of the hypothalamic function may be due at least in part to a direct central action of cytokines abnormally produced by transformed lymphoid cells. On the basis of the fact that the possible existence of a functional hypothalamic damage can be indirectly documented by the relief of changes in pituitary hormone secretions,the present study was carried out to evaluate the hypothalamic-pituitary-pineal interactions in patients (pts)affected by HD with or without systemic symptoms. The study included 24 untreated pts ,13 of whom without and 11 with systemic symptoms. For endocrine detections,venous blood samples were collected during the morning before the start of therapy. In each blood sample, the serum levels of the pineal hormone melatonin (MLT) and those of beta-endorphin (END) were measured with the RIA method. The results were compared with those obtained in a group of 42 age-matched healthy subjects. Abnormally high concentrations of MLT and END were seen in 3/24 (12.5%) and in 4/24 (16.7%) pts,respectively. MLT mean levels were higher in pts without than in those with systemic symptoms (26 $\pm$ 6 vs 15 $\pm$ 4 pg/ml;$\bar{x}$ $\pm$ SE);on the contrary,pts with systemic symptoms had higher concentrations of END than those without symptoms (49 $\pm$ 6 vs 31 $\pm$ 7 pg/ml). However,none of these differences was statistically significant. These results,which have to be confirmed on a greater number of patients,would suggest the existence of differences in the functionless of the pineal gland and of the opioid system in HD between pts with and without systemic symptoms. Further studies will be required to better define which relation exists between neurohormone secretions and systemic symptomatology in HD.

P 7 Detection of Residual Mediastinal Hodgkins Disease by using Gallium Scanning.

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It is well recognised that in some patients a residual mediastinal mass (MM) following initial therapy for Hodgkin's Disease (HD) indicates residual active disease whilst in others an abnormal CXR or CT scan may persist for many years without evidence of relapse. Thus there exists the need for a reliable non-invasive technique to demonstrate residual disease. In this study we evaluated Gallium (Ga) scanning in 69 patients with biopsy proven HD in an attempt to determine the place of this procedure in monitoring disease activity and in particular within the mediastinum. Patients were scanned following an injection of 370 MBq Ga-67 citrate using triple height pulse analysis. 41 had a Ga avid MM at presentation and were re-scanned following the completion of planned therapy. The mean age was 36 years and there were 23 males and 18 females. Post treatment results and disease status with a mean follow of 39 months is as shown:

	Ga POSITIVE	Ga NEGATIVE
All Patients	9 deaths	17 CR
	6 PD (1 now Cr)	3 PD
	1 CR	4 Relapse (now CR)
		1 death *
Residual MM	4 deaths	7 CR
	4 PD (1 now CR)	3 relapse (now CR)
		2 PD**
No MM	5 deaths	10 CR
	2 PD	1 PD
	1 CR	1 relapse (now CR) **
		1 death

* Studied during chemotherapy (1) and ** within 4 weeks (3).

Ga Scanning provided excellent differentiation of patients with persistent active disease after treatment ($p < 0.001$). The predictive value of a positive Ga scan was 94% with only 2 patients now in CR. The predictive value of a negative scan was 69% although 4 patients were studied too soon after the completion of chemotherapy (< 6 weeks) and 2 others have undergone late relapses (4 & 6 Years).

Therefore Ga scanning is an accurate non-invasive prognostic indicator of outcome after initial therapy for mediastinal HD independent of a MM. A positive scan is a particulary bad prognostic factor and may indicate the need for further/alternate therapy.

P 8 A NUMERICAL PROGNOSTIC INDEX FOR CLINICAL USE IN IDENTIFICATION OF POOR RISK PATIENTS WITH HODGKIN'S DISEASE AT DIAGNOSIS.

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The aim of this study was to assess the feasibility of using objective data obtained at diagnosis of Hodgkin's disease to predict those patients who were likely to die of progressive disease within four years of diagnosis.

Ninety-two consecutive patients from one centre (Newcastle upon Tyne), were used to construct a numerical index based on disease stage (Ann Arbor), age, haemoglobin and absolute lymphocyte count. Weight was assigned according to a predictive value in univariate and multivariate analyses based on survival. The index produced was then validated on a separate patient set (455) from other centres within the Scotland and Newcastle Lymphoma Group (SNLG) on whom the same prospective information was available. The index produced provided a useful separation of those patients destined to die of disease. In 101 patients index >0.5 62(61.4%) were dead at four years, whereas with index <0.5 61(18%) of 336 patients were dead at four years. The index includes Ann Arbor stage but possesses additional practical prognostic value which allows identification of patients with early stage destined to die of disease. Of 149 patients with Stage I and II disease, 15 patients had index >0.5, and 9 (60%) have died, whereas the remaining patients had survival of 90% and 85% respectively

This numerical index is applicable to all patients at diagnosis and in the SNLG population gives better predictive survival at four years than stage alone, and provides a basis for selecting patients for more aggressive therapy.

P 9 RADIOTHERAPY VERSUS CHEMOTHERAPY IN PATIENTS WITH EARLY STAGE HODGKIN'S DISEASE (PATH. STAGE I-IIA). A PERSPECTIVE RANDOMIZED TRIAL. REPORT AFTER 6.5 YEARS OF FOLLOW-UP.

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The authors will present the updated results of the randomized trial comparing MOPP chemotherapy (CT) with extended field radiotherapy (RT) in 89 early stage (path. stage I-II A) Hodgkin's disease (HD) patients. The previous data (presented also at the '87 Lugano Conference) have been confirmed. In particular, a trend was demonstrated toward a shorter survival for patients treated with CT (DFS about 65%) as opposed to those treated with RT (DFS about 80%). Similar differences are evident for overall survival. Relapsing patients were salvaged twice as frequently in the RT arm than in the CT arm.
No acute life-threatening complications were registered in the two treatment arms. Infections caused by Herpes Zoster virus have been to date evident in 15.5% of the RT-treated patients as opposed to 14% for the CT-treated ones (salvage treatment given before the infectious episode being not taken into account). Infertility was much more frequent in CT treated patients (100% vs 0% for males and 50% vs 10% for females).
A case of acute non lymphoblastic leukemia was registered among the CT treated patients.
More mature data seem to confirm that early stage HD should not be treated with chemotherapy only.

P 10 RESULTS OF TREATMENT OF CLINICAL STAGES (CS) IA TO IIIA HODGKIN'S DISEASE. THE H81 PROTOCOL.

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Between 10/80 and 09/85, 159 patients (pts.) with previously untreated HD CS IA-IIIA were entered on H81 trial. 152 pts. are evaluable : mean age 30 years (range 13-69 y, 25 pts. > 40 y, male 81, female 71 ; histology LP 18, NS 70, MC 59, unclass 5 ; CS IA 33, IIA 58, IB 4, II B 39, III A 18. Contiguous extranodal disease 9 CS II, infradiaphragmatic presentation 9 pts. All pts. were treated with combined modality (CMT). CS IA-IIA were treated by 3 MOPP cycles (Prednisone first cycle only), CS IB-IIB-IIIA were randomly assigned to receive 4 cycles of MOPP (33 pts.) or 4 cycles of MOPP alternating with ABVD (28 pts.) Adriamycin 30 mg/m2 IV days 1, 8 ; Bleomycin 2 mg/m2 SC days 2-5 ; Vinblastine 6 mg/m2 IV days 1, 8 ; DTIC 200 mg/m2 IV days 1, 8. Irradiation (40 Gy) consisted of : involved fields for CS I-II in complete remission (CR) after chemotherapy (CT): localized areas 31 pts., mantle 38 pts., inverted Y 2 pts. ; extended fields for CS I-II in partial remission (PR) after CT and CS IIIA : mantle spleen and paraaortic 63 pts., inverted Y spleen and mantle 18 pts., without mediastinum in 8 pts. with infradiaphragmatic presentation. After CT 8 pts. (3 PR and 5 failures) underwent surgical restaging, with splenectomy, abnormal in 1 pt. After CT, CR percentage was 60 % (IA-IIA 71.4 %, IB-IIB 37 %, IIIA 55 %), PR percentage was 35.5 %, failure 4.5 %. After CT + RT, CR percentage was 97 % (IA-IIA 100 %), IB-IIB 93 %, IIIA 94.4 %). Response rates were similar according to MOPP or MOPP/ABVD regimen. 14 pts. relapsed (in situ : 2, non irradiated lymph node areas : 2, nodal and extranodal : 10) after 1 to 71 months of CR, 5 pts. reached a second permanent CR, 1 PR. 15 pts. died (initial failure : 4, relapsing pts. : 7, deaths in first CR : 4, including 3 acute leukemia and 1 aplasia after MOPP/RT). RT complications were hypothyroidism (3), thyroidism (1), myelitis (1), sigmoid stenosis (1). Other toxicities were : Bleomycin pneumonitis (1), NHL (1), acute leukemia (1 pt in CR), dysmyelopoiesis (1 pt in failure).In January 1990, the median follow-up is 64 months. Actuarial survival and disease free survival of all pts. are 87 % and 85 % respectively, IA-IIA 90 % and 87 %, IB-IIB 75 % and 80 %, IIIA 87 % and 62 %.

