ABSTRACTS

PRESENTATION BY TITLE ONLY

ABSTRACTS - Third International Conference on Malignant Lymphoma, Lugano

T 1 PHENOTYPIC AND GENOTYPIC STUDIES ON SPORADIC BURKITT'S LYMPHOMAS (sBL).

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The biopsies from 22 patients with sBL (17 pediatric, 5 adult) were analysed with T and B cell specific monoclonal antibodies. The DNA from 10 cases was also studied by Southern blot hybridization with probes specific for the TCRß, JH, C-MYC genes, and for EBV genome. Phenotypically all cases were HLA-DR+, CD2-, CD5-, Y29.55+, SmIg+; 83% were CD10 (CALLA)+ and 90% CD24+. Cases positive for FMC7, SmIgM, SmIgD were 77%, 80%, 71% respectively. 10% of cases were unreactive with the anti- Burkitt Mab 38.13, of the remaining 60% were strongly reactive, 30% weakly. 5/5 cases were CD19+, CD22+, CD23-, CD37+. With regard to the pediatric group, all treated with the same protocol, no significant clinical presentation and survival rate differencies were observed when the cases were split into CALLA+ and CALLA- subgroups. The genomic studies revealed that the TCRß was, in all cases, in the germ line configuration; conversely JH and C-MYC were rearranged, with multiple bands detected in two cases. The size of the rearranged C-MYC bands varied from case to case. The hybridization of EcoRI digested DNA blots with JH and C-MYC showed that in two cases the rearranged fragment size of both genes had the same M.W.. EBV sequencies were detected in one case only. Overall, the sBL have a B cell phenotype characterized by a common expression (or absence) of the CD19+, CD22+, CD23-, CD37+, Y29.55+ determinants and can be dissected into subgroups according to the differential reactivity with CD10, CD24, FMC7, 38.13. They all have c-myc rearranged and only rarely EBV genome can be found in them.

T 2 KARYOTYPE ABNORMALITIES IN NON-HODGKIN LYMPHOMAS (20 CASES).

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We have attempted to correlate histo-immunological and cytogenetic aspects in 20 non-Hodgkin's malignant lymphomas :

- 6 nodular B-lymphomas
- 6 diffuse lymphomas
- 8 T-lymphomas

Recurring chromosome abnormalities specific of particular types of lymphomas and complex chromosome abnormalities were found.

In the nodular B-lymphomas, we noted specific chromosome abnormalities such as t(8;21), (q24;q32) in a case of Burkitt's lymphoma, t(14;18)(q32;q21) in a follicular lymphoma and frequent involvement of chromosome 14 at band 14 q32 in the various chromosome rearrangements. In the mixed-cell nodular lymphomas, in one same tumor we found several abnormal cellular clones with different chromosome abnormalities. This may, we feel, be explained by the fact that the different clones reflect the morpho-functional variation of varied cell types within the B proliferation.

In the diffuse lymphomas, no specific chromosome abnormality of malignant grade was noted in these tumors. A 6q21 deletion associated with other chromosome abnormalities was found in a case of centroblastic lymphoma. The 11q23 deletion, associated with other chromosome abnormalitieswas observed in two cases of immunoblastic lymphomas. We suggest that chromosome abnormalities such as del.6q21 and del.11q23, specific to certain histological types, modify, when associated with other chromosome abormalities, the phenotypical aspect of the lymphoma with which they are usually associated.

In the T-lymphomas, we noted that a trisomy 19 was always present in large-cell lymphomas. We also recorded, in 80 % of these lymphomas, abnormalities in structure and in the number of chromosome 3.

In our study, various structural abnormalities of chromosome 1 recurred particularly often in T-lymphomas : Iso 1q, del.1q, inv. peric. 1, dup.1q.

An oncogene, situated somewhere in a region of the long arm of chromosome 1 may be involved in the T-lymphomas.

T 3 BIPHENOTYPIC EXPRESSION OF MYELOID AND B CELL ANTIGENS ON MONOCLONAL EBV POSITIVE CELL LINES DERIVED FROM NORMAL DONORS.

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Cell lines grown from 5 normal donors either spontaneously or induced by B95 cell culture supernatant containing Epstein-Barr virus (EBV) were studied with respect to surface markers and immunoglobulin gene rearrangements. Antigens were determined repeatedly by an indirect enzyme-immunoassay using an alkaline phosphatase conjugated secondary antibody on adhesive slides. 70-90% of the cells were positive with B1- and B2-antibody (CD20) wherease the proportion of VIM-D5 positive cells (CD 15) varied between 3 and 90% among the cell lines. Both markers were found on the same cells by means of a double marker technique employing consecutive stains with fast blue BB- and fast red TR- salt and interposed blocking of the enzyme by HCl (2 M) which allowed the simultaneous detection of 2 determinants without destruction of antigens. Clonality was assesed by Southern blot technique: DNA of the cell lines was digested by Hind III and hybridized to a µ-specific probe, demonstrating monoclonal rearrangements of the µ chain immunoglobulin gene.
These data indicate that immortalization of normal B cells by EBV produces clones which, besides B antigens, express myeloid antigens at a constant individual degree. It can only be speculated if clones with high proportion of biphenotypic antigen expression represent cells with disturbed differentiation or transformed precursor cells of earlier progeny.

T 4 PROGNOSTIC SIGNIFICANCE OF CYTOGENETIC STUDIES IN ANGIOIMMUNOBLASTIC LYMPHADENOPATHY (AILD).

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AILD is a lymphoproliferative disease considered so far as a hyperimmune reaction or as prelymphoma. Previous cytogenetic studies revealed chromosome aberrations in the majority of the cases.
In the present study the prognostic significance of the chromosome findings should be evaluated.

Our series comprises 34 cases, including 16 yet unpublished cases. 27 of these cases (79 %) showed chromosome abnormalities in lymph node cultures. The abnormalities were monoclonal in 13 cases, both clonal and non-clonal in 7 cases. Only single cell abnormalities were found in 7 cases, only normal metaphases in another 7 cases. There were always normal mitoses besides the aberrant ones.
The most frequent findings were trisomy 3 (14 cases), trisomy 5 (8 cases), and aberrations of the X-chromosome (11 cases).

Cytogenetic findings of 19 cases were compared with survival data. Patients with clonal abnormalities had a median survival time of 14 months. In this group (n=10) only one patient is still alive. Patients with normal karyotypes had a median survival time of 21 months. The group with single cell abnormalities does not markedly differ from the group with normal karyotypes. In the group without clonal abnormalities four out of nine patients are still alive. The number of mitoses studied was equal in all groups.

This indicates that cytogenetic findings may be of prognostic value in AILD.

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T 5 TRANSLOCATION 2/8 (p 12:q 24) IN TWO CHILDREN WITH BURKITT LYMPHOMA.

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In Burkitt type lymphoma the most frequently seen chromosomal abnormality is 14 q+; t 8/14 (q 23;q 32) (Zech et al. 1976, McCaw et al. 1977). However t 8/22 (q 23;q 12) is sometimes revealed, as well as the rare abnormality t 2/8 (p 12; q 24) (Philip et al. 1980).

In our study of children with malignant lymphoma treated at the Belgrade University Children's Hospital from 1976 to 1986 we have assessed that 30% of them had Burkitt type lymphoma. In these children we have studied initial presentation of the illness, clinical and laboratory findings, therapy and evolution.

Cytogenetic study of bone marrow using G Band technique was made in 10 children. Of these, in two a rare chomosomal abnormality t (2p;q8) (p 12;q 24) was confirmed. The authors point out the significance of cytogenetic studies in Burkitt lymphoma in which changes on chromosome 8 are apparently a significant marker for tumor cells, identically as Philadelphia chromosome is for chronic myeloid leukaemia.

T 6 CHROMOSOMAL REARRANGEMENTS IN LYMPHOBLASTOID CELL LINES (LCL's) FROM PATIENTS WITH HODGKIN'S DISEASE (HD) AFTER IN VITRO TREATMENT WITH CYTOSTATIC DRUGS USED IN HD THERAPY.

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Epstein-Barr virus transformed B lymphoblasts (= lymphoblastoid cell lines = LCL's) from patients with HD as well as from healthy controls were used either for long term or for short term experiments. In long term investigations the cell lines were treated 5 times for 2 hours each over a period of 3-6 months. For short term experiments the cell culture was exposed only once for the last 24 hours before harvesting the cells. Afterwards, chromosome preparations were performed and chromosome bands involved in structural rearrangements were analyzed from about 100 metaphases of each culture. After long term in vitro treatment with activated cyclophosphamide in a LCL from a HD patient, a clonal aberration, namely a translocation between the long arm of chromosome 1 and the short arm of chromosome 17 was found. After treatment with bleomycin the same LCL showed other clonal rearrangements: a translocation t(1;11)(q21;q23/25) and a translocation t(3;5)(q27/29;q31). The significance of these chromosomal aberrations is discussed and it is emphasized that in malignant disorders like acute nonlymphocytic leukemia and non-Hodgkin lymphomas which often occur as secondary malignancies after HD, the same chromosomal regions are involved in marker formation as in our HD derived LCLs after in vitro treatment.

T 7 HODGKIN - STERNBERG-REED-CELLS IN VITRO PRODUCE ROSETTE INHIBITING FACTORS.

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The Hodgkin derived cell line L 428 generates a factor, capable of suppressing the capacity of T-lymphocytes from normal donors to bind sheep red blood cells (SRBC). The factor (RIF = rosette inhibiting factor) does not interfere with the binding sites of OKT11 or Leu7a monoclonal antibodies and does not change the expression of OKT4, OKT8, or OKT11 antigens. RIF suppresses the rosetting capacity of about 50 % of the T-lymphocytes; the suppressed cells can be found in both OKT4 and OKT8 fractions. RIF is active in an 37 C assay system, but not at 4 C. The activity is stable to heating up to 56 C and does not tolerate acidic (pH6) or alkaline (pH9) pH or trypsine treatment. It can bind to lipoproteins. RIF was partially purified by affinity-, ion-exchange- and molecularsieve-chromatography and has an apparent molecularweight of 25 KD.

T 8 MOLECULAR CHARACTERIZATION OF HODGKIN'S DISEASE DERIVED CELL LINES.

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The origin of Hodgkin (H) and Sternberg Reed (SR) cells is still not clear. The availability of cell lines with characteristic properties of H and SR cells allows molecular analyses to characterize the cells. We have analyzed the organization and expression of immunglobulin (Ig)-, T-cell receptor (TCR)- and IL2-receptor genes and certain proto-oncogenes. Our results indicate that two Hodgkin's derived cell lines have rearrangements and expression of TCR genes. A third line however shows rearrangements and expression of Ig genes. All three cell lines express IL2-receptor mRNAs. In addition the expression of the proto-oncogenes c-myc, c-raf, p53, N-ras, Ha-ras1, Ki-ras2 and c-myb were detected by northern blotting experiments. These results indicate that the cell lines resemble immature lymphoid cells, but express antigens (CD30, IL2-receptor), which habe been detected on activated lymphoid cells only.

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T 9 IN HODGKIN'S DISEASE ONLY REED-STERNBERG CELLS HAVE AN ABNORMAL KARYOTYPE.

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Altough the histogenesis of Reed-Sternberg cell still has remained a subject of controversy there is substantial evidence of the neoplastic nature of Reed-Sternberg cell. In this study of one case of Hodgkin's disease we show that only Reed-Sternberg cells have an abnormal karyotype.

A biopsy of a left supraclavicular mass in a 21 years old man revealed a histology of Hodgkin's disease of nodular sclerosis type. In a cytocentrifuge preparation stained with May-Grünwald-Giemsa the differential count showed 2% mono- or multinuclear Reed-Sternberg cells and >90% small lymphocytes. In addition there were some eosinophils, macrophages and epithelioid histiocytes. 71% of the small lymhocytes were positive for pan-T antibody (Leu 4), 37% for combined kappa+lambda antibodies and 0% for an antibody against Reed-Sternberg cells (Ber H-2, prof.H.Stein). 86% of Reed-Sternberg cells were positive for Ber H-2, 73% for combined kappa+lambda antibodies and none for Leu 4. The conventional chromosome analysis revealed a clone of 72 chromosomes with several structural and numerical changes in 10 mitoses. Fifteen mitoses had a normal karyotype of 46,XY.

A combined analysis of morphology, immunocytology and karyotype with the new MAC (**M**orphology **A**ntibody **C**hromosomes; Blood 1984;64:1116, Cytogenet Cell Genet 1985; 39:70, Am J Clin Path 1986;85:602) method showed that all the 9 analyzeable mitoses positive for Ber H-2 had an abnormal karyotype with 72 chromosomes. A normal karyotype was found in all 30 mitoses positive for Leu 4 and in two mitotic cells of small lymphocyte size positive for kappa+lambda. 12 mitotic cells of Reed-Sternberg cell size were also positive for kappa+lambda and contained 72 chromosomes. None of the mitotic cells of Reed-Sternberg cell size with 72 chromosomes were, however, positive for pan-B antibody (Leu 14) indicating that these big cells were not B-cells, but rather Reed-Sternberg cells containing immunoglobulins. There were no mitoses positive for antibodies against natural killer cells (Leu 11) or interleukin-2 reseptors (IL 2).

