ABSTRACTS

PRESENTATION BY TITLE ONLY

ABSTRACTS - Fourth International Conference on Malignant Lymphoma, Lugano

T 1 DOCTORS DELAY AND SURVIVAL IN MALIGNANT LYMPHOMA.

R. Obrist, M. Klöti, and J. P. Obrecht, Div. of Oncology, Dept. of Internal Medicine of the University, Kantonsspital, CH-4031 Basel, Switzerland

Only little and contradictory data are available on the impact of doctors delay (DD) on cancer patient (pt) survival. We therefore retrospectively evaluated the interval between the first doctor - patient contact and the establishment of a final histological diagnosis in 1845 pts, who were seen and died at our outpatient clinic between 1972 and 1987. The correlation of DD with age, gender and survival was analyzed for Hodgkin's disease (HD, 67 pts), Non-Hodgkin's lymphoma (NHL, 126 pts) and multiple myeloma (MM, 45 pts). Median DD for all cancer types was 31 days, 46 days for HD, 37 for NHL and 50 for MM. No significant differences were seen in DD for pts older than 65 years as compared to those younger than 65 years in HD and NHL (HD, 51/42; NHL, 38/36), whereas in MM a strong trend was obvious (59/41). In contrast to the overall population, where no difference was obvious, men with NHL had their final diagnosis established 0.3 months earlier than women. This difference is not statistically significant. In pts with NHL the median survival was 37 months with a DD of less than 30 days, 31 months with 31 - 180 days and 28 months with more than 180 days of delay (for HD the respective median survival was 52/71/24 months and for MM 37/35/32 months). These results indicate that outcome of NHL and MM pts is only marginally dependent on DD, whereas in HD a steep drop is observed with delays in excess of 180 days. The lack of effect in the former groups may be due to selection of a prognostically bad subgroup (those, who have died), or an irrelevant effect of an earlier (or later) begin of therapy. In addition, the retrospective nature of the analysis may further obscure reality, e.g. by shifting histological diagnostic criteria and changing therapies during that long time interval.

T 2 SPORADIC BURKITT'S LYMPHOMA AND VARIANT CHROMOSOMAL TRANSLOCATIONS. OUR RESULTS OF A CYTOGENETIC STUDY.

E.Stojimirović, I.Vuković, V.Deretić. University Children's Hospital, 11000 Belgrade, Yugoslavia

In patients with Burkitt's lymphoma specific chromosomal abnormalities are significant in the study of the activating process of myc oncogen and initiation of oncogenesis. In 1972 G.Manolov and Y.Manolov have discovered 14q+ anomaly in Burkitt's lymphoma which Zech confirmed as reciprocal translocation t(8:14)(q 24:q32) in 1976. About 80% cases of Burkitt's lymphoma show this translocation. Other 15% reveal t(8:22)(q 24:q 11), while t(2:8)(q 11:q 24) is found in only 5% (C.Groce et al., 1986). The authors present the results of a cytogenetic study in children with Burkitt's lymphoma. Classic bone marrow culture and G band technique were used. The assessed frequency of a rare variant of 2/8 translocation was considered significant. In the delevopment of the cytogenetic markers of the disease geographical influence has been suggested as a possible cause.

T 3 MOLECULAR ANALYSIS OF A CHRONIC T-CELL LYMPHOPROLIFERATIVE DISORDER WITH NEUTROPENIA

M.F. Fey, A. Tobler, G. Brun del Re, Institute of Medical Oncology and Central Haematology Laboratory, Inselspital, 3010 Bern, Switzerland

Chronic T-cell lymphoproliferative disorders (T-LPD) usually represent clonal neoplastic processes. While T-cell surface markers are not suitable to demonstrate clonality in T-LPD, this is now possible by immunogenotyping with T-cell receptor (TCR) gene probes. We studied the clonal composition of T-cells in an unusual case of T-LPD diagnosed on morphology as a T-chronic lymphocytic leukaemia or a Non Hodgkin's lymphoma (IWF A).
A 60yr-old male patient had recurrent fever, hepatosplenomegaly, lymphadenopathy, lymphocytosis (mean 5.3x109/l, range 0.9-10.0), polyclonal increase of IgG and cryoglobulinaemia (monoclonal IgMλ anti-IH) and severe chronic neutropenia (mean 0.1x109/l, range 0-0.6) complicated by purulent anal fistulas. Infiltrates of small to medium sized non-granular lymphoid cells were noted in bone marrow (20-80%), lymph nodes and spleen. Prednisone pulses resulted in transient increases of neutrophil counts, but cyclophosphamide and vincristine failed to induce remission. The patient died 4 years after the initial diagnosis.
Immunophenotyping of lymphocytes in blood and bone marrow showed a 1.5-2.4 x increase in absolute T4 and T8-counts, but a normal T4/T8-ratio (1.85). There was preferential activation of T8-cells (HLA-DR+T-cells: T4+ 13%, T8+ 35%). Natural killer cells were not increased (0.2-0.3x109/l). Southern blot hybridisation of *Bam* HI, *Eco* RI and *Hind* III digests of DNA from peripheral blood leucocytes (containing less than 2.5% granulocytes) with molecular probes for Ig genes as well as TCR β, γ and δ genes revealed no evidence of clonal gene rearrangements.
Whilst the clinical course and the morphology suggested a clonal lymphoid malignancy in this case, surprisingly, molecular analysis indicated a polyclonal T-LPD of unknown cause. Immunogenotyping thus permitted this unique case to be clearly distinguished from T-LPD reported as clonal in the literature, such as Tγ-LPD or other types of mature T-cell leukaemias.

T 4 CYTOGENETIC MARKERS IN PERIPHERAL T-CELL LYMPHOMA

Anna Montaldi*, Teodoro Chisesi**, Vincenzo Stracca-Pansa***, Paola Celli*, Michele Vespignani** and Mario Stella*
* Service of Immunology, Blood Transfusion and Human Genetics Center for the Human Genetics
** Division of Hematology *** Division of Patology
Ospedale "San Bortolo" Vicenza ITALY

Histological, immunological and cytogenetic analysis on the same neoplastic tissue have been performed on eight patients with peripheral T-cell lymphomas (PTCL).
All cases, except the two in which the diagnosis of T helper chronic lymphocytic leukemia (Thp-CLL) on peripheral blood and bone marrow files was made, were classified as PTCL, according to the Working Formulation and expressed CD3 surface antigen.
Molecular study showed, in the six patients examined, rearrangement of the β-chain of the T-cell receptor.
Anti-HTLV-I antibody and/or monoclonal integration of HTLV-I proviral DNA were not found.
Cytogenetic studies were performed on specimens of lymph node for the six patients without bone marrow infiltration; for the other cases, with bone marrow infiltration, chromosomal analysis on specimens of bone marrow were done.
Six out of eight patients examined had complicated abnormal chromosomes such as derivatives and markers of unknown origin whereas two had a normal karyotype.
Three chromosome markers were present in the malignant cells from several patients: the first is a rearrangement of band 14q11.2 ,the second a trisomy for the long arm of chromosome 8, the third a rearrangement of band 6q21.
Although we have analyzed only eight patients, four cases showed rearrangements of band 14q11.2 (three had inv(14) (q11.2;q32), one t(14;19)(q11.2;p13)). It seems to be well documented that inv(14) is a characteristic T-cell marker and that the break in q11.2 is closely correlated with malignant T-cell disorders.
Combining molecular and cytogenetic studies, it has been shown that the α-chain gene of the T-cell receptor was rearranged in inversions and translocations at 14q11.2. Numerical or structural abnormalities of chromosome 8 were observed in five of our patients. Partial or total trisomy 8 in T-cell diseases has also been observed by other authors. It seems reasonable to assume that genes that are of impor-tance for the development or early progression of T-cell tumours are located on chromosome 6q (21). This assumption could be explained by assuming that trisomy 8q affects the cellular proliferative capacity, allowing to develop by the gain of chromosomal material involved in neo-plastic transformation. Three cases involved the chromosome 6 with breakpoint at band q21. In this region (6q21->q22) had mapped the oncogene ROS1, with tyrosine phosphokinase activity, and functional similarities with EGF receptor. It is demonstrated that only a limitated number of breakpoints were regularly involved in chromosomal aberrations in human neoplasia, and postulated that these regions might contain genes of special importance for the carcinogenic process. The data indicated that breakpoints of malignant diseases affecting similar cell types might cluster to specific chromosomal regions. Caryological studies of more patients with peripheral T-cell lymphomas will be required to confirm the association of those breakpoints, either singly or in combination, with development of these malignancies.
Our data indicate that breakpoints of malignant diseases affecting similar cell types might cluster to specific chromosomal regions, and that can be helpful in recognizing and classifying PTCL.

This work was supported by grant from the Italian Association for Research on Cancer (AIRC, Progetto Finalizzato "Nuove strategie terapeutiche").

T 5 BCL-2 REARRANGEMENTS AND t(14;18) IN 4 PATIENTS WITH B-ALL.

M.H. Kramer, S. Raghoebier, G.C. Beverstock, D. de Jong, G.J.B. van Ommen, G.J. den Ottolander, R. Willemze, Ph.M. Kluin, J.C. Kluin-Nelemans. Dept. of Hematology, University Leiden, The Netherlands

The chromosomal translocation t(14;18) characterizes >90% of the follicular lymphomas. The BCL-2 gene at chromosome 18q21 is a proto-oncogene involved in the translocation t(14;18), which results in its subsequent deregulation of expression. Assumably, this translocation already takes place at the pre-B cell stage during immunoglobulin heavy chain gene rearrangement. Recently, we encountered 4 patients with B-cell acute lymphoblastic leukemia (ALL) in which 18q21 rearrangements and other chromosomal abnormalities were found. In three patients, morphology and immunophenotype suggested Burkitt-like ALL except for the lack of immunoglobulin expression. This absence was explained by involvement of both IgH genes in chromosomal translocations or deletions.

	cytogen.	phenotype	morphology and comments
man 44 yr	t(14;18) t(8;14)	CD10+,CD19+ TdT+, sIg-	L2/3 clonally related follicular lymphoma (composite lymphoma)
man 33 yr	t(14;18) 14q+ other abn.	CD10+,CD19+ TdT-, sIg-	L3 paratrabecular follicle center cell lymphoma with areas of Burkitt-type lymphoblasts
man 59 yr	t(14;18) -14	CD10+,CD19+ TdT-, sIg-	L3
man 35 yr	t(14;18) t(8;14)	CD10+,CD19+ TdT-, sIg-	L3

Three patients died within six months after diagnosis and standard induction chemotherapy. One patient is in remission three months after induction chemotherapy. In conclusion, ALL with translocation t(14;18) may occur more frequently than previously described, and must be considered in cases with L3 morphology and absence of immunoglobulin-expression. This type of ALL seems to have a extremely poor prognosis.

T 6 THE USE OF NUCLEAR ANTIGEN EXPRESSION IN CELL CYCLE ANALYSIS OF MALIGNANT HEMATOPOIETIC CELLS.

G. Roos, G. Landberg, J. Lindh. Departments of Pathology and Oncology, University of Umeå, S-90187 Umeå, Sweden.

Cell cycle analysis of malignant lymphomas has previously shown that the fraction of S-phase cells is an independent prognostic factor. More detailed cell kinetic information of malignant hematopoietic disorders is needed to better evaluate and understand tumor progression and respons to treatment. For this purpose we studied the expression of two proliferation associated nuclear antigens using flow cytometric (FCM) multiparameter analysis.

Hematopoietic cell lines and cells from non-Hodgkin's lymphomas were studied after fixation in cold ethanol or after detergent treatment only. The S-phase related expression of proliferation cell nuclear antigen (PCNA), also called cyclin, was detected using an autoantibody and a fluoresceinisothiocyanate-labeled anti-human antibody. The Ki-67 antigen, which is increasingly expressed in cycling cells during the S-phase and with a maximum in the M-phase, was detected using a monoclonal antibody and a phycoerythrin-conjugated anti-mouse antibody. These stainings were combined with a DNA stain (7-amino actinomycin D) and the three fluorochromes were simultaneously recorded by a FACScan flow cytometer (Becton-Dickinson) and data in list mode were analyzed using the FACScan software.

Four cell populations, representing G_1, S, G_2 and M, could be demonstrated in the cycling cells in cell lines as well as in most lymphomas. Also, G_0 cells could be discriminated from G_1 cells. Low grade malignant lymphomas showed mainly G_0 cells and a small fraction of cycling cells. High grade malignant lymphomas had a larger fraction of cycling cells and S-phase cells were easily distinguished from cells in other cell cycle phases.

By this technique valuable cell kinetic information can be obtained using a simple triple staining procedure.

T 7 KI 67 ANTIGEN IS NOT ALWAYS EXPRESSED IN PROLIFERATIVE LYMPHOID CELLS.

N. SHEN, M. FFRENCH, F. BERGER, P.A. BRYON. Laboratoires de Cytologie analytique et d'Anatomie Pathologique, Hôpital Edouard Herriot, LYON, FRANCE.

Ki 67 antibody is known to recognize the proliferative compartment of a cell population. We report a case of NK-cell CD 56 and CD4 positive malignant lymphoma. It was classified as diffuse mixed according to the Working Formulation and numerous mitoses were observed on lymph node biopsy.

A double immunoenzymatic staining on frozen section with CD56 antibody (Leu 19) recognizing malignant cells (APAAP technique) and with Ki 67 antibody (immunoperoxydase technique) was performed. A labelling by Ki 67 antibody was observed on reactive non malignant cells while less than 5 % of malignant cells were marked.

A cell suspension of the same lymph node was studied by flow cytometry after a double staining of DNA by propidium Iodide and CD56 by immuno fluorescence. A high proliferative activity of malignant cells was observed, with a percentage of cells in S phase at 16 %.
This discrepancy illustrates a tissue dependance of the labelling level by the Ki 67 marker which may not be ignored.

T 8 MDR PHENOTYPE IN 25 PTS. WITH CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) AS DETECTED BY IMMUNOFLUORESCENCE (FACS) AND NORTHERN BLOT ANALYSIS.

G.Wulf, H. Kluding, A.D.Ho and W. Hunstein. Med.Klinik and Poliklinik V, Hospitalstr.3, 69 Heidelberg, Germany

Multi Drug Resistance (MDR) is closely related to overexpression of a plasma membrane associated glycoprotein (gp 170), which functions as an efflux pump for various chemotherapeutic agents. It has been suggested that an increased level of gp 170-expression is responsible for the development of chemotherapy resistance in initially responsive tumors. Acquired resistance is a problem especially in the treatment of Non-Hodgkin-Lymphomas of low malignancy. We therefore studied gp 170-expression in 25 pts. with Chronic Lymphocytic Leukemia (19 B-CLLs, 3 Prelymphocytic Leukemias, 2 Hairy Cell Leukemias and 1 Plasma Cell Leukemia). At least 7 pts. were still untreated. Methodology included flow cytometric detection (FACS) of indirect immunofluorescence with Moabs c219 and JSB-1 and Northern Blot analysis of mRNA expression for gp 170. FACS analysis showed, that the lymphocytes of 24 out of 25 pts. were positive with the Moabs c219 and JSB-1, 1 was negative (B-CLL, still untreated). To further subdivide the MDR phenotype in CLLs we tested the pts.´cells with Moab 494 (kindly provided by G.Bradley, Ontario Cancer Institute, Toronto, Canada), which in contrast to Moabs c219 and JSB-1, is specific for the MDR3 gene product. Northern Blot analysis of the mononuclear cells of 19 of the CLL-pts. using a MDR3-probe (5´ 1.02 kB fragment of the human mdr3 cDNA clone 3.27 (van der Blick et al., Gene 1988;71:401-411)) showed, that 9 pts. were MDR3-posistive, while 10 were negative. Why gp 170-expression with c219 and JSB-1 was detectable in all but one pts.´ lymphocytes regardless of stage and pretreatment, while normal control lymphocytes were negative, is not clear at the moment. Possibly gp 170-expression does not determine the responsiveness of these tumor cells to chemotherapy and the acquisition of resistance in CLL-pts. might be due to mechanisms independent of gp 170-expression.

ABSTRACTS - Fourth International Conference on Malignant Lymphoma, Lugano

T 9 LEVELS OF myc PROTEIN, AS ANALYZED BY FLOW CYTOMETRY, CORRELATE WITH CELL GROWTH POTENTIAL IN MALIGNANT B-CELL LYMPHOMAS.

H. Holte, T. Stokke, E.B. Smeland, H.K. Blomhoff, O. Kaalhus, S. Kvaløy and R. Ohlsson. Institute for Cancer Research, N-0310 OSLO 3, Norway

We have analyzed c-myc protein expression during the cell cycle in malignant B-cell lymphomas by dual flow cytometric detection of a fluoresceinated polyclonal anti-myc antibody and propidium iodide which binds stochiometrically to DNA. The data obtained were correlated to other parameters of cell activation such as histopathological grading, expression of the activation antigen 4F2, light scatter (proportional to cellular volume), DNA synthesis and percentage of S-phase cells. The c-myc protein level was strongly correlated to parameters of DNA-synthesis/content. In addition, the oncoprotein level was largely unvarying from the late G_1 phase through the rest of the cell cycle in both malignant cells and normal purified B cells stimulated to proliferate in vitro.

T 10 DIFFERENT TUMOR BIOLOGY BETWEEN PERIPHERAL T-CELL LYMPHOMA AND DIFFUSE B-CELL LYMPHOMA-- IMPLICATION ON TREATMENT POLICY

A.L. Cheng, I.J. Su, C.H. Wang, et al. Division of Hematology-Oncology, Department of Internal Medicine and Department of Pathology, National Taiwan University Hospital, Taipei, Taiwan, R.O.C..