P 11 RESULTS OF THE POF H81/12 TRIAL FOR HODGKIN'S DISEASE, CLINICAL STAGES (CS) I + II.

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From 1.10.81 to 30.09.88, 274 patients (pts) with CS I + II were prospectively treated according to the POF H 81/12 protocol. Lymphangiography was performed in all pts. No laparotomy-splenectomy was performed except in 2 cases for diagnosis purpose. Initial characteristics of the pts were : Sex: M 143, F 131 ; age: mean 32.9, range 15-65 ; histology: LP 21, NS 180, MC 52, LD 4, ND 17, CS:IA 57, IIA 143, IB 10, IIB 64 ; contiguous lesions: Lung 23, sternum 5, iliac bone 3, vertebra 2 ; 34 pts had a bulky tumor : mediastinal widening/thorax width) 0.44 (26 pts), lumboaortic and pelvic involvement (8 pts). 3 monthly courses of ABVD-MP (mg/m2, IV, days 1 and 15 : Adriamycine 25, Bléomycine 10, Vinblastine 6, Dacarbazine 375, Methylprednisolone 120) were administered to all pts (except non-mediastinal CSIA : one course only). Pts with complete remission (CR) or partial remission were given extended focal plus prophylactic lombo-aortic and splenic irradiations (involved areas 40 Gy, non involved areas 30 Gy). As of December 1rst 1989, median FU was 45 months (range 12-98)
Results of this protocol are summarized in the table :

	CS I+II	Sympt. A	Sympt. B	P Logrank.	Tumor Burden No Bulk	Tumor Burden Bulk	P Logrank.
Patients	274	200	74		240	34	
CT CR (%)	82.4	87	70	0.001	85	61	<10-3
RT CR (%)	98	99	96		99.2	91	
SV (%)	94	95	90	NS	96	79	<10-3
FF P (%)	90	94	82	0.01	96	57	<10-6

(CT: post chemotherapy ; RT: post radiotherapy
SV: 8-year survival, FFP : Freedom from first progression).
Initial failures : 5 (2 deaths) ; Relapses : 14 (in situ/marginal +/- visceral 11, visceral 2, non irradiated nodes 1), median delay after CR 15 months, (deaths 4) ; deaths in CR : 4 (melanoma, ovarian cancer, sudden death, car accident). Fertility was maintened in all pts < 35 yrs. This protocol gives optimum results in the 240 pts without bulky disease. In the 34 pts with bulky disease, treatment needs to be more intensive (supported by AREMAS).

P 12 COMBINED MODALITY TREATMENT OF "BULKY" HODGKIN'S DISEASE: REPORT OF 55 CASES.

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Of the 270 patients affected by Hodgkin's disease we have diagnosed over the last 15 years, 55 (25 males and 30 females) had a bulky disease, mostly (80%) of mediastinum. The median age at diagnosis was 26 years (range 10-74). They were staged as follows: 4 stage I, 39 II and 12 III. Nodular sclerosis histology was present in 41/55 patients (74%). The follow-up median is 60 months (range 6-180).
Treatment. 48/55 patients were treated with chemotherapy, on average 6 cycles of MOPP (18 patients) or alternating MOPP/ABVD (30 patients) plus radioterapy (17 Involved Field, 17 Mantle Field, 8 Subtotal Lymphoid Irradiation, 6 Total Lymphoid Irradiation, 30 to 45 Gy); 5 received only chemotherapy (8 cycles of MOPP or alternating MOPP/ABVD); 2 patients were treated with radiotherapy alone (Subtotal Lymphoid Irradiation).
Results. Overall CR was obtained in 51/55 patients (92,7%); relapse occured in 7/51 cases (13,7%), in four out of seven in the site of bulky. At present 43/51 patients (84%) are in continous complete remission, the actuarial survival and disease free survival curves showing a ten-year plateau of 73,3% and 80,3%, respectively.
The cure rate was 78%. Of the 48 patients treated with chemotherapy plus radiotherapy, 44/48 (91,7%) obtained CR.
So far one patient (splenectomized at diagnosis) developed acute non Lymphoblastic leukemia 4 years after chemotherapy plus radiotherapy (MOPP plus Total Lymphoid Irradiation)
Conclusions. The presence of bulky mass is currently considered a poor prognosis factor in Hodgkin's disease and needs a more aggressive treatment. Combination therapy including MOPP±ABVD plus radiotherapy appears effective in achieving complete remission and preventing relapse.

P 13 HODGKIN'S DISEASE WITH BULKY MEDIASTINAL INVOLVEMENT : EARLY RESPONSE TO CHEMOTHERAPY DELINEATES HIGH-RISK PATIENTS.

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Between 1977 and 1985 a series of 38 patients with localized bulky mediastinal Hodgkin's disease were clinically staged and received combined modality treatment. All patients had mediastinal tumour measuring at least 1/3 of the width of the maximum thoracic diameter. Treatment consisted of three courses of MOPP followed by sub-TNI radiotherapy (mantle, lumbo-aortic and splenic fields). This series included 1 patient with Stage I, 27 patients with Stage II and 10 with Stage III (Stage III_1 was defined as subdiagraphagmatic disease restricted to the spleen and/or upper aortic nodes). B symptoms were present in 23 (60%) cases. The sex ratio was 1/1 and the median age was 28 years (range 15-60). The histological subtypes were nodular sclerosis in 30 cases (79%), mixed cellular in 7 (18%) and lymphocyte depleted in 1. Complete response after the three initial courses of chemotherapy was referred to as CR3, and as CR if it occurred after completion of the combined treatment. Analysis was performed in December 1989.

The CR3 rate was 47% and the CR rate 87%. 54.5% of CR patients had reached CR3. The overall 8 y-survival and disease free survival (DFS) were 64% and 78%, respectively. 5 non-CR3 patients failed to respond to combined modality treatment, 4 of whom died. 6 CR patients relapsed, 5 of whom were non -CR3 patients, and 4 died despite salvage treatment. Median time to relapse was 28 months. Failures and relapses were limited to above the diaphragm. 1 CR patient died from acute leukemia without evidence of recurrent Hodgkin's disease. Thus, among the 9 non-surviving patients, 4 died from failure and 4 from relapse. Among the 11 patients with unfavourable Hodgkin's disease (i.e.5 failures and 6 relapses) 10 were non-CR3. Finally, 8 y-survival was better for CR3 than for non-CR3 patients : 100% vs 37% ($p < 0.001$). DFS rates also differ between CR3 and non-CR3 patients: 87% vs 65% ($p < 0.02$). Survival and DFS rates were not affected by other factors such as age, stage, B symptoms and histology.

On the basis of these results a new strategy was devised in which non-CR3 patients were treated with three courses of chemotherapy (cyclophosphamide, methyl-GAG, etoposide, methotrexate) interspersed with three courses of 15 gy mantle radiotherapy over a period of 3 months, followed by lumbo-aortic and splenic irradiation. CR3 patients were treated as previously. The results on 40 patients treated in this way since 1986 will be presented.

P 14 MOPP + EXTENDED FIELD RADIOTHERAPY COMPARED TO ALTERNATING CHEMOTHERAPY IN STAGE II B AND III B HODGKIN'S DISEASE.

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From January 1982 to June 1989 a series of 100 patients were clinically staged as II B or III B Hodgkin's disease and were consecutively enrolled in the following non randomized treatment programs:
* until December 1985 (45 patients): 6 MOPP plus extended field radiotherapy 36 Gy (subTNI for stage II and TNI for stage III).
* from January 1986 (55 patients): a minumum of 6 courses of 1/2 MOPP - 1/2 ABVD (MA/MA) followed by radiotherapy limited to bulky areas.

Median age was 39 years (range 14-74). No statistical difference was seen between the two consecutive series for median age (38 vs. 39), male sex (49% vs. 58%), stage III (42% vs. 38%), E involvement (18% vs. 16%), bulky mediastinal mass (40% vs. 35%), advanced histology (MC+LD: 35% vs. 31%), more than two B symptoms (31% vs. 32%) and presence of fever (71% vs. 81%).

Results are as follows:

	MOPP+RT	MA/MA	p value
C.R. after 3 cycles	59 %	75 %	0.06
Final complete remission	77 %	93 %	0.03
Disease free survival	78 %	78 %	0.54
Overall survival	62 %	83 %	0.03
Event free survival	56 %	69 %	0.15

Treatment program variations due to bad compliance or toxicity were more frequent in patients planned to be treated with MOPP+RT than in patients entered the MA/MA protocol (28% vs. 6%).

Results of combined modality therapy with MOPP+RT are worse than those of MA/MA in terms of tollerance, final remission rate and overall survival. So far disease free survival of patients achieving final complete remission is not different between the two groups.

P 15 THE RESULTS OF THE TREATMENT OF 538 HODGKIN'S DISEASE PATIENTS WITH MOPP OVER 19 YEARS - THE BNLI EXPERIENCE.