Our results indicate that Reed-Sternberg cells (Ber H-2 positive mitoses) have an abnormal karyotype and are thus neoplastic. The other cells have a normal karyotype and were mostly T-cells, rarely B-cells. Further patients will be analyzed and presented.

T 10 PROGNOSTIC FACTORS IN HODGKIN'S DISEASE. THE SPECIAL VALUE OF HISTOLOGIC AND CYTOLOGIC ASPECTS AND OF LEU M1 EMA MARKERS.

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The study was carried out on 155 cases of Hodgkin's disease treated at Grenoble between 1975 and 1985 (representing 69 % of all patients seen for Hodgkin's disease during this period).
The histology was reviewed and the slides classified into 4 types according to the Lukes classification. Among the type 4 (21 %), a sub-type was individualized, called atypical Hodgkin (type 4'), based on architectural criteria : an elevated number of malignant cells with invasion of the lymphatic sinuses, and vascular emboli (16 patients or 10 %).
The cytology slides (touch preparations) permitted the distinction of typical forms from atypical forms based on characteristics of the Sternberg cell : considerable nuclear dystrophy, cytoplasmic hyperbasophilia, and absence of edema of the chromatin (17 patients or 12 %).
These cases of Hodgkin's disease were also classed according to the positive reaction of Sternberg cells to the following monoclonal antibodies : Common Antileucocyte (CAL) PD 7/26 DAKO (128 cases positive = 83 %) Antikeratin (KL-1) immunotech (0 case positive/155). LEU M1 B.D. (143 cases positive = 92 %) and EMA DAKO (32 cases positive = 21 %). The combination of markers LEU M1 and EMA permitted the definition of 4 phenotypes : LEU M1+ EMA- (76 %) ; LEU M1+ EMA+ (16 %) ; LEU M1- EMA+ (5 %) ; LEU M1- EMA- (3 %). The first phenotype corresponds with the typical morphological form of Hodgkin's disease, while the other three are highly correlated with the atypical forms as well as with an unfavorable prognosis.
A multifactorial analysis of the prognostic factors in the population studied showed that 5 factors of poor prognosis are preponderant and complimentary : age > 50 yrs, atypical histology, atypical cytology, stage IV of the Ann Arbor classification, and EMA+. They determine 2 groups : patients who have none of these characters (94 cases or 61 %) for whom only one death was observed (1,1 %) and those presenting one or several of these characters (61 cases or 39 %) for whom 29 deaths (48 %) were observed.

T 11 ANTIPROLIFERATIVE EFFECT OF THE MONOCLONAL ANTIBODY HD37 (CD19, p95) ON NON-HODGKIN'S LYMPHOMA CELLS.

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The introduction of monoclonal antibodies (MoAbs) proved to be a powerful tool for the precise classification of hematological malignancies, especially with respect to lineage specificity and differentiation stage. In addition, with MoAbs it was possible to study and define antigens functioning as receptors for biological activities or as binding sites within cell-to-cell interaction. We investigated the possible functional role of the CD19 antigen, representing the broadest B lineage specific marker by using the MoAb HD37 (IgG1, CD19). Our target cells were B lymphoma cell lines (free of EBV transformation) expressing the CD19 antigen. Both cell lines have been derived from patients with high grade malignant lymphomas. The cell lines were established from a bone marrow aspirate and a lymph node biopsy. In a semisolid clonogenic culture assay (methylcelluose 0.9%, human plasma 30% and 2 ME 2 $x10^{-5}$M) the functional effect of HD37 added to the culture system in a concentration between 0.01 and 1 ug/ml was assessed. For the NHL cell lines tested a reduction of 35-55% in the number of colonies in comparison to the controls could be demonstrated. Similarly, the mean ^{3}H-thymidine uptake in the presence of HD37 in identical concentration was between 40-60% compared to the controls in a 72 hrs culture period. For those experiments 1 x 10^{4} cells/ml were plated in flat bottom microwells in RPMI supplemented with 1-10% fetal calf serum. The ^{3}H-thymidine was always added 16 hrs before cell harvest. In all experiments control MoAbs of the same IgG class were included to rule out any unspecific effects.
In summary we conclude that the CD19 antigen is functioning within the regulatory network of neoplastic B cell growth and proliferation. In addition, Pezzutto et al. demonstrated similar effects of HD37 on normal B cells of peripheral blood and tonsils. With our future studies we try to elucidate the biological mechanisms, so that HD37 might be used in the treatment of patients with B cell malignancies as a new immunomodulatory drug.

T 12 CYTOSTATIC TREATMENT OF NUDE MOUSE TUMORS INDUCED BY ESTABLISHED HUMAN HODGKIN CELL LINES

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Although a variety of chemotherapeutic regimens exist for the treatment of refractory or recurrent Hodgkin's disease, the results have in general been up to now disappointing. We therefore decided to establish a preclinical model for the testing of various schemes of treatment of Hodgkin's disease.
The investigations were performed in two long term in vitro Hodgkin cultures (L428, L540). The cell line L540 induces both intramuscular (i.m.) and intracerebral (i.c.) tumors in the nude mouse, the L428 produces i.c. tumors only. In the i.m.-system the success of therapy was judged by the reduction in tumor volume, in the i.c.-system by the prolongation of survival time compared to a control group. 9 different cytostatic drugs were tested as monotherapy in a variety of doses.
With the cell line L540 similar results were obtained with regard to sensitivity and resistance in both the i.m. and i.c.-systems. DTIC and procarbazine proved to be the most effective drugs, both produced complete remission of i.m. tumors, no relapses occured within the observation period of a hundred days (4/4 and 5/5 respectively). The animals with i.c.tumors had a median survival time of 26 days following therapy with DTIC and 12 days following therapy with procarbazine, the controls survived 6,25 days. In these animals, in contrast to the i.m.group, death was due to tumor relapse. CCNU produced a reduction of tumor volume of the i.m. tumors of 50 %, 2 out of 5 animals entered complete remission. In the i.c.-model CCNU prolonged survival to 26 days. Bleomycin as well as methotrexate therapy resulted also in tumor reduction or increase of survival. No effect was seen with vinblastine, IFF or cisplatin therapy.
In the L428 cell line only cisplatin produced a response with intracerebral tumors. Median survival was prolonged to 22 days in contrast to 12 days in the control group.
The effectiveness of DTIC and procarbazine in the L540 line is in contrast to the clinical experience, where progression occurs under therapy with COPP/ABVD. We will discuss the probability that the dosages of some of the effective drugs in rapidly alternating therapy regimens may be too low. The effectiveness of CCNU and methotrexate is in good agreement with clinical experiences in treatment of relapses. These results form the basis for the testing of new cytostatics and for the development of new treatment regimens.

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T 13 IMMUNOCHEMICAL EVIDENCE FOR MU HEAVY CHAIN DISEASE PROTEIN IN A CASE OF GASTRIC LYMPHOM

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Mu Heavy Chain Disease Proteins are defined as incomplete polypeptide chains of IgM class devoid of light chains.

Such an immunological abnormality was detected in the serum of 54 years old woman suffering from gastric lymphoma.

The abnormal protein escaped detection by routine electrophoresis and immunoelectrophretic analysis by antiserum to whole human serum. It was subsequently detected in the serum (but not in concentrated urine) by immunoelectrophoresis using anti-IgM antibodies. as supplementary arc of Beta-1 mobility under normal IgM precipitin line. This dual precipitation was not revealed by anti-Kappa and anti-Lambda antibodies.

Because of the scarcity of patient's serum. the abnormal protein was isolated by affinity-chromatography using successive passage over anti-IgM and anti-Kappa-Lambda light chain Sepharose-4B columns.

The eluted protein still expressed IgM antigenic determinants and migrated in S.D.S-polyacrylamide gel rods as unique band of 35.000 daltons molecular weight.

No decrease in molecular weight was noted after reduction and alkylation. These results suggest the presence of monomeric form of Mu Heavy Chain Disease Protein.

T 14 ASSESSMENT OF IMMUNOLOGIC STATUS IN CHILDREN WITH MALIGNANT LYMPHOMA AFTER COMPLETED TREATMENT AND LATE EFFECTS OF ANTICANCER THERAPY.

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During the application chemotherapy and radiotherapy in the long term treatment of malignant diseases depression of cellular and humoral immunity as late effects have been reported (Borella et al. 1971, Green et al. 1973, Hitzig et al. 1976, Stojimirović et al. 1985). Today when new therapeutic approaches enable long term survival, great significance is laid on the quality of life, specially in paediatric patients. Impaired immunosurveillance may produce increased susceptability toward infection and may play a role in the development of secondary cancer.

At the Belgrade University Children's Hospital we have followed the status of cellular and humoral immunity in 24 children with malignant lymphoma (14 Hodgkins and 10 Non Hodgkins) 6 months to 6 years following the discontinuation of the therapy. The study involved estimation of absolute lymphocyte count, estimation of T cell count using T rosette method with sheep red blood cells, and quantitative estimation of total number of T lymphocytes. . T helper (inducer) and T suppressor (cytotoxic) subpopulation were assessed using monoclonal OKT4 and OKT8 antibodies. B cell count was obtained by detecting membrane immunoglobuline bearing lymphocytes and concentrations of IgM, IgG and IgA in the serum determined.

Investigation results showed that absolute lymphocyte count was decreased in the substantial number of children due to the decreased T lymphocyte count. T helper/suppressor ratio was statistically significantly decreased. In most children B cell count was within the normal limits. The decreased rate of serum IgM was statistically significant and it correlated with disorders of T lymphocytes ans T lymphocyte subpopulations. Concentration of IgG and IgM in the serum was not significantly impaired.

The difference between our results and reports by other authors may be explained, to our opinion, mainly by the differences in the used protocoles.

T 15 PHARMACOKINETIC STUDY OF FOLINIC ACID IN CEREBROSPINAL FLUID.

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Folinic acid (D,L,5-formyltetrahydrofolate, CHO-THF) and its active metabolite (5-methyltetrahydrofolate, CH3-THF) were measured in the blood and CSF of normal volunteers after a single i.v. administration. CHO-THF and CH3-THF were analyzed by HPLC (paired ion and UV detection). Three dose regimens were compared: 50 mg, 100 mg and 250 mg. Coupled samples were collected 1,2, 6 and 24 hours after injection. There were three subjects per time and dose (total 36). Results showed that:

1. only CH3-THF penetrates CSF (maximum at 6 hours)
2. the AUC CH3-THF CSF/AUC CH3-THF plasma ratio is around 10%
3. there is a significant linear increase between the dose and AUC CHO-THF in plasma, AUC CH3-THF in plasma, and AUC CH3-THF in CSF
4. CH3-THF is cleared more slowly from CSF than from plasma

These data appear useful for rational management of methotrexate treatments with folinic acid rescue, particularly in patients with malignant lymphoma and CNS involvement.

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T 16 PHORBOL MYRISTATE ACETATE INDUCES LOW-AFFINITY FUNCTIONAL INTERLEUKIN 2-RECEPTORS ON A PRE-B LEUKEMIC CELL LINE.

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The human pre-B leukemic cell line (Reh-6) does not constitutively express IL2-receptors (IL2-R), but cell incubation with Phorbol Myristate Acetate (PMA) induces expression of IL2-R in a dose-and time-dependent manner. IL2-R expression on Reh-6 cells requires de novo DNA, RNA and protein synthesis. Binding experiments with radiolabelled recombinant IL2 (rIL2) revealed low-affinity IL2-R. However, IL2-R-bearing Reh-6 cells absorbed rIL2 in a dose-dependent manner. This absorption was inhibited by a monoclonal antibody against IL2-R (anti-Tac). rIL2 also allowed a time-dependent "down-regulation" of IL2-R. Moreover, rIL2 enhanced colony formation from PMA-induced Reh-6 cells which could also be inhibited by anti-Tac.

These findings indicate that the Reh-6 cell line can be induced to express low-affinity but functional IL2-R after PMA incubation, and may provide a convenient model to study the molecular and biochemical mechanisms which regulate their expression on immature B cells.

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T 17 ENDOGENOUS LECTINS IN HUMAN HODGKIN CELLS.