To test if immunophenotypes could be of use in deciding treatment strategy for non-Hodgkin's lymphoma(NHL), 42 cases .of peripheral T-cell lymphoma(PTCL) and 46 cases of diffuse B cell lymphoma(DBCL), consecutively admitted between 1983 and 1989, were reviewed. Under homogeneous chemotherapy, complete remission(CR) rates were 59% and 60% for PTCL and DBCL, respectively. PTCL had an overall survival worse than DBCL($p<.01$). Grade-to-grade comparisons revealed a trend toward poorer survival of PTCL, especially in the intermediate grade. Early death within one year of diagnosis occurred in 37% and 13% of PTCL and DBCL, respectively ($p<.05$). Major causes of early death in PTCL were primary failure, sepsis and hepatic failure. Relapse rates for complete responders were 25% and 48% for PTCL and DBCL, respectively ($p=.15$). Induction of second CR was achieved in 17% of PTCL and 77% of DBCL ($p<.05$); survival after relapse was also better in DBCL ($p<.05$). Long survival after relapse was often possible in DBCL, but not in PTCL. For patients who did not obtain a rapid remission in 4 courses of induction chemotherapy, the outcome was significantly perturbed only in PTCL ($p<.025$). We conclude that DBCL represents the extension of a continuous spectrum from their follicular/low grade counterpart, and retains to some extent, the clinical features of higher relapse rate, better retreatability, better survival after relapse and less importance of a rapid remission. On the other hand, PTCL presents a classical picture of aggressive lymphoma, for which prognosis is highly dependant on a rapid remission induced by intensive chemotherapy.

T 11 Functional Antigens and Clinical Pictures in Adult Non-Hodgkin's Lymphoma (NHL).

M ITAMI, T TAKENOUCHI, J TAMARU, K HARIGAYA, A MIKATA. Department of Pathology, Chiba University School of Medicine, 280 Chiba, JAPAN.

Various functional antigens expressed on the surface of NHL cells are thought to have roles in forming clinical features through the cell-cell interactions. To clarify this, we studied the relationship between immunohistochemical phenotypes and clinical course. [Materials and Methods] We selected 24 monoclonal antibodies which recognized well known functional molecules and immunostained fresh frozen materials obtained from 46 adult NHL cases for such antigens. [Results] 1. Tumor cells displayed aberrant antigen combinations not seen in normal counterparts. 2. Mu-chain and CD25 (IL-2 receptor) expression correlated significantly with bone marrow involvement ($p<0.02$, $p<0.09$ respectively) and clinical stage ($p<0.08$, $p<0.03$, respectively). 3. No relation was observed between LFA-1 (adhesion molecule) expression and clinical stage, while bone marrow involvement tended to occur in the patients without LFA-1 expression. 4. B2 (CD21) and Ki-67 have significant correlation with serum LDH value ($p<0.003$, $p<0.02$ respectively). 5. The expression of Ki-67 more than 35 % of the tumor cells indicated unfavorable prognosis ($p<0.03$). 6. The patients without B2 expression had tendency to show unfavorable prognosis. 7. Intranuclear c-fos expression had no significant correlation with the prognosis and clinical pictures. [Discussion] The bone marrow involvement was found to be associated with mu, CD25, and LFA-1 expression. Also we found the positive relationship between the level of serum LDH and Ki-67, B2 (CD21). From this clinicopathologic study, some functional antigens expressed on the surface of lymphoma cells may play some roles in the development of specific clinical courses.

T 12 CLINICAL AND HISTOPATHOLOGICAL FEATURES OF B-CLL AND LOW-GRADE B-CELL LYMPHOMAS: A COMPARATIVE ANALYSIS.

F.d'Amore', L.Agertoft, N.T.Pedersen', B.E.Christensen'
'Dept. of Haematology, Odense University Hospital, Odense, DK 'Dept. of Pathology, Odense University Hospital, Odense, DK

ABSTRACT

In spite of the advent of advanced modern investigation techniques the clinical hæmatologist and the pathologist may in some cases still find it difficult to differentiate among low-grade B-cell malignancies. We here present a comparative analysis of the clinical and histopathological features of 91 consecutive cases of B-CLL and 109 consecutive cases of low-grade B-cell lymphoma (LL) diagnosed in the period 1984-1988. Twenty-eight % of patients with LL and 3% of those with CLL were aged < 50 years. Male to female ratios were respectively 0,7 and 1,7. Disseminated disease (stage IV) was found in 61% and localized disease (stage I) in 18% of cases with LL. Using the International Staging System, 63% of CLL patients were in stage A, 24% in stage B and 13% in stage C. The majority of patients in stage A (77%) were over the age of 60 and the male to female ratio in this group was 1,7. The pattern of lymphnode involvement and the occurrence of clinically detectable splenomegaly was similar for CLL and LL. The mean leukocyte (%lymphocyte) count in the peripheral blood was 108 x 10^9/l (86%) for CLL with 4% of cases having <15 x 10^9 leukocytes/l and 9 x 10^9/l (23%) for LL where 5% of cases had>15 x 10^9 leukocytes/l. Serum lactate dehydrogenase activity was elevated (<450U/l) in 30% of patients with LL and in 35% of patients with CLL. There was clinical evidence of hæmolysis associated with a positive direct Coomb's test in respectively 2 and 9% of cases. Paraproteinemia, mostly of IgM type, was found in 7% of LL cases and 13% of CLL cases. Furthermore results of a comparison of bone marrow infiltration patterns will be shown as well as a clinicopathological characterisation of the young patient population (<45 years) virtually only present in the LL group.

T 13 *A PREVIOUSLY NOT DESCRIBED, NON BLASTIC, NON BLASTOID, B-MEDIUM SIZE CELL LYMPHOMA.*

G. Mathé, J.L. Misset & M. Delgado. DMSIT & ICIG, Hop. Paul-Brousse, Villejuif, France.

Between 1976 and 1989, we have observed 13 cases of a yet undescribed lymphoma. 1) Its cells are of homogenous medium size; nuclei are not cleaved; chromatin is neither blastic nor blastoid; cytoplasm is not hyperbasophilic, not ribosome rich, and not vacuolized). 2) The immunologic cell phenotype is SIgM+ or G+ and EBNA-, and the serology is EBV-CMV-, HIV (1 and 2)-. 3) The histologic pattern is always diffuse. The last cases were shown to be CD_5+ and carrying chromosomal abnormalities: case 1, t (11;14), (q^{13}; q^{32}) and -19; and case 2 was del. (8) (q^{23}), -19 and -17. The molecular study showed no rearrangement of c-myc oncogene, HTLV-1 and EBV-, two rearranged bands of the heavy-chain immunoglobulin genes (JH) of t (11;14) with two putative oncogenes (Bcl-1, ets-1). This lymphoma mainly affects adults (contrary to endemic Burkitt's tumor which affects young children, and non endemic Burkittoid NHL which most often affects young adults or HIV+ subjects). It predominates at the age of 40-50 years. It is most often rapidly converted into a leukemic NHL, the cells of which nearly resemble those of the so-called Galton's "prolymphocytic" leukemia, which is not prolymphocytic as its cells are Sig M+ or G+. The incidence of CR is 77%. The survival at 3 years is 60% and a half, and seems to go down to 0% at 5 years. The median duration of DFS is 1 year. The NIH meeting on NHL gave a bimodal age curve to what was called "small cell non cleaved NHL": we think that the presently described B-NHL type corresponds to the adult type of what was erroneously called "small cell non cleaved type", which, as it was described, is a heterogeneous type.

T 14 CELL PROLIFERATION IN B-CELL MALIGNANT LYMPHOMAS (ML). RELATIONS WITH CLINICAL AND BIOLOGICAL FEATURES.

M. FFRENCH, C. SOUCHIER, F BERGER, J.P. MAGAUD, P.A. BRYON. Laboratoires de Cytologie Analytique, d'Anatomie Pathologique et d 'Hématologie. Services d'Hématologie, LYON, FRANCE.

Cell proliferation was analysed in 164 cases of B-ML (101 males and 63 females). 129 cases were studied at diagnosis before any chemotherapy. The other 35 cases were relapses. Pathologic review was done by two hematopathologists according to the Working Formulation.
Cell suspensions was performed from lymph node biopsies for immunologic phenotyping and cell kinetics in all the cases. Cell proliferation was studied by flow cytometry after a double staining of DNA with Propidium iodide and proteins with FITC. Five variables were studied S, G2+M, S+G2+M, mean cell protein content and the level of ploidy.

An aneuploidy was observed in 147 cases with a tetraploidy in 12 cases. In 16 cases aneuploidy did not allowed the determination of the cell cycle variables.
Significant differences were found for S, S+G2+M and the mean cell protein content between histological classes ($P < 0.01$). Cell kinetics variables were analysed according other clinical and biological features for the whole population of patients and for each histological classes.
Globaly we found a positive correlation between S phase and the transferrin receptor expression ($P < 0.01$) and between S phase and the mean cell protein content ($P < 0.01$). The correlation between S phase and the (LDH level was less strong ($P < 0.05$).
A negative correlation was observed between S+G2+M and the IgD expression ($P < 0.01$).

Relations between cell proliferation and immunological markers was analysed separately for each histological classes. In the low and high grades of prognosis no difference was found for cell proliferation according to blood or bone marrow involvements and the obtention of CR. In the intermediate grade of prognosis bone marrow and/or blood involvements were more frequently observed for low S+G2+M or S phase values ($P < 0.01$) and complete remission was more frequent for high S or S+G2+M values ($P=0.0565$). Survival was studied according to treatments : For the patients studied at diagnosis, survival was significantly longer when S+G2+M was lower even when only aggressive ML were considered ($P<0.05$). Pronostic value of S+G2+M was compared to other prognostic criteria.

T 15 ALTERATIONS OF SIGNALLING ENZYME SYSTEM IN HIV INFECTED CELLS FROM DRUG ABUSERS.

G.A.Losa, L.Leoni, R.Graber. Laboratorio di Patologia Cellulare, Istituto cantonale di Patologia 6600 Locarno, Switzerland

Drug abusers infected with HIV were subdivided into distint groups by considering the level of membrane 5'-nucleotidase (5'-NT) and soluble deoxynucleotidyl transferase (TdT) measured in PBMN cells and the absolute value of T8 suppressor cells. These indipendent variables might provide clues on the functional and biochemical capacity of lymphoid cells and also on the evolution toward a clinically manifest AIDS. Indeed probands with a positive TdT , extremely low level of 5'-NT and altered T8 cells value at the presentation were associated with a higher probability to develop a clinical disease within relative short time. When manifest, both enzyme activities were no longer detectable in analogy to what observed in patients who had clinical AIDS at first examination. Changes of the enzymatic properties imply peculiar modifications of chemico-physical and biochemical properties of lymphocyte plasma membrane which in turn might perturb the regular reception and transmission of immune signals and other antigenic stimuli in cells infected by HIV. Actually the membrane surface of infected cells appeared as more acidic than the plasma membrane of control peripheral blood mononuclear cells,as could be infered from pH optimum values shifted toward acidic values for 5'-NT (pHo of 6.0 versus 7.5) and for PtdInositol Phospholipase-C (pHo of 5.7 and 6.2 versus a unique value of 6.2 in normal cells). Nevertheless, activity values of both enzymes measured at these pHo were found still lower than the levels measured in control cells at the corresponding pHo. This might be related to a changes in membrane lipids known to extensively regulate enzymes and other membrane constituents involved in the immune response. Whether or not i.v. drugs assumption might induce biochemical changes at the membrane molecular level and eventually affect the functional integrity of lymphocytes previous any HIV infection,is currently under investigation.

T 16 PATTERNS OF PERIPHERAL BLOOD MONONUCLEAR CELLS (E-RFC, YC-RFC, M-RFC, MONONUCLEAR PHAGOCYTES) DISTRIBUTION IN LYMPHOPROLIFERATIVE DISORDERS

Milica Marinković,Dušanka Miloševlć,Svetislav Jelić and Vesna Jovanovlć, Institute of Oncology and Radiology,1000 Beograd, Yugoslavia

The heterogenity of malignant lymphoproliferative disorders and transformation processes that take place in the course of disease hamper the impact both morphologic and immunophenotypic diagnostic procedures.
In the present study we analysed peripheral blood mononuclear cells(PBMC) subpopulation in order to obtain adltional diagnostic parameters.The study included 31 patients with chronic lymphocytic leukemia (CLL),14 patients with acute lymphoblastic leukemia (ALL) and 36 patients with non-Hodgkin lymphomas (NHL),before the treatment and during two years of follow up.The percentage of PBMC subpopulation was determined in Lymphoprep isolated lymphocytes by the tests of: E rosette forming cells (E-RFC),yeast complement rosette forming cells (YC-RFC), mouse E rosette forming cells (M-RFC) and yeast particle phagocyting cells. The cells not identified by these tests were designed as "0" cells.
We found a typical PBMC percentage pattern for each of the se three major disease types.The typical PBMC patterns could be summarised as follows:CLL-high percentage of M-RFC and "0" cells and low percentage of E-RFC,YC-RFC and monocytes; ALL-high percentage of "0" cells and extremely low percentage of all other cells(although some cases with slight increase of "0" cells consequently to slight decrease of the percentage of other cells was observed);NHL-increased percentage of monocytes and low percentage of E-RFC YC-RFC and M-RFC.The same typical pattern was seen in CLL and NHL before treatment and in subsequent course of disease not withstanding cytostatic therapy.Disagreement of PBMC pattern type with diagnosis was observed in cases of: CLL presenting with immunoblastic transformation,Hodgkin lymphoma raising in a patient with CLL(diagnosis made by both morphologic and immunophenotypic procedures),and CLL with an initial ALL-cytology,neuroleukemia and 30%CALLA+ cells.
The results of the present study point to a typical PBMC pattern for each major lymphoproliferative disease type which remains constant in the course of disease.Disagreement of PBMC pattern with the diagnosis could predict an atypical course, or the transformation of one to another type of disease.

ABSTRACTS - Fourth International Conference on Malignant Lymphoma, Lugano

T 17 HODGKIN'S DISEASE AND NON HIV-ASSOCIATED KAPOSI'S SARCOMA: A FORGOTTEN ENTITY?

C.C. de Bruyn, V.B. Jogessar - Department of Haematology, King Edward VIII Hospital and University of Natal, Durban, South Africa.

Non-Hodgkin's Lymphoma and Hodgkin's Disease in association with Kaposi's Sarcoma is currently commonly seen in the setting of HIV-Infection. However, the association of malignant lymphomas, particularly Hodgkin's Disease with non HIV-associated Kaposi's Sarcoma was well documented in the literature of the 1950's and 1960's with a decline in the early 1970's.

We would like to present a further case of this seemingly forgotten association and postulate reasons for its apparent decline.

A 27 year old Zulu male presented with multiple skin nodules having developed these over a 6 month period. Night sweats, weight loss and pruritis were present. Eight months prior to admission he presented with inguinal lymphadenopathy to a peripheral hospital where biopsy showed lymphocyte predominant Hodgkin's Disease (LPHD). He declined further treatment. No skin nodules were present at that time.

Multiple biopsies of the skin nodules showed Kaposi's Sarcoma. Repeat inguinal lymph node biopsy confirmed LPHD. CT scan showed mesenteric lymphadenopathy - no other sites appeared involved. HIV and HTLV-I serology was negative. Absolute CD4+ lymphocyte count was increased with a normal number of CD8+ lymphocytes. Chemotherapy with COPP/ABVD regimen resulted in resolution of both the Kaposi's Sarcoma and the Hodgkin's Disease.

The possible pathogenesis of this once common association and reasons for its apparent decline will be discussed.

T 18 IL-6 mRNA EXPRESSION IN TAC POSITIVE MALIGNANT LYMPHOMAS.

S. Diebold°, M. Peuchmaur°, D. Emilie*, P. Solal Céligny+, P. Galanaud*
° Service d'Anatomie Pathologique, Hôpital Antoine Béclère; + Service d'Hématologie, Hôpital Beaujon;
* INSERM U 131, Clamart, FRANCE

We recently demonstrated (1) that IL-2 is produced by reactive T cells in Tac positive Malignant Lymphomas (ML). Using *in situ* hybridization, we investigated IL-6 mRNA expression in these Tac + ML. The ML tested included 12 Tac + ML (9 anaplastic large cell lymphomas expressing T (n=5), B (n=2), or non T non B (n=2) phenotype and 3 B-diffuse large cell lymphomas). Five Tac negative ML were studied as controls.

We showed that IL-6 producing cells were present in all these ML. The density of such producing cells was heterogeneous from case to case. However, 3 cases of Tac + ML showed a dramatically higher density of IL-6 producing cells (mean 54,3 ± 8,1 IL-6 producing cells/ 10^4 cells) as compared to either the 9 remaining cases of Tac + ML (6,03 ± 2,1/10^4 cells) or the 5 Tac negative ML (5,84 ± 2,49/10^4 cells) .

Morphological and topographical datas suggest that several types of cells including fibroblasts, macrophages and endothelial cells may synthesize IL-6. We cannot exclude that tumor cells participate in this IL-6 production.

As IL-6 acts as a lymphoid growth factor and induces IL-2 receptor expression, our results indicate that it may play a major role in the proliferation of these ML.

1. M. Peuchmaur, D. Emilie, M.C. Crevon, P. Solal-Céligny, M.C. Maillot, G. Lemaigre, P. Galanaud: IL-2 mRNA expression in Tac positive malignant lymphomas. Am. J. Pathol. 1990, 136, (in press).

T 19 PROLIFERATION AND LYMPHOKINE-ACTIVATED KILLER (LAK) ACTIMVITY OF T CELL CLONES FROM PATIENTS WITH MALIGNANT LYMPHOMA.