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Between 1970 - 1983, 538 patients with advanced Hodgkin's disease (89% Stage III/IV) were entered into BNLI randomised trials and studies and treated with MOPP. MOPP consisted of Mustine 6 mg/m² (max 15 mg) i.v. day 1 & 8, Vincristine 1.4 mg/m² (max 2 mg) i.v. day 1 & 8, Procarbazine 100 mg/m² (max 200mg) orally daily for 10 days, Prednisone (or Prednisolone) 25 mg/m² (max 60 mg) orally daily for 14 days. Repeated every 28 days.

The results for the series of 538 patients were as follows:- the CR rate was 61%: the disease-free survival (DFS) was 29% at 15 years: the relapse-free survival of patients achieving complete remission was 48% at 15 years: and the overall survival was 45% at 15 years.

The series included an appreciable number of patients who failed to receive 6 courses of MOPP, due to lack of response with or without progression of disease and early death. A further group of 'slow responders' in the series received more than 6 courses, the DFS of those who received more than 8 courses being less than 20%.

The DFS of those patients who received second line treatment was less than 25% at 15 years from time of start of second line treatment. The overall survival of those patients who failed to achieve CR from their second line treatment was less than 3% at 14 years.

The major prognostic factor for overall survival was age at presentation. However many of the deaths occured in patients in CR, and appear unrelated to HD.

P 16 STAGE IIIB/IV HODGKIN'S DISEASE: A RANDOMIZED TRIAL OF CHEMOTHERAPY VS. RADIOTHERAPY FOR REMISSION CONSOLIDATION AFTER THREE DOUBLE CYCLES OF CYCLOPHOSPHAMIDE, VINCRISTIN, PROCARBAZINE, PREDNISONE (COPP) AND DOXORUBICIN, BLEOMYCIN, VINBLASTINE, DACARBAZINE (ABVD).

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Two-hundred-and-seventy-four consecutive patients (pts.) in stages CS (205 pts.) or PS (69 pts.) IIIB (145 pts.), IVA (32 pts.) and IVB (97 pts.) received 3 double cycles of monthly alternating COPP+ABVD. Patients in complete remission (CR) were then randomized to receive either IF radiotherapy 20 Gy or another double cycle of COPP+ABVD. Pts. not in CR after 3 x (COPP+ABVD) received salvage radiotherapy for persistant nodular or CEVD-chemotherapy (Pfreundschuh et al., 71:1203, 1987) for persistant diffuse or organ involvement. The CR rate after 3 x COPP+-ABVD was 58% and the overall CR rate including salvage therapy was 76% (IIIB 79%, IVA 72%, IVB 73%). There were three treatment related and one intercurrent deaths. Twenty-seven pts. (10%) progressed. Fifty-two pts. in CR after 3x (COPP+ABVD) were randomized for IF radiotherapy and fifty-three for a fourth double cycle of COPP+ABVD. Freedom from treatment failure (FFTF; median time of observation 33 months) events show no differences between the two arms. Relapse-free survival (median time of observation of 21 months) was 81% in the chemo-radiotherapy arm (10 relapses) and 87% in the chemotherapy-only-arm (7 relapses). Analysis of subgroups according to initial stage or site of involvement showed no differences between the two arms, either. We therefore conclude that for patients with stage IIIB/IV Hodgkin's lymphoma IF radiotherapy and additional chemotherapy are equally effective for the consolidation of remission achieved after 3 double-cycles of COPP+ABVD.

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P 17 RESULTS OF COMBINED MODALITY TREATMENT FOR STAGES IIIB-IV HODGKIN 'S DISEASE AT SAINT-LOUIS HOSPITAL. THE H81 PROTOCOL.

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From 01/81 to 02/86 76 patients (pts.) with advanced HD were treated according to H81 protocol consisting of 4 cycles of chemotherapy (CT),MOPP versus MOPP/ABVD, and nodal extended fields radiotherapy(RT 40 Gy) for major responses, additional CT before RT for partial responses (PR). 70 pts. are evaluable: 53 males, 17 females, mean age 35 years (range 13-69; 21pts. > 40 years 40) .Pathology included NS:32 pts, MC:32pts, LD:1 pt,unclassified:5 pts. 69 pts. were clinically staged,and one after laparotomy. Stage distribution was IIIB 35, IVA 3, IVB 32. Extranodal disease was present in 6 stages IIIE and bone marrow-10, liver-10, lung-6, bone-7, skin-1,and several-6. Pts. were randomly assigned to receive 4 cycles of MOPP or 4 cycles of MOPP alternating with ABVD (Adriamycin 30mg/m2 IV days 1,8 ; Bleomycin 2 mg/m2 SC days 1,8 ; Vinblastine 6 mg/m2 IV days 1,8 ; DTIC 200mg/m2 IV days 1,8). 47 pts. received 4 cycles (MOP 22 pts.,MOP/ABVD 27 pts.), 2 pts received less than 4 cycles because of toxicity, 21 pts.received additional CT ABVD or other regimens (13 PR and 8 failures). After CT, 16 pts in PR underwent surgical restaging. RT consisted of mantle plus inverted Y fields in 42 pts., plus spleen in 31/42 non splenectomized pts.,mantle plus para-aortic and spleen in 20pts., mantle alone in 3 pts. No RT was delivered in 4 failures and one early death. 56 pts. received a total dose of 40 Gy,9 pts received a reduced dose (15-30 Gy) over supra and/or infradiaphragmatic fields. After CT the major response rate was 85.7%(25.7% CR and 60% PR ≥ 75%) Results were similar after MOP and MOP/ABVD. The CR rate was 81.4% after CT+RT and 82.8% after additional CT. Initial failures and early death represent 15.7%. 9 pts. relapsed after 2 to 44 months of CR, 4 pts. reached a second permanent CR. 21pts. died, initial failure : 9; relapsing pts. : 4; deaths under treatment 2 pts.; deaths in first CR:3 pts. (2 acute leukemia after MOPP/ABVD/RT);other 3 pts. Hematologic toxicity grade 3 or 4 with prolonged cytopenia was observed in 20% of the pts. In January 1990 the median follow up is 64 months. Actuarial survival and disease free survival of all pts. are respectively 62% and 70% (IIIb 80% and 80%, IV 45% and 52%).Adjuvant RT seems beneficial for advanced HD but comparison with CT alone needs prospective randomized trial.

P 18 MOPP/ABV HYBRID CHEMOTHERAPY FOR ADVANCED HODGKIN'S DISEASE (HD). 7 YEARS EXPERIENCE AT A SINGLE CENTRE.

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MOPP/ABV was our standard therapy from April 1981 to June 1988 for untreated, advanced HD patients (pts) aged 16 to 65.

Nitrogen Mustard	6 mg/m²	iv	d1	Repeat every 28 days
Vincristine*	1.4 mg/m²	iv	d1	
Procarbazine	100 mg/m²	po	d1-7	
Prednisone	40 mg/m²	po	d1-14	
Doxorubicin	35 mg/m²	iv	d8	
Bleomycin	10 mg/m²	iv	d8	
Vinblastine	6 mg/m²	iv	d8	

*Maximum 2.0 mg

Planned treatment was as follows:

Stage	Comments	Chemotherapy	Radiotherapy
IIB, IIIB, IVB, IIIA2, IVA IIA, IIIA	- - >5 splenic nodules	CR plus 2 cycles (min 8)	If localized Residual at 6 cycles
All other stages	Mediast >1/3	6 cycles	+ Involved Field
Except IA, IIA	Nod sclerosing + Mediast >1/3	3 cycles	+ Mantle

Of the 170 pts (101 male, median age 34, B symptoms in 88) 119 had nodular sclerosing, 34 mixed cellularity 3 lymphocyte predominant, 5 lymphocyte depleted and 9 unclassified HD, not otherwise specified. 54 had a mediastinal mass greater than one third (>1/3rd) of the thoracic diameter.

Follow up is from 1 to 7 years (median 4). Projected 7 year overall survival (OS) and failure free survival (FFS) - failure defined as primary progression, relapse or death from any cause -are:

		n	OS	FFS		n	OS	FFS
Stage	2A	14	88	70	Symptoms			
	2B	26	82	80	A	82	70	61
	3A	53	80	76	B	88	80	70
	3B	35	81	69	Mediastinum			
	4A	15	93	78	0	47	66	60
	4B	27	82	70	<1/3rd	69	89	78
	All	170	77	62	>1/3rd	54	86	64

OS is higher than FFS as some relapses can be salvaged. 46% (of 21 relapses) are "second failure free" 3 years from relapse. 5 solid tumours (1 lung, 2 cervix, 1 pituitary and 1 skin) and 2 haematologic malignances (1 acute leukaemia, 1 non-Hodgkin's lymphoma) occurred during follow up. There were 4 toxic deaths (2 neutropaenic sepsis, 1 embolus, 1 pneumocystis).

MOPP/ABV (± irradiation) is highly successful for advanced Hodgkin's disease irrespective of stage, presence of B symptoms or bulky mediastinal disease.

P 19 ALTERNATING CHEMOTHERAPY IN STAGE IV HODGKIN'S DISEASE.