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The origin of the malignant cell in Hodgkin's disease is unkwown. Long term in vitro cultivation of Hodgkin- and Sternberg-Reed-cells provides reproducable material for membrane analyses. Endogenous lectins (carbohydrate-binding proteins) of tumor cells are supposedly involved in growth regulatory and recognitive processes, relevant to tumor growth and spread (1). Potential clinical applications of such lectins in therapy as targets by controlled drug delivery or diagnosis require thorough analysis of the different types of lectins present on tumor cells. As a first step to infer the presence of such membrane lectins in human Hodgkin cells (cell lines L428, L540 (2)), we have employed cell surface labelling fluorescent neoglycoproteins. Lectin-mediated uptake of neoglycoproteins as a step to drug targeting was then measured by inhibition of DNA sythesis, effective in the presence of certain drug-neoglycoprotein conjugates. Possible participation of lectins in intercellular interactions was determined by sugar dependent inhibiton of rosette formation with trypsinized, glutaraldehyde treated erythrocytes. Biochemical analysis using affinity chromatography on supports with immobilized sugar or glycoproteins reveals the presence of a beta-galactoside-specific lectin at apparent molecular weight of 14 kDa, an alpha-fucoside-specific lectin at apparent molecular weight of 22 kDa, an alpha-glycoside-specific lectin of apparent 30 kDa and a sialic-acid-binding protein at apparent molecular weight of 11 kDa.
The presence of membrane lectins in malignant Hodgkin cells provides a rationale for further studies to test their usefulness in improvement of clinical management of this tumor type.

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T 18 RECOMBINANT ALFA INTERFERON IN THE TREATMENT OF MYCOSIS FUNGOIDES.

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From November 1985 to December 1986 in an ongoing study 17 patients with Mycosis Fungoides (M.F.) or Sezary's Syndrome were treated with recombinant alfa-2a interferon (ROFERON-A Roche). Up to date 15 patients are considered evaluable. The study design included patients with MF or Sezary's syndrome refractory to previous treatments (PUVA or chemotherapy or both) and patients previously untreated with stage more than II detected by Cohen's system. The protocol consisted of daily interferon administration in excalating dose from 3 MU to 18 MU for 3 months. After this time all patients underwent other 6 months therapy with 18 MU three times weekly. Both preliminary response and tolerance are reported.
Fifteen patients entered the study (13 MF and 2 Sezary S.) with median age 53 y; 12 were previously treated and 3 untreated. Among pretreated patients two obtained a pathologic complete remission documented with skin biopsy, 7 obtained more than 50% (60% to 90%) reduction of skin detectable lesions or circulating Sezary's cells and 3 a minor response (< 50%). Among untreated patients 2 obtained a pathologic complete remission (CR) and one a partial remission. Side effects included fever (15/15), flu-like syndrome (12/15), nausea-anorexia (10/15), itching (1/15), paresthesia (1/15), somnolence (4/15). Haematological toxicity included thrombocytopenia $< 50X10^3/ml$ (1/15) or $<100 \times 10^3/ml$ (4/15), neutropenia < 2000/ml (10/15). Protocol violations included a reduction of scheduled dose in 8 patients: temporary interruptions were necessary in 5 patients of which 4 for clinical intolerance and 1 for haematological toxicity. No deaths related therapy were recorded.

T 19 RECOMBINANT LEUKOCYTE ALFA-2A INTERFERON (r IFN α-2a) IN UNTREATED CUTANEOUS T-CELL LYMPHOMAS.

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Since February 1986, 15 patients with histologically confirmed Mycosis Fungoides (MF) or Sezary Syndrome (SS) have been treated with subcutaneous r IFN α-2a (Hoffmann - La Roche) as single agent. r IFN α-2a was administered daily with dose escalation from 3 to 18 million units during a 12 week induction, and thereafter 3 times weekly at maximal tolerated dose. Patients induced into complete (CR) or partial (PR) remission were given r IFN α-2a for 6 more months after achievement of maximal response; patients with progressive disease were withdrawn. Patients with stable disease during induction were re-evaluated after 3 more months of treatment: then, only responding patients were kept on protocol as above. There were 12 males and 3 females with a median age of 63 (range: 20-76). Two patients had SS, 8 had T1-T2 skin lesions, and 5 had cutaneous tumor; none had positive node biopsy or visceral involvement on abdominal sonogram. Median percentage of OKT4 and OKT8 lymphocytes was, respectively, 36% (range: 14-44) and 13% (range: 4-28). All patients were untreated but one, who had received local radiotherapy. Liver toxicity was dose limiting in 4 patients, fatigue in 3, leukopenia in 2, and diarrhea in one. Flu-like syndrome was transiently experienced by all patients. Psoriasis flare led to withdrawal of one patient from protocol. Among 12 evaluable patients, 5 are in CR, 6 are PR, and one progressed during the first 12 week treatment: median time to response was 5 months (range: 4-6). Clinical CR was confirmed by pathological re-staging: no biopsy showed persistence of T-cell infiltration. CR was achieved by all patients receiving 100% of scheduled induction dose. All patients showed an increase of OKT8 lymphocytes number, which was more evident in CR patients. No patient has relapsed so far. These initial results are very encouraging: r IFN α-2a as administered in this study is well tolerated, and induces a significant response in a high percentage (CR + PR= 92%) of patients. A longer follow-up period is necessary to evaluate the long term result of r IFN α-2a in cutaneous T-cell lymphomas.

T 20 RECOMBINANT INTERFERON 2B IN COMBINATION WITH CHLORAMBUCIL IN THE TREATMENT OF NON-HODGKIN'S LYMPHOMA (A PHASE II STUDY).

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The evaluation of response and the efficacy of recombinant interferon Alpha 2b (Intron A) in combination with Chlorambucil has been studied in 22 pretreated or relapsed pts., with non-Hodgkin's low-intermediate grade lymphoma. The treatment schedule consisted of Interferon 3 Mu/m2 thrice weekly and Chlorambucil 10 mg daily for three weeks, with a week's rest. Treatment continued for up to six cycles. Two complete remission (CR), 12 good partial remission (GPR), 7 no remission (NR) and one stable disease were obtained. According to histology, we observed a response in 8/10 follicular lymphoma (2 CR and 6 GPR), in 3/5 diffuse and 3/7 diffuse mixed. The median follow up is of 12 mos. (range 6-18); the median duration of response is 8.4 for pts. in maintenance regimen and 4.6 mos. for pts. without therapy. There are 5 pts. under maintenance therapy consisting of 5 Mu/m2 weekly. Two pts. relapsed at 3 mos. and one at 8 from the end of therapy: all of them were retreated with the same regimen and responded. The major toxicity consisted of fever and nausea. Hematologic toxicity was generally mild and occurred between the third and fourth cycle. These results allowed to us to consider this regimen as effective for relapsed or resistant non Hodgkin's lymphoma. Against this background we started a first line randomized study to compare in pts. with follicular histology the response to Chlorambucil + IFN versus a conventional regimen with Chlorambucil alone. This protocol is now under evaluation as first line therapy in a cooperative study group.

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T 21

A phase II study with Interferon beta (IFN-B) in lymphoproliferative syndromes. A.M.Liberati, M.F.Martelli, B.A.Falini, M.Fizzotti, S.Cinieri, L.Cini, M.Schippa, G.Federici, F.Grignani. Clinica Medica I, Policlinico Monteluce, Univ. Perugia, 06100 Perugia, Italy.

Since the antitumor activity of different IFN species may be correlated with their aminoacid sequence, as is shown by the fact that the biochemical IFN system is heterogenic, it would seem that the various IFN species exert differential natural functions. So far, few studies have investigated IFN-B activity in patients with lymphoproliferative syndromes. Twenty-two patients with lymphoproliferative diseases recieved treatment with IFN-B (6 pts were treated with IFN-B produced by the Pharmacological Inst. Sclavo and the remaining 6 pts with the IFN-B provided by the Serono company). IFN-B (6 x 10^6 IU/sqm, 6 hour IV infusion) was administered x 7 days with 7 day intervals x 3 cycles (induction therapy). Then, IFN-B at the same dose was given twice/week by IV bolus x 12 wks and by 6 hour IV infusion x additional 12 wks (maintenance therapy). Partial remission (> 5% residual hairy cell in the bone marrow biopsy) was achieved in 5 out of 6 hairy cell leukemia (HCL) pts who had completed the entire therapeutic regimen. There was a significant reduction in spleen volume and striking improvement in the hematological counts within the first 6 wks of treatment in all 5 of these pts . After treatment discontinuation, remission duration ranged from 3 to 10 + months. There has also been a significant improvement in the clinical and hematological parameters during the course of induction therapy in the additional 5 evaluable HCL pts at present on treatment. The only HCL pt who failed to respond to IFN- B did not benefit from a 2nd treatment with rIFNα-2. Response was observed in a radiotherapy- and chemotherapy resistent Sezary syndrome patient during the course of the induction therapy and in another polymorphic T-cell skin lymphoma during the first week of treatment. The clinical response was non-significant in 4 chemotherapy resistent multiple myeloma (MM) pts, while it was not evaluable in the 3 MM patients still in the course of induction therapy. Neither was a response obtained in a pt with prolymphocytic leukemia after induction or during the first 6 wks of maintenance therapy. IFN-B is, therefore, like IFNs α a useful palliative treatment in certain lymphoproliferative syndromes.

T 22

Synergic effect of natural Interferon beta(nIFN-B) and recombinant Interleukin-2(rIL-2) on NK cell function in hairy cell leukemia patients. A.M.Liberati, M.Fizzotti, S.Cinieri, L.Cini, M.Schippa, G. Federici. Clinica Medica I, Univ. Perugia, 06100 Perugia, Italy.

Hairy cell leukemia (HCL) pts generally have very low NK cell activity levels, that may reflect either a true depletion of overall NK cell fraction (pre-NK cells and mature functionally NK cells) or a reduction in the number of cytolitically mature NK cells. If the 2nd hypothesis were true, immunomodulators known for their NK-cell booster activity might be able to correct the NK-cell defect that occurs in HCL pts. We, therefore, tested the in vitro activity of low doses of nIFN-B (10 IU/ml), rIFNα-2 (10 IU/ml) and rIL-2 (5 IU/ml) on NK-cell function. A significant increase of NK-cell activity was exerted by nIFN-B in 8 of 20 experiments and by rIFNα-2 in 4 of 6 assays. IL-2, however, at the dose used, was able to boost NK-cell function in 3 instances. When effector cells were incubated overnight with both nIFN-B and IL-2 , synergic or additive effect of these molecules was observed in 8/20 and in 4/20 experiments respectively. Although there were no apparent differences in the NK-cell booster activity of 10 IU nIFN-B or rIFNα-2 when used alone, synergic or additive effect was observed, when rIFNα-2 and IL-2 were used together, only in 2 of the 6 pts tested. In addition the effect was less marked than that observed with the nIFN-B in the same mononuclear cell preparation. Similarly, in another 2 instances, the NK-cell activity of the same effector cell preparation was additively or synergistically boosted by the nIFN-B and IL-2 combination, but not by rIFNα-2 and IL-2 combination. The finding of synergistic effect between low doses of nIFN-B and IL-2 suggests that these two molecules affect different NK-cell subsets. Preliminary results of a series of experiments designed to identify the target cells of the combined effect of nIFN-B and rIL-2 and the mechanism underlying the synergism of these two molecules indicate that : 1) the target cells are Leu7+ and Leu11+; 2) rIL-2 may act by increasing the number of IFN-B receptors (incubation of effector cells with rIL-2 followed by incubation with nIFN-B is more effective than the reverse sequence); 3) the addition of a MoAb reactive with the IL-2 receptor before or during the incubation of effector cells further increases the synergic effect.

Natural IFN-B was kindly provided by the SCLAVO and SERONO Pharmaceutical companies.

T 23

AROTINOID-TREATMENT IN ADVANCED CUTANEOUS T-CELL LYMPHOMAS. K. Meissner, E. Hoting, H. Voigt*, Dept. of Dermatology, University of Hamburg, Hamburg, FRG, and *Max-Brauer-Allee 52, Hamburg 50, FRG

Up to now, prognosis of advanced cutaneous T-cell lymphoma is very poor, particularly in intensively pretreated patients. This prompted us to study the effect of arotinoid ethyl ester (Ro 13-6298) on the clinical course of 6 patients with advanced cutaneous T-cell lymphomas.

The patients (female:2, male:4) with a median age of 58 years were found to have stage IB(n=1), IIB (n=2), III (n=1), and IVA (n=2). All patients had had extensive photochemotherapy and/or X-ray pretreatment and revealed progressive disease. Starting dose was 0.3 mg p.o. daily (≙ 0.004 mg/kg/day) and was modified according to clinical response and to toxic side effects. Median treatment duration was 64,7 weeks (2-104 weeks). Response parameters were evaluated in 4 weeks intervals.

1/6 patient (stage IVA) had a complete remission lasting for more than 59 weeks at present. 2/6 patients (stage IVA, stage III) had a partial remission with a median duration of 33 weeks. 1/6 patient (stage IIB) had a stable disease at 2 weeks and had to be retired from further study due to persistant cephalgia. 2/6 patients (stage IIB, stage IB) had disease progression at 4 weeks and were subsequently excluded.- Toxic side effects were: skin desquamation, atrophy, and vulnerability (6/6), cheilitis (6/6), exsiccation of oral mucosa (6/6), nail dystrophy (4/6), effluvium (4/6), rhinitis sicca (3/6), conjunctivitis (1/6), hypertriglyceridemia (1/6), persistant cephalgia (1/6). In 4/6 patients dose reduction was necessary due to toxic side effects. Overall treatment's tolerance was moderate.