C.Y. Jiang, P.H. Tang, N.W. Zhang et al. Institute of Basic Medical Sciences, P.O. Box 130 (3), Beijing 100850, P.R. China

Peripheral blood mononuclear cells (PBMC) were isolated by Ficoll-Hypaque gradient centrifugation from seven patients with malignant lymphoma. Cultured in semisolid medium containing recombinant IL-2 for 6~7 days, PBMC of all patients could be developed colony formation units for T lymphocytes (T cell clone). The growth rates of T cell clones that depended upon the doses of rIL-2 and the number of PBMC were about 109±24/1×10⁴ PBMC, as similar as that (117±37/1×10⁴ PBMC) from healthy adults, in the optimal concentrations both of rIL-2 of 500~10000 u/ml and PBMC of 2~5×10⁴/ml added into cultures. T cell clones proliferated well and expanded continuously for over 2 months while the cell numbers undergo an average 10⁴-fold expansion in rIL-2-containing liquid medium with cell density 5~10×10⁵/ml. Using a short term (4-hr) ^{51}Cr release assay for cytotoxicity, about 20% of T cell clones showed significant LAK activity against either NK-sensitive erythroleukemic cell line K562 or NK-resistant human liver cancer cell line H7402 in a ratio-dependent increase in E/T ratios of 1.25~5. The percentage of specific lysis of K562 and H7402 were 23.4~54.1% and 10.3~24.5% respectively, even at E/T as low as 5. Jurkat cells (T-lymphoma cell line) were also killed by the T cell clones with lytic values as high as 41.8~53.1% at the ratio of 5. Phenotypic analysis by flow cytometry showed that these T cell clones with LAK activity carried CD3, CD8 and CD25 antigens. Recombinant IFN-γ (concentrations of 100~1000u/ml added), but not recombinant TNF (concentrations of 1000~10000 u/ml added), incubated with these T cell clones with LAK activity for 3 days, could up-regulated the cytotoxicity for targets as mentioned above. These data indicated the possibility of T cell clones with LAK activity from patients with malignant lymphoma employed in killing of Fresh autologous malignant lymphoma cells.

T 20 P 55 IL 2 RECEPTOR EXPRESSION ON PERIPHERAL BLOOD LYMPHOCYTES FROM PATIENTS WITH HODGKING'S LYMPHOMA AND WITH SOLID MALIGNANCIES.

G. Mantovani, A. Macciò, G. Pusceddu, E. Proto, G.P. Sanna, G. Sulis, M.V. Zucca, M.P. Cogoni, A. Balestrieri, G.S. Del Giacco.
Department of Clinical Oncology, University of Cagliari, Via San Giorgio 12 - 09124 Cagliari, Italy.

The aim of the study was to assess the possible existence and the extent of an impaired p 55 IL2 receptor (IL2R) expression in Hodgkin's Lymphoma (HL) and in some widespread solid malignancies (SM) in which a secondary immune deficiency arises in the course of disease. In HL and in most SM a defective IL2 production has been already found. 7 HL, 6 head and neck, 3 breast, 3 lung (NSCLC), 3 colorectal, cancer patients, as well as 6 normal subjects, were studied. Both a cytofluorimetric and a cultural assays were carried out, the last culturing the PBL in presence of PHA, IL2 and PHA+IL2 either with or without the non FITC-conjugated anti p 55 MoAb and assessing the ^{3}H TdR uptake, the former evaluating the percentage of fluorescent cells in cultures undergoing the same stimulation, after addition of FITC-conjugated anti p 55 MoAb. The results showed a full competition between IL 2 and MoAb for the p 55 IL2R, being the MoAb more avid for the ligand in such a way to prevent almost completely the binding of IL2. The flow cytometry assay indicated a p 55 expression significantly lower in HL PBL, at later times (72 h), compared to normal and SM PBL: this may suggest that also the p 55-75 heterodimer could be expressed at significantly lower levels in HL PBL, so providing new insights for the severe T cell immune impairment of HL. The almost normal pattern of p 55 expression in PBL of SM may support the perspective of the usefulness of IL2 administration in these patients.

Work supported by CNR, A.P. "Oncology", Grant N.88.00624.44.

T 21 Interleukin-2 receptor levels in patients with non Hodgkin lymphoma. Correlation to histological degree of malignancy and prescence of constitutional symptoms.

Jon-Magnus Tangen, Hematology section, Ullevål Hospital, Oslo, Norway,
Arne Foss Abrahamsen, The Norwegian Radium Hospital, Oslo, Norway,
Bjørn Østenstad, Oncology department, Ullevål Hospital, Oslo, Norway,
Jann Bergheim, Oncology department, Haukeland Hospital, Bergen, NOrway.

Serum interleukin 2 receptor (Il-2R) levels were measured in 28 untreated patients with stage III/IV non Hodgkin lymphoma (low grade lymphoma: 11 patients, high grade lymphoma 17 patients).
Markedly higher levels of Il-2R were found in these patients compared to an age- and sexmatched control group. Significant differences were also found between the high grade group and the low grade group, and between patients with and without constitutional (B) symptoms.
It has previously been shown that Il-2R levels vary according to tumor burden in patients with non Hodgkin lymphoma. Our data indicate that histological degree of malignancy as well as prescence or abscence of B symptoms may also influence Il-2R levels in these patients.
All three parameters should therefore be taken into account when the clinical significance of Il-2R levels is evaluated.

T 22 PRELIMINARY RESULTS OF RECOMBINANT INTERLEUKINE-2 (rIL2) IN REFRACTORY LYMPHOMAS.

JM. Tourani, C. Audroin, S. Roithman, JM. Andrieu. Oncology and Hematology, Laennec Hospital, 75007 Paris, France.

Objective: to observe the toxicity and efficacy of recombinant interleukine-2 in réfractory lymphomas.
Patients and methods: from 6/88 to 12/89, 9 patients (pts) with lymphomas (Hodgkin's diseases (HD) 4, high grade non Hodgkin's lymphomas (HGNHL) 5) were treated with rIL2 (Cetus corp) $18*10^6$ IU/m²/D continuous infusion day 1 to 5 and day 12 to 16. After 3 weeks rest, in the absence of undue toxicity or disease progression, a second cycle of treatment was administered.
Results:

Presentation and Response

Pts	histology	previous TT	pre IL2 CS	response
1	HD	CT	II failure	failure
2	HD	CT+RT	II failure	failure
3	HD	CT+RT	II failure	failure
4	HD	CT+RT	IV failure	failure
5	HGNHL	CT	IV failure	failure
6	HGNHL	CT+RT	IV failure	failure
7	HGNHL	CT+RT	IV failure	failure
8	HGNHL	CT+RT	IV failure	failure
9	HGNHL	CT+RT	IV failure	failure

CT: chemotherapy RT:radiotherapy TT:treatment
CS: clinical stage (Ann Arbor)

Toxicity grades (WHO)

	skin	GI	renal	fever	BP	hematological
I	2	5	6	-	1	1
II	3	1	2	1	2	2
III	4	-	1	8	2	-
IV	-	-	-	-	-	-

GI:gastro intestinal toxicity BP:Blood pressure

No treatment was interrupted due to toxicity. On the other hand, 4 patients received only 1 cycle because of early disease progression. No response was observed with rIL2 among the 9 HD or HGNHL who were initially non responders to chemotherapy ± radiotherapy.

T 23 IMMUNOCYTOCHEMICAL STAINING OF VARIOUS MARKERS FOR MALIGNANT HISTIOCYTOSIS.

Ji Ya You, Liu Yan Fang, Wang Bo Yun. Department of Pathology, Fourth Military Medical College, Xi'an, Shaanxi, People's Republic of China

In order to understand the characteristic of malignant histiocytosis (MH), we collected 36 MH autopsy cases to study the distribution of α_1-antichymotrypsin (ACT), α_1-antitrypsin (AT), lysozyme (LYS), ferritin (FER), S-100 protein (S100) and ricinus communis agglutinin (RCA) by double peroxidase anti-peroxidase and make comparison for these markers.

The results of the staining for various markers were showed in Table 1 and Table 2.

Table 1. Positivity rates for various markers in MH

Marker	Positive case	Total	Positivity rate (%)
ACT	33	36	91.67
AT	28	36	77.78
LYS	34	35	97.14
FER	36	36	100.00
S100	27	36	75.00
RCA	33	34	97.06

Table 2. Comparative immunocytochemical staining for various markers in MH

Quantities of positive tumor cells*	ACT	AT	LYS	FER	S100	RCA
-	3	8	1	0	9	1
+	14	18	5	13	18	2
++	11	6	17	9	3	15
+++	8	4	12	14	6	16
Total	36	36	35	36	36	34

*-: no tumor cell stained, +: positive tumor cells were less than 10% of total tumor cells, ++: positive tumor cells were between 10 and 30%, +++: positive tumor cells were more than 30%.

Although the four types of MH tumor cells showed the positive reaction for these markers, there were obviously different. Most of well-differentiated histiocytes and prohistiocytes represented FER, ACT, LYS and RCA positive. AT was mainly presented in atypical histiocytes. Phagcytosis often associated with the presence of ACT, RCA and FER. Positive cells for LYS were almostly not phagcytosis. S100 was seen both in well-differentiated histiocytes and atypical histiocytes.

T 24 DIFFERENT EBV-EXPRESSION IN LYMPHOMAS FROM IMMUNOCOMPROMISED AND IMMUNOCOMPETENT PATIENTS.

B. Borisch Chappuis, C. Nezelof, H. Müller, H. K. Müller-Hermelink. Institute of Pathology, University Bern, 3010 Bern, Switzerland, and Institute of Pathology, University Würzburg, 8700 Würzburg, FRG

Eighteen tissue samples from lymphoproliferative lesions and lymphomas in immunodeficiency states were investigated for their content of EBV-genome by dot-blotting and for the distribution of EBV in tissue sections by in situ-hybridization. Fourteen lymphomas from AIDS-patients and four children with disorders of the immune system were available. For control reasons, six cases of infectious mononucleosis (IM) and eight Burkitt's lymphomas (BL) from malaria-free regions of Africa were included in the study. Two different patterns of EBV-distribution are described: heterogeneous scattered EBV-positive cells, as originally seen in IM and therefore called the IM type pattern and a BL type pattern seen in endemic Burkitt's lymphoma with homogeneous EBV-positive cells all over the tumor. In lymphomas in patients with inborn immunodeficiencies an IM type pattern was found. In lymphomas from AIDS-patients, the two different patterns were found. There were lymphomas with the IM type pattern as well as some with the BL type pattern. In some AIDS-associated lymphomas both patterns occured in one tumor. The findings suggest that it is not the disease process that is the distinguishing feature between the two patterns of EBV infection but the patient's underlying disease and the extent of this disease.

ABSTRACTS - Fourth International Conference on Malignant Lymphoma, Lugano

T 25 THE QUALITY OF SURVIVAL IN CHILDREN WITH HODGKIN'S DISEASE (HD). TEN YEARS AFTER TREATMENT.

G. Petrič-Grabnar, B. Jereb, B. Kragelj, et al. The Institute of Oncology and the University Clinical Center, Ljubljana, Yugoslavia

Patients treated between 1970-1980 for HD as children have been evaluated by means of physical examination, endocrinological and intellectual testing as well as evaluation of their psycho-social adjustment to their environment. Of the 31 patients who were 3-15 years old at the time of treatment, 8 have died (4 of HD, 3 of sepsis and one in rhabdomyosarcoma). Included in our study are patients who were at least 15 years old at the time of investigation. All had been treated with IF irradiation and all except one had chemotherapy (MOPP, LOPP).

Ten patients (4 female, 6 male) have completed testing until January 1990. Late sequelae of irradiation were found in all patients: atrophy of the neck and shoulder girdle soft tissues in 9, scoliosis in 1 and low sitting height in 3. Except for latent hypothyreosis in one patient there were no endocrinological deficits found as were no chromosomal aberrations.

Except for one, who is suffering from neurotic symptoms and emotional instability, they are socially very well adjusted. All of them have finished primary schooling, 7 have vocational schooling, 2 are college graduates and one woman is an unqualified physical worker. Three females are married, three have produced 4 children. One patient has been operated for cancer in situ of the uterine cervix (13 years after combined treatment for HD and after having given birth to 2 children).

Ten years after treatment for HD our small sample of patients is well adjusted socially, the endocrinological and physical sequelae of treatment are not severe. However, the incidence of secondary tumors (2 out of 23) is already rather high.

T 26 LATE EFFECTS ON LINEAR GROWTH, BODY PROPORTIONS AND GONADAL FUNCTION OF CHEMOTHERAPY AND INFIELD RADIOTHERAPY FOR CHILDHOOD HODGKIN'S DISEASE.

Lamkin VA, Shafford EA, Malpas JS, Kingston JE, Savage MO and Plowman PN. Department of Paediatric Oncology, St Bartholomew's Hospital, London.

Extended field radiotherapy for childhood Hodgkin's Disease is associated with poor linear growth. In an attempt to minimise the effect on growth, combined modality treatment with ChlVPP chemotherapy (Chlorambucil, Vinblastine, Procarbazine, Prednisolone) and infield radiotherapy was given to 35 children between 1977 and 1984. Height, body proportions and fertility were evaluated in 14 (9 males) who had completed growth. Minimum follow up was 4 years, 8 months (median 8 years, 11 months). 13 received radiotherapy (RT) to the neck, of whom 9 also had RT to the mediastinum, 1 received RT to the mediastinum alone and 2 in addition to the para-aortic nodes. Height standard deviation scores (SDS) were normal in all subjects (range -1.2 to +1.8). In 8 of the 14 patients sitting height (SH) was below average; median -1.3 SDS (range -0.7 to -1.9) with subischial leg length correspondingly increased; median +0.8 SDS (range 0 to +3.3). 7 of these 8 patients had radiotherapy to the mediastinum compared to 3 of 6 patients with normal SH. Median age at diagnosis was comparable although the median dose of radiotherapy was 3250 cGy in the low SH group and 2500 cGy in the normal SH group. 8 of 9 males have elevated plasma FSH levels (range 17.4 to > 50 u/l, N < 7 u/l) and 4 out of 5 tested are azoospermic. The 5 females have normal menstruation, 1 being fertile.

In patients who received combined treatment with ChlVPP chemotherapy and infield radiotherapy, final adult height was normal, although spinal growth was impaired resulting in disproportion of upper and lower segments. Impaired gonadal function with elevated FSH and infertility was present in most males.

T 27 PEDIATRIC NON-HODGKIN'S LYMPHOMA ABDOMINAL PRESENTATION: A COMPARATIVE STUDY BETWEEN TWO TREATMENT REGIMENS.

S.Abdel-Hadi, A.Abou-Gabal, O.El-Tannir, M.H.Hussein, A.El-Haddad, I.Attia, S.Aboul-Naga, S.El-Badawi, M.R.Hamza, N.Gad-El-Mawla. National Cancer Institute, Cairo; Departments of Pediatric Oncology and Radiotherapy

In Egypt, abdominal presentation of pediatric non-Hodgkin's lymphoma (NHL), are usually extensive locally. They are accordingly rarely amenable to complete surgical resection. This may be due to a delay in the diagnosis of these patients due to the non-specificty of their presenting manifestations.

Chemotherapy is the hall mark of treatment for pediatric NHL. Treatment of various types of this disease including intra-abdominal NHL in children with so many various protocols, have not exceeded 54% two years disease free survival.

We have attempted to study and compare the effects of two treatment regimen upon two groups of previously untreated with abdominal NHL, who presented to the Pediatric Oncology Unit, at the NCI, Cairo. The first group included 18 children who presented in 1983, and were treated by a modified St. Jude regimen. The second group of patients were comprised of 19 children who presented in 1985, and were treated by a new protocol. This consisted of two alternating cycles of chemotherapy, cycle A, and cycle B, for 4-8 cycles. Cycle A; cyclophosphamide, high dose Ara c, adriamycin, and vincristine. Cycle B; ifosfamide, methotrexate, and VP 16, with intrathecal methotrexate.

The two groups will be compared with respect to various patient charecteristics, response to therapy, and both disease free survival, and overall survival.

T 28 BURKITT'S LYMPHOMA WITH AFRICAN TYPES FACIAL TUMORS (JAW+ORBIT) IN TURKISH CHILDREN

A.O. Çavdar, S. Gözdaşoğlu, G. Yavuz, E. Babacan, E.Ünal, Ö. Uluoğlu, S, Cin, Ankara TURKEY

Pediatric Hematology-Oncology Research Center of Ankara University, Ankara TURKEY

Sixty-four Turkish children with Burkitt's lymphoma (BL) observed within a period of 20 years (1968-1988) have been analysed retrospectively from clinical and therapeutic point of views. The diagnosis was established histologically according to WHO criterias. BL represented 47.4% of NHL in this series. The patients were staged according to Ziegler's system. The median age of patients was 5 years with a sex (M/F) ratio of 3.3/1. The most common primary site of tumor involvement was abdomen (68.8%) which was followed by facial tumors in particular jaw and orbit (51.5%). There were 18 cases with jaw (28.1%) and 15 cases with orbital involvement (23.4%) at initial presentation. The majority of the patient (84.4%) were in advanced stages (C and D) at initial diagnosis. Facial tumors observed in Turkish children with BL were more similar to African Burkitt's lymphoma rather than American or European cases. High titer of antibodies against VCA of EBV was also shown in our recent cases of BL (g.mean for anti VCA titer: 1/493). Two main treatment regimens namely single agent chemotherapy with cyclophosphamide (CYX) (1968-1988) and three drugs (COM) combination chemotherapy with CYX, VCR, MTX were used consecutively (1974 1988). COM have been shown to produce better results than single agent with 42.8% over all survival rate at 96 months, whereas none of the patients survived in CTX treated group beyond 12 months. Currently we have started to use multiagents (8 drugs) rotating chemotherapy for BL, with good results. The clinical presentation of BL in Turkish children appears to be between African and American BL in this series. Studies related to viral genome and cytogenetic, are under way to determine biological caracteristics of this tumor in Turkish children.

ABSTRACTS - Fourth International Conference on Malignant Lymphoma, Lugano

T 29 E.C.1.1.1.27 AND SERICAL COPPER AS POTENTIAL MARKERS IN CHILDREN WITH HODGKIN DISEASE.