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From January 1982 to June 1989 a series of 86 patients with stage IV Hodgkin's disease were treated with a minimum of 6 courses of the following chemotherapy regimens:

* MOPP/ABVD (MM/AA) until December 1985 (42 pts.).
* 1/2MOPP-1/2ABVD (MA/MA) from January 1986 (44 pts.).

Radiotherapy 36 Gy was delivered to bulky areas only. Clinical features at diagnosis were: median age 41 (range 13-69) - presence of B symptoms 61 (71%) - bone marrow involvement 38 (44%) - hepatic involvement 41 (48%) - lung involvement 17 (20%) - unusual extranodal involvement (thyroid, bone etc.) 13 (15%) - two concomitant extranodal involvement 37 (43%).

Complete remission (CR) rate was 71%. 8-yr actuarial survival and disease free survival (DFS) were 46% and 70% respectively.

Age, sex, histology, number of systemic symptoms, number and site of extranodal involvement and delivery rate of drugs were not significantly different in MM/AA and MA/MA groups. Moreover no differences in CR, survival and DFS rates were observed in the two treatment groups. The analysis of prognostic factors was therefore conducted in all patients. The clinical outcome was not statistically influenced by sex, number of B symptoms and number of extranodal involvement. Patients older than 45 had a lower remission rate (54% vs. 82% - p=0.01), with a better DFS (85% vs. 50%). CR was lower in patients with bone marrow involvement (59% vs. 82% - p=0.03). Patients with lung disease had a higher remission rate (93% vs. 65% - p=0.04), but relapses were more frequent (DFS 34% vs. 70% - p=0.04). For a better evaluation of the influence of prognostic features on untoward events the event free survival analysis was performed, but the event free survival was not related with the clinical characteristics analyzed so far.

P 20 PROLONGED FOLLOW-UP OF A RANDOMIZED TRIAL COMPARING MOPP/ABVD/RT TO MOPP/MOPP/RT IN HODGKIN'S DISEASE (HD) WITH POOR PROGNOSTIC FACTORS.

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Bulky disease, B symptoms, or extensive abdominal HD are poor risk factors requiring combined treatment. Furthermore, the administration of two non-cross-resistant regimens could prevent the occurrence of resistant tumor cells. With these concepts in mind, we devised to randomly allocate 51 pts with stage IIA bulky (2), IIB (16), III_{1-2} A&B (8), III_3 A&B (25) HD to receive either MOPP/ABVD (M/A) or MOPP alone (M/M) for 6 courses, alternated in both cases with a ping-pong modality to STNI (stage IIA, IIB, III_{1-2}) or TNI (stage III_3) to a total dose of 33 Gy/field. All but 5 pts (90%) achieved a CR with the planned therapy. A grade 3 leukopenia was more frequently seen among M/A pts (80%) than in M/M pts (60%), while anemia (13% vs 25%) and thrombocytopenia (13% vs 30%) were more frequently observed among M/M pts. As a consequence, 24% of pts treated with M/A received ≥ 2/3 of the planned dose of HN_2 or ADM, while 57% of M/M pts received this amount of HN_2. With a follow-up ranging from 13 to 100 months, the 5-year results showed no significant differences between M/A and M/M treated pts in terms of overall survival (72% vs 77%), survival of CRs (78% vs 89%) and disease-free survival (76% vs 89%). Occurrence of relapse was not related in our series to the actual amount of drugs received by pts. However, because the dose intensity of treatment is still a controversial issue, we think that new chemotherapy approaches including the classic MOPP and ABVD are needed in order to increase the intensity of treatment actually given to pts.

P 21 MOPP versus MOPP/ABVD IN THE TREATMENT OF ADVANCED HODGKIN'S LYMPHOMA.

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We retrospectively reviewed 312 patients treated with MOPP±Radiotherapy (RT) and 126 patients treated with MOPP/ABVD±RT. Before 1980 stage II-IV patients with high risk disease due either the to presence of symptoms or to bulky disease were treated with MOPP followed by extended field RT; after 1980 we introduced ABVD regimen to be administered alternatively or sequentially to MOPP+RT on bulky disease. Patients have been evaluated after 84 months of observation with a minimum follow-up of two years. Overall survival of the patients treated with MOPP/ABVD is 85% versus 75% of the patients treated with MOPP (p=0.005). Stage II patients had the same survival (85%) in both groups treated by MOPP or MOPP/ABVD; stage III patients treated with MOPP had an overall survival of 72% versus 85% of patients treated by MOPP/ABVD (p=0.001): MOPP-treated stage IV patients had an overall survival of 45% versus 78% of the other group (p=0.004).
In conclusion combined chemotherapy with 8 drugs (MOPP/ABVD) was more effective in increasing the overall survival of stage III-IV Hodgkin's disease patients, even if it has been associated with lower dose and less extended RT.

P 22 RANDOMIZED STUDY IN ADVANCED STAGE HODGKIN'S DISEASE (HD) COMPARING TWO ALTERNATING CHEMOTHERAPIES: MOPP/ABVD vs. OPP/ABVD.

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From May 1983 at our Institution there is an ongoing study in wich patients affected by advanced stage HD are randomly allocated to receive 8 cycles of MOPP/ABVD (VCR 1,4 mg/sqm i.v., H2N 6 mg/sqm i.v. on days 1 and 8; PCB 100 mg/sqm/day; PDN 40 mg/sqm/day orally on days 1-15; ADR 25 mg/sqm; BLM 10 mg/sqm; VLB 6 mg/sqm and DTIC 375 mg/sqm i.v. on days 43 and 56) versus OPP/ABVD (VCR 1,4 mg/sqm i.v. on days 1,8,15; PCB 100 mg/sqm/day, PDN 40 mg/sqm/day orally on days 1-21; same dosage and schedule for ABVD). Patients in complete remission (CR) after chemotherapy are treated with consolidation radiotherapy on involved fields (20 Gy total dose) plus spleen area (40 Gy total dose). Mecloretamine, an alkilating agent with high mutagenic activity, was removed from the OPP scheme following the aim to reduce the incidence of secondary leukemias and sterility. Dose intensification of VCR and PCB was also carried out to improve therapeutic results versus standard MOPP/ABVD. At present 184 patients are evaluable with 89 in the MOPP/ABVD group (30 stage IIB, 33 stage IIIB, 24 stage IV A/B) and 95 in the OPP/ABVD group (4 stage IB, 27 IIB, 33 IIIB, 31 IVA/B). Clinical characteristics are comparable between the two groups and median follow-up is 34 and 31 months, respectively. Overall response rate was 93% in MOPP/ABVD group (CR 81%, PR 12%) and 94% in OPP/ABVD (CR 82%, PR 12%). All patients in partial remission (PR) after chemotherapy have obtained CR with radiotherapy. Hematologic toxicity has been comparable in two groups whereas neurotoxicity (peripheral neuropathies) have occurred more frequently in OPP/ABVD patients. Both overall (OS) and disease-free survival (DFS) curves at 60 months do not show any statistical difference in the two arms of the trial (OS 85%, DFS 80% in MOPP/ABVD; OS 85%, DFS 88% in OPP/ABVD). Acute non lymphoid leukemia has occurred in two patients treated with MOPP/ABVD. Major complications are discussed into detail. These data indicate the equal effectiveness of both chemotherapies. Longer follow-up is required to confirm the results and to evaluate the incidence of long-term complications.

P 23 CHEMOTHERAPY (HALF MOPP ALTERNATED WITH HALF ABVD) FOLLOWED BY RADIOTHERAPY IN STAGES IIA TO IV HODGKIN'S DISEASE.

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Between 1/85 and 11/89, 88 patients with Hodgkin's Disease, 41 males and 47 females with a median age of 35 years (range 15-64), were admitted to the study. All the pts underwent staging procedures inclusive of total body CT scan and laparoscopy; laparosplenectomy was performed only in selected pts (6 cases). Subsequently the pts. Were administered chemotherapy followed by radiotherapy. Chemotherapy consisted of 3 to 6 cycles; every cycle was inclusive of half course of MOPP alternated with half course of ABVD.
With the exception of the stage IV pts and of 6 other pts, radiotherapy (20 Gy if there was no "residual" disease at the CT scan or 40 Gy in the other cases) was administered after the completion of chemotherapy to all the involved field; in stage II and III pts, radiation was administered also to the paraaortic nodes and to the spleen.
Stages were: IIA in 23 (bulky in 18), IIB in 10, IIIA in 18, IIIB in 20, IVA in 8, IVB in 13 pts. Until now 73 pts are fully evaluable for response and toxicity: after the combined treatment the complete remission was achieved in 60 pts (82,2%).
For those pts who completed treatment, the median follow up is 30 months and up to now 6 pts have relapsed and 2 of these (not previously irradiated) obtained prolonged secundary remission after radiation therapy alone.
Main toxicities: one non fatal pneumonia from pneumocistis carinii, one fatal interstitial pneumonia in a non-responsive pt, one myelodisplasia occurring two years after the completion of treatment. This combined program is feasible, but approximatly 20% of the pts still await for more effective treatment.