At 4 weeks in 4/6 patients control biopsies were taken for assessment of histological alterations. In 3/4 biopsies, the epidermis as well as the subepidermal grenz zone were found to be cleared from mononuclear cell infiltration. Immunohistological examinations (three step immunoperoxidase method)did not reveal preferential reductions of certain T-cell subsets; in the epidermis, helper T-cells representing the mononuclear infiltrate had disappeared.

Arotinoid treatment appears to offer a promising approach to the treatment of advanced cutaneous T-cell lymphomas, even in prognostically very unfavourable patients. Despite extensive radiotherapeutic pretreatment of all patients significant improvement could be observed in 3/6 patients, particularly in erythrodermic manifestations. Histological manifestations suggest that arotinoid may act on the lymphocytic infiltrate via influencing the epidermis. Though the number of patients in this pilot study is small, the experiences presented warrant further study.

T 24

LYMPH NODE AND CIRCULATING T LYMPHOCYTE COLONY STIMULATING AND INHIBITING ACTIVITY OF GRANULOPOIESIS FROM PATIENTS WITH MALIGNANT LYMPHOMAS. M.P. Piccinni, J.J. Sotto, Thierry Bonnefoy, M.C. Jacob, Brigitte Pégourié, P. Couderc. Groupe de recherche sur les lymphomes malins - Service d'Hématologie - CHU - BP 217 X - 38043 GRENOBLE Cédex.

The goal of this study was to examine the role of T. lymphocytes (TL) in the stimulation of granulopoiesis during certain malignant lymphoid hemopathies giving rise to polynucleosis (neutrophilic and eosinophilic) in the peripheral blood and to lymph node granulomas. The TL were isolated from lymphoid tumors after suspension, filtration on Sephadex G 10 and AET rosetting. A purity of 92 ± 5 % was achieved. Conditionnel media (CoM) were produced by culturing the TL for 7 days with or without stimulation by mitogens (PHA - ConA). The granulopoietic colony stimulating activity (CSA) and inhibiting activity (IA) of these CoM were tested with normal bone marrow cultures depleted of adherent cells.

CSA is expressed in number of units per microliter of CoM as compared to the dose-response curve of a reference CoM of placenta.

IA is expressed as a percentage in proportion to the reduction of placenta activity of reference.

The results show that whatever the sample studied TL, non-stimulated by mitogen, do not secrete CSA. As for stimulated TL from normal blood : CSA = 5 U ± 0,5 and IA = 34,5 % ± 16.

Stimulated TL from lymph nodes in Non Hodgkin's lymphoma (NHL) B constantly showed CSA = 0 in the 6 cases studied. TL from the corresponding peripheral blood showed a normal CSA = 5.46 U.

TL from lymph nodes as well as from corresponding peripheral blood of T NHL showed no CSA (4 cases).

Stimulated TL from lymph nodes of Hodgkin's disease (7 cases) showed an elevated CSA of 6.0 ± 6 U. Two groups were distinguished :

* 5 cases with a CSA of 8.51 ± 3 U
* 2 cases with CSA = 0

The IA of TL was 9 % ± 9 (6 cases).

TL from the peripheral blood of Hodgkin's disease showed a very elevated mean CSA of 14.76 U in 5 cases. Two groups were distinguished :

* 2 cases with a normal CSA of 5 U
* 3 cases with a very elevated mean CSA of 21.27 U

In all cases a close correlation was observed between the extent of the granuloma, the degree of leucocytosis, and the type of cell involved (neutrophil, eosinophil, macrophage).

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T 25 MEDIASTINAL B CELL LYMPHOMAS WITH SCLEROSIS: CLINICAL STUDY OF 14 CASES.

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A highly malignant type of B mediastinal non Hodgkin lymphoma has been recently described, histologically characterized by the presence of large cells and fine compartimentalizing fibrosis (*).
From January 82 to December 86 we observed 14 cases (7 males, 7 females) of such mediastinal large cell lymphoma.
These cases were clinically characterized by:
- the young age of patients (median 29 yrs.);
- SVCS and/or thoracic pain frequently present (12/14);
- absence of superficial limph-node involvement (histological diagnosis could consequently be made only through mediastinoscopy or thoracothomy);
- absence of bone marrow and CNS involvement at diagnosis;
- spread to unusual sites (kidney in 5, adrenal tissue in 2 cases).

Follow up in 13 patients (1 patient is not yet evaluable) ranges from 5 to 35 months (median 14).
Treatment was heterogeneous: all patients received chemotherapy, 5 according to conventional regimens (like CHOP), 8 with more aggressive schedules (MACOP-B = 6, m-BACOD = 2, F-MACHOP = 1); in all but 1 patient IF radio-therapy was performed.
6/13 evaluable patients achieved CR (46%), 5 PR, 2 NR. Clinical response well correlated with overall survival; no correlation between stage and response to therapy could be demonstrated. CR was obtained only in patients (6/8) treated with aggressive regimens.
This type of non Hodgkin mediastinal lymphoma appears therefore to be a distinct immunohistological and clinical entity, and needs to be treated intensively.

(*) Histopathology 1986, 10 : 589

T 26 PRECLINICAL AND CLINICAL LIQUID CELL CULTURE ASSAY TO MEASURE THE IN VITRO ELIMINATION OF BURKITT CELLS FROM THE B.M.

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Bone marrow purging procedures, by complement lysis using a cocktail of pan-B monoclonal antibodies, have been proven to allow 4 to 5 log depletion of Burkitt (BL) cells from the bone marrow (BM) on artificial models using BL cell lines (1). Such methods, when applied in clinics, have been proven to be non toxic but pilot trials are still required to prove the benefit of this approach, specially the risk of graft contamination by BL cells before the purging procedure and their elimination after the procedure. We therefore developed a liquid cell culture assay which allows the growth of less than 10^{-5} BL cells (either EBV positive or negative) and therefore their detection in a cytologically normal BM (2). We currently use this assay to evaluate the number of residual BL cells in the BM before and after the purging procedure, either in preclinical assays or during the therapeutic procedures.
In preclinical assays, the purging procedure was shown to allow a full inhibition of BL cell growth in 3 cases; in the fourth one, malignant cells taken in relapse were sensitive to the complement lysis whereas they were resistant when taken in progressive disease.
In the 4 therapeutic assays, the procedure allowed the full elimination of malignant cells; one purged autograft was reinjected, the patient relapsed 2 months later outside the BM.
Such clinical pilot studies which permit an accurate quantitation of residual malignant cells before and after the purging procedure for each individual patient are needed before starting extensive multicentric studies.

(1) Favrot M.C. et al., Br. J. Haematol., 1986, 64, 161-168.
(2) Philip I. et al., J. Immunol. Meth., in press.

T 27 S-PHASE CELLS IN BLOOD IN NON-HODGKIN'S LYMPHOMAS. Correlation with morphology, leukemisation and prognosis.

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142 consecutive patients with non-Hodgkin's lymphomas were investigated with respect to morphology according to the Kiel classification, clinical stage, evidence of B-cell monoclonality in blood (MBCB) and the fraction of S-phase cells determined by flow cytometry in blood mononuclear cells. In addition, we also studied DNA S-phase in tumor material in 50 of these patients. 112 previously untreated patients without any other malignancy were evaluated in a survivalanalysis. Results: 46 patients (=32%) were MBCB pos. and 37 (=80%) out of these 46 patients were in clinical stage IV. The fraction of S-phase cells in blood was significantly higher ($p<0.001$) in the MBCB pos. group (mean value: 1.4%) than in the MBCB neg. group (mean value: 0.7%). No difference was found between high and low grade malignancy lymphomas. Only a weak correlation between S-phase in blood and tumor material was found in the MBCB pos. patients, no correlation was found in the MBCB neg. group. In the survival analysis MBCB pos. patients with high S-phase value in blood (> 1.5%) seemed to have a less favourable prognosis than patients with low S-phase (< 1.5%) ($p=0.01$). This difference in survival was not found in the MBCB neg. group. 44 previously untreated patients, analysed on both blood and tumor material , were followed 2-5 years and 2-year survival rate was determined. Patients with low S-phase values both in blood (< 1.5%) and tumor (≤ 4.0%) were found to have a significantly higher survival rate (71 %) than the rest of the patients (30 % 2-year survival). These results indicate that elevated S-phase values in blood in non-Hodgkin's lymphomas might depend on proliferating tumor cells in blood. In blood, as well as in tumor material, DNA S-phase seems to be a prognostic factor in these patients.

T 28 MORPHOLOGIC & IMMUNOLOGIC CHANGES OF HAIRY CELL LEUKEMIA UNDER INTERFERON TREATMENT.

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We describe a patient with morphologic and immunologic features of hairy cell leukemia (HCL), who changed lymphoma cell morphology to prolymphocytic leukemia (PLL) under recombinant &-2 interferon (&-2-IF) therapy. Lymphoma cell surface antigen expression at diagnosis was B 1, FMC 7 positive and Leu 1, Ig-G, Ig-M, Ig-D, kappa- and lambda-chain negative. Under &-2-IF the surface antigen expression switched to B 1, Leu 1, FMC 7, Ig-D and lambda-chain positive. Gene rearrangement studies showed 3 bands on Southern Blot before treatment and two bands after the morphologic change under &-2-IF treatment.
We conclude that this was a biphenotypic lymphoma before treatment. Under 2-&-IF the HCL came into remission and the PLL remained.

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T 29 EXPRESSION OF TRANSFERRIN AND INTERLEUKIN-2 RECEPTORS IN CUTANEOUS T-CELL LYMPHOMAS.

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Cutaneous T-cell lymphomas (CTCL) represent a neoplastic proliferation of helper T-cells. It is postulated that T-cell stimulation and regulation in the skin is triggered by epidermal signals (skin associated immune system). Interleukin-2 (IL2R) and transferrin (TR) receptors are markers of T-cell activation and proliferation. TR^+ cells have been found in the large majority of CTCL in contrast to large plaque parapsoriasis, a postulated precursor disease of CTCL. IL2R expression has been reported to be very variable and even negative in CTCL. This prompted us to examine the expression of both receptors in CTCL and in a control group of benign dermatoses to address the following questions: (1) which is the distribution of $IL2R^+$ and TR^+ cells in dermis and epidermis of CTCL; (2) is the IL2R expression on the cellular skin infiltrates reflected in the IL2R expression on peripheral blood mononuclear cells (PBMC); (3) may one of the mentioned markers be used in the differentiation between CTCL and benign dermatoses?

Up to now, cryostat sections of 16 cases with CTCL of various stages and of 11 cases with benign dermatoses as well as PBMC of 7 cases (from the above mentioned 16) with CTCL were exposed to the monoclonal antibodies OKT9 and Clonab IL2R. Antigen binding was visualized either by a 3-step or, in the case of PBMC examination, a 2-step immunoperoxidase technique. Positive cells were calculated as numbers per mm^2 of tissue section or as numbers per nl, respectively. Statistical analysis was performed with Spearman's test and with the step by step analysis of discrimination.

$IL2R^+$ and TR^+ cells were present in the epidermis of CTCL as well as in all layers of dermal infiltrates. In benign dermatoses, the expression of TR was often negative. All cases of CTCL exhibited $IL2R^+$ as well as TR^+ skin cells. The expression of IL2R was significantly correlated ($p<0.01$) with the expression of TR in CTCL. A statistically significant correlation ($p<0.005$) could also be observed between $IL2R^+$ cells in the skin and in the peripheral blood. In CTCL, the numbers of both TR^+ ($\bar{x}=315.4$) and $IL2R^+$ ($\bar{x}=228.3$) cells were significantly increased ($p<0.01$) in comparison with the control group of benign dermatoses ($\bar{x}$ (TR^+ cells)=52.5; $\bar{x}$ ($IL2R^+$ cells)=82). Nevertheless, step by step analysis revealed that neither IL2R nor TR can be used as a clear cut marker for the discrimination between CTCL and benign dermatoses.

In conclusion, these results point out that (1) all cases of CTCL examined exhibited $IL2R^+$ and TR^+ cells , though in a rather variable number, (2) in spite of significantly increased numbers of TR^+ and $IL2R^+$ cells in CTCL, none of both antigens is a clear cut marker for discrimination between CTCL and benign dermatoses, (3) hypothesis is questionable that (solely) the skin delivers signals for triggering activation and proliferation of T-cells in CTCL.

T 30 CLINICAL CHARACTERISTICS OF 15 PERIPHERAL T CELL LYMPHOMA.

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15 T cell lymphomas excluding mycosis fungoides and lymphoblastic lymphoma are described.