M.Bălan(1), C.Nistor(1), M.Onigor(1), D.Rădulescu(1), S.Neamțu(1), R.Rădulescu(1), E.Ciuleanu(1), V.Nistor(1), D.Isai(1) M.Ujică(2), C.C.Nistor(2), V.Trică(2), T.Ban(3), M.Dan (1), R.Mălai(1), M.Timiș(1); (1.Oncolog.Inst.Cluj Napoca; 2.Interdisc.Labor.Univ.Cluj Napoca; 3.Districtual Hospital Reșița; Reșița ; România)

We studied the dinamic variation of LDH (E.C.1.1.1.27) and serical copper (SC) in 12o childrens with Hodgkin disease (CHD), using usual standardized methods. The results showed an increase of values of LDH with 8o-1oo % about normal values intervals and an increase of SC in the interval of 18o - 22o µ.g % (28,3 - 34,62 µmol/1). The dinamical variation of LDH, SC and the correlations between their variations in CHD, were studied with the automatic statistical correlations programmes (CORRELLA), for the use as potential tumor markers. After the complex treatment applied in CHD, the continnuing increase of LDH with 18o-2oo % about normal values intervals, and of SC about 35o µg % (55,o9 µmol/1) and the maintaniance in time at this level is an index a bad prognose for the evolution of CHD, and for the efficacity of the complex treatment applied, this correlated with a short survival. The decrease of LDH and SC after the complex treatment applied in CHD and the tendency to reduction toward normal values, correlated with other 19 biochemical parameters, may constitute an index of positive prognose. In conclusion the quantitative determination of LDH and SC, and correlations between their in CHD, are used as biochemical oncological markers, and for the prognostic of the efficacity of the complex treatment applied in CHD.

T 30 CLINICAL FEATURES AND RESULTS OF TREATMENT OF HODGKIN'S DISEASE IN PRE-SCHOOL SAUDI CHILDREN.

Z. Nasserallah, R. Sabbah, R. Aur and K. Sackey, Department of Oncology, King Faisal Specialist Hospital and Research Centre, Riyadh 11211, Kingdom of Saudi Arabia

The purpose of this study is to describe the clinical features and results of treatments of pre school Saudi children, (<6 years of age) with the diagnosis of Hodgkin's disease. The study includes 34 patients seen at King Faisal Specialist Hospital and Research Centre (KFSH & RC) over a period of 14 years (1975-1989). There were 28 boys and 6 girls (M:F 4.7/1). The age range was 18 to 66 months (median: 42 months). Presenting complaints included lymphadenopathy in 33 patients, anemia in 15 patients and constitutional (B) symptoms (fever, night sweats, weight loss and/or pruritis) in 13 patients. Histological subtypes included mixed cellularity in 22 patients (65%), nodular sclerosis in 10 patients (29%), lymphocyte depletion and lymphocyte predominance in one patient each. Clinical stages were: stage I-6 patients (18%), stage II - 10 patients (29%), stage III-15 patients (44%) and stage IV-3 patients (9%). Treatment consisted of chemotherapy only in 29 patients (85%) and radiotherapy only in 4 Stage I patients (12%) and one patient (3%) received both. Conventional MOPP was delivered as front line therapy. Nineteen of the 34 patients (56%) survive disease-free for a period of 8 to 135 months (median: 48 months), 4 patients (12%) relapsed and were treated with alternate regimens, 2 patients (6%) died and 9 patients (26%) were lost to follow up while in complete remission. Alternate treatments included ABVD, ABVD + MOPP, and ChlVPP. This study demonstrates that childhood Hodgkin's disease in pre school children tends to be more advanced at diagnosis, and that the mixed cellularity form is predominant just as in older children from the same population. Also, the treatment modalities were similarly tolerated without prohibitive side effects, and the overall therapeutic response is as good as the one obtained in older children.

T 31 TREATMENT OF STAGE III AND IV B LYMPHOMAS IN ADULTS BY THE PEDIATRIC PROTOCOL LMB 01/84

R. Meckenstock, P. Biron, E. Bouffet, H. Bonnefoy, Ph. Colombat, C. Dauriac, B. Salles, T. Philip - Centre Leon Berard Lyon (France).

20 patients (15 men, 5 women) 16 to 54 year-old suffering from a immunologically proved B-Lymphoma (Burkitt 12, Immunoblastic high grade 2, Lymphoplasmocytoid low grade 1, Intermediate grade of the WF 5) were treated by the LMB 01 84 protocol : Cop - Copadem x 2 - either Cym x 2 or Cam + Mini-Bact and 2 arms one short with only one more course and one long arm with 4 maintenance courses. 5 patients were treated outside of our center.

At diagnosis 13 presented a stage III and 7 a medullary stage IV in the Murphy classification. Initial site was abdominal in 14 cases including all Burkitt lymphomas, and mediastinal in 4 cases.

18 patients are evaluable and 2 are not yet evaluable. 14 achieved a CR (78 %) ; one of them died of AIDS 6 months later. Another one relapsed at 8 month and is in 2nd CR with the same protocol and BMT for 5 months +. The 12 other patients are disease free from 2 + to 68 + months.

3 patients relapsed and died 2 to 3 months after assumed CR which was probably only a PR. The only toxic death (septicemia) in our series occured in a patient (HTLV 1+) having a pathological PR after the first Copadem course.

CR was generally achieved after the 2nd Copadem or the 1st Cym. In 5 of 8 evaluated patients tumor regression was 50 % after the initial Cop. Aplasia occured in all cases after Copadem and not always after Cym courses. Extramedullary toxicity was rare and transient and mostly linked with high dose MTX. At this time 14 patients (70 %) are alive with a median survival of 31,7 months.

We conclude that LMB 84 is an effective and safe protocol which can be applied to adult patients.

T 32 ADULT BURKITT'S LYMPHOMA: HIGH RESPONSE RATE WITH A PEDIATRIC REGIMEN

A. Delmer, B. Rio, F. Ajchenbaum, E. Perez, J.P. Marie, R. Zittoun.
Service d'Hématologie, Hôtel-Dieu, 75181 Paris cédex 04

During a five year period, we have treated in our institution 18 patients (pts) with Burkitt's lymphoma (BL). The median age was 29 years (range 15-55). Eight pts were infected with HIV. In these pts, the lymphoma represents the first manifestation of AIDS in all cases.

Among HIV negative pts, 7 had advanced disease (stages III and IV) and 3 had localized disease (stages I and II). Eight pts received induction therapy according to the previously published FPOS (French Pediatric Oncology Society) LMB protocol (J Clin Oncol 1986, 4: 1219) and 2 received miscellaneous regimens. Complete remission (CR) was achieved in 9 pts (90%) and 7 remain free of disease with a median follow up of 24 months (range 7-46). Four pts received intensive consolidation with high dose cyclophosphamide and TBI followed by autologous (3 pts) or allogeneic (1 pt) bone marrow transplantation (BMT).

Among pts with HIV related BL, 6 presented with disseminated disease and 2 with a localized axillary lymphadenopathy. These 2 pts received short chemotherapy with 3 courses of modified ProMACE MOPP followed by involved field radiotherapy (40 Gy), and remain in first CR at 16 and 24 months. Stage IV pts were treated with either LMB or LNH 84 (J Clin Oncol, 1989, 7: 1018) protocols. Three achieved CR but all died from progressive disease (median survival 4 months).

Our results deserve some comments:
- The LMB protocol initially designed for pediatric pts is a well-tolerated and highly efficient regimen in young adults.
- The place of intensive consolidation followed by BMT remains to be defined in BL.
- In HIV pts with localized BL, a conservative approach seems to fit well with the opportunistic infections risk of high dose chemotherapy.
- The poor prognosis of HIV pts with disseminated BL is confirmed.

ABSTRACTS - Fourth International Conference on Malignant Lymphoma, Lugano

T 33 RICHTER'S SYNDROME: 14 CASES AMONG 359 CHRONIC LYMPHOCYTIC LEUKEMIA.

B. Desablens[1], J.F. Claisse[2], P.Mouillard[1], S. Bonnay[1], I. Quiquandon[1], M.F. Gontier[3], J. Delobel[2] - [1]Maladies du Sang, [2]Lab. Hématologie, [3]Lab. Anatomie Pathologique - CHRU 80030 AMIENS, FRANCE.

Fourteen patients developed a Richter's syndrome among 359 CLL (3.9 %) treated at our institution from 1970 to 1988. There were 9 men and 5 women and median age was 58.7 years at time of CLL diagnosis. The interval from diagnosis of CLL to Richter's syndrome ranged from 9 to 138 months (median: 50 months). The five-year and ten-year actuarial risks are respectively 9.6 +/- 4.4 % and 8.8 +/- 12.2 %. Three predictive variables are detected at the 10 % level: age < 60 years, enlarged retroperitoneal areas and diffuse bone marrow involvement whereas others parameters are without significance (sex, stage and number of enlarged areas according to the Binet's system, splenomegaly, blood and bone marrow lymphocytosis, haemoglobin and platelets values).

Histology is the following:
- 1 true Hodgkin's disease with lymphocytic predominance (clinical stage IA),
- 1 EBV-associated Burkitt's lymphoma (stage IIBE),
- 6 diffuse mixed cells lymphomas (1 stage IIIB and 5 stages IVB with hepatic, medullary and/or osseous involvement). Two patients had an hypercalcemia and two a monoclonal component,
- 4 diffuse large cells lymphomas: 3 apparently localized to the digestive tract and the last with enlarged retroperitoneal lymph nodes and contiguous gastric involvement,
- 2 immunoblastic lymphomas with ureteral compression (stage IIBE).

One patient expired before therapeutic programm and 2 were not treated because of age. One patient received a COP regimen without efficiency (survival: 3 months) and 2 a CHOP regimen (doxorubicin: 40 mg/m2) with a failure (survival: 5 months) and a partial response (survival: 7 months). Seven patients received the VACP regimen (doxorubicin: 80 mg/m2): 3 died before evaluation, 1 failed (survival: 3 months) and 3 had a partial response (2+, 2+ and 9+ months). Median survival is less than 3 months and only the patient with Hodgkin's disease treated by 3 ABVD and radiotherapy according to the POF H81/12 trial, seems to be cured (survival: 59 months).(Work supported by APREMS).

T 34 LYMPHOPLASMACYTOID/PLASMACYTIC MONOCLONAL GAMMAPATHY WITH HIGH IgG OR IgA PARAPROTEIN LEVELS: A DISTINCT CLINICOPATHOLOGICAL ENTITY OF LOW GRADE MALIGNANCY.

JJ Michiels, CA de Leeuw, FWJ ten Kate Dept. of Hematology and Clinical Pathology University Hospital Molewaterplein 40 3015 GD Rotterdam.

A case of IgG-kappa monoclonal gammapathy with a very high paraprtein level (76g/L) was diagnosed as multiple myeloma. Treatment with melphalan/prednisone and subsequent combination chemotherapy induced partial remissions of less than 50%. Reinstitution of melphalan was complicated with myelotoxicity. Neither osteoporosis nor lytic bone lesions developed. However, the pleiomorphic lymphoplasmacytoid/plasmacytic infitration of the bone marrow with the coexistance of IgG-kappa surface membrane positive lymphoplasmacytoid and IgG-kappa cytoplasmicpositive plasmacytic cells was very suggestive for a Waldenstrom-like diease. A high IgG synthetic rate of 44 pg/24 hour/plasma cell was indicative for a low tumour burden. Subsequent treatment of progressive disease with liver involvement and abdominal lymphomas with chorambucil was effective.
The clinical, morphological and immunological findings in our case and twelve reported case histories of pleiomorphic lymphoplasmacytoid plasmacytic monoclnal gammapathies with high serum IgG or IgA paraprotein levels were analysed. It appeared that this condition, which usually runs a benign course, is featured by relative lymphocytosis in the peripheral blood, lymphadenopathy and/or spenomegaly in the absence of bone lesions, renal impairment and hyperviscosity syndrome. These data are in support of the concept that the pleiomorphic lymphoplasmacytoid/plasmacytic proliferation of B cells secreting large amounts of IgG or IgA paraproteins constitute a distinct clinicopathological condition of low grade malignancy, in which chrorambucil/prednisone or cyclophosphamide/prednisone is the treatment of choice.

T 35 Response to two different doses and schedules of IFN-β in hairy-cell leukaemia.

A.M. Liberati, B. Falini, M. Fizzotti, F. Di Clemente, M. Senatore, M.F. Martelli, F. Grignani. Istituto di Clinica Medica I, Policlinico Monteluce, 06100 Perugia, Italy.

Thirteen hairy-cell leukaemia (HCL) patients were treated with $6x10^6$ IU/m² IFN-β for 7 days during alternate weeks for 3 cycles. IFN-β was then continued at the same dose twice a week for an additional 24 weeks. Treatment was discontinued in two non-responders and two partial responders; one, a haematological PR (haem-PR), because of death unrelated to IFN, the other, a pathological PR (path-PR) due to increased liver enzymes. The objective response in the 9 patients who completed the planned therapy was 66% (1 CR, 3 path-PR and 2 haem-PR). The CR and one path-PR were observed 23 and 12 months after termination of therapy and confirmed by later bone marrow biopsies (4 biopsies for the CR and 2 for the PR patient). Another 2 patients achieved MR for an overall response rate of 88%. Responses lasted from 5 to 45+ months. After 3 weeks of IFN therapy had reduced spleen size by 50% and so allowed splenectomy to be performed, a 14th patient, who was not part of the formal study, achieved CR (21+). Seven patients, 4 newly diagnosed and 3 in relapse after discontinuation of IFN-β therapy ($6x10^6$ IU/m²) were treated with a lower dose of IFN-β ($2x10^6$ IU/m²). The objective response to this lower dose was 57% (3 path-PR, 1 haem-PR). One additional patient obtained an MR for an overall response rate of 71%. No patients have relapsed 7-12 months from termination of therapy (12+ months in the MR patient, 8+ months in the haem-PR, and 9+ and 14+ months in 2/3 of path-PR who had completed the 12 months of therapy). Since IFN-β was well tolerated, especially at the lower dose, and no chronic toxicity was observed, it may be proposed as an alternative treatment for HCL.

T 36 EXPERIENCE WITH ALPHA-INTERFERON AS MAINTENANCE TREATMENT FOR MULTIPLE MYELOMA.

R. Jacobson, D. St. Germain and F. Smith, Divisions of Hematology and Oncology, Georgetown University Hospital, Washington D.C., U.S.A.

Concern about the leukemogenic effects of prolonged alkylating agent chemotherapy in multiple myeloma (MM), has led to the practice of discontinuing treatment when patients with MM enter a remission. However, the remissions are usually short-lived and relapse is accompanied by an increased morbidity and mortality. Recent interest has focused on prolonging the remission with alpha-interferon (α-IFN). We report here our experience of the past 2 years with α-IFN as maintenance treatment in 8 patients with MM. The patients were selected on the basis of having entered a remission following a minimum of 12 months of chemotherapy. The pulse regimen of melphalan and prednisone was used in all patients. Two patients required localized radiation therapy to painful skeletal lesions and 3 patients were also treated with other combination chemotherapy, which included cyclophosphamide, doxorubicin and vincristine. The patients' age range at the time of the MM diagnosis was 37 to 78 years (mean 58 years) and 4 patients had IgG myeloma, 2 kappa light chain disease and 1 each with IgA and IgD myeloma. The plasma cell dyscrasia had been initially diagnosed from 1 to 6 years prior to the start of α-IFN. The patients were considered to be in remission when their myeloma-related symptoms had abated and when the abnormal serum and urine immunoglobulin or light chain determinations were not detectable or had decreased by greater than 75% and had stabilized for at least 3 months. Seven patients with normal renal function were treated with α-IFN at a dose of 3 million units/M² sub-cutaneously injected 3 times weekly. The dose was reduced because of symptoms of fatigue and weakness or because of leucopenia (<2000/dl). The patient with IgD myeloma has renal failure and requires hemodialysis. He has received α-IFN at a dose of 0.5-1.0 million units. The 8 patients have been treated with α-IFN for 6 to 20 months and no patient has had a relapse of MM. Specifically no new osteolytic lesions have been detected, the hematologic parameters are stable and renal function in 7 has been well preserved. Two patients have a trace of free kappa chains in their urine (total protein <150 mg/24 hour urine) and the patient with IgD MM still has a detectable monoclonal protein in his serum. In one patient the α-IFN had to be stopped because of rising liver enzymes (SGOT and SGPT > 150 units) and a pruritic skin rash. These preliminary findings are encouraging and strongly support a role for α-IFN as maintenance therapy for multiple myeloma.

T 37 PLASMA- AND CELLULAR PHARMACOKINETIC OF PREDNIMUSTINE (STERECYT®) AND ITS COMPONENTS.

E.Musch, M. Malek, E.Hügl, U. Loos, A. Alléra, Dep.Internal Medicine Univ. of Bonn, D-5300 Bonn,FRG.

Prednimustine (PM) the 21-prednisolone (P) ester of Chlorambucil (CLB) has been synthesized with the aim of a facilitated uptake into tumor cells. In a cross over study comparing the kinetics of PM (300 mg) with its constituents CLB (30 mg) + P (50 mg) we did not find the intact PM in plasma. However we measured lower peak- and longer persistent plasma concentrations of CLB, phenylacetic mustard PAAM and P from PM than from its single components. The availability of CLB in PM was 14 %, of PAAM 21 % and of P 22 % of the value found when equimolar doses of CLB + P are given. The availability of CLB was still only 62 % even when refered to the actual therapeutic doses of PM (300mg) and CLB (30 mg). Because these kinetic data were discrepant to reports of an equal/superior therapeutic effect of PM compared to CLB+P administered separately we performed studies of the intracellular kinetics of PM versus CLB + P to see if there is intracellular sequestration of PM. In lymphocytes from healthy volunteers as well as from patients with CLL and WDLL incubated with PM (5 µg/ml) we could identify by HPLC intracellular PM as the integer P-ester of CLB. The lymphocytes exhibited a more pronounced uptake of PM than of CLB. As a mean the AUC of PM + CLB in the PM incubated lymphocytes amounted 274 ± 99 [µg/ml xh] while only minor intracellular AUCs of CLB 46 ± 18 [µg/ml xh] could be detected in the CLB+P incubated lymphocytes.A similar difference could be observed in our in vivo study of cellular kinetics with lymphocytes from patients with CLL and WDLL before and after oral uptake of either PM or CLB + P. The lymphocytes of the PM treated patients showed intracellular AUC of CLB+PAAM 1,6 x higher than the intracellular AUC of patients treated with CLB+P. We succeeded to identify chromatographically a substance peak which was related to PM therapy. This peak was not detectable in any of the lymphocytes of CLB treated patients. Further analytical work for chemical identification of the PM related chromatographic peak is going on.

* Supported by the Ministerium für Wissenschaft und Forschung des Landes Nordrhein-Westfalen.