P 24 NOVP: A NOVEL CHEMOTHERAPY REGIMEN FOR TREATMENT OF HODGKIN'S DISEASE (HD) WITH MINIMAL TOXICITY.

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Treatment of patients (pts) with early staged HD results in high cure rates, with 75-85% of pts relapse-free, and survival rates of 85-95%. For pts with favorable disease characteristics, radiotherapy (XRT) alone provides good results; however, combined modality therapy including chemotherapy is necessary to assure good disease-free survival results for pts with unfavorable features. However, both MOPP and ABVD are associated with various risks of toxicity, both acute (nausea, vomiting, alopecia, myelosuppression) and chronic (sterility, leukemia, cardiopulmonary). We designed NOVP (Novantrone 10 mg/m2 day 1, Oncovin 2 mg day 8, Vinblastine 6 mg/m2 day 1, Prednisone 100 mg day 1-5) given q 3 weeks for 3 cycles in an effort to provide effective and minimally toxic chemotherapy without alkylating agents prior to XRT for pts with unfavorable presentations of stages IA-IIB and for stage III HD. We have treated 31 pts (16 stage I-II, 15 stage III) with 3 NOVP and XRT. The complete remission and partial remission rates were similar to that obtained with MOPP. Tolerance to therapy has been excellent. Acute problems were minimal. Most pts experienced nausea, grade 1; 1 had phlebitis, grade 1; 2 reported alopecia, grade 1. Three had transient paresthesias or myalgias, but all resolved within 7-10 days of onset. Median nadir granulocyte count was 600, with no thrombocytopenia. Duration of neutropenia was short and no pts experienced neutropenic infection or fever. No cardiopulmonary complications have occurred. Five of 6 males studied experienced azo- or severe oligospermia following the third dose of NOVP, but immediately after the third course, sperm counts began to rise. At 3-5 months, the median counts of 7 men analyzed were .1-10 mil/ml. At the end of therapy, 3/7 are normospermic and 4/7 are moderately oligospermic. Genotoxicities of MOPP and NOVP were compared by examining chromosome breaks and sister chromatid exchanges (SCEs) in lymphocytes of pts during treatment. In vitro bleomycin treatment was also used to unmask single-stranded DNA breaks induced by these regimens. Results show that MOPP causes elevated levels of SCEs but not chromosome breaks, although it causes elevated levels of single-stranded DNA breaks. By contrast, NOVP did not cause elevation of chromosome or single-stranded DNA breaks, or SCEs. From these early results, NOVP is a very well tolerated chemotherapy regimen, with side effects that appear less severe than those associated with MOPP or ABVD. Early results of treatment also are comparable to that seen with 2 cycles of MOPP prior to XRT.

P 25 ALFA 2b RECOMBINANT INTERFERON (INTRON) IN HODGKIN'S LYMPHOMA.

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In an ongoing multicenter randomized study we are evaluating if alfa-2b-IFN-R is usefull in high risk patients with Hodgkin's disease in preventing relapse after achievement of remission and in preventing infections namely those mediated by Herpes Virus. From December 1987 a total of 125 patients, stage II-IV with poor prognostic factors, were enroled. The study design consists, after induction treatment (MOPP±ABVD±Rxt, ABVD±MOPP±Rxt), of alfa-2b IFN-R or no further therapy. Alfa 2b IFN-R was administered at 3 MU/day over 3 months and 3 MU/three times a week over 9 months. Up to December 1989 105 patients are evaluable with a minimum follow-up of 3 months; 58 patients received alfa-2b-IFN-R and 47 didn't. Data concerning age, sex, clinical presentation, stage and histology were similar in both groups. Three relapses occurred in the group treated by alfa-2b IFN-R (5%) and 3 in the other group (6.5%). Herpes Zoster occurred in 2 patients treated by alfa-2b IFN-R (3.5%) and in 2 patients who didn't (4.2%). Tolerance to alfa-2b IFN-R was defined good in 52% of patients, 38% of patients had moderate hematological or clinical toxicity which was reversible by the temporary discontinuation of the drug administration, 18% of patients definitely stopped the drug administration because relapse (3%), clinical intolerance (13%) or hematological toxicity (2%). A faster recovery of T4/T8 ratio was demonstrated in the group of patients treated by alfa-2b IFN-R ($P<0.05$). To our knowledge this is the only study finalized to see of IFN has a role in Hodgkin's disease; obviously the data are too preliminary to drawn firm conclusion out of the feasibility of the protocol.

P 26 LATE RELAPSES IN EORTC EARLY STAGE HODGKIN'S DISEASE PROTOCOLS.

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From 1964 to 1981, 1,057 patients with supradiaphragmatic clinical stage (CS) I-II Hodgkin's disease were treated on 3 successive protocols. Treatment consisted of mantle irradiation (MRX) +/- 2 years vinblastine (VLB); subtotal nodal irradiation (STNI) +/- 2 years VLB and procarbazine; total nodal irradiation (TNI); or combined modality treatment (MOPP x 6 and MRX (MOPP). 377 (36%) patients underwent a staging laparotomy. 3 subgroups were defined: 1) patients who never relapsed (NR); 2) patients who early relapsed (ER); and 3) patients with late relapse (LR) more than 60 months post-treatment start. The Cox model was used to compare these 3 groups with adjustment on initial characteristics (age, sex, B symptoms, ESR, number of nodal areas involved, mediastinal involvement, and histology), and initial treatment. Patients were prospectivelly followed and data were up-dated December 1, 1989.

1,044 (98.8%) patients reached a complete remission (CR). Overall, 340 (32.6%) patients relapsed: 304 (29.2%) with ER, and 36 (3.4%) with LR. According to initial treatment, cumulative proportions of ER and LR, and relative risks (RR) of relapse were:

	No of pts	Early Relapse		Late Relapse	
No LAP MRX	142	57%	RR=10.1***	6%	RR=3.1
No LAP MRX + VLB	127	39%	5.9***	1%	0.3
STNI	198	33%	4.0***	4%	1.2
Negative LAP STNI	98	22%	3.5***	5%	2.3
Negative LAP MRX	100	22%	3.3***	9%	4.9*
TNI	152	28%	3.0***	8%	2.6
STNI + VLB/PCZ	96	14%	1.5	1%	0.3
MOPP + MRX	144	11%	1.0	4%	1.0

* $p<0.05$, *** $p<0.001$

There were 7 (10%) cases of nodal in-field LR, 17 (47%) cases of nodal out-field LR, and 12 (33%) cases of extranodal LR. Of these 36 LR patients, 29 (81%) reached a 2nd CR. Compared to ER patients, sites of relapse and percentages of 2nd CR were not statistically different. The 10-year survival rates after relapse were 73% in LR, and 47% in ER ($p<0.001$), while in the NR group the 10-year survival rate was 89%.

Conclusions: These findings indicate that 1) LR are rare and have a better outcome than ER; 2) With more aggressive therapies proportions of LR are not modified; and 3) Types of LR do not differ from that of ER.

P 27 "Classical" management of relapsed advanced Hodgkin's disease

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In the period 1977-1986 63 untreated patients (pts) with Hodgkin's disease (HD), clinically stage IIIB-IV were seen in our Institute: stage IIIB 37 pts, and stage IV 26 pts. All were treated with a combined modality regimen. Up to 1981 6 courses were given of alternating MOPP and CHVmP (Cyclofosfamide 600 mg/m^2, Doxorubicine 25 mg/m^2, Etoposide 60 mg/m^2, intravenous on day 1, Prednison 40 mg/m^2 orally day 1 to 5, q 25 days). In the later years standard MOPP or a MOPP-ABVD combination was used. Iceberg radiotherapy (RT) was added to all previously involved areas after MOPP-CHVmP, and to areas with bulky or slowly regressing lesions only, after MOPP or MOPP-ABVD. A dose of 20 Gy was applied to areas in complete remission (CR) at time of RT. For partial remission (PR) and stable disease (SD) a higher dose was given.

There were 31 progressions/recurrences (St. III: 16, St. IV:15) with a 5 year actuarial diseasefree survival (DFS) of 51% for the total group, and a total survival (S) of 75%. Progression during initial planned chemotherapy occurred in 7 pts, who all had multiple unfavourable prognostic factors (bulky lesions, more than 4 regions involved, ESR > 50 mm and age above 40 yrs). One pt only was salvaged and had extensive RT. Relapse within 18 months of start of treatment occurred in 9 pts and after 18 months in 15 pts. Sites of relapse were nodal only in 16 pts of whom 12 were previously involved and 3 only in previously irradiated areas. New areas were adjacent to previously RT. In 4 pts nodal and extranodal relapse were combined, 4 others had extranodal relapse only.

Almost half of the progressed/relapsed pts could be salvaged by classical management. Further treatment was by chemotherapy followed by iceberg RT if feasible, only 1 pt had ABMT. Of these 31 progressed or relapsed pts 5 yr DFS and S is 33% and 40% respectively. For pts with progression or early relapse within 18 months of commencing first treatment, the 5 yr S is 21% with a 2 yr S of 40%. For pts with late relapse the 5 yr S is 56%.