They were studied morphologically and immunologically with E Rosettes and a panel of monoclonal antibodies reactive with T cell differentiation antigen in frozen tissues or in fresh separated cells. All were diffuse mixed cell lymphomas with common findings of T cell type (eosinophils, plasmacells, epithelioid histiocytes and prominent vessels). T cell origin was confirmed by T immunologic marker with 7 CD4 +, 4 CD4 CD8 +, 1 CD8 +. Median age was 57 (34-72). The sex ratio M/F was 11/4. Initial staging was I or II in 5 cases and III or IV in 10 cases, clinical evolutivity "B" in 5 cases. Skin was involved in 6 cases. These lesions disappeared spontaneously in 4 cases. Excluding 2 cases of classical Japanese T lymphoma leukemia who had initial bone marrow involvment, 5 others presented secondary bone marrow infiltration at the moment of progressive disease. 3 presented increase of gammaglobulinemia polyclonal, 1 a malignant increase of calcemia.

Two clinical evolutions could be described : an indolent and an aggressive form.

The first form occured in 10 patients : 2 did not receive any chemotherapy with a survival of + 13 m and + 36 m. 2 were treated after 6 m and 12 m evolution because of progression of the disease. All these patients received COP or MOPP or CHLORAMBUCIL alone. Survival was (+ 3 m, + 9 m, + 13 m, + 13 m, + 24 m, + 24 m, + 36 m, + 96 m). 2 deaths : 19 m (lymphoma) and 24 m (2 th carcinoma).

The aggressive form occured in 5 patients "B" in the initial staging. They were treated with chemotherapy with anthracyclin. The survival of the 2 leukemia lymphoma was 4 m and 24 m and the 3 others + 9 m, 13 m, 18 m.

This morphological entity is very heterogeneous in clinical features and evolution.

T 31 Levels of zinc in serum of patients with Hodgkin's disease and non-Hodgkin's lymphoma.

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Multiple studies have been done on zinc in cancer and other diseases. Results have been variable and sometimes contradictory (Schwartz MK, Cancer Res 1975,35:3481-3487). Few studies on zinc in lymphomas seem to exist in the literature. Gobbi et al.(Haematologica 1978,63:143-155) found lower zinc levels in Hodgkin's disease with B symptoms. Babacan et al.(Boll Ist Sieroter Milan 1977, 56:228-234) reported decreased zinc values in 24 children with Hodgkin's disease, there was no variation with treatment.

The purpose of this paper is to study zinc levels in the serum of patients with different types of lymphoma.
A flame atomic absorption method was used to determine the zinc in serum.
56 cases of Hodgkin's disease, 15 untreated and 41 in remission complete in most of them, showed values of 90 µg/dl ± 12 and 83 µg/dl ± 15 respectively (p:N.S.).
47 patients with non-Hodgkin's lymphomas (mostly diffuse histiocytic and diffuse lymphocytic poorly differentiated), 19 untreated and 28 in remission complete in most of them, had values of 83 µg/dl ± 20 and 86 µg/dl ± 15 respectively (p:N.S.).
Our normal controls (50 people) had a mean value of 89 µg/dl ± 13, there was no statistically significant difference between this figure and any of the previous ones.

Our results seem to indicate that zinc values in the serum of patients with lymphoma show no significant variations either in active disease or in remission complete or incomplete.

T 32 TUMOR MARKER - LDH (SERUM LACTATE DEHYDROGENASE) WITH ISOZYMES IN LYMPHOMAS.

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In 90 patients with lymphomas total serum LDH activity and LDH isozymes were determined before primary treatment. We wanted to know: 1) Correlation between increased LDH activity and histology, stage, presence of bulk disease. 2) Which of the five isozymes is elevated when total LDH activity is increased? 3) Which of the five isozymes is increased in the case of liver, lung or bone-marrow involvement? Kiel classification and Ann Arbor staging was used for non-Hodgkin lymphomas (NHL). Bulk disease was defined as a tumor mass 10 cm in diameter. Results: There were 70 patients with NHL, of these 42 low grade (LG-NHL), 28 high grade (HG-NHL) and 20 patients with Hodgkin disease (HD). Total LDH was increased in 10% patients with LG-NHL, 68% patients with HG-NHL and 10% patients with HD. In stage I+II no one with LG-NHL, but 57% patients with HG-NHL had increased LDH. In stage III+IV, LDH was increased in 12% patients with LG-NHL and in 74% patients with HG-NHL. Increased LDH was found in only 2 of 20 patients with HD and in 1 of 7 patients with bulk disease. Isozymes of LDH were always normal in spite of liver, lung or bone-marrow involvement. Conclusions: An increased level of serum LDH correlates well with HG-NHL and high proliferative rate (LDH was elevated in higher percentage in HG-NHL even in localized disease). It seems that there is no correlation between increased LDH and bulk disease. Although LDH was increased, isozymes were always normal regardless liver, lung or bone-marrow involvement. The number of increased LDH in HD was too small to allow any conclusion.

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T 33 SEMIOLOGIC AND PROGNOSTIC VALUE OF SERUM FERRITIN, BETA-2 MICROGLOBULIN (B2 M) AND LACTICDEHYDROGENASE (LDH) IN NON HODGKIN'S LYMPHOMAS (NHL).

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Serum levels of ferritin, B2M and LDH were measured in 205 patients with NHL at diagnosis in the same institution. Correlations were studied with histology according to the working formulation, dissemination and tumor mass, and obtention of complete remission (CR) and survival. Low grade patients were treated with conventional therapy (90 cases) and most of patients with intermediate or high grade with high dose CHOP-Bleo chemotherapy (115 cases).

The distribution of levels was very asymetric and we used non parametric methods of analysis.

	Median	Mean	Range
Ferritin man (ug/L)	230	403	30 - 5 000
___ woman	159	277,5	10 - 1 900
B2M (mg/L)	2,45	3,01	1,12- 9,8
LDH (UI/L) (N = 140-330)	354	369	125 - 2 520

Ferritin, B2M and LDH levels were not correlated together. Serum ferritin was not related with histology nor with tumor mass and was of borderline prognostic value (survival : p = 0,03, log rank test). B2M and LDH were not correlated with histology and immunologic phenotype (B or T) of NHL, but were correlated with disease extension, tumor mass and hemoglobin levels. Low levels of B2M and LDH were significantly related to high CR rate and long survival but the levels of significance were higher in the low grade (survival : p = 0,005) than in the intermediate or high grade NHL (survival : p = 0,02 to 0,15). This discrepancy between histologic grades might be linked to the more intensive chemotherapy used in aggressive NHL.

T 34 GALLIUM-67 SCINTIGRAPHY IN MONITORING LYMPHOMA RESPONSE TO TREATMENT.

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The clinical value of Gallium-67 scintigraphy (GaS) in patients (pts) with lymphoma has been compared with simultaneous clinical and radiologic evaluation, however few studies have had the benefit of long-term follow-up. We evaluated the utility of GaS in monitoring response to treatment in 26 consecutive pts presenting with lymphoma in the years 1984-1985. GaS was performed in each patient before, during, and at the end of therapy (ET). In some pts, additonal GaS were performed periodically thereafter. GaS results were compared with concomitant (within a month) chest x-ray, CT and physical examination. Nineteen pts had Hodgkin's disease and 7 non-Hodgkin's lymphoma. Twenty-three pts were defined as complete responders (CRs) and all had follow-up of at least 15 m after ET. In 22 of 23 CRs GaS became negative during treatment or at ET, while CT returned to normal in 10/21 and chest x-ray in 6/13 CRs. Of those pts whose CT and/or chest x-ray remained positive at ET, the residual mass disappeared in 4 pts within 4-13 m from ET. In 8 pts a mass could still be detected, of these 6 had no evidence of active disease, 8-17 m after ET, however 2 pts with residual mediastinal mass and a negative GaS at ET had relapsed within 4 months. Thus, GaS was falsely negative in those 2 pts. Five additional CRs relapsed after ET in previously uninvolved sites (time to relapse after ET was 6-18 m). Three pts in whom GaS remained positive, did not achieve complete remission and subsequently died of disease. In one patient, GaS was positive at ET, but subsequently (after 2 m) became negative and the patient remained free of disease for 22 m after ET. The specificity of GaS as an indicator of long-term complete remission was 91%. In contrast, the specificity of chest x-ray and CT were approximately 50%. In conclusion, GaS appears to be a better indicator of lymphoma response to treatment (especialy in the mediastinum). This is probably based on the fact that Gallium uptake depends on tumor cell viability, while CT and chest x-ray show tumor mass, which may contain fibrotic or necrotic tissue.

T 35 DEOXYTHYMIDINE KINASE: HIGHER CLINICAL SIGNIFICANCE AS SERUM MARKER IN MALIGNANT LYMPHOMAS THAN BETA-2-MICROGLOBULIN AND NEOPTERIN.

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Searching for additional aids in the monitoring of the treatment of malignant lymphomas we have studied the clinical relevance of deoxythymidine kinase (dtk), $ß_2$-microglobulin ($ß_2$m) and neopterin (npt) as serum markers in 76 untreated and treated patients (pts) with malignant lymphomas.

Recent clinical studies have shown elevated serum levels of dtk, $ß_2$m and npt in various benign and malignant lymphoproliferative diseases in the latter being of prognostic and therapeutic relevance.

Serum levels of dtk, $ß_2$m and npt have been simultaneously determined in 53 pts with non-Hodgkin-lymphomas (NHL) (12 pts with untreated or progressive diseases, group 1; 29 pts in partial remission (PR), group 2; 12 pts in complete remission (CR), group 3) and in 23 pts with Hodgkins disease (HD) (5 untreated or relapsed pts, group A; 4 pts in PR, group B; 14 pts in CR, group C). Dtk-determinations were performed as a radioenzyme assay (Prolifigen®, AB Sangtec Medical, Bromma, Sweden); $ß_2$m and npt were measured by radioimmuno assays (Phadebas $ß_2$microtest, Pharmacia Diagnostics, Uppsala, Sweden, and Neopterin-RIAcid®, Henning GmbH, Berlin, W.-Germany, respectively). In group 1 serum concentrations of dtk showed a mean 7-fold increase, whereas those of npt were only 2.8.-times and those of $ß_2$m only 1.4 times above their respective normal upper limits. Normal serum levels of all three markers have been found in groups 3 and C, moderate elevations have been observed in groups 2 and B (mean: 1.1 - 2.5 times above their respective normal limits). In conclusion, serum concentrations of $ß_2$m and npt are significantly less elevated compared to dtk at least in untreated or progressive NHL-pts (group 1). Furthermore since serum concentrations of $ß_2$m and npt rise considerably with increasing renal insufficiency, whereas dtk serum levels are unaltered by disturbances of renal functions, dtk represents a serum marker of superior clinical significance at least in malignant NHL. Updated results of this ongoing comparative study will be presented.

T 36 DEFINITION OF THE FAVORABLE STAGE OF CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) ACCORDING TO THE LYMPHOCYTE DOUBLING TIME (LDT).

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The prognostic significance of LDT in CLL has previously been reported (Galton et al. 1966, Jaksic et al. 1981, Montserrat et al. 1986). In this study we have retrospectively studied the LDT in a series of 99 previously untreated CLL patients in order to analyse the prognostic value of this parameter as well as to investigate whether it was correlated with, or independent from, other prognostic features such as age, sex, lymphocyte count, bone marrow failure and clinical stage. The analysis extended to the whole population of CLL patients showed clear cut-off differences in the life expectancy between patients with LDT equal or lower than 12 months (median survival, 36 months; relative death rate, O/E, 1.57) and those with LDT higher than 12 months (median survival not yet reached at 13 years, O/E, 0.37) ($P < 0.001$). Similar trends were seen when the cut-off was established at 6 months ($P < 0.001$). The LDT was a prognostically significant factor even after adjustment was made for age, sex, peripheral blood lymphocytosis, bone marrow failure. The lack of statistical significance after adjustment for Binet's clinical stage is not surprising if we consider that clinical stages were not distributed homogeneously; high LDT being associated with less advanced and low LDT with more advanced forms of disease ($P < 0.001$). The influence of LDT was also clear when we took into account therapy-free survival. This analysis, in which the events are not represented by death but by requirements of treatment, shows that patients with low LDT have a more progressive disease and require early therapy ($P < 0.001$). Finally, taking into account the value of LDT, patients of low and intermediate risk (A and B stages of International Classification) could be divided into two subgroups with a different prognosis: the first one with a median survival not yet reached at 13 years and the second with a median survival of 36 months, not statistically different from stage C (22.5 months). In conclusion, LDT is a prognostic variable of useful in clinical management of CLL which appears to predict the progression rate. This is true for the whole population of CLL patients as well as for those of the low and intermediate risk who are more difficult to classify from a prognostic point of view.

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T 37 IMMUNOHISTOCHEMICAL CHARACTERIZATION OF A SIGNET RING CELL LYMPHOMA.