T 38 RECOMBINANT ALPHA INTERFERON IN THE TREATMENT OF LOW GRADE NON-HODGKIN'S LYMPHOMA: RESULTS OF A COOPERATIVE PHASE II TRIAL IN 31 PATIENTS.

L.Mantovani*, C.Guglielmi*, M.Martelli*, A.Chierichini**, L.Deriu**, M.R.Sertoli***,A.Ardizzoni***,F.Mandelli*. * Ematologia, Dip.Biopatologia Umana, Univ."La Sapienza", via Benevento 6, 00161 Roma; ** Div.Ematologia, Ospedale S.M.Goretti, Latina; *** Ist.Naz.Ricerca sul Cancro Ist. Oncologia, Genova, Italy.

Thirty-one previously untreated adult patients with advanced stage of favourable histology non-Hodgkin's lymphomas were entered into a multicenter phase II trialwith highly purified recombinant alpha A interferon (IFN-rA) as single agent. The drug was kindly provided by the Hoffmann-La Roche. IFNrA was administered intramuscularly in doses of $6x10^6$ UI/m^2 three times per week for 12 Weeks. Dose escalation was applied, in the absence of toxicities greater than WHO grade II, in patients not responding after 4 weeks. In responding patients treatment was continued at the same dose by weekly maintenance schedule for 12 additional weeks. Objective responses (4 complete, 10 partial) were obtained in 14 of the 27 evaluable patients (52%). A complete response was obtained only in NLPD and NM histologic categories. The actuarial proportions of patients alive or free from treatment failure at 34 months are 0.84 and 0.16 respectively. Hematological toxicity was irrelevant and never hastened the administration of interferon. Extrahematological side effects were generally moderate and manageable. The majority of responding patients (10/14) did so after 8 weeks of treatment. However dose escalation of IFN-rA to $12x10^6$ UI/m^2 resulted in an improvement of response in 6/15 patients. The duration of response was not significantly correlated with the onset of response nor with the escalation of IFN-rA dosage. Three patients have died, while on chemotherapy for NHL refractory or relapsed after IFN-rA, of the following causes:progressive drug-resistant lymphoma, severe bleeding, sepsis. Treatment was discontinued in three patients because of side effects and one patient refused therapy after 3 weeks.

T 39 Biological effects of Roferon-A in malignant non-Hodgkin's low-grade lymphomas.

A.M. Liberati, M.A. Horisberger, F. Di Clemente, L.Fedeli, M. Schippa, D.Adiuto, S. Cinieri, M.F. Martelli, F. Grignani. Istituto di Clinica Medica I, Policlinico Monteluce, 06100 Perugia, Italy.

Patients with low-grade non-Hodgkin's lymphomas (NHL) resistant to standard chemotherapy are being treated with increasing doses (3,6 and $9x10^6$ IU) of r-IFNα 2a for 12 weeks. IFN is given every other day and the dose increased every four weeks. After the first 12 weeks of therapy, CVP is administered during the 1st week of each month and followed by IFN at the maximum tolerated dose for the remaining 3 weeks. The following biological and immunological responses to IFN and the effect of chemotherapy on these responses are evaluated. Biochemical: serum levels of B2-microglobulin (B2-M), Neopterin (Np), 2-5 oligoadenyilsynthetase (2-5 OAS), human-Mx protein (Hu-Mx). Immunological: in vitro synthesis of PHA-indiced IFN-γ, NK activity, percentages and absolute numbers of circulating CD57+,CD59+,CD16+ cells. Six patients are presently evaluable for the biological effects induced by IFN in the first 12 weeks of therapy. Both serum levels of Np and B2-M increased 48 hours after the 1st IFN administration and remained elevated during the whole period of IFN administration. 2-5 OAS was measured in both the serum and the cell lysates. The serum and intracellular levels of this enzyme increased 2-fold 48 hours after the 1st IFN administration. There was a marked continuous rise in 2-5OAS serum levels, which seemed to be correlated with the increasing doses of IFN injected. Intracellular 2-5 OAS levels remained high during the following weeks of IFN therapy and further rises were small. Immunologically, there was a significant rise in PHA-induced IFN-γ. NK activity increased in 4/6 patients, while absolute numbers and percentages of CD57+, CD59+, CD16+ cells decreased. The unusual constitutional synthesis of Hu-Mx rose sharply in all patients tested after 48h of IFN therapy and levels of this protein remained elevated for the whole IFN administration period. In only one half of patients were the host biochemical and immunological responses reduced in the week following chemotherapy administration.

T 40 COMPARISON OF OUTCOME OF RESPONDING AND NONRESPONDING NON HODGKIN LYMPHOMA PATIENTS USING DIFFERENT STATISTICAL METHODS;

R.Heinz, B.Schneider, 3rd Med.Dept. and Ludwig Boltzmann Institute for Leukaemia Research and Haematology, Hanusch Hospital, A-1140 Vienna, Austria

The common practive of comparing the survival of responders and nonresponders when reporting outcome of patients with NHL is biased in favor of responders and the results are usually interpreted as providing evidence that response prolongs survival and/or that treatment applied is effective. We investigated NHL patients treated at the 3rd Medical Department of Hanusch Hospital Vienna during the last decade. As NHL are a heterogenous group of diseases and though different forms of treatment were used we subdivided our collective into three main groups with significant different prognosis ($p<0.0001$). Group 1 comprises NHL of good prognosis i.e. B lymphocytic lymphoma usually CLL, and lymphoplasmocytic immunocytic lymphoma, and CB/CC follicular subtype according to the Kiel classification. Group 2 the group with intermediate prognosis comprises CB/CC diffuse subtype, CC, immunocytoma of lymphoplasmocytoid und polymorphic subtype. In group 3 high grade NHL (CB, IB, LB, high grade unclassified, anaplastic PTCL, Ki-1 lymphoma) were evaluated. Treatment consisted of irradiation in localized disease and mild chemotherapy with alcylating agents in group 1 and 2 and in anthracycline containing induction regimen regardless of the initial stage of the diseases in group 3. Influence of response to different treatment modalities and outcome of responding and nonresponding patients were evaluated with 2 different valid statistical methods published recently.

T 41 PROGNOSTIC FACTORS FOR HISTOLOGIC PROGRESSION AND EARLY DEATH IN FOLLICULAR LYMPHOMAS.

B. Coiffier, Y. Bastion, F. Berger, P. Felman, J.D. Tigaud, J.J. Viala, P.A. Bryon. Centre Hospitalier Lyon-Sud, 69310 Pierre-Bénite, France.

127 patients (pts) treated from 1975 to 1985 for a follicular lymphoma were reviewed and analyzed for the risk of histologic progression and early death (<5 y). All slides have been reviewed and classify in the 3 groups of the Working Formulation: FSC, <10% large cells, 41 pts; FM, 10-50% large cells, 50 pts; FLC, >50% large cells, 30 pts. Histologic parameters included in the analysis were: percentage of large cells and of diffuse areas, mitotic rate, fibrosis, type of large cells. 18 pts were stage I, 20 stage II, 26 stage III, and 63 stage IV. 15 pts had B symptoms and 57 a bone marrow infiltration. Clinical parameters included in the analysis were age, stage, symptoms, number and type of extranodal localizations, largest diameter of the tumor, hemoglobin, ESR, serum albumin, LDH and ß2-microglobulin levels. Treatment was radiotherapy in 23 pts, chlorambucil in 7 pts, CVP in 30 pts, CHOP-like regimens in 43 pts, C-MOPP in 20 pts, and other chemotherapy in 4 pts.

80% of the pts reached CR and 47% of them relapsed. Median survival is 111 months with a median follow-up of 9 y. The relapse rate and death rate are constant with 8% of the pts relapsing and dying each year. No plateau was obtained with a follow-up >12 years. 33 pts had an histologic progression, 26% of all pts & 46% clinical progressive pts. 80% of these histologic progressions occurred during the first 6 y after diagnosis with a constant rate during this period. Histologic progression is associated with bone marrow infiltration, stage IV, high tumor mass, ≥2 extranodal sites, high mitotic rate, absence of fibrosis, and partial response to treatment. Patients with early death without proven histologic transformation had the same characteristics plus high LDH and ß2-microglobulin levels and a low serum albumin level. A multiparametric regression study isolates absence of fibrosis (p=.0002), ≥2 extranodal sites (p=.0296) and bone marrow infiltration (p=.0839) as parameters highly correlated with an histologic progression during the first 6 years after diagnosis. Early death is highly correlated in a multiparametric analysis with LDH level (p=.0002), absence of fibrosis (p=.0004), ≥2 extranodal sites (p=.0218) and stage IV (p=.0725).

Early death with or without histologic progression occurs in 50% of follicular lymphoma patients and is characterized by the presence of some clinical, histologic and biologic parameters. Patients with those characteristics should probably be treated with more intensive chemotherapy at diagnosis.

T 42 IDENTIFICATION OF PROGNOSTIC GROUPS IN LOW GRADE NON-HODGKIN'S LYMPHOMA (LGNHL) - A MULTIVARIATE ANALYSIS.

R. Leonard, L. Hayward, R. Prescott et al for the Scotland and Newcastle Lymphoma Group (SNLG), Edinburgh, UK

Between 1979 and 1987, 463 patients with Working Formulation LGNHL registered with SNLG and were treated with conventional radiotherapy and chemotherapy. Median available follow-up was 46 months. Clinical, haematological and pathological data were analysed by multivariate prognostic (PROG) index (Cox) (treatment variables excluded). 163 Edinburgh patients were excluded to provide an independent test group. The best model was based on (rank order): performance status, clinical stage, presence of fever, sex and age with best survival predicted in fit, apyrexial middle-aged women with stage 1 disease. Both younger and older patients appeared to have worse PROG. Estimates of relative risk for deviations from this best survival produced a simple PROG index. Patients fell into 3 PROG groups according to their index score. Tested on the independent sub-group, 22% had good PROG, plateau survival of 79%. 52% had intermediate (INT) PROG, 5-year survival 57%, median survival of 64 months. 26% had poor PROG, median survival 17 months and 5-year survival of 33%. INT & good PROG had no plateau; 7-year survivals were both 21%. For Edinburgh patients <70 years, the index gave similar separation of PROG groups. Simple clinical features at presentation, appropriately weighted, allow selection of poor risk patients for novel or intensive therapies.

T 43 PROGNOSTIC FACTORS IN LOW AND INTERMEDIATE GRADE NON-HODGKIN'S LYMPHOMA (NHL): A MULTIVARIATE ANALYSIS.

M. Hallek, L. Wanders, H.D. Schick, R. Busch, R. Senekowitsch, B. Emmerich, J. Rastetter. Medizinische Klinik Innenstadt, University of Munich, D-8000 Munich 2, FRG.

The prognostic value of different laboratory and clinical parameters was assessed in 209 patients (pts) with low and intermediate grade NHL (27 to 84 yrs, 84 female, 125 male) included in the study between January 1987 and October 1989. Histopathological entities according to the Kiel classification were distributed as follows: 140 pts with chronic lymphocytic leukemia or immunocytoma, 54 pts with centrocytic-centroblastic lymphoma and 15 pts with other low grade NHL. Pts on radio- or chemotherapy were excluded. Progressive disease was defined as progression of tumor parameters (e.g. thrombocytopenia, lymph node size) by > 25 % within 2 months. An univariate and multivariate analysis (Cox's regression model) of progression-free survival was performed in 97 pts evaluable, using the following parameters determined at inclusion in the study: age, sex, platelet count, WBC, hemoglobin, serum thymidine kinase (s-TK), serum $ß_2$-microglobulin, serum lactate dehydrogenase, presence of B-symptoms, number of lymph node areas involved and Karnofsky index (KI). Of these variables, all except WBC, age and sex showed a significant relationship to progression-free survival. Using a multivariate analysis on all variables, the platelet count was found to be the best factor predicting progression-free survival. Significant additional information was provided by s-TK ($P<0.01$), KI ($P=0.05$), WBC and age ($P<0.05$ for inclusion in the model). In conclusion, a limited number of clinical and laboratory parameters seems to provide sufficient prognostic information on the clinical course of low and intermediate grade NHL.

T 44 FOLLICULAR LYMPHOMAS. A PROSPECTIVE HISTOLOGICAL STUDY OF 180 CASES.

N. Brousse°, M. Peuchmaur°, P. Solal-Céligny+
°Service d'Anatomie Pathologique Hôpital Necker-Enfants Malades, Paris, +Service d'Hématologie Hôpital Beaujon, Clichy, and GELF: Groupe d'Etude des Lymphomes Folliculaires, France.

The major aim of the GELF study is the evaluation of different therapeutic trials, depending in part upon a strict pathological estimation. All the biopsy specimens of the patients included in the GELF are reviewed by a panel of 3 independent pathologists. The cytohistological analysis of follicular lymphomas (FL) included the architecture (purely follicular or follicular and diffuse) and the percentage of large non-cleaved cells (< 5%, 5-15%, 15-30%, 30-50%); the large cell FL (>50%) are excluded.

Three years after the beginning of the study, 180 cases have been reviewed. The diagnosis of FL was not confirmed in 20 (11%) cases (3 non-tumoral conditions, 5 diffuse small cell lymphomas, 4 large cell lymphomas, and 8 lymphomas involving non lymph-node organs and not proved to be follicular). In the 160 (89%) remaining cases, there were 140 cases (87.5%) of pure follicular architecture and 20 cases (12.5%) of both follicular and diffuse architecture. The ability of pathologists to recognize the growth pattern was reproductible in 71% of the cases reviewed three times. The cytologic analysis disclosed 28 (17.5%) small cleaved FL, 12 (7.5%) mantle zone lymphoma and 120 (75%) mixed FL. The percentage of large non-cleaved cell was evaluated in the range of 5-15, 15-30 and 30-50% in respectively 48%, 16%, 4% and was not determined in 6% of the cases. The reproductibility among the pathologists in the evaluation of the cytology subclassification was 53%.

These preliminary results emphasize: i) the importance of a review for definite diagnosis (11% of non FL). ii) The impossibility of affirming the diagnosis of FL on a non lymph-node tissue. iii) The moderate concordance of cyto-architectural appraisal, outlining the necessity of strict cytohistologic criteria. All the results presented will be correlated with clinical data after longer follow-up for the evaluation of prognostic factors.

This work is supported by a GELF grant.

T 45 THERAPY OF LOW GRADE NON HODGKIN'S LYMPHOMAS. A RANDOMIZED STUDY OF α 2 IFN + CHLORAMBUCIL VERSUS CHLORAMBUCIL ALONE: A PRELIMINARY REPORT.

T. Chisesi, L. Rancan, G. Capnist. Department of Hematology, S. Bortolo Hospital, Vicenza (Italy) for NHL Cooperative Study Group (NHLCSG) A. Contu (SS), V. Rizzoli (PR), A. Porcellini (PS), G. Santini, A.M. Congiu (GE), R. Sertoli (GE), P. Coser (BZ).

On the basis of the previous study conducted in our institution confirming the efficacy of association α2 IFN + Chlorambucil in relapsed or resistent pts with low grade NHL, a randomized study has been performed in a larger cooperative group (NHLCSG) to verify the import of this schedule in first line therapy. From June '86 to November '89 71 pts have been enrolled, 38 arm A 33 arm B, the median age is 61 (range 38-84). The pts were cathegorized as III (10) or IV (61) with histology B-C-D of W.F.. The pts were assigned randomly at maintenance. The schedule of therapy consisted of α2 IFN 5Mu/m2 thrice weekly plus Chlorambucil .5mg daily for 3 weeks with a week rest. At the response 2Mu/m2 thrice weekly for at least one year. We registered a response rate of 60.6% in arm A (Chlorambucil) and of 60,4% in arm B (α2 IFN + Chlorambucil) without significative differences in the different arms. According to the duration of response we were not able to find out any advantage from maintenance therapy. When considered the differences in pts aging > 60 years we obtained a higher rate remission in the older pts treated with combination of α 2 IFN + Chlorambucil. In conclusion this combined regimen seems more effective on duration of remission. We need more long observation to draw out a definitive conclusion about maintenance therapy.

T 46 RECOMBINANT INTERFERON ALPHA-2b AFTER PROMACE-CYTABOM IN THE TREATMENT OF FOLLICULAR SMALL CLEAVED CELLS N.H. LYMPHOMAS.

V. Pitini, D. Palmara, C. Arrigo, G. Chillè, M. Zanghì, P. Rizzotti and A. d'Aquino. Institute of Oncology and Research on Cancer, University of Messina, C.da Papardo - Sperone , 98010 Messina, Italy.

Still today the treatment for patients affected by NH lymphoma (Follicular Small Cleaved Cells) is one of the most controversial questions in Oncology, because of the fact that the responses to the various therapeutic agents in both mono and polychemotherapy do not last much.
However, it appears evident that aggressive treatment at diagnosis can permit a great percentage of patients to obtain a longer period of disease free survival, even if the Molecular Biology analysis highlight the persistence of the malignant cellular clone which furthermore seems to be the precursor of the relapse.
From an evaluation of the data reported in literature that indicates good responses obtained in the treatment of low-grade non-Hodgkin's lymphomas with Interferon, we have treated 6 patients affected by Follicular Small Cleaved Cells Lymphoma with recombinant Alpha - 2b Interferon after chemotherapy with PROMACE/CYTABOM.
Of the 6 patients, 4 were males and 2 were females, ages ranged from 45 to 50. Disease stage: 4 patients IV B, 2 patients IV A.
The Interferon dose was optimized from 9 to 12.000.000 U.I. according to individual tollerance. This treatment was subministered for 6 months.
At the end of this treatment all patients underwent analysis for the detection of minimal residual cells carrying the (+14;18) by the DNA sequence amplification.
This analysis has permitted to document the persistence of the neoplastic clone in all patients. This indicates that the treatment with Interferon is unsuccessfull in eradicating the neoplastic clone and therefore that further studies will have to be concentrated in this direction.