Conclusion: the reported survival figures of "classical management" for relapse of advanced Hodgkin's disease, can compete with data published for agressive chemotherapy with autologous bonemarrow support.

P 28 ADRIAMYCIN AND ETOPOSIDE CONTAINING COMBINATION CHEMOTHERAPY FOR RELAPSED HODGKIN'S DISEASE.

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Forty-four patients with relapsed or resistant Hodgkin's disease were treated with Adriamycin 40 mg/m^2 IV on day 1, vincristine 1.4 mg/m^2 IV on days 1 and 8, prednisolone 40 mg/m^2 orally days 1-8, etoposide 200 mg/m^2 orally days 1-4 according to the nadir white cell count, and bleomycin 10 mg/m^2 IV days 1 and 8 (HOPE-Bleo). Median age was 27 years (range 12-71). When stage was considered according to all sites currently or previously involved by Hodgkin's disease (cumulative stage) 26 patients (59%) had stage IV, 13 (29%) stage III, and 5 (11%) stage II disease; 33 (75%) had B symptoms. All patients had received previous chemotherapy and 18 (41%) had received two or more regimens. Twenty-six patients (59%) achieved CR and 10 (23%) PR. Median follow-up of surviving patients was 52 months (range 28-74). The median duration of CR was 22 months and median survival for all patients was 48 months. Eight patients remain in continuous CR: 6 of these were from a group of 19 patients who had relapsed from CR achieved by a single previous chemotherapy regimen. The HOPE-Bleo regimen was generally well tolerated, WHO grade I/II and III/IV toxicity occured as follows: leukopenia 41% and 23%; infection 16% and 22%; nausea and vomiting 53% and 7%; alopecia 21% and 50%; neuropathy 41% and 5%, there were two toxic deaths, one due to neutropenic sepsis, the other to acute peritonitis. The HOPE-Bleo regimen is an effective treatment for relapsed or resistant Hodgkin's disease and because of its low probability of carcinogenesis and infertility deserves further evaluation as primary treatment for Hodgkin's disease. There was a substantial proportion of durable CRs in patients relapsing from CR induced by primary chemotherapy which suggests that it may be unnecessary to expose such patients to the toxicity and risks of high dose salvage regimens incorporating bone marrow transplantation.

P 29 TREATMENT OF REFRACTORY HODGKIN'S DISEASE WITH HIGH DOSE CYTOSINE ARABINOSIDE AND MITOXANTRONE IN COMBINATION (HAM). RESULTS OF A CLINICAL PHASE II STUDY OF THE GERMAN HODGKIN STUDY GROUP.

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In the present study the activity and side effects of high-dose cytosine arabinoside (HD-Ara-C) and mitoxantrone (Mitox) (HAM) were evaluated in 32 patients with refractory Hodgkin's disease. Therapy consisted in HD-Ara-C 3g/m^2 q 12 hrs days 1 and 2 and Mitox 10 mg/m^2/day days 3-5. Subsequent escalations comprised 6 and 8 doses of HD-Ara-C on days 1-3 and 1-4, respectively, and 4 doses of mitoxantrone from days 2-5. Eighteen of the 32 patients (56%) responded with 5 complete and 13 partial remissions, 13 cases (31%) had refractory disease and 4 patients died from infectious complications. Ten of the responding 18 patients underwent subsequent autologous (n = 9) or allogeneic bone marrow transplantation. Seven of these cases are currently alive at 5+ - 22+ months, 6 of them without evidence of disease. From the remaining 8 patients, 3 are alive at 6+ - 19+ months, 2 in ongoing remissions of 2+ and 5+ months' duration. The median survival for all treated patients is 6,2 months. These data indicate that HAM has a significant activity in refractory Hodgkin's disease but also bears substantial side effects. Further application therefore requires modification in timing and dosage as well as the addition of hematopoietic growth factors (GM-CSF) to compensate especially for myelosuppressive complications.

P 30 HIGH DOSE CHEMOTHERAPY (HDC) WITH AUTOLOGOUS BMT (ABMT) IN 113 ADVANCED RESISTANT HODGKIN'S DISEASE PATIENTS. AN ITALIAN STUDY GROUP REPORT.

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Current primary treatment for untreated, advanced stage Hodgkin's disease may cure a high porportion of patients However, patients who fail a first line therapy do not have a favorable outlook. Patients refractory to/or relapsing soon after second and third line protocols are rarely cured and the prognosis is very poor. Between July 1981 and December 1989, 113 patients (36 females, 74 males, median age 25 years, range M - 51 years) were treated with HDC and ABMT as a treatment modality for advanced resistant Hodgkin's disease. 89 pts had B symptoms. 40 pts had progressive disease during alternating MOPP/ABVD protocol. 7 pts were in CR. 51 pts had a CR with first line therapy but later relapsed and all received salvage therapy; 16 pts achieved no response or progression ("resistant relapse"patients) and 35 responded partially or completely ("sensitive-relapse patients). HDC consisted of a modify CBV protocol: Cyclophospamide (3 g/mq/day for two days), Etoposide (300 mg/mq/d x 2 days) and Carmustine (300 mg/mg/day for two days). In the last 48 patients, the total doses of Etoposide and Carmustine were escalated to 250 mg/mq/day and 200 mg/mq/day, for 4 days and ABMT was given on day +7, after a rest period of two days. CR occured in 49.5% of patients with a median duration of 28 mo. and 26% of patients achieved PR with a median duration of 8 mo., for an overal response rate of 69.5%. 16 pts failed to respond and died. Toxicity was significant including infections, liver enzymes and alkaline phosphatase elevations while carmustine lung toxicity was present in 6 pts; all these 6 pts died. There were 13 other treatment-related deaths: 4 pts died of cardiac failure, 3 of unknown causes, 3 pts of candida pneumonitis, 2 of aplasia and one patient of viral hepatitis.

P 31 HIGH DOSE CHEMOTHERAPY (HDCT) AND AUTOLOGOUS BONE MARROW TRANSPLANTATION (ABMT) IN RELAPSED AND REFRACTORY HODGKIN'S DISEASE (HD)

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Despite combination of chemo and radiotherapy some patients with advanced HD have a bad prognostic. We performed HDCT (BCV regimen : BCNU 300 mg/m^2 D-7, CYCLOPHOSPHAMIDE 1500 mg/m^2 and ETOPOSIDE 125 mg/m^2 X 2 D-7 D-6 D-5 D-4) followed by infusion of cryopreserved bone marrow (22 pts) or peripheral stem cells (5 pts) in 27 patients with advanced HD. 12 pts were considered as refractory after at least two non cross-resistant chemotherapy regimens and radiotherapy in 8. 15 pts had a poor prognostic relapse in visceral sites (10 pts) and/or in irradiated lymph nodes (7 pts) after complete remission and they received chemotherapy before HDCT and ABMT. The mean time between diagnosis and transplantation was 34 months (8 to 107 months).
Before HDCT and ABMT, 4 pts had progressive disease and did not respond to HDCT and died from persistent HD 3 to 12 months post ABMT.
From the 23 remaining pts, 11 were in PR and 12 in CR after second or third line chemotherapy regimen before HDCT and ABMT. Median time to bone marrow recovery was 22 days. There was one toxic death with interstitial pneumonitis due to CMV infection. 3 months after HDCT and ABMT, 20 pts were in CR, 2 in PR. After CR, 5 pts relapsed from 6 to 18 months and 15 pts are in persistent remission from 8 to 34 months after ABMT. Survival is significantly better in patients with relapsed HD than in refractory pts.
At two years, the probability of survival was 70 % with a disease free survival of 60 %.
These results are encouraging in patients with bad prognostic factors but sill responding to chemotherapy.

P 32 HIGH-DOSE MITOZANTRONE AND ETOPOSIDE CONDITIONING IN ABMT FOR RELAPSED HODGKIN'S DISEASE.

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A percentage of patients with relapsed Hodgkin's disease (HD) now achieve long-term remission following ABMT. Anthracyclines are effective in HD but cardiotoxicity has previously precluded dosage escalation. Mitozantrone (MTZ) has reduced cardiotoxicity and we have now conditioned 6 patients with refractory HD for ABMT with high-dose MTZ (100-120 mg/m^2) and high-dose etoposide (2000 mg/m^2). Both agents were given by continuous infusion through a central venous catheter on alternate days in 2 divided doses. Plasma levels of MTZ were measured daily by ELISA assay.

Sex/Age	Dose MTZ/m^2	Day of ABMT	MTZ level at ABMT (ng/ml)	Days to neutrophil recovery	Days to platelet independence
M/39	100	+9	3.4	28	17
M/21	100	+7	7.8	24	27
F/25	120	+6	7.9	Death ARDS day +24	
F/24	100	+7	10.5	41	31
F/30	100	+7	NA	13	13
M/28	100	+9	3.1	21	29

(NA=not available)

Of 5 surviving patients 3 achieved CR and 2 PR. Delayed engraftment and graft failure occurred in the 2 patients with highest plasma MTZ levels at the time of marrow reinfusion. Peak MTZ levels occurred immediately post infusion and showed exponential decay with marrow toxic levels for 7 days. No cardiotoxicity was evident on ECG monitoring and MUGA scanning post-ABMT.