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The signet ring cell lymphoma is a rare lymphoma described in 1978 by Kim et al. as a variant of follicular center cell lymphoma. This term is used to define the morphology of lymphoma cells characterized by a cytoplasmic mass displacing the nucleus at the periphery, similar to that ascribed to the mucin-producing cells. Immunohistochemistry demonstrated that these cells are immunoglobulin producing cells; therefore their appearence is due to an abnormal production of immunoglobulins. Twenty five cases are reported in the literature, however at present little is known about the differentiation pathway of this peculiar variant of B cells. In the present study we have characterized the immunophenotype of signet ring cells, using a large panel of monoclonal antibodies. A 61 year old male patient presented with generalized peripheral adenopathy and hepatosplenomegaly. Chest x-rays revealed mediastinal widening and a bone marrow biopsy showed multifocal infiltration of lymphocytes and signet ring cells. An abdominal computerized axial tomographic study demonstrated no evident alterations. A diagnosis of signet ring cell lymphoma based on morphologic and immunohistochemical features was made on an axillary lymph node. The lymph node architecture was effaced by a diffuse proliferation of centrocytes and centroblasts with intermingled signet ring cells which account for 15% of the total cell population. Some B cell follicles (To15+/HLA-DR+), devoid of signet ring cells, were still present with an irregular meshwork of DRC1+/LeuM3+ dendritic cells. The main cytologic feature of the signet ring cells was the presence of round eosinophilic cytoplasmic inclusions intensively PAS positive. Signet ring cells were cytokeratin negative and showed a restricted positivity for lambda light chain and IgA/IgM heavy chains. The large majority of the signet ring cells were markedly T10+/T200 negative/HLA-DR negative/To15 negative. Few mitotic figures were observed (14/10 oil fields); the number of Ki67 positive cells was higher (336/10 oil fields). Typical signet ring cells were always Ki67 negative. Our results indicate that the signet ring cells express surface markers closely similar to the normal plasma cells and that the abnormal production of immunoglubulins is not associated with phenotypic modifications of mature B cells.

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T 38 SEZARY SYNDROME WITH SUPPRESSOR PHENOTYPE.

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Introduction

We report a case of Sézary Syndrome (SS) with suppressor phenotype. The mature T-helper cell phenotype of the cutaneous infiltrate in mycosis fungoides and the SS was determined, with the use of monoclonal antibodies to T-cell subsets. Suppressor cell function of neoplastic T cells of skin lesions may be found in adult T cell leukemia - lymphoma; this also is not generally seen in mycosis fungoides and its leukemic variant SS.

Case Report

S.L., male, 71 years old, was admitted to the Dermatological Division, S. Chiara Hospital Trento, because of generalized pruriginous exfoliative erythrodermia of six month's duration. Sezary's cells were seen in peripheral blood smears. A skin biopsy was performed. The upper dermis was infiltrated by medium sized mononuclear cells, with occasional cerebriform nuclei, inconspicuous nucleoli, and a narrow rim of cytoplasm. These cells intimated only focally with the overlying epidermis. Pautrier's microabscesses were absent. The study of peripheral blood lymphocytes revealed only slight alteration of T cell subsets. The total number of T cells was normal, T helper lymphocytes were slightly augmented (T4 + : 48%, range 37-47), suppressor cells were slightly decreased, with a T4/T8 ratio of 2.23 (range 1.3-1.9). The cells infiltrating the skin were identified as T cells by the monoclonal antibody OKT 11; more than 80% of these cells were OKT8+, OK1A1+, OKT4-, Leu 10-. No Smlg were demonstrable. The patient was treated with combined therapy Retinoid-Puva. Good clearance of cutaneous lesions after 4 weeks of treatment was obtained. A year later the patient was free of disease.

Comment

Mycosis fungoides and SS are commonly described as a malignant proliferation of T helper lymphocytes. Only few cases have been reported up to date in which the malignant clone was T8+. Unusual features of the present case of SS were: T-helper cell phenotype of the cutaneous infiltrate, indolent course of the disease, the very limited involvement of epidermis and the absence of Pautrier's microabscesses. In our opinion, the SS include a wide range of immunologically heterogenous malignant proliferations of T lymphocytes, with different clinical behaviour.

T 39 SJOGREN'S SYNDROME: A HUMAN MODEL FOR LYMPHOMA DEVELOPMENT.

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Sjogren's syndrome (SS) is an autoimmune disease characterized by focal lymphoplasmacytic infiltration initially of the exocrine glands and eventually of other extrasalivary organs. SS can present as primary SS when it occurs alone or as secondary when it accompanies other autoimmue diseases i.e. rheumatoid arthritis, lupus erythematosus, scleroderma etc. Immunologically, SS is expressed by a polyclonal B-cell activation with a variety of circulating autoantibodies. During the course of the disease a number of patients with SS, develop serum or urinary monoclonal immunoglobulins which probably represent the first step of the transformation from the benign polyclonal activation to a malignant lymphoproliferation.

For the last few years, we are investigating the presence of monoclonality in patients with primary SS and the incidence of pseudolymphoma or lymphoma development. Fifty-eight patients who were diagnosed and followed-up in our Department for a period of 1-6 years were studied. These patients were also compared with 47 American SS patients who were treated at the National Institutes of Health, in Bethesda, U.S.A between 1967-1979.

High resolution agarose gel electrophoresis combined with immunofixation was used for the detection of monoclonal proteins. In patients with extraglandular involvement, serum monoclonal immunoglobulin and/or light chains were detected in 100% (Americans) and 70% (Greeks) of them. 100% of the Greek patients had also monoclonal light chains excreted in the urine and 37% of them had detectable amounts of mixed cryoglobulins in the serum containing exclusively an IgMk monoclonal immunoglobulin.

Three Americans and one Greek patient had developed pseudolymphoma in a mean time of 4 years after the diagnosis of SS; new or progressive lymphadenopathy, splenomegaly and a lymph node biopsy which showed benign reactive lymphoreticular hyperplasia were the main features of these patients. In addition, 3 Greek patients developed non-Hodgkin's lymphomas 2 of low-grade and one of intermediate malignancy (positive for IgMK); one patient had immunocytoma (stage II), another had immunocytoma in the minor salivary gland with bone marrow infiltration and the last patient presented with lymphoma of the nasopharynx.

In conculsion, SS is an autoimmue disease which can serve as a fascinating model for the transformation of a chronic benign polyclonal activation to a malignant monoclonal lymphoproliferation.

T 40 TWO UNUSUAL CASES WITH CUTANEOUS LYMPHOMA AS A SOLITARY NODULE.

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The appearance of malignant lymphoma as a solitary lesion confined to the skin is rare and incorrect diagnosis often occurs. The present report describes two unusual cases with solitary lymphoma of the skin. **Case 1.** A 59-year-old man was referred to our clinic for evaluation of a 13 x 7 mm dark brown ulcerated nodule on the right ear of a month duration. He denied any abnormalities in his general condition. The nodule was poorly demarcated and appeared to be invading the underlying tissue. The superficial lymphnodes were not enlarged. H.E.-staind image of this tumor was so primitive that even the origin could not be decided. We performed dopa reaction and various immunohistochemical stains. Malignant melanoma was excluded because of a negative dopa reaction. The tumor cells did not react with antiserum to keratin which reflects an epithelial character. A diagnosis of large cell lymphoma of B-cell type was made through positive staining with B-cell-specific Leu10 and antisera to κ light chain and λ light chain. No invasion of visceral or skeletal organs was detected by thorough systemic examinations including CT scan and Ga-scintigram. Excision of the tumor and local radiotherapy of 4000 rads have clinically freed the patient from the disease more than one year, to date. **Case 2.** A 48-year-old woman was seen with an asymptomatic ø 20 mm ulcerated nodule on the finger of a two-months history. The nodule presented a dome-like appearance with a reddish halo and the central ulcer was covered with bloody crusts. The superficial lymphnodes were not enlarged. In spite that the macroscopic appearnce of the lesion suggested a squamous cell carcinoma or sporotrichosis, the nodule was histopathologically disclosed as malignant lymphomà. Thorough systemic investigations for staging detected no other involvement. The lesion then disappeared spontaneously and the patient has been clinically free of disease for more than eight months.

Although spontaneous regression of malignant lymphoma has been noted by several authors, clinicians should be aware of cutaneous lymphoma as a solitary nodule to conduct its appropriate therapeutic management in view of its unfavorable prognosis.

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T 41 WALDENSTROM'S MACROGLOBULINEMIA(WMG). Report of a case with pulmonary involvement as a sole demonstrable presenting clinical manifestation.

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We report a case of WMG presenting with a large basal mass of the left lung. Peripheral blood studies revealed moderate anemia and lymphoplasmocytic cell infiltration, and a monoclonal IgM protein in excess of 9 g/dl. Pulmonary biopsy showed a heterogenous population of mature lymphocytes, as well as plasmacytoid forms and plasma cells By immunologic typing of tumoral tissue from the lung we found 80% B cells lymphocytes. 20% of cells showed positive especific intracytoplasmic immunofluorescence with Ig IgM.
The diagnosis of WMG was based on the finding of the abnormal protein plus the immunolo y and histopathology of the tumor. There was an excellent clinical response after 11 months of therapy with chlorambucil as was evidence by disapearance of symptoms and decrease in values of the paraprotein to about 0.5 g/dl.
The following case presented a challenging pulmonary diagnostic problem, and emphasizes the need of considering the possibility of WMG in patients with pulmonary infiltrates and a monoclonal IgM gammopathy in whom bone marrow and clinical examination have failed to establish a diagnosis. Clinicians' familiari y with WMG pulmonary syndromes will undoubtedly result in the more frequent recognition of this treatable tumor, which has a good response to monochemotherapy; thus avoiding the unnecessary risks of multiple drugs commonly used in other types of malignant tumors of the lung.

T 42 Mediastinal diffuse large cell lymphoma with sclerosis: a poor prognosis condition.

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18 cases are reported (14 females, 4 males). Median age was 33 y (17-53). Initial symptoms were thoracic pain and/or vena cava syndrom. Cervical or axillary nodes were noted in 7 cases, and B symptoms in 7. In all patients, but one who had kidney involvement, the disease was confined to supra-diphragmatic areas at the time of initial diagnosis. Pericardial, pleural or chest wall invasion was noted in 12 cases. In each of the 9 cases analysed for cell lineage, a B cell phenotype was demonstrated. All patients received 3 courses of an anthracyclin-containing 5-drug combination, followed by mantle radiotherapy (35-45 g). In 7 patients (38 %) the disease resisted to chemotherapy and to subsequent radiotherapy as well; 6 died within 14 months, 1 is on salvage therapy. Complete response was obtained in 11 patients (62%). 3 had early relapse (< 12 months) with recurrent intrathoracic disease (1 died, 2 are on salvage therapy). 1 patient experienced a late relapse (36 months) and died with disseminated disease. 7 patients are alived free from relapse, 3 being over 3 y. The 3 y. disease free survival of the entire group is 28 %. Localized mediastinal lymphoma with sclerosis is a highly malignant subset of large cell lymphomas in which standard treatment approaches are unsuccessfull.

T 43 *CD8 T LYMPHOMA ASSOCIATED TO HTLV-I.*

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We report on the case of a 42 year old caucasian woman who was referred to our Service with a major splenomegaly and pantycopenia. The suspected diagnosis from the hospital of origin where she had already been submitted to spleen biopsy was Hairy Cell Leukemia (HCL). However the review of bone marrow aspirates containing 30% of abnormal lymphoid cells which were Tartrate resistant acid phophatase negative showed that these cells were morphologically identical to so-called "prolymphocytes". The patient had to be submitted to splenectomy (the spleen weighed 2460g) and monoclonal antibody phenotype determination on spleen cells, both in cell suspension and frozen sections confirmed the T lineage and CD8 phenotype of the tumor cells (sER+, Leu4+, T4-, T8+). In microscopic sections, the leukemic cells filled the red pulp cords and sinuses and encroached upon or obliterated the white pulp; the pattern of involvement was strikingly similar to that in HCL. The leukemic cells were of medium size and had round to oval nuclei. In routine histologic sections, the chromatin pattern appeared open and the nucleolus was often obscured unless examined under oil immersion. Irregularities in the nuclear contours, including deep identations, were noted in a few of the cells. In the touch imprints prepared from the spleen, however, the moderately coarse chromatin pattern, the single centrally located nucleolus, and the moderate to abundant pale-blue cytoplasm were clearly evident and were similar to the leukemic cells of Galton's prolymphocytic leukemia. Despite the cytological involvement of the bone marrow by the same cells, no excess of CD8 cells could be demonstrated in the marrow. Frozen serum had IgG antibodies to HTLV-I. The absorbence ratio of patient serum to standard negative control serum was 8.4. No HTLV-III proteins were detected in the western blot system. ELISA assay for HTLV-II was negative. The patient was treated with prednisone, vincristine, L-asparaginase and doxorubicin, followed by maintenance therapy with 6-mercaptopurine, methotrexate and vindesine, and by intensification therapy every three months. The agents used for intensification therapy were doxorubicin and vincristine, with either cyclophosphamide or cytosine arabinoside given alternately in every other intensification course. The patient remained clinically well for 21 months, after which she had a bone marrow relapse during which she died early from sespis. No postmortem examination was performed. This clinicopathologic entity represents a new variety of peripheral T cell malignancy.