T 47 BENEFITS OF AN ASSOCIATION OF ALPHA-INTERFERON (IF) AND CHEMOTHERAPY IN PATIENTS (pts) WITH HIGH-TUMOR BURDEN FOLLICULAR LYMPHOMA

(F. L.). Ph. Solal-Céligny , E. Lepage , N. Brousse , M. Peuchmaur , C. Glasselbrecht, P. Brice , C. Haioun, M. Le Porrier, F. Reyes, B. Colffier for the "Groupe d'Etude des Lymphomes Folliculaires" (GELF) Paris, France.

Since January 1987, the GELF multicenter group has initiated a trial in pts with F.L. 221 pts with a confirmed diagnosis of FL were registered. Among them 147 were considered to have a high-tumor burden because they fulfilled at least 1 of the following criteria : involvement of 3 or more lymph node sites, each with a diameter of at least 3 cm (35 %), one nodal or extranodal tumor site of a least 7 cm in diameter (62 %), FL involvement with a risk of local complication (pleura, retro-orbital, epidural, peritoneum,....) (29 %), B symptoms (26 %), peripheral blood lymphoid cell count greater than 50 x 10^9/l (3 %) cytopenia (Hb < 10 g/dl or PMN < 1.5 x 10^9 /l or pts > 100 x 10^9/l) (11 %). Their mean age was 53 ±10 yrs. There were 80 males and 67 females. According to the Ann Arbor Classification, the stage distribution was I + II ± E = 8 %, III = 12 % and IV = 80 %. 63 % of these pts had BM involvement. 30 % had increased serum LDH levels. These pts were randomly treated either with chemotherapy alone (72 pts) (ADR 25 mg/m^2, VM 26 60 mg/m^2, CPM 600 mg/m^2 all on D1 and Prednisone 40 mg/m^2 D1 to D5, 1 cycle every 4 wks during 6 months then 1 cycle every 8 wks during 12 months) or with the same regimen associated with IF alpha-2b 5 MU x 3 per wk SC during 18 months (75 pts). At the first interim analysis (03/89), the median follow-up was 12 months. The response rate (CR + PR > 50 %) was 56 % in pts treated with chemotherapy alone and 75 % (p = 0.08) in pts treated with chemotherapy + IF alpha-2 b. 6 pts stopped IF treatment because of toxicity. There were only 2 pts with grade 4 neutropenia. These results suggest that (1) IF alpha may be safely associated with cytotoxic drugs for which in vitro tests suggest potentialization (2) such an association may improve the response rate in FL. The second interim analysis (03/90) will be presented.

T 48 INTERFERON-ALPHA TREATMENT IN PATIENTS WITH LOW GRADE NHL.

H.L. Seewann, G. Gallhofer, R. Zikulnig, Ch. Schmid. Department of Internal Medicine III. County Hospital and Institute of Pathology, University of Graz, A 8036 GRAZ, AUSTRIA.

11 pts (4 m, 7 f) aged 37 - 70 (m = 60) years with low grade NHL were treated with IFN-Alpha. Histological classification of NHL revealed: lymphocytic 1, CLL 2, prolymphoc. leukemia 1, immunocytic 4, centroblastic-centrocytic 2, angioimmunoblastic lymphadenopathy 1. Clinical staging: 10 pts showed marrow infiltration, 1 pt was CS III with spleen involvement. Duration of disease prior to treatment with IFN was 0 - 60 mos (m = 12 mos). 5 pts had been pretreated (4 with COP or CEOP, 1 pt with Prednimustin-monotherapy).

Causes for initiation of IFN treatment were: increasing lymphocyte counts (leukemic blood changes) in 4 pts (1 PLL, 2 CLL, 1 IC), enlarged lymphnodes and/or spleen size 4 pts (1 LC, 1 AILA, 1 IC, 1 CBCC) and cytopenia due to marrow infiltration 3 pts (2 IC, 1 CBCC). Treatment regimen consisted of IFN-Alpha 3 x 2 to 5 x 5 mio/U weekly for at least 3 mos. Duration of treatment was 3 to 13 mos (m = 7 mos). Criteria of response were decline of lymphocyte count in the leukemic patients, regression of lymphnode enlargement or spleen size and improvement of cytopenia respectively (in most cases thrombocytopenia).

Results:
According to general leukemia and lymphoma response criteria there was no CR or PR; minimal changes were seen in 3, stable disease in 2 and progression in 6 pts. Out of the latter group 4/6 pts were pretreated with cytostatic agents compared with only 1/5 pretreated pts in the combined minimal change & stable group.
Low dosage IFN-Alpha showed only limited effectivity in most of our investigated cases of low grade NHL. Side effects were tolerable in most cases. Further studies are necessary to define efficacy of a combined treatment schedule of IFN-Alpha with cytostatic agents.

ABSTRACTS - Fourth International Conference on Malignant Lymphoma, Lugano

T 49 MITOXANTRONE IN COMBINATION WITH PREDNIMUSTINE (NOSTE) IN LOW GRADE MALIGNANCY NON-HODGKIN LYMPHOMA (LNHL)

K. Landys, U. Wannholt, L. Röckert* and E. Holmberg**, Departments of Oncology and Pathology*, Sahlgren's Hospital and Regional Cancer Center**, S-413 45 Göteborg, Sweden

Mitoxantrone (Novantrone®) and prednimustine (Sterecyt®) have shown therapeutic activity in monotherapy studies in LNHL. This phase II study was undertaken to evaluate the efficacy and toxicity of NOSTE in LNHL. Twenty-five patients with advanced recurrent or therapy requiring initially diagnosed LNHL were entered into the study between August 1984 and June 1986. Eligibility criteria included: -histopathologically proven disease as determined by Kiel classification; -WHO performance status ≤3; -previous therapy discontinued at least four weeks ago. Median age was 61 years, range 40-78. Nineteen patients were previously treated: 13 with doxorubicin-containing regimen, 3 with CVP, 2 with prednimustine monotherapy and 1 with MEV. Six patients were previously untreated. Mitoxantrone was administered at a dose of 8 mg/m^2 IV on day 1 and 2 and prednimustine as an absolute dose 100-150 mg orally on days 1 through 5. The regimen was repeated every 4th week. The number of courses per patient ranged from 2 to 10. Complete response was assessed in 17/25 patients (=68%, 95% confidence interval was 46 - 85%). No response was seen in 8 previously treated patients. Hematological toxicity was predictable, non-hemotological toxicity was rare and mild and overall tolerance was good. Twelve of 17 complete responders relapsed. The median time to relapse (TTR) was 27 months, range 2.6 - 58.9. There are 5 disease-free survivors, the median relapse-free survival (RFS) is 4.5 years, range 4.0 - 4.9. The overall 4-year survival was 55%. NOSTE represents a suitable therapy for LNHL. The TTR, RFS together with the low toxicity are promising and deserve further analysis in a randomised study.

T 50 RANDOMIZED STUDY COMPARING PREDNIMUSTINE (PM) VS. CHLORAMBUCIL (CLB) + PREDNISOLONE (PDN) IN ADVANCED LOW GRADE NON HODGKIN LYMPHOMA.

E. Hiller, R. Herrmann, E. Musch, R. Schlag, T. Lipp, W. Wellens, B. Emmerich, A.D. Ho, E. Hügl, H. Rückle, C. Manegold, B. Termaneder, B. Nilsson and E. Thiel. Medizinische Klinik III, Klinikum Grosshadern der Universität München, D-8000 München 70, FRG.

The purpose of this study was to evaluate the efficacy and safety of PM, a PDN-ester of CLB, in comparison with the regimen of KNOSPE, i.e. CLB/PDN. Patients with chronic lymphocytic leukemia (CLL), RAI stages III and IV or immunocytoma (IC, Kiel classification), with clinical stages III and IV were eligible for this study. Patients with lower stage disease were eligible if they had rapidly progressive disease. 186 patients were randomized to receive either PM 200 mg/day for 3 consecutive days or CLB 0.2 mg/kg/day + PDN 50 mg/day for 3 consecutive days. Cycles were repeated every 2 weeks with 10% increments of daily PM and CLB, respectively, each following cycle until effect or toxicity was noted. Treatment groups were well matched for patient and disease characteristics. 44 patients had received prior chemotherapy, but not within the last 6 months. 168 patients were evaluable for response. CR or PR were achieved in 80% on PM and in 71% on CLB/PDN (not significant). At the present time 78 patients have died, whereas 61 patients are still on study. There was no significant difference between treatment groups regarding median time to response or to progression and median survival (PM 37.5 months, CLB/PDN 37 months). Toxicities other than neutropenia and thrombocytopenia were rare, WHO grade 3-4 neutropenia (41 vs. 31%) and thrombocytopenia (32 vs. 22%) was somewhat more common with PM than with CLB/PDN. In conclusion, PM is at least as effective as CBL/PDN, it is well tolerated, but is associated with slightly more hematologic toxicity.

T 51 TREATMENT OF CHYLOTHORAX ASSOCIATED WITH LOW GRADE NON-HODGKINS LYMPHOMA WITH INTENSIVE CHEMOTHERAPY.

S. ANAND, R. CHISHOLM, O.G. WARNER, J.J. MARSHALLECK, Departments of Medicine, Thoracic Surgery and Pathology, Division of Medical Oncology, Howard University Hospital, Washington, D.C., U.S.A.

Chylothorax is a rare complication of malignant lymphoma which is characterized by the accumulation of chyle in the pleural space. Management of this complication generally includes tube drainage, pleurodesis and dietary replacement of lost medium chain triglycerides. Administration of radiation and/or chemotherapy had not been considered beneficial (Fairfax, et al: Thorax: 1986:41:880-885). However, Kondo, et al(Jpn. J. Clinic. Hematol. 29(7):1093-1096,1988) recently described a case in which combination chemotherapy resulted in a marked resolution of chylothorax in a patient with malignant lymphoma.

We report here another case of chylothorax which responded to aggressive chemotherapy. A 69 year old female with follicular small cleaved lymphoma presented with massive abdominal and thoracic lymphadenopathy and an associated large left chylous effusion. The latter was treated initially with tube drainage and total parenteral nutrition. However, no reduction in chyle output was observed. On day 24 of the treatment, a modified m-BACOD (methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine and dexamethasone) regimen was initiated. Within two weeks of institution of chemotherapy, her thoracic chyle output, which had ranged between 350-500 ml/day decreased to negligible amounts and the chest tube was able to be removed. A sclerosing agent was not administered. The chest x-ray and CT scan confirmed the response. A partial remission of her abdominal lymphadenopathy was also noted.

It is concluded that intensive chemotherapy may benefit patients with chylothorax associated with malignant lymphoma.

T 52 TRADITIONAL CHEMOTHERAPY VS RADIOCHEMOTHERAPIC PROTOCOL IN THE TREATMENT OF THE GERMINAL CENTER-CELL LYMPHOMAS.

M.Lombardo,F.Angrilli,T.Filippini,M.T.Leva,M.Cirillo. Department of Haematology Chieti Pescara, Italy (Dir. Prof. G.Torlontano).

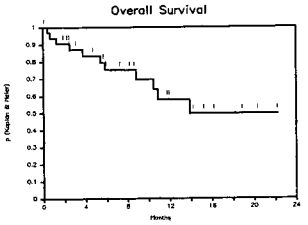
From January '76 to December '89 154 patients suffering from Germinal center cell non-Hodgkin's lymphomas have been treated at the Haematological Division of Pescara Hospital. According to the Kiel Classification, we recorded 21 ML Centrocytic (Cc), 67 ML Centroblastic-centrocytic (Cbl-Cc) and 66 ML Centroblastic (Cbl). The distribution of patients according to the stage was: I 18, II 23, III 40 and IV 73. At diagnosis, the accurence of systemic symptoms was in 82 patients. The therapeutic approachment has been performed according to two modalities:
-traditional protocols (COP, CVP, CVP+VP16, CHOP) in 55 patients;
-aggressive polichemotherapy, including the use of antraciclines, plus, if necessary, radiotherapy (BACOP ± MTX + ARA-C ± LSA2L2 modified, MACOP-B, PROMACE-CYTABOM), in 99 patients.

We have achieved 106 Complete Remissions (CR)(69%), 12 Partial Remission (PR)(8%) and 36 Non Remission (NR)(23%). Complete Responders have been 26 (47%) in the former group and 80 (81%) in the latter. Overall survival was 49% at 12 years; while 60% of the patients treated with aggressive therapy (survival and disease free survival, respectively, 62% and 60%, in case of Cc+Cbl-Cc, 53% and 45% in case of Cbl)and 19% of the patients treated with traditional protocols survived in the same period observation. After an aggressive therapy, survival and disease free survival, were, respectively, 62% and 60%, in case of Cc+Cbl-Cc, while were 53% and 45% in case of Cbl. Now, after a long period of observation we can say that all cases of Germinal center-cell lymphomas must be treated with a more aggressive therapy, including induction and re-induction cycles, plus radiotherapy. This treatment seems tobe so effective in high grade as in low grade non-Hodgkin's limphomas. We can achieve, in ML Cbl constant values of plateau by this treatment either for the overall survival or for the disease free survival. Moreover, in case of ML Cc and Cbl-Cc we have obtained a higher survival rate of patients treated with aggressive therapy and a better quality of life without illness.

T 53 PREDNIMUSTINE AND MITOXANTRONE (PmM) IN PATIENTS WITH CLL, PLL, IMMUNOCYTOMA (IC) AND CENTROCYTIC /CENTROBLASTIC NHL.

M. Freund (1), S. Wunsch, H. Link, H. Wilke, J. Wysk, M. Schäfers, H. Poliwoda (1). (1) Department of Haematology and Oncology, Hannover Medical School, D-3000 Hannover, FRG

Anthracycline-containing treatment can improve the prognosis of CLL in advanced stages with impaired haemopoiesis (Rai 3 and 4, Binet C). Based on previous favourable experiences, we have performed a study with mitoxantrone 8 mg/m² IV d 1+2, and prednimustine 100 mg/m² PO d 1-5 in pretreated patients with disseminated low grade NHL or CLL and in patients with Rai stage 3 and 4 CLL and IC without pretreatment. 33 patients have been enrolled (21 male, 12 female). 9 patients had CLL, PLL or lymphocytic NHL, 13 IC, 10 centrocytic/centroblastic, and one centrocytic NHL. The mean age was 62 (44 - 78) yrs. In NHL remission criteria were as usual. In CLL partial remission was defined as recovery from Rai stage 3 or 4, complete remission as absence of detectable tumor. Two patients are too early for evaluation. The results in the other 31 are as following: 6 CR (18 per cent; 1+ - 11 mo), 11 PR (33 per cent; 1+ - 13+ mo), 3 MR (9 per cent), and 4 NC (12 per cent). Six (18 per cent) patients had progressive disease, another died from infection. Median survial is 14 months. The main toxicity was hematologic: WHO grade 3 and 4 thrombopenia occurred in 31, granulopenia in 34, and infections in 18 per cent of the patients. Other side effects were rare with no grade 3 and 4 vomiting and with no significant alopecia. Dose reductions below 85 per cent had to be done in 40 per cent of the cycles for mitoxantrone and in 14 per cent for prednimustine. We conclude that PmM is effective and is subjectively well tolerated in low grade NHL, but its hematotoxicity is significant.



T 54 NATURAL HISTORY OF HODGKIN DISEASE (HD) AND NON HODGKIN LYMPHOMA (NHL). A 12 YEAR STUDY.

A. Nouel, N. Balliache-Marcano, E. Santos*, H. Yanez-León. Universidad de Oriente, Hospital Ruiz y Páez, *Hospital Dr. Héctor Nouel Joubert. Ciudad Bolívar. VENEZUELA.

We have studied the bio-clinical characteristics of 154 patients with malignant lymphoma diagnosed in the 2 main hospitals of Ciudad Bolívar from 1976-1989, with the purpose of comparing these characteristics with the ones reported in developed countries.
A discrete prevalence of NHL 1.7:1 (98 cases) over HD (56 cases) was found.
HD. Age ratio adult to children 1.2. 31 adult cases (55.4%) more frequent in the fourth decade (38%), 25 cases in children (44.6%), 80% diagnosed in the first 10 years, with slight predominance of males (2.3:1). Histologic Subtypes (Rye). MC: 56% in children, 48.3% in adults; NS: 22% in children, 29% in adults; LD was only seen in adults 22.5% and LP in children 12%. The most frequent complain was lymphadenopathy 51 cases (91%), predominantly cervical 72.2%, followed by inguinal localization 18.5%. Extranodal 3.6%. B Symptoms: Adults 74.2%, children 52%. Clinical Stage:79.1% of children had stages I and II, with only 38.8% of adults at those stages. Laboratory: Lymphopenia in 71.4% of adults related to advanced disease (75%) and B symptoms (85%) and in children 44% related to B symptoms 72.7%, but not with advanced disease (18.1%). ESR was raised in 66.6% of children and 86.3% of adults. Increase in FA was found in 1/4 of children and in almost half of adult cases. Blood group distribution was as follows: O (nv 60.6%): 75% in the whole group, A (nv 25.8%): adult 25%, children 15%;B (nv 11%): nil; AB (nv 2.4%): children 10%.
NHL. 75 adults (76.5%) and 23 children (23.4%) (3.2:1). 82.6% of children were in the first decade of life, and 81.3% of adults were in the 5th-8th decades. A marked prevalence of males was seen in children (3.6:1). In adults there was a discrete prevalence of males in patients with lymphomas of more aggressive histology (1.5:1), with a female prevalence in patients with lymphomas of indolent histology (3:1). Histologic Subtypes. (Rappaport): Adults: DHL: 49.3%, DLPD: 20%, IM: 9.3%, only 4% of LL and 12% of Lymphomas of low grade histology (DLWD, NLPD, NM) was found. In children: 34.78% LL, 13% LL, 13% HL and 39% DLPD (first years of study). Initial presentation was nodal in 73.6% of adult cases (cervical 39.6%, inguinal 32%), and extranodal in 69.5% of children, most frequently gastrointestinal (81.25%). Bone pain was present in 21.7% of children and 12.3% of adults. Clinical Stage: In children there was no significative statistical difference between localized and advanced disease. 71.6% of adults did have advanced disease. Laboratory: 67.5% of adults patients with aggressive histology had marked lymphopenia, in 84% directly related to advanced stages, and to B symptoms in 88% of the cases. 27.2% of patients with lymphomas of intermediate histology had lymphopenia, with prevalence of B symptoms and advenced disease in 66.6%. In indolent lymphomas the frequency was 11.1%. In children 37.5%, not related to stage or B symptoms. A high ESR in 80% of adults and 50% of children. Increase in F.A. value in 1/3 of adult patients. The frequency of blood groups was: O 58.8%, A 19.6%, and B 21.5% in adults; and 70% O, 25% A and 5% B in children.