This regimen appears to be safe and effective in refractory HD and shall now be evaluated in a larger group of patients. Non-cardiotoxic anthracycline derivatives with a shorter in vivo half-life would permit earlier marrow reinfusion and subsequent engraftment.

ABSTRACTS - Fourth International Conference on Malignant Lymphoma, Lugano

P 33 ABMT IN PATIENTS WITH MORBUS HODGKIN - A RETROSPECTIVE EVALUATION OF 393 PATIENTS ACCORDING TO VARIOUS CRITERIA OF TRANSPLANTATION CENTRES.

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In our department, we investigated 306 randomly selected patients between the ages of 12 and 50 years for ABMT according to different criteria recommended by four well-known transplantation groups. Seattle recommends ABMT for all patients who fail MOPP while a group in UK suggests ABMT for patients resistant to primary therapy. Similar criteria are applied in Germany and Italy. However, all these groups describe patients with a rather short observation period so that the longterm outcome is not evaluable. The median observation period of our patients was 90 months. In our retrospective evaluation more than 50 percent of the patients with second line therapy achieved long term CR. The median survival time of high risk patients i.e. patients who had more than 3 chemo-therapy cycles was 135 months.
Because of these results with conventional chemo- and radiotherapy the question arises whether such a high risk procedure as ABMT is justified. We had to identify this small group of patients by a score relating to 14 well established risk factors. Because of the very bad outcome of patients having a score of more than seven ABMT is recommended as salvage therapy . Bone marrow harvesting should be carried out for all patients with a score over five.

P 34 HODGKIN'S DISEASE (HD) IN THE ELDERLY.

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Between 1968 & 1988, 52 elderly (age>60) patients (pts) with HD were evaluated at the Lahey Clinic (age range 60-88 years (yrs), median 68 yrs). They represented 22% of the HD population. Few underwent staging laparotomy. Elderly pts were predominantly male (62%), 50% had B symptoms (sx), and often had advanced stage HD (Stage I 17%, II 23%, III 15%, IV 44%). Twenty-seven per cent had HD limited to subdiaphragmatic sites. Stage I & II pts were primarily treated with extended field (EF) (mantle or inverted Y) radiotherapy; stage III and IV pts received combination chemotherapy (MOPP).

THe median follow up is 16 months (mo) (range 1 mo - 15 yrs). The mean absolute survival was 4 yrs with a median of 1.3 yrs. Seven pts are alive without evidence of disease (NED), 9 died NED, 31 died of progressive or recurrent HD, and 3 died of treatment complications. Two pts were diagnosed at autopsy and excluded from survival analysis. Pts with Stage I & II HD had a significantly better freedom from relapse (FFR) rate and survival rate (SR) than pts with Stage III & IV HD (median FFR 1.75 vs 1 yrs, p=.03; median survival 4.95 vs 1 yrs, p=.02). Asymptomatic pts had a better FFR rate and SR than pts with B sx (median FFR 21 mo vs. 8 mo, p=.01; median SR 5.09 yrs vs. .55 yrs, p<.01). Pts with nodular sclerosis and mixed cellularity HD had a significantly better median FFR rate and SR than pts with lymphocyte depleted histology (FFR 3.47 yrs vs. .51 yrs, p<.01; SR 4.55 yrs vs. .55 yrs, p<.01). Gender, erythrocyte sedimentation rate, and supra- vs. subdiaphragmatic presentation were not significant factors in predicting FFR or survival. Elderly pts with Stage I & II HD tolerate EF radiotherapy well; FFR rates may be improved by treating with subtotal lymphoid irradiation. Treatment programs for elderly pts with Stage III & IV HD and B sx should be individually tailored given the overall poor prognosis.

P 35 AGE (<50 vs > 50 YEARS) AS A PROGNOSTIC FACTOR IN 1624 PATIENTS WITH STAGE I & II HODGKIN'S DISEASE ENTERED IN EORTC CLINICAL TRIALS SINCE 1964.

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From 1964 to 1988, 1624 patients with clinical stage (CS) I-II Hodgkin's disease (HD) were treated on 4 consecutive prospective clinical trials. The age upper limit entry for these trials was 70 years. Treatments consisted in mantle irradiation (MRX) +/- vinblastine for 2 years (467 pts); subtotal nodal irradiation +/- vinblastine and procarbazine for 2 years (518 pts); total nodal irradiation (152 pts); or combined modality treatment associated MOPP x 6 and MRX (322 pts) or ABVD x 6 and MRX (165 pts). Moreover 508 (31%) patients underwent a staging laparotomy. 1486 (92%) patients were aged 49 years or less at diagnosis, and 138 (8%) were aged 50 to 70 years. Patients were prospectivelly followed and progressions, relapses, treatment side-effects, and death recorded. Data were up-dated December 1, 1989. Time at risk for progression, complication, and death started at treatment initiation. The Cox model was used to compare survival curves between the 2 age groups (< 50 and > 50 years) with adjustment on treatment and initial characteristics, such as sex, B symptoms, ESR, number of nodal areas involved, mediastinal involvement, and histology. At diagnosis, there were less females (p=0.05), more CS I (p= 0.001), less mediastinal involvement (p 0.001), and more NC histological type (p 0.01) in the group of patients aged 50 years or more. Response rates to initial therapy were similar in the 2 age groups, as were freedom from progression rates: at 5 years, 74% in the yougers and 72% in the olders. By contrast, the 10-year survival rate was significantly lower in the olders (47% vs 81%, p 0.001), with a relative risk (RR) of death (all causes) of 3.73 (p 0.001). By Cox analysis, age >50 years was found to be the most important prognostic factor for cause-specific mortality: RR-2.12 (p=0.002) for deaths as a consequence of disease progression; and RR-5.94 (p< 0.001) for deaths from other causes. After a progression/relapse occured, survival in older patients was very poor as compared to the youngers: 5-years survival rates 26% vs 61%, respectively (p 0.001). Older patients also developed more second malignancies: the 10-year cumulative proportions were 33% and 5% respectively (p < 0.001). For ANLL these proportions were 5% and 1% (p 0.01); for NHL they were 2% and 1% (p 0.20); and for solid tumors they were 28% and 3% (p 0.001). For other complications such as pericarditis, cardiac failure, ulcer, or bowel occlusion syndrome, there were no significant differences between the 2 groups. Patients aged 50 years or more represent a small proportion of CS I-II HD entered in prospective EORTC trials. Although the response rates were similar to those observed in youngers, patients 50 years or more appear to be at higher risk of death, partly as a consequence of the poor rescue rate that can be reached after progression/relapse, and partly as a consequence of second malignancy risk. These findings should be taken in consideration when therapy is planned in these patients.

P 36 HODGKIN'S DISEASE IN ELDERLY PATIENTS: THERAPEUTIC APPROACH AND CLINICAL OUTCOME.

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From January 1982 to June 1989 clinical data from 523 untreated patients with Hodgkin's disease were recorded in the Piemonte Hodgkin's Disease Study Group (PHDSG) Registry. 394 (75%) patients were enrolled in the HO82 and HO86 protocols, while 129 (25%) entered an alternative staging procedure or treatment program. 58 (11%) patients were older than 65 years. Clinical stages and presence of B symptoms were similar both in patients over 65 and in younger ones. Histology was statistical different between the two groups, with a predominance of mixed cellularity versus nodular sclerosis in elderly people (MC: 63% vs. 31% - NS: 30% vs. 58% - p=0.001). Only 41% of the elderly group were enrolled into the therapeutic protocols, compared with 80% of younger group (p=0.0). Elderly patients had also an higher incidence of subsequent protocol violations/interruptions due to bad compliance or toxicity (34% vs. 10% - p<0.01). So far 20 elderly patients have died, with a high incidence of toxic deaths (45%).
No differences were seen in terms of complete remission, disease free survival, overall survival or event free survival between elderly patients treated according to the protocols and those who entered an alternative program. Results for age groups are as follows:

	<65 years	>65 years	p value
complete remission	87 %	62 %	0.000
8-yr dis. free survival	71 %	58 %	0.859
8-yr survival	71 %	53 %	0.001
8-yr event free survival	56 %	33 %	0.001

Our data show that elderly patients achieve complete remission less frequently than younger ones, mainly due to the high incidence of bad compliance and toxicity. However disease free survival is not worse than that of younger patients. Alternative regimens with lower incidence of adverse effects could improve the outcome of this group of patients.

P 37 Patterns of survival in Hodgkin's Disease (HD) following relapse in patients treated at a single centre over a 21 year period.