T 44 *HISTOLOGIC, CYTOLOGIC AND HISTO-CYTO-IMMUNOLOGIC CATEGORIZATION OF T NON-HODGKIN'S LYMPHOMAS (NHL). ACTUALIZATION OF WHO CLASSIFICATION.*

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For T lymphoma-leukemia categorization, one can, at first microscopic look, distinguish small cell, medium cell and large cell groups.
1) In the T-small cell group, two types can be recognized:
(a) The CD4+ helper type which has convoluted nuclei and is serologically HLV-I or II+;
(b) The CD8+ cytotoxic/suppressor cell type of which we have observed one case with splenic hypertrophy predominance, with HTLV-I+ and HIV+ serology, and of which the survival is longer (>36m).
2) In the T-medium size cell group, one can easily recognize:
(a) Mycosis fungoides-Sezary disease, owing to its "Pautrier abcesses" at histology and its HTLV-I and II negative serology;
(b) The HTLV-I+ or II+ type which is not dermatotrope and present more cells with convoluted nuclei than the preceeding one. Its prognosis is much more severe.
3) In the T-large cell group, we have observed two types:
(a) The CD4+ pleiotropic type with many cells resembling T immunoblasts and with a rapid evolution;
(b) The CD8+ type contains more T-immunoblasts and the evolution of which is rather less severe than that of the preceeding one.
At electron microscopy, monoclonal antibodies labelled with colloidal gold can precisely identify the CD4 and CD8 types, the nature of which can be suggested by the cell appartenance (the CD8 cells show more abundant cytoplasm with a richer organular pattern).

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T 45 IMMUNOREACTIVITY FOR T11 (CD 2) IN HISTIOCYTOSIS X CELLS OF LETTERER-SIWE DISEASE.

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Langerhans cells (LCs) and histiocytosis X cells (HCs) present several ultrastructural, enzymatic and antigenic similarities. It is generally believed that LCs and HCs are bone-marrow derived cells which are closely related to the histiocytic lineage; nevertheless, cell origin and differentiation pathway of these cells are still largely unknown. We have recently observed a lymph node localization of Letterer-Siwe disease in a 11-month-old female infant and a prominent dermatopathic lymphadenitis in a 9-month-old male infant with hyper-IgE syndrome. The lymph nodes were studied by conventional histology, by immunohistochemistry on frozen sections, and by immunocytochemistry on cytocentrifuge smears prepared from the lymph node cell suspensions. In both cases, conventional histology revealed the presence of large sheets of cells whose morphology was consistent with that of LCs. In dermatopathic lymphadenitis, LCs proliferation was confined to the paracortex with preservation of the lymph node structures; in Letterer-Siwe disease, the lymph node histology was completely effaced by a diffuse proliferation of HCs. On frozen sections, LCs and HCs were weakly ANAE+ and were markedly T6+/T4+/HLA-DR+. However, HCs differed from LCs because of their additional expression of T11, Leu-11 and OKM-1 antigens which are consistently expressed also by cells of the natural killer (NK) lineage. Immunostaining of cytocentrifuge smears allowed us to investigate the morphological aspect of positive cells. It could be demonstrated that, in both pathological conditions, immunoreactivity for T6 was not restricted to cells with LC morphology, but was also present on several lymphocyte-like cells and on medium-sized cells with monocytoid morphology. Myeloperoxidase and Leu-M1 antigen were not detected in T6+ cells. The macrophage antigens Leu-M3 and PAM-1 were expressed by some medium-sized and large cells whose morphology was consistent with that of HCs. Our findings suggest that both pathological conditions are characterized by the presence of LCs or HCs exhibiting different degrees of maturation. Furthermore, the demonstration of T11 reactivity on HCs and the observation of T6+ cells with lymphocyte morphology may contribute to further distinguish LCs/HCs from those belonging to the myelo-monocytic lineage.

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T 46 IMMUNOHISTOCHEMISTRY OF MACROPHAGE SUBSETS IN HUMAN LYMPH NODES

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It is well accepted that mononuclear-phagocytic cells are widely distributed and that functional and phenotypic differences are present among human mononuclear-phagocytes from different sites. The heterogeneity of these cells may reflect either the influence of environmental factors stimulating monocytes to differentiate in a distinctive manner, or the existance of different subsets of macrophages (MØ). In this study we show that MO and sinus lining cells, from different areas of human nodes, express different phenotypes. Cryostat sections, immunostained with a large panel of MoAbs, were prepared from 36 human nodes: 17 with follicular and 19 with sinusal lymphadenitis. Control tissues included 5 spleens and 3 tonsils with reactive lymphoid hyperplasia,3 livers, 3 hearts and 2 thymuses of fetuses; 3 normal skin biopsies were also used as control. Our investigation has demonstrated that Mo present in B germinal centers display an immunophenotype different from that of MØ populating T-areas. Actually germinal centers are populated by PAM-1 and OKM-1 negative MØ, whereas Leu M3+ cells, showing a follicular distribution, are particularly numerous. MØ of T- paracortical areas have an immunophenotype (PAM-1+,Leu M3+,OKM-1+) similar to that of MØ present in other non lymphoid tissues like liver, skin and heart. In sinusal lymphadenitis the number of PAM-1+ MØ increases as compared to follicular lymphadenitis; furthermore sinus MØ become much more positive for T4 and T9 MoAbs. Sinuses of human lymph nodes are lined by cells characterized by PAM-1, Leu M3 and OKM-1 markers, which are present on tissue MØ. Furthermore sinus lining cells of nodes with sinus hyperplasia, express the T4 antigen, which is present on cells involved in antigen presentation. In lymph nodes with sinusal lymphadenitis, sinus lining cells were also positive for RFF-VIII:/2 MoAb which detects an endothelial cell antigen. This observation suggests that sinus lining cells of human lymph nodes express MØ and endothelial markers when activated as in sinusoidal lymphadenitis, and indicates that they may be considered as a subset of specialized MØ with endothelial morphology. In conclusion our data suggest, on immunohistochemical grounds, that macrophages populating B and T dependent areas as well as sinuses of human nodes, may modulate their immunophenotype according to environmental and antigenic influences.

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T 47 STROMAL MACROPHAGE-HISTIOCYTES IN HODGKIN'S DISEASE: THEIR RELATION TO FEVER.

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Fever remains an important adverse parameter of Hodgkin's disease (HD) in this post-MOPP era. However, its pathophysiology is unclear. Neither the number of Interleukin-1 containing cells nor inflammation and/or necrosis of the tumor correlated with the occurrence of fever in our material.

Con A-binding macrophage-histiocytes (M-H) were studied in diagnostic specimens of 140 untreated patients with HD (72 asymptomatic, and 68 with B-symptoms). Fever was the most common symptom (57/68).

Three morphological types of M-H were recognized: medium-sized cells similar to those seen in reactive follicles, characterized by distinct cytoplasm and cell borders, and uniform nuclei (Type A); damaged-appearing Type A cells marked by rarefied or ragged cytoplasm, indistinct cell borders, and varying-sized nuclei (Type B); and large spindling or stellate cells (Type C).

Type A cells were predominant in 52 patients; Type B cells in 51; Type C cells in 7; and Type A cells mixed with Type B in 30. Fever was present in 1 of 52 patients with Type A predominance; 43 of 51 with Type B; 0 of 7 with Type C; 13 of 30 with mixed Type A and B cells. Logistic regression analysis showed that the association of fever with Type B cell predominance was highly significant, and was not attributable to the known association of fever with other variables.

Morphological evidence suggests that fever in HD may be a clinical manifestation of M-H injury rather than an acute-phase response of inflammatory or immune reaction.

T 48 IMMUNOPHENOTYPIC EVOLUTION OF A T-CELL LYMPHOBLASTIC LYMPHOMA.

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A 34 year old woman was refered to the Institut J. Bordet for the treatment of a lymphoblastic lymphoma. Two weeks before admission, she had been operated for a mediastinal malignant lymphoma with a $T6^+T10^+T4^+T8^+TDT^+$ phenotype. On admission, examination revealed a pleural effusion containing 99% lymphoblast expressing the same immature phenotype. Lymphopenia was present at diagnosis with a normal T4/T8 ratio. Bone marrow (BM) cytology and biopsy were normal. However, the immunophenotyping evidenced 50% of $T6^+T10^+T4^+T8^+$ lymphocytes. The patient was treated according to EORTC ALL protocol with CNS prophylaxis. A first transient response was observed. Two months later, the pleural effusion recurred with an homogeneous population of atypical lymphocytes but the immunophenotype had changed for a more mature phenotype ($T11^+T3^+T4^+TDT^-$). At that time, the marrow was still morphologically and phenotypically normal. However, a similar $T11^+T3^+T4^+$ cell population progressively infiltrated the marrow and the peripherial blood. An ocular myasthenia, evidenced by electromyography, was observed at that time. Cerebral CT scan and lumbar puncture were normal. A pathological review of the slide excluded a concomittant thymoma. Since the pleural effusion was progressing, another chemotherapy regimen was initiated which produced a second remission. The malignant nature of the $T11^+T3^+T4^+$ lymphocytes was not evident on morphological basis. Their caryotype was normal and was thus not helpfull to ascertain their malignant nature. However, a DNA analysis of these ($T11^+T3^+T4^+TDT^-$) cells for the T-cell receptor gene showed a rearrangement which disappeared during the second remission. In addition, these T-cells have been maintained in culture for 10 weeks suggesting that a T-cell line had been established. Both facts lead us to conclude on the tumoral nature of those cells. In conclusion, the present observation on T-cell lymphoblastic lymphoma is compatible with either one or the other of the 2 following hypothesis : (1) The tumour was biclonal T at diagnosis but the $T11^+T3^+T4^+TDT^-$ population could be demonstrated only after chemotherapy. (2) A tumour cell maturation has been induced by chemotherapy.

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T 49 POLYMORPHOUS LYMPHOPROLIFERATIVE LESIONS OF THE THYROID GLAND: Report of 4 cases.

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We present 3 cases which could not be diagnosed with confidence as thyroid lymphoma by the routine microscopic examination alone. Another case in which a similar histological appearance to those of the 3 cases coexisted with immunoblastic sarcoma in the same thyroid gland is also presented.

A 59 years old man (case 1) had been under treatment for hyperthyroidism for 3 years. A nodule of the rt. lobe appeared in June 1979. After 2 months partial thyroidectomy was done. A 70 years old man (case 2) and a 49 years old woman (case 3) noticed a rapidly growing thyroid tumor in 1985 and 1986 respectively. They underwent an open biopsy. A 49 years old woman (case 4) had been receiving medical treatment for Hashimoto's disease since 1982. In 1986 her struma increased rapidly. Total thyroidectomy was performed in July 1986.

Grossly, a whitish nodule (0.5cm in diameter) was observed in case 1. In case 2 and case 3 the rt.lobes of the thyroid glands were enlarged, though there were no distinct nodules in the glands on the inspection at surgery. In case 4 the whitish and enlarged gland contained a poorly circumscribed tumor (3cm in diameter). Microscopically, small lymphocytes, medium sized lymphoid cells, mature and immature plasma cells and immunoblasts proliferated among lymph follicles or thyroid follicles in case 1, 2 and 3. In case 4 polymorphic cells above mentioned were numerously observed adjacent to the tumor, while the tumor were mainly composed of large cells with immunoblastic features. Using ABC methods, paraffin embedded sections were stained for cytoplasmic immunoglobulin. Monotypia for kappa light chain was clearly demonstrated in case 1, 2 and 3. In case 4 the cells with kappa light chain were numerically greater than those with lamda light chain to some extent.

Case 1, 2 and 3 histopathologically lacked the monotonous lymphoid infiltration and either loss of normal germinal centers or nearly complete effacement of the thyroid architecture. These histological features are said to be required for the diagnosis of malignant lymphoma of the thyroid gland. However, these 3 cases may be considered as neoplastic disorder rather than Hashimoto's disease because the thyroid lesions of these 3 patients were focal not extendig throughout the gland and the immunoperoxidase method showed monotypic cytoplasmic immunoglobulin. They are probably consistent with LP immunocytoma. It remains undetermined whether the polymorphocellular proliferation adjacent to immunoblastic sarcoma in case 4 is a part of lymphoma or not.

T 50 TWO TYPES OF RICHTER'S SYNDROME.

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The occurrence of histiocytic non-Hodgkin lymphoma (NHL) in a patient with chronic lymphocytic leukemia (CLL) is termed Richter's syndrome.

The demonstration of identical immunoglobulin (Ig) heavy and light chains on the surface of CLL and NHL cells of patients with Richter's syndrome has led to the conclusion that Richter's syndrome may represent transformation of the malignant CLL clone to a larger cell type (Am.J.Clin.Pathol. 1981; 76: 308). However expression of similar Ig light chains by two B-cell malignancies in one patient does not prove identical monoclonality, since the statistical likelihood of two independent clones expressing the same Ig light chain is more than 50%. Southern blot analysis to detect Ig gene rearrangement appears to be the most accurate method to prove or exclude the clonal origin of B-cell neoplasms.

Previously we demonstrated different Ig heavy chain gene rearrangements in a case of Richter's syndrome with different Ig light chains on the CLL and the NHL cells and concluded that in this CLL patient the NHL most likely should be considered as an independent B-cell malignancy (Blood 1984; 64: 571).