T 55 The Epidemiologic and Pathologic Features of Malignant Lymphomas(ML) in China

Prof. Song Shao-zhang, Cancer Institute/Hospital, Chinese Academy of Medical Sciences, Beijing

The mortality rate: According to our National Survey in 70s, the mortality rate of ML/10^5/yr was 1.16, about 1/3-4 that of western countries and 1/2 of Japan.

The type distribution: In analyses of 3,366 cases of ML occurring in 12 regions from 1978 to 1982, HD(Hodgkin's disease) was found to be 10.9% (6.7-18.4%). Among cases of NHL(non-Hodgkin's lymphoma), B cell type occupied 67.9% with follicular architecture only 4.4% and T cell type 26.1%.

Composition of NHL in selected areas (1978-1982):

Area	No. of cases	% T	% B	% Undetermined
Sheng yang	42	47.6	45.2	7.2
Nanjing	684	40.2	57.0	2.8
Beijing	111	35.1	57.7	7.2
Qingdao	265	29.8	65.7	4.5
Changsha	226	27.6	69.5	3.5
Chengdu	439	26.9	72.0	1.1
Lanzhou	96	24.0	66.7	9.3
Fuzhou	205	22.4	67.3	10.3
Kunming	87	21.8	63.2	15.0
Wuhan	220	15.0	82.7	2.3
Hainan	152	14.5	73.7	11.8
Nanning	472	10.2	77.1	12.7
Total	2,999	26.1	67.9	6.0

Distribution of immunologic types (ABC method with monoclonal antibodies) of 183 cases of NHL in 4 regions (1984-1986)

Area	No. of cases	% T	% B	% Others
Suzhou	94	47.9	44.7	8.4
Shengyang	56	8.9	73.2	17.8
Nanjing	23	47.5	39.1	17.3
Qingdao	10	50.0	50.0	0
Total	183	35.5	53.0	11.6

After seroepidemiological studies on HTLV-I antibody in sera of normal donors in various regions, essentially negative results were obtained indicating no clustering of HTLV-I in China.

T 56 NON-HODGKIN'S LYMPHOMA

Hend A.Shalaby**, M.Hayat**, M.S.Sabbour*, Mahy M.El Teheawy***
Department of Medicine Ain Shams University*, Institut Gustave Roussy France**, Department of Epidemiology and Community Medicine Ain Shams University***, Cairo, EGYTPT

Analysis of 169 patients with Non-Hodgkin's lymphoma to assess the relationship between histologic criteria and clinical presentation and course; utilizing Kiel classification for the clinical extent of the disease before treatment, and staging according to the Ann Arbor classification, is presented. Nodular lymphomas constituted 10.7% of the entire group and diffuse lymphomas 82.2%. Although 52.07% of the patients had stage IV disease at presentation, localized forms (stage I,II) were observed in 37.9%. Extralymphatic involvement occurred more often in patients with diffuse than nodular lymphomas. The most frequently observed sites of extralymphatic involvement were bone marrow (31.8%),lung (29.5%) and gastrointestinal (20.5%).
Most nodular lymphoma patients had pathological stage (PS) III (33.33%) and IV (33.33%), most diffuse lymphoma patients had PS IV (55.40%).
Mean age was lower for Burkitt's lymphoma and lymphoblastic lymphoma patients. Systemic symptoms occurred in 26.62% of patients with diffuse and 11.11% of those with nodular lymphomas. Complete remission rate (CRR) correlate strongly with the pathologic stage and presence or absence of B-symptoms. Survival rate strongly correlated with pathologic stage and architectural pattern of lymphoma; patients with nodular lymphoma survived significantly longer than those with diffuse lymphoma. In stage I, excellent results were obtained with extended field radiotherapy (complete remission rate 100%, no relapse and 11.11% toxicity rate); followed by regional radiotherapy protocol (CRR) 72.73%, (relapse rate 12.5%). In stage II patients, the prognostic impacts of histology became prominent. In favourable histologic types, excellent results were obtained with the same protocols of stage I. On the other hand, with unfavourable histologic types the alternating protocol proposed by the Institut Gustave Roussy permitted early administration of both CT and RT in full dose and it gave good results.
In patients with stage II & IV disease with favourable histologic types, the higher complete remission rate was obtained with CVP protocol. In stage III & IV patients with unfavourable histologic types the complete remission rate was obtained with PROMACE-MOPP protocol followed by CHOP-bleo protocol but with relapse rate 50% for the second.

ABSTRACTS - Fourth International Conference on Malignant Lymphoma, Lugano

T 57 RETROSPECTIVE ANALYSIS OF HODGKIN'S LYMPHOMA IN NEW DELHI, INDIA.

A.Ranganathan, S.Singhal, G.K.Rath, V.Kochupillai. Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi - 110029. India.

A retrospective analysis of 256 patients of adult Hodgkins Disease seen at this Hospital over a eight-year period (1980-1988). Histologically, the mixed cellularity type was the most common (63.2%), followed by lymphocytic predominant (10.9%). Majority of the patients (58.5%) presented in Stages III and IV. The incidence of systemic symptoms was significant (59.7%) in all stages. The nodular sclerosis variety occured in only 9.7% patients with males exceeding the females by a ratio of 1.7 : 1. Bone Marrow biopsies were found positive in 27 patients (of a total 220 sampled) of which only 5 were in Stages I and II. 21 of the 27 positive patients had mixed cellularity or lymphocytic depletion varieties of Hodgkin's Lymphoma. 26 of 69 Stage I patients and 26 of 71 Stage II patients (37%) were upstaged by various invasive and noninvasive staging procedures. The clinical stage and histopathological type of the disease bear a good correlation with significant impact on treatment responses and total survival. The incidence of complete remission with the use of chemotherapy, radiotherapy or both, was 92.5% in Stage I, 63.6% in Stage II, 56.2% in Stage III and 58.7% in Stage IV. The overall response rates (complete plus partial remission) were 97.5% in Stage I, 95.4% in Stage II, 93.7% in Stage III, and 88.7% in Stage IV. Details of survival data and the modalities of treatment used, will be discussed.

T 58 Clinico-pathological Correlations in Non-Hodgkin's Lymphomas

D. Rădulescu, N. Galatăr, E. Marinca, C. Nister
Oncological Institute , Cluj-Napoca, Romania

We made clinico-pathological correlations in 100 patients with Non-Hodgkin lymphomas, classified according to the "Working Formulation" , in the evidence and treatment of the Oncological Institute, between 1980-1989. Correlations were made between made histology on one hand, and clinical staging at presentation, the presence of systemic signs, the degree of lymphatic nodes' involvement (including the Waldeyer's ring), the most common extranodal sites of involvement (including the bone marrow), the incidence of blood discharge, on the other hand. The great majority of Non-Hodgkin's lymphomas presented in advanced stages, with generalised adenopathies. Systemic signs were encountered with high-frequency in the lymphoblastic (100%), the immunoblastic (82%), followed by the intermediate - grade diffuse lymphomas (45-60%); their incidence was low in the small lymphocytic lymphomas (18%). Involvement of Waldeyer's ring had a high incidence in the diffuse large - cell, mixed - cell and small cleaved lymphomas (20-28%). The highest incidence of extranodal involvement was present in the immunoblastic (73%), lymphoblastic (50%) and small lymphocytic lymphomas (39%). The bone marrow was often involved in the small lymphocytic (64%), and lymphoblastic lymphoma (66%). We observed a high incidence of blood discharge in the diffuse large-cell and mixed-cell (40-57%), the lymphoblastic (50%) and small lymphocytic lymphoma (39%). In conclusion we defined different patterns of clinical evolution for the different pathological subgroups of malignant lymphomas, a fact with important therapeutic implications.

T 59 COMBINATION CHEMOTHERAPY WITH COBDP IN MALIGNANT LYMPHOMA : AN ANALYSIS OF 64 CASES.

Jin Xingquan, Xu Yuexiang, Zhao Tiping, Department of Chemotherapy, Cancer Hospital, Shanghai Medical University, 200032 Shanghai, P.R.China

From Feb.1986 to Feb.1989,64 evaluable patients with malignant lymphoma were treated with cyclophosphamide, vincristine,bleomycin A5,cis-diaminedichloroplatin and prednisone (COBDP regimen) in our hospital.There were 46 males and 18 females.The ages ranged from 7 to 75 years with a median age of 38.The scales of Karnofsky Performance Status in 62 cases was >70.Among them,there were 7 cases with Hodgkin's lymphoma and 57 cases with non-Hodgkin's lymphoma (NHL) based on Rye classification (1965) and Modified Working Formulation classification (Chengdou,1985).According to Ann Arbor staging system (1971),patients were staged I,5 staged II,22 staged III, 30 staged IV.70% of 57 cases with NHL had unfavorable (intermediate- and high-grade) histology.
The COBDP regimen consisted of cyclophosphamide 600mg, iv,on days 1.8;vincristine 2mg,iv,on days 1.8;bleomycin A5 10mg im,on days 1.4.8.11;cis-diaminedichloroplatin 20mg,iv drip on day 1-5;prednisone 10mg,po,tid,on day 1-14.After two weeks intervals,the course mentioned above was repeated.All patients received two or more than two courses.
The results showed that 22 patients had complete remission (CR),33 partial remission (PR),2 no change,4 progressive disease or died of complications within two months after treatment.The overall objective response rate to COBDP regimen was 90%(CR 37% plus PR 53%).The CR rate was 56% in 25 patients untreated previously,28% in 39 patients with prior chemotherapy with or without radiotherapy, the difference was statistically significant ($P<0.05$), but no statistically differences were found in median CR duration (>12 months v >9 months) and median survival for CR patients (>16.5 months v >15 months).The median survival after CR was significantly longer than PR for previously untreated and treated patients ($P<0.05$).
The common toxicity and side effects caused by COBDP regimen included anorexia,nausea,vomiting,alopecia and leucopenia.There were no treatment-related deaths and pulmonary toxicity.
The data showed that COBDP regimen is one of the satisfactory first line combination chemotherapy regimen.

T 60 GROUP RISK CLASSIFICATION OF NON-HODGKIN'S LYMPHOMAS.

A.Avilés, L.Rodriguez,JDíaz-Maqueo, R.Guzmán, E.L.Garcpia, A.Talavera. Hospital de Oncología, Centro Médico Nacional, I.M.S.S.,MéxicoD.F. Mexico.

One hundred and sixty-two patients with Non-Hodgkin's lymphoma were treated with cyclophosphamide,adriamycin, vincristine and prednisone (CHOP) or CHOP-Bleo (CHOP plus bleomycin); and evaluated according to a multiple regression analysis model, which was the following three factors associated to bad prognosis: clinical evolution (less than three months), bone marrow infiltration and high levels of lactate dehidrogenase (LDH).
The Cox model of analysis also agreed that the clinical evolution and high levels of LDH were bad prognostic factors. These two factors were associated with poor remission rates and short survival. A mathematical model was built based on the last two factors.
Five groups of patients were observed with increasing risk of a poor response and a short survival rates,which allowed us to identified three prognostic groups with clear differences in both the duration of remission and survival. The three groups were classified as low-, intermediate- and high-risk.
These results will have important clinical implications for the desing of the prospective clinical trials in patients with malignant lymphoma.

T 61 PROGNOSTIC FACTORS IN AGGRESSIVE LYMPHOMAS: DESCRIPTION AND VALIDATION OF A PROGNOSTIC INDEX THAT COULD IDENTIFY PATIENTS REQUIRING MORE INTENSIVE THERAPY.

B. Coiffier, E. Lepage, C. Gisselbrecht, J.O. Armitage, H. Tilly, R. Herbrecht, A. Bosly, J.M. Vose, for the G.E.L.A. Centre Hospitalier Lyon-Sud, Pierre Bénite, France.

The 737 patients treated with LNH-84 regimen (J Clin Oncol 1989;7:1018) were analyzed for prognostic factors for response to treatment, relapse, FFR survival, and overall survival. Histological types were according to the Working Formulation D 3%, E 2%, F 15%, G 52%, H 19%, I 4%, and J 4%. Factors having an adverse prognostic significance (p<.0001) for survival in univariate analyses were: age ≥65, stage III and IV, B symptoms, PS ≥2, tumor mass ≥10 cm, ≥2 extranodal sites, weight loss, bone marrow infiltration, serum albumin ≤30 g/l, and increased LDH level. In Cox model, stage, bone marrow involvement, number of extranodal sites, and LDH level retain prognostic significance for FFR survival. For overall survival, LDH and albumin levels, stage, number of extranodal sites, tumor mass, and age retain prognostic importance. A prognostic index was construct with these parameters. Age and serum albumin level did not increase the value of the index and were dropped out.

Index	Mass ≥10	≥2 sites	Stage ≥III	Increased LDH
1	-	-	-	-
2	1 or 2 adverse factors			-
2	-	-	-	+
3	+	+	+	-
3	1 to 3 adverse factors			+

This index partition our patients in 3 subgroups with good, intermediate and bad prognosis (p<.00001): CR rates 93%, 83%, 61%; relapse rates 12%, 25%, 45%; 4-year FFR survival 79%, 61%, 34%; 4-year survival 84%, 73%, 51%. This index was applied to 155 patients treated with CAP-BOP regimen in Nebraska. The 3 groups had 4-year DFS survival of 71%, 40%, 25% (p=.0002); 4-year survival of 70%, 54%, 30% (p=.005). Use of this index in patients with aggressive lymphoma could identify patients requiring intensive treatment and those who could be treated with classic regimens. For example, young patients with index 3 could be included in prospective trial testing ABMT in first CR.

T 62 EVOLVING PROGNOSTIC FACTORS IN 151 CONSECUTIVE PATIENTS WITH AGGRESSIVE NON HODGKIN'S LYMPHOMA.

A.R. Bianco, P. Tagliaferri, A. Contegiacomo, F. Caponigro, R. Calderopoli, R. Lauria, V. Montesarchio, I. Falco, R.V. Iaffaioli, G. Palmieri. Division of Oncology, University of Naples, Medical School II.

We have reviewed the pretreatment characteristics of 151 consecutive patients (pts) with aggressive non Hodgkin's lymphoma, who were observed at our Institution from 1977 to 1989. The patient population was divided into three groups according to time of diagnosis: group I, pts diagnosed between 1977 and 1981 (n=41); group II, pts diagnosed between 1982 and 1985 (n=54); group III, pts diagnosed between 1986 and 1989 (n=56). All pts were treated with ongoing chemotherapy programs.

We evaluated the following pretreatment characteristics, which are thought to represent the most significant prognostic factors in aggressive non Hodgkin's lymphoma: age, stage, B symptoms, bulky disease, LDH levels, Hb levels, bone marrow involvement, number of extranodal sites. Results of our analysis are shown below:

	Group I	Group II	Group III	
Age < 40	12.2%	24%	33.9%	
" 41-60	48.8%	44.4%	33.9%	
" > 60	39%	31.6%	32.2%	p < 0.01
Stage I-II	31.8%	38.9%	35.7%	
" III	21.9%	11.1%	12.5%	
" IV	46.3%	50%	51.8%	
B symptoms	24.4%	29.6%	41.1%	
Bulky disease	17.1%	22.2%	41.1%	p < 0.05
LDH > 240	26.8%	24.1%	66.1%	p < 0.001
Hb < 10	9.8%	14.8%	8.9%	
Marrow involv.	12.2%	27.7%	12.5%	
0 extranod. sites	65.9%	29.6%	32.1%	
1 "	26.8%	46.3%	44.6%	
> 1 "	7.3%	24.1%	23.3%	p < 0.001

Our results seem to indicate a changing pattern in the presentation of aggressive lymphomas, with an increasing incidence of some unfavorable prognostic factors. If our observation is confirmed by other Institutions, it may lead to a reconsideration of the therapeutic programs of this group of diseases.

T 63 STAGE I HIGH GRADE NON-HODGKIN'S LYMPHOMAS: A RETROSPECTIVE ANALYSIS.

F. Gherlinzoni, P. Mazza, G. Poletti, M. Bocchia, S. Tura. Istituto di Ematologia "L. e A. Seràgnoli", Università di Bologna.

37 consecutive patients (pts) with high grade non Hodgkin's lymphoma (NHL) clinical stage I (excepted for lymphomas arising from gastrointestinal tract) treated between 1983 and 1988 have been retrospectively analyzed. Mean age was 46 yrs (range 16-75); histolgy was: centroblastic lymphoma in 18 pts, immunoblastic lymphoma in 10 pts, lymphoblastic lymphoma in 6 pts and anaplastic large-cell lymphoma (ki-1 positive) in 3 pts. Nodal involvement was found in 9 pts, extranodal involvement in 18 pts.. Sites of extranodal disease were: Waldeyer's ring, skin, bone, paranasal sinus, testis, thyroid and larynx. 10 pts presented with bulky disease.

Treatment consisted of radiotherapy (RT) alone in 19 pts, RT with adjuvant chemotherapy (CT), in 14 pts, CT alone in 3 pts. 1 pt had no other therapy after diagnostic biopsy. All the pts with bulky disease had adjuvant CT after RT. At a median follow-up of 27 months, overall survival is 83% and 7 yrs projected freedom from relapse is 81%. No differences were recorded neither between nodal or extranodal lymphomas nor between pts treated with RT alone or with RT and CT. This study suggests that clinical stage I high grade NHL can be successfully treated by RT alone. CT before RT may be recommended in NHL subgroups with higher relapse rate, i.e. pts with bulky disease.

T 64 PHASE II TRIAL OF m-BNCOD IN NON-HODGKIN LYMPHOMA (NHL)

J. Fernandes, A. Sousa, V. Mesquita, M. Bernardo, A. Pereira, J. Veiga, I. Ribeiro, J. Oliveira, M. Sousa, A. Gonçalves, I. Costa e J. Gouveia; Unidade de Hematologia, Hospitais Civis de Lisboa, Lisboa, Portugal.