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520 previously untreated adults with confirmed HD (91 stage I, 177 stage II, 147 stage III and 105 stage IV) were treated at St. Bartholomew's Hospital between 1968 and 1984 with what was considered to be appropriate therapy (extended field irradiation or MVPP based chemotherapy). The overall median survival is 18.3 years. Clinical remission (R = complete remission plus complete remission, uncertain; ref: Lister et al J Clin Oncol 1989;7:1630-1636) was induced in 442 (85%); the median survival of remitters has not been reached. Fifty eight patients achieved responses less than R with initial therapy (partial response) or had progressive disease, the median survival of this group being 1.4 years. 20 patients died before completion of therapy. With further therapy, R was subsequently induced in 10; 5 are still alive, 5 have died between 1.9 years and 14.3 years. 146 of the remitters following initial therapy have relapsed over a median follow up period of 13 years (minimum 5 years). 143 patients were treated following relapse (105 chemotherapy, 28 radiotherapy, 6 combined modality treatment and 4 surgery). Second remission was induced in 109/143 (76%). There was a strong trend towards better second remission induction in patients whose first remission was longer than 1 year ($p = 0.06$). The median duration of second remission is inferior to first remission duration ($p < 0.001$). There was no correlation between duration of first remission and survival following relapse or with duration of second remission. There is no significant difference in duration of second remission between patients who were initially treated with radiotherapy or chemotherapy. The median survival following second remission is 12.0 years, being the same for patients with initially localized disease (stages I and II) treated with radiation alone and for patients with advanced HD (stages III and IV) treated with chemotherapy. Survival after relapse is significantly better for patients under 50 years at the time of relapse ($p < 0.001$). 46 patients relapsed a second time, third remission being reinduced in 22, the median survival of the remitters being 5.1 years. These results illustrate the importance of prolonged follow up in defining the clinical course of patients with HD and are vital for planning experimental chemotherapy at the time of treatment failure or relapse.

P 38 Second malignancies following Hodgkin's Disease.

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During 1968-1985 1177 patients with Hodgkin's disease (HD) from all parts of Norway were admitted to The Norwegian Radium Hospital. 68 patients developed a second primary cancer ≥ 1 year after diagnosis of HD and 6 of them subsequent developed still another cancer rendering the total number of second primary cancers 74. These included 56 solid tumors, of which 10 were lung cancers, 9 non-Hodgkin's lymphomas (NHL) and 9 acute non-lymphocytic leukemias (ANLL). The median intervals between the diagnosis of HD and that of second lung cancer, NHL and ANLL were 10.4, 7.0 and 5.8 years, respectively. The overall relative risks (observed/expected ratio) of developing lung cancer, NHL and ANLL were 3.3, 8.4 and 24.4, respectively. Nine of ten cases of lung cancer arose in patients treated with radiotherapy (RT) and were located within radiation field. For the development of NHL, no particular therapy received dominated. Only 4 of 9 patients were heavily treated. (Either RT to both sides of the diaphragm, combination chemotherapy (CCT) more than 6 cycles or a combination of RT to one or both sides of the diaphragm + CCT used cyclically). All the patients that developed ANLL had received CCT with alkylating agents and Procarbazine. Eight of 9 patients were heavily treated. 60 %, 33 % and 22 % of the patients with lung cancer, NHL, and ANLL respectively had splenectomy. This does not support the hypothesis of an increased risk of developing ANLL after splenectomy. The treatment trend of the Norwegian Radium Hospital to use radiotherapy rather than agressive chemotherapy may explain the rather low numbers of second ANLL. The increased risk of developing a second primary cancer after treatment of HD will be discussed.

P 39 THE ROLE OF PREGNANCY IN THE PATHOGENESIS OF HODGKIN'S DISEASE: A CASE-CONTROL STUDY

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To evaluate the role of pregnancy in the etiopathogenesis and in the clinical course of Hodgkin's disease (HD), a case-control epidemiological study included a series of 165 women aged 17 to 50 years at the time of diagnosis. Data on socio-economic status in childhood, and on parity were obtained from 120 patients who are still alive and from the relatives of 45 deceased patients, as well as from 321 population-based controls matched by residency and year of birth. The data on the parity of controls were considered only till a woman reached the age at diagnosis of her corresponding HD patient. When compared to controls, patients tended to have their first child at an older age, possibly attributable to their slightly longer education; on the other hand, a non-significant excess of nulliparous women was seen in the control group. Within the first 6 months after delivery, HD was diagnosed in 14 cases, a figure which is significantly higher ($p<0.05$) when compared to expected 6.5 cases, or to occurence of HD in other 6-month intervals after delivery. The clinical course of HD diagnosed in pregnancy or soon after delivery did not seem worse than otherwise. After treatment and in complete remission, 31 children were born to 25 mothers; only one of these patients later died of disease progression. We conclude: 1. previously reported protective effect of pregnancy on the risk for HD (Abramson et al, JNCI 61:307, 1978) could not be confirmed; 2. puerperium may be a period of an enhanced expression of HD; 3. pregnancy does not have an adverse influence on patients in remission.

	patients		controls
No.	165		321
nulliparous,%	35.7		45.2
nulliparous, age>30 years,%	19.2		12.2
children born prior to age of dx	167		387
mean age at first delivery, years	25.0		22.5
diagnosis of HD[1] during pregnancy	5		9
diagnosis of HD[1] during puerperium[2]	14	$p<0.05$	13

[1]for controls, reaching the age (in months) of her corresponding HD patient
[2]within 6 months after delivery

P 40 INCIDENCE OF "SECON TUMORS" IN PATIENTS TREATED FOR HODGKIN'S DISEASE: An analysis of 1060 cases.

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In recent years, owing to the better knowledge in the field of oncology and to the use of more adequate and aggressive diagnostic and therapeutic protocols better results, in terms of disease free and overall survival, have been achieved in patients suffering from malignant disease. At the same time, the incidence of undesired "jatrogenic related", acute or late, effects increased: some out of those effects are compatible with a good quality of life, whereas others may be life-threatening. Among those latter effects, "second tumors" are particularly important.
MATERIALS, METHODS and RESULTS: We reviewed the clinical records of 1060 patients treated for Hodgkin's disease and followed between 1960 and 1990 at the University and Hospital Departments of Radiotherapy. The 0.2% of "second tumors" appeared before the diagnosis of HD, the 0.4% was synchronous and the 3.8% was metachronous. No correlation was found between the incidence of the second tumors and the following clinical findings: sex, age, histology, clinical and pathological stage, laparosplenectomy, number of involved nodes, sites of involved areas, bulky disease.
The incidence of 2nd tumors was 5.5% in the group of patients treated with RT alone, 2.7% in the group treated with RT plus CHT and 3.4% in the group treated with CHT alone.
2.17% of 2nd tumors appeared in the irradiated area and 1.1% out of the irradiated volume.
When the 2nd tumor was a "solid tumor" the mean latent period since treatment was 10.1 years for patients treated with RT alone, 9 years for patients treated with RT plus CHT and 3 years for patients treated with CHT alone.
When the 2nd tumor was a "liquid tumor" the mean latent period was 5.5 years for patients treated with RT plus CHT and 1 year for the patients treated with CHT alone.

P 41 HIV-ASSOCIATED HODGKIN'S DISEASE(HIV-HD) CLINICAL OUTCOME. THE EXPERIENCE OF THE FRENCH REGISTRY OF HIV-ASSOCIATED TUMORS. S.Roithmann. B.Desablens. B.Dupont. J.Dumont. M.Gentilini. B.Tallian. J.M.Tourani. J.M.Andrieu. Oncology-Hematology. Laennec Hospital - 42. rue de Sèvres - 75340 Paris - CEDEX 07 - France.

From 1/1987 to 11/1989. 34 patients(pts) with HIV-HD were recorded by the registry. Data from 28 pts were available for clinical outcome analysis. Initial characteristics were: sex M 25 F 3. age 25-50. median 30: risk groups homosex 11. IVDA 11. both 1. others 5: HIV clinical status asympt 14. PGL 7. ARC 5. AIDS 2. CD4 cell count (19 pts) median 270/ul (99-800/ul). HD histology LP 1. NS 13. MC 10. LD 2. unclassified 2: HD clinical stages(CS) I 4. II 5. III 11. IV 8 (liver 5. bone marrow 5. CNS 1). Treatment: radiotherapy 1. chemotherapy 16 (MOPP and/or ABVD. 3-6 cycles. median 4). chemo plus radiotherapy 11. Follow-up: 4 to 52 months. median 13. 2 pts(CS IIB and IV) progressed under treatment. 24 pts entered in complete remission(CR).1 pt relapsed(CS IV. 7 months after therapy). 2 pts were not evaluable due to early death from opportunistic infection(O.I.).Out of the 26 initially non-AIDS patients,12 developed AIDS: 8 pts during HD therapy (O.I. 6. Kaposi's Sarcoma(KS) 1. O.I.+KS 1). and 4 pts(O.I.) within the 3 months following treatment. Overall 2-year actuarial survival was 48% (CS I+II 67%. CS III+IV 39%). Freedom from progression rate (events are initial failure and relapse) was 84% (CSI+II 88% and CS III+IV 79%). AIDS progression rate was 58% at 10 months and stable thereafter.Conclusions: 1. Treatment of HIV-HD gives a particularly high rate of CR. with a low relapse rate. 2. Infectious complications are extremely frequent during therapy and shortly after. 3. These findings should be taken into account for future prospective trials and individual management of HIV-HD.(Supported by AREMAS and Ligue Nationale contre le Cancer).