Here we present a case of Richter's syndrome which expressed identical Ig heavy (μ) and light (κ) chains on the CLL cells and the NHL cells. The CLL cells were samll lymphocytes and expressed the CD5 antigen and the B-cell antigens CD19, CD20 and CD24. The NHL cells which were large cells with prominent nuclei,also expressed these B-cell antigens, but were negative for the CD5 antigen. Southern blot analysis revealed that the CLL cells and the NHL cells had identical rearranged Ig heavy chain genes.

Based on these data it is concluded that there are two types of Richter's syndrome: one characterized by two different B-cell clones in a susceptible host and another one in which the B-NHL arises from transformation of a pre-existing malignant B-cell clone.

T 51 FAMILIAL MALIGNANT LYMPHOMA - DUNCAN'S SYNDROME

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In 1975, Purtilo described a family in which 6 out of 18 male members had died from lymphoproliferative diseases. All had acquired Epstein-Barr viral infection and showed immune deficiencies. Since only males were affected, an X-chromosomal inheritance was proposed ("X-linked lymphoproliferative syndrome" or "Duncan's disease"). Following immunopathogenetic mechanisms have been discussed: upon infection EB virus induces polyclonal proliferation of B lymphocytes. Due to an immune defect, there may be an insufficient production of specific antibodies and suppressor T lymphocytes to eliminate EBV infected B cells which in a second step may converse to monoclonal malignancies probably by gene rearrangements of cytogenetic alterations.

In this report we present a family with 3 sons who had lymphogranulomatosis and died at the age of 12, 20 and 25 years from Hodgkin's disease stage II B/IV B. The fourth son, 19 years old, was followed up for suspected Hodgkin's disease. A biopsy led to the diagnosis of a polymorphic lymphoplasmacytoid immunocytoma. A constant lowering of immunoglobulins, a moderately elevated EBV antibody titer and EBV DNA in a lymph node was detected. In concert with the history of the family we conclude the diagnosis "Duncan's syndrome". No evidence of HLA-linkage of the lymphoproliferative disorder could be shown. Although there was no numerical aberration of B and T cells and their subpopulations an areactivity by MLC-testing could be demonstrated. This suggests a functional T cell defect which may favour the development of a lymphoproliferative disease upon EB viral infection. From two of the patients lymphoid B cell lines have been established in vitro. The cells harbor the EB viral genome in multiple copies, express EB viral antigens, and show rearrangement of Ig heavy chain joining region. The oncogene c-fgr is highly expressed while other oncogenes tested (Ha-ras1, Ki-ras, myc, p53, fos) are expressed at the same level than quiescent peripheral blood lymphocytes.

T 52 HISTO-IMMUNOPATHOLOGY RELATED TO SURVIVAL IN A REGIONAL REGISTRY OF NON-HODGKIN'S LYMPHOMAS (NHL)

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In the region covered by the CCCW, a population based registry of >90% of all NHL (ALL, CLL, primary cutaneous T cell lymphoma and myeloma excluded), yielded 381 new cases between 1981 and 1985. All NHL from 15 hospitals have been reviewed according to the Kiel classification by a panel of 3 pathologists. Only NHL with immuno- and enzyme-histochemistry on initial, frozen material (available in 75%) have been classified. Many biopsies were of extranodal origin (44%). The frequencies for B-, T-NHL and Histiocytic NHL (HIS) were 88%, 7% and 6%, respectively. In 212 patients (follow-up up to 56 months), differences in survival were found for NHL of low (n=54), intermediate (n=119) and high malignancy grade (n=39) according to the Internarional Working Formulation (p=0.001). The low grade NHL included few lymphocytic (n=4) and Immunocytic NHL (n=8) because of exclusion of clinically overt CLL and frequent lack of frozen material from bone marrow. However, low grade Immunocytomas showed a relatively bad survival, not different from the polymorphic variant (n=14; 50% survival 22.5 months). This was confirmed by the association of a shorter survival for low grade NHL with intracytoplasmic Ig. (p=0.01). In Centroblastic/Centrocytic (CB/CC) NHL (n=68), a follicular pattern (n=46) was related to better survival (p=0.02). No differences in survival were observed between CB (n=80) and B-Immunoblastic lymphoma (n=13). Twelve cases were considered as NHL HIS by the presence of a diffuse activity of acidic phosphatase and non-specific esterase with absence of B- and T- cell markers. Although their histiocytic nature may be doubted, they do not compare with NHL CB, as they show differences in age (mean age 50 versus 62 yr), localisation and survival (50% survival 7 against 25 months; p=0.01).
Apart from the significance of sIgD on tumor cells, discussed elswhere, the absence of HLA-Dr on B-NHL (n=6 out of 135 analysed) seems to be related to extremely bad prognosis (50% survival of 5 months).

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T 53 PERCUTANEOUS LIVER BIOPSY IN PATIENTS WITH CLINICAL STAGE I-II NON-HODGKIN'S LYMPHOMAS.

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The percutaneous liver biopsy was performed in 103 patients with untreated non-Hodgkin's lymphomas clinical stages I and II. There were 51 histiocytic lymphomas, 48 lymphocytic and 4 lympho-histiocytic lymphomas (Rappaport). The purpose of this study was to determine the frequency of lymphomatous liver involvement in first two clinical stages of non-Hodgkin's lymphomas. All the biopsy specimens were histologically and cytologically analyzed. Lymphomatous infiltration was confirmed in 13.7% of patients with histiocytic lymphomas (7/51), only in 4.2% patients with lymphocytic lymphomas (2/4) and in 50% of patients with lympho-histiocytic lymphoma (2/4). In total, the liver was involved in 10.7% (11/103) of the patients. In the whole group of patients, there were non-specific liver changes: 13 chronic persistant hepatitis, one chronic aggressive hepatitis, 11 liver steatosis, 4 liver hemosiderosis and one cirrhosis. Based on these results, it can be concluded that liver involvement with lymphomatous tissue was confirmed by percutaneous biopsy in every ninth patient with non-Hodgkin's lymphomas clinical stages I and II. Knowledge of this is relevant for clinical staging and the treatment program. These findings also confirm that percutaneous liver biopsy is a valuable diagnostic procedure in the staging of malignant lymphomas.

T 54 ENHANCED DIAGNOSTIC ACCURACY OF B-NHL IN FINE NEEDLE ASPIRATES BY ANALYSIS OF CLONAL EXCESS.

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Fine needle aspiration (FNA) cytology is a valuable tool in diagnostic and staging procedures in patients with NHL. These tumours are often multicentric and involve sites not easily accessible to surgical biopsy such as the liver and spleen.

The lymphoma cells might be difficult to recognize in an admixture of normal lymphocytes.

The aim of this study was to determine the diagnostic value of adding clonal excess analysis to the morphological evaluation of FNAs.

MATERIAL AND METHODS. 121 FNAs from 100 adult patients with NHL or unclear lymfadenopathy were examined. The membrane immunoglobulin light chain distribution was analysed in direct immunofluorescence by flow cytometry. Incongruence between the K and L light chain distribution was considered to indicate clonal excess, i.e. lymphoma cells.

RESULTS. Sufficient material was obtained in 2/3 of the aspirates.

In 19 FNAs performed as part of staging in patients with NHL, the morphological evaluation was inconclusive or normal. In seven (37%) of these NHLinvolvement was detected by clonal excess .

In 14 FNAs performed in primary diagnostic procedures the morphological evaluation showed poorly differentiated tumours of undetermined origin. In five of these (36%) a B-NHL was defined by restricted light chain expression.

In 33 FNAs the morphological diagnosis was NHL, which was confirmed by clonal excess analysis in 16 (48%). Data will be discussed.

CONCLUSION.

The diagnostic precision was enhanced by combining morphological and immunological evaluation of FNAs in adults with NHL. The diagnostic gain was confined to the low grade malignant group (according to Kiel). The clinical value of enhanced staging accuracy will require long term follow up.

T 55 PHENOTYPIC SUBPOPULATION STUDIES ON NON HODGKIN LYMPHOMA (NHL) BY FLOW CYTOMEMETRY.

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65 specimens from NHL patients were characterized by a panel of monoclonal antibodies to leukocyte differentiation antigens (T, B and Monocytic antigens as well as the HLA-Dr (Ia) related antigen).

20 specimens were classified as B cell, 6 as T cell, 19 as null-cell and 20 as mixed (expression of more than one lineage markers).

Studies of the physical characteristics (volume and light scatter) by a Becton-Dickinson flow cytometer indicated that distinct differentiation stages are related to various size and light scatter parameters. Four patterns were distinctly shown to occur 1) Well differentiated B-lymphoma cells, small size, agranular cells 2) Null-type Ia^+ or Ia^- cells small size-agranular 3) T cells small-agranular 4) Cells of mixed phenotype small and large, granular or agranular.

It appears that physical properties of lymphoma cells are related to various differentiation stages when assened by the expression of leukocyte monoclonal antibodies and flow cytometry.

T 56 LOW FIELD STRENGTH (0.08 Tesla) MAGNETIC RESONANCE IMAGING OF LYMPH NODES IN PATIENTS WITH LYMPHOMA.

M.A. Richards, R.H. Reznek, J.A.W. Webb, S.E. Jewell, P.F.M. Wrigley, T.A. Lister. ICRF Department of Medical Oncology and Department of Radiology, St. Bartholomew's Hospital, London EC1A 7BE.

Magnetic resonance imaging (MRI) of mediastinal (12 patients) and abdominal (26 patients) lymph node masses has been performed in patients with known lymphoma. The mean spin lattice relaxation time (T_1) of each mass was calculated. The influence of histology on nodal T_1 was evaluated. Serial scans were performed on 6 patients with mediastinal masses and on 8 patients with abdominal lymphadenopathy. Changes in T_1 were compared with response to therapy documented by conventional methods. The size of abdominal lymph nodes measured by MRI was compared with that measured by CT scanning.

The mean T_1 of abdominal lymph nodes in patients with untreated HD ranged from 330-422 msec (mean 387 msec). The range for follicular NHL was 391-413 msec (mean 402 msec) and that for diffuse NHL was 412-509 msec (mean 464 msec). The mean for patients with diffuse NHL was significantly higher than that for patients with either HD ($p < 0.001$) or follicular NHL ($p < 0.05$). However, in the mediastinum, no difference in nodal T_1 was observed between patients with untreated HD and those with high grade NHL.

A marked decrease in nodal T_1 (in the mediastinum and abdomen) was observed in all patients undergoing serial scanning who showed objective evidence of response to treatment. Nodal T_1 was unchanged or increased in 3 patients who failed to respond to treatment. The implications for the use of MRI in detecting and monitoring lymphadenopathy will be discussed.

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T 57

LOW FIELD STRENGTH MAGNETIC RESONANCE IMAGING OF THE SPLEEN IN PATIENTS WITH MALIGNANT LYMPHOMA. M.A. Richards, J.A.W. Webb, R.H. Reznek, S.E. Jewell, P.F.M. Wrigley, T.A. Lister. ICRF Department of Medical Oncology and Department of Radiology, St. Bartholomew's Hospital, London EC1A 7BE.

Magnetic resonance imaging (MRI) of the spleen at 0.08 Tesla with spin lattice relaxation time (T_1) measurement was performed in 19 lymphoma patients (15 HD, 4 NHL) prior to splenectomy (18 patients) or autopsy (1 patient). The characteristics of normal spleens on T_1 images and the normal range of spleen T_1 were established by scanning 79 volunteers. Diffuse inhomogeneity of spleen T_1 or focal 'hot spots' were observed on the images of 25 (32%) of the volunteers. Such findings were therefore considered to be normal variants. Mean spleen T_1 for the volunteers ranged from 362-420 msec (mean 385 msec).

Six of the patients had spleens which appeared enlarged on MRI. In each case the spleen weighed more than 450 gms. The other 13 spleens appeared normal in size on MRI and each weighed less than 250 gms.

Eight patients (5 HD, 3NHL) had histological evidence of splenic lymphoma. Two patients with HD in the spleen had normal spleen T_1, in the other 3 T_1 was below normal. Two of the 3 patients with NHL in the spleen had prolonged T_1, the third was normal.

Eleven of the patients had no evidence of lymphoma in the spleen. Eight of these had normal spleen T_1. In the other 3 the spleen T_1 was below normal. Each of these 3 had recently undergone lymphography and one had received prior chemotherapy.

The sensitivity of T_1 measurement by MRI for the detection of splenic lymphoma was therefore poor and contrasts with the results for the detection of hepatic lymphoma found using the same system[1]. Possible explanations for these findings will be discussed.

[1] Richards, M.A. et al. BMJ, 1986, 293 : 1126-1128.

T 58

Non Hodgkin lymphomas of high and intermediate malignancy with primary involvement of the Waldeyer's ring and maxillary sinus. Treatment and clinical course.

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While Hodgkin lymphomas involve the Waldeyer's ring in only about 1% of the cases, initial