The efficacy of the m-BACOD regimen (Skarin, Canellos et al, 1983) for diffuse large cell (DLC) NHL is well demonstrated. In an attempt to lower toxicity, keeping the same efficacy, we started in June 1986 a Phase II trial replacing Doxorrubicin (DXR) for Dihydroxianthracenedione (DHAD) at 10 mg/m^2; until November 1989, 49 patients (pts.) with histologically proven NHL, non HIV related, were treated. Pts. were 37 male, median age 54 (16 ⩾65), PS 0-2 37; histology was 37 intermediate (20 DLC), 10 high and 2 low grade. Ann Arbour stage was 18 I-II (16 bulky), 24 stage IV; extra-nodal sites (ENS) were bone marrow (BM) 16, digestive tract 10, other sites 17; 13 pts. had previous CT ± RT (7 relapsed, 6 refractory). Pts. were treated on an outpatient basis. 45 pts. are evaluable.

Main toxicity was hematological with leucopenia II-III in 28% of cycles (84/291), thrombocytopenia II-III 8% (24/291); mucositis II-III 7% (20/291); peripheral neuropathy I-II 9% (4/45); alopecia was II in 22% pts. (10/45); transient EKG abnormalities occurred in 2 pts.; another pt. had congestive heart failure after DXR 550 mg/m^2 and DHAD 45 mg/m^2 with previous normal echocardiogram. Lethal toxicity was 3/45 (6,5%), 2 infectious non-neutropenic, 1 G-I toxicity with diarrhea and uremia. The q21 day schedule was accomplished only in 57% of cycles, the remainders delayed to q28 day.

Overall RR was 95% (43/45) with CR 44% (20/45) and PR 51% (23/45). There is a trend toward lower CR in pts. ⩾65, PS 3-4, high grade histology, BM involvement. In 4 pts., disease progressed on treatment after CR or PR (3 in CNS and 1 in primary nodal bulky site), 3 of them with Methotrexate < 75% of predicted dose. 4 pts. relapsed off treatment, 3 in nodal sites primarily involved, non-bulky, and 1 in nodal and ENS not primarily involved (3 were previously treated pts.). Survival of the whole group and of CR patients is 52% and 72% respectively at 26 months. The median time to progression of the 43 responding patients is 24 months. These results, similar to those obtained by others, must be validated with a longer follow-up.

T 65 BRIEF CHEMOTHERAPY (ACOPB) PLUS INVOLVED FIELD RADIOTHERAPY (IFRT) IN LOCALIZED STAGE OR EXTRANODAL DIFFUSE LARGE CELL LYMPHOMA (DLCL): PRELIMINARY RESULTS.

L.Orsucci, U.Vitolo, M.Bertini, A.Levis, L.Depaoli, F.Ficara, R.Ghio, D.Rota-Scalabrini, E.Scassa and L.Resegotti. MRSGNHL, c/o Div. of Hematology, Molinette Hosp, Torino, Italy.

In localized stage DLCL RT alone gives high complete remission rates (CR), unfortunately between 25 and 60% of CRs relapse. Chemotherapy (CT) as CHOP +/- RT was proved to be more effective, however 20-30% of pts still relapse. More recently a new 6-week CT called ACOP-B has been proposed (Connors et al) for this group of lymphomas. Therefore from September 1987 we tested the efficacy of this more intensive sequential CT + IFRT. ACOPB was given as originally proposed with the following schedule: Doxorubicine 50 mg/sqm iv and Cyclophosphamide 350 mg/sqm iv on day 1 of weeks 1,3,5; Bleomycin 10 U/sqm iv and Vincristine 1,4 sqm iv on day 1 of weeks 2,4,6; Prednisone 50 mg po daily throughout 6 weeks (tapered on the last week), cotrimoxazole 1 DS tab po BID and oral nystatin daily for 6 weeks. One month after CT ended IFRT 36 Gy in 20 fractions was given to the site of initial disease. Till now 32 pts were treated: 17 males and 15 females with a median age of 56 yrs (range 28-78). Histologic subtypes were: diffuse mixed 12, diffuse large 12 and immunoblastic 8. Stages were: IA 4, IAE 13, IIA 7 and IIAE 8. Sites of extranodal disease were: gastric 10, small bowel 1, lung/pleura 2, bone 4, skin 1, ENT 4, soft tissue 4. 5 pts had bulky disease. After ACOPB all pts but one achieved a CR. The only one in PR after CT was converted to CR with the subsequent IFRT. With a median follow-up of 13 months, only one relapsed. There were no deaths due to lymphoma. One died of unrelated disease. Toxicity was graded according to WHO and was generally mild: mucositis grade 1-2 in 12 pts, peripheral neuropathy grade 1 in 11, moderate bronchial infection in 2. No cardiac or lung toxicities nor toxic deaths occurred. Hematological tolerance was good: neutropenia <500 in only 3 pts, Hb <10 gr/dl in 3 and no cases of thrombocytopenia. Even pts over 60 (44%) tolerated the program fairly well. A longer follow-up is needed to draw definite conclusions, however these preliminary results suggest that ACOPB + IFRT is a brief, effective and well tolerated treatment for localized stage DLCL.

T 66 CEOP/PEB ALTERNATED CHEMOTHERAPY IN ADVANCED STAGE NON-HODGKIN'S LYMPHOMAS (NHL) WITH UNFAVORABLE HISTOLOGY.

P.Comella, G.Abate, G. Di Finizio, A.Mineo, D.Zarrilli. National Tumor Institute, Cappella dei Cangiani, 80131 Naples, Italy.

Twenty-four pts (M/F=13/11) affected by NHL in advanced stage were treated with CEOP (CTX 750 mg/mq i.v., EDX 50 mg/mq i.v., VCR 1.4 mg/mq i.v. d 1, PDN 100 mg p.o. d 1-5) alternated every 21 d with PEB (CDDP 100 mg/mq i.v. d 1, VP-16 100 mg/mq i.v. d 1-3, BLM 15 mg i.v. d 1&8). Twenty-three evaluable pts received a median of 8 courses of therapy. We observed 16 CRs (69%), 2 PRs (9%) and 5 PD (22%). CR rate was affected by grade of malignancy according to W.F. (intermediate=12/15, high=4/7), stage of disease (III=6/6, IV=10/17), bulky disease (yes=10/16, no=6/7). All pts experienced vomiting of grade 2-3 and alopecia. Grade 1-3 leukopenia and anemia were observed in 79% of pts, and grade 2 thrombocytopenia in 8% of pts. Grade 1-3 hepatic toxicity was seen in 25% and infection in 33% of pts. Six of 16 CRs subsequently relapsed within 1-15 (median, 6) months. After a follow-up ranging from 7 to 29 months, the probability of overall survival was 48% and the projected disease-free rate was 33% after 20 months from the end of therapy. CR rate in this study was somewhat better with respect to our previous experience with CEOP alone (Haematologica, 73, 509, 1988), considering that most pts had extranodal or bulky disease, but hematologic toxicity was also increased and the compliance of pts to CDDP-including regimen was poorer. More pts and a longer follow-up are needed to assess the actual effectiveness of this approach of therapy.

T 67 THE TREATMENT OF NON-HODGKIN'S LYMPHOMA WITH IFOSFAMIDE-MEV.

L.M. Zetina Toache, Dept. of Internal Medicine, Roosevelt Hospital, Guatemala, C.A.

16 newly diagnosed patients with high-grade non-Hodgkin's lymphoma (7 females and 9 males) were treated with Ifosfamide: 1.5 g/m2 daily for 3 days: Methotrexate: 35 mg/m2 on days 1 and 8, Etoposide: 100 mg/m2 for 3 days and Vincristine: 1.4 mg/m2 on days 1 and 8. To avoid haemorrhagic cystitis Uromitexan (Mesna) 200 mg/m2 iv was administered at 0.4 and 8 h after Ifosfamide (IFO-MEV). All patients received 6-8 cycles of IFOMEV. Median age was 30 years with a range from 8 to 60 years. Stage IV: 6 patients, Stage III: 6 patients and Stage II: 4 patients. 81 % of pts. had B symptoms. The median follow up is 22 months. 56.2 % (9) achieved a complete remission and 31.2 % (5) achieved a partial remission, with a overall response of 87.4 %. The relapse-free survival remained for 8 and 12 months in two patients with CR, and the other 7 patients are still in CR. The major toxicity of this regimen was leukopenia. Four patients had leucocyte nadir below 1.000/cmm, but none had life-threatening infection. Thrombocytopenia and anemia were mild. Other toxicities were alopecia (12); nausea and vomiting (6); paresthesia (3); transient hepatic damage (1); mild haemorrhagic cystitis (2). This regimen has been effective in treatment of patients with high-grade non-Hodgkin's lymphoma as front line chemotherapy. These preliminary results are very exciting (87.4 % CR + PR) and warrant further studies.

T 68 EFFİCACY AND TOXICITY OF CYLOPHOSPHAMİDE MİTOXANTRONE-VİNCRİSTİNE-PREDNİSONE COMBİNATİON CHEMOTHERAPY İN ADVANCED DİFFUSE LYMPHOMAS-2-YEAR-RESULTS.

E.Büyükünal,S.Serdengeçti, F.Demirelli,N.Mandel,U.Derman,B.Berkarda.İstanbul University,Cerrahpaşa Medical Faculty,Deparment of Medical Oncology,İstanbul,Turkey.

We tested the efficacy and toxicity of the combination of mitoxantrone ($10mg/m^2$),cyclophosphamide ($750mg/m^2$),vincristine ($1.4mg/m^2$) and prednisone ($50mg/m^2$ D_1-5) as first line treatment for patients with advanced agressive-non-Hodgkin's lymphoma.

Among 30 evaluable patients,36 % complete and 44 % partial responses were observed,for an overall response rate of 80 %.The median duration of response and survival was 14 (R:3-24+) months;disease-free-interval was 11 months (R:4-24+).

Myelosupression and neuromuscular toxicity of moderate degree were the two major side effects,however the regime was generally well tolerated.

These results indicate that the combination regimen can play a significant role in the treatment of advanced agressive lymphomas.

T 69 MIMEV - FIRST LINE TREATMENT FOR HIGH RISK LYMPHOMAS NON-RESPONSIVE TO CONVENTIONAL CHEMOTHERAPY.

F.C. Duarte, L.H. Cisne, C. Ferrera, F. Muñoz, H. Aguilar. Hematology-Oncology Service, Hospital Escuela, Boulevard Suyapa, Tegucigalpa, Honduras.

We determined the response, survival time and toxicity after treatment with a combination of Mesna, Ifosfamide, Methotrexate, Epidophyllotoxin and Velba (MIMEV), in 25 patients, age between 14 and 17 years (median= 35), predominantly female (female/male ratio= 1.8), classified as high risk lymphomas (17), relapsing lymphomas or Hodgkin's Disease (9), or lymphomas unresponsive to conventional therapy (3).
In the cases of high risk lymphomas, the combination was used as first line therapy. Ninety per cent of the cases were in clinical stage III and IV, uniformly distributed in the Karnofsky scale (10-80%).

Twenty patients (83%) had complete remission, two patients (8%) had a partial remission and two (8%) had no change. Fifteen cases (68%) presented remission after one cycle, three cases (14%) after two cycles and four cases (18%) after four (18%) after four cycles. Five cases (23% of remissions) had a relapse. The median of the survival time was seven months, with a range from 0.6 to 24 months. The cumulative survival rate was 60% at 12 months, and 20% at 24 months.

The most common side effects were nausea and vomiting (92%), alopecia (60%), leukopenia (60%) and Thrombocytopenia (34%). Eighteen patients developed complications: infections (72%), central nervous system involvement, deep vein thrombosis, cachexia, bleeding and tumor lysis.

We conclude that this regimen is effective, as first line treatment, in patients with high risk lymphomas; and that it is an alternative in the treatment of patients with non-responsive or relapsing lymphoma and Hodgkin's Disease.

T 70 MULTICENTER COMBINED CHEMOTHERAPY PROTOCOL FOR LARGE CELL ADVANCED NON HODGKIN'S LYMPHOMA.

J. Dumont, P. Charpy-Validire, V. Mosseri*, JC. NATALI, B. Asselain*, Institut Curie (*unité de biostatistiques) Paris, J. Gabarre, V. Missenard, JL Binet, CHU Pitié Salpétrière, Paris, C. Bellanger, F. Dreyfus, B. Varet, CHU Cochin Paris, F. Turpin, M. Janvier, Centre René Huguenin St Cloud, F. and F. Teillet, CHU Colombes, FRANCE

72 patients with stage III and IV non Hodgkin's lymphoma, large cell type, were treated with an alternating chemotherapy regimen including weekly: Cure A: Adriamycin (50mg/M²), Vincristine (1,4mg/m²), Cyclophosphamide (400mg/m²), Bleomycin (10mg/m²), IT Methotrexate (10mg/m²) and Cytarabine (20mg/m²). Cure B: IV Methotrexate (500mg/m²) followed by leucovorin rescue. Cure C: Adriamycin (50mg/m²), Ifosfamide (1,5g/m²), Etoposide (120mg/m²), IT MTX and ARA-C idem cure A. Cure D: idem cure B. Complete responders after 3 cycles A,B,C,D, were given 18 Gys cranial irradiation and randomised between 1 additional cycle or 3 monthly CHOP.
Among 66 evaluable patients, 45 achieved a complete remission (CR 68,2%) and 8 a partial remission (12,1%). There were 5 non-responders and 8 early deaths during initial phase, mostly due to septic problems. Despite this relative toxicity, 4 patients, non included in the 66 patients group because of age (older than 70 years) were able to tolerate this regimen and to achieve a durable complete response. 34 of the 45 CR patients (75,5%) have remained free of disease with a median follow-up of 18 months (1-49). 7 among the 10 relapses occurred during the first year, the 3 others at 15, 19 and 41 months respectively. There was 1 unrelated death. The 2 year survival was 68,7% for the whole group, and 84,1% for the CR group. No difference until now was observed between the two groups with different additional modality treatment.
In order to avoid early relapses, our present regimen includes a consolidation phase with intensive chemotherapy (BEAM) and autologous bone-marrow transplantation, for patients with initial unfavourable pronostic factors : for patients who achieved only partial response (> 75%) after the two first cycles, and for stage IV patients if associated with LDH> 500 U.I./l, or if there is an involvement of bone marrow, or central nervous system, or breast, or testis, or at least 2 other non-lymphoide organs.

T 71 CHOP-VA-MB SEQUENTIAL INTENSIVE CHEMOTHERAPY FOR PATIENTS WITH AGGRESSIVE NON-HODGKIN LYMPHOMAS. A NON-RANDOMIZED PHASE II/III STUDY.

C. Lindemalm & M. Björkholm for the Swedish Lymphoma Study Group. Dept of Oncology and Division of Hematology, Karolinska Hospital, S-104 01 Stockholm, Sweden

Within the last decade the potential cure for patients with non-Hodgkin lymphomas (NHL) of high grade malignancy has been recognized. It has also been claimed that multiple regimens administered in short intervals between drug delivery might improve the cure rate. Based on this assumption the Swedish Lymphoma Study Group investigated the effects of combination chemotherapy given in the following 15 weeks schedule:

Cyclophosphamide	350 mg/m² i.v.	Day 1, weeks 1,4,7,10,13
Doxorubicin	60 mg/m²	
Vincristine	2 mg i.v.	
Prednisone	75 mg p.o.	Days 1-10, w. 1,4,7,10,13
Etoposide	100 mg/m² i.v.	Days 1-3, w. 2,5,8,11,14
Cytarabine	100 mg/m² i.v.	
Bleomycin	10 mg/m² i.v.	Day 1, w. 3,6,9,12,15
Methotrexate	250 mg/m² i.v.	

Leukovorin rescue was initiated 24h after the methotrexate infusion. Fourty-nine patients, 35 men and 14 women with a median age of 54 years (range 18-80 years) in clinical stages II-IV entered the study between November 1985 and November 1986.
RESULTS:
Sixty per cent of the patients achieved a complete remission (CR) and 77% of the patients stayed in unmaintained CR for >2.5 years. However, toxicity was marked. Leuko- and thrombocytopenia was noted in 50% of the patients as well as mucositis. Three patients achieved pulmonary toxicity probably related to bleomycin.
CONCLUSION:
Combined chemotherapy of this aggressive model could be safely administered with the potential of cure for a substantial number of patients.

T 72 PRELIMINARY RESULTS OF MeNCOP-B REGIMEN IN INTERMEDIATE GRADE LYMPHOMAS.

M. Rochon, M. Lépine-Martin, P. Beauregard, B. Longpré, D. Bergeron, G. Bisson, S. Massé. Service d'hématologie, Centre hospitalier universitaire de Sherbrooke, Sherbrooke, Québec, Canada, J1H 5N4.

Recent induction regimens for the treatment of agressive lymphomas are reputed to produce more complete remissions but are responsible for a 5% - 10% fatality rate. Moreover, multiorgan toxicity is of concern in people over 55. Since February 1986, a modified MACOP-B regimen was initiated in 24 patients median age 60 (39 - 77); essentially mitoxantrone (novantrone) 10 mg/m² replaces doxorubicin (adriamycin) thus the acronym MeNCOP-B. During treatment 17 patients experienced grade 3 or 4 leucopenia and 4 patients developed bacterial infections. Mucositis grade 1 or 2 occurred in 10 patients, no mucositis greater than grade 2 was observed. After 8 weeks of continuous steroid therapy 4 patients required transfusions for gastrointestinal bleeding. There were no toxic deaths. Out of 19 previously untreated patients with advanced intermediate grade lymphomas an objective response was achieved in 79% (15/19) of patients (CR 3 pts, PR 12 pts) when measured 16 weeks after beginning of treatment. Subsequent radiotherapy converted 4 partial remissions to CR. There were 4 primary failures in patients with adverse prognostic features (bone marrow involvement: 3, high LDH: 2, poor performance status: 1), all died within one year of diagnosis. An alternate regimen is needed in patients with adverse prognostic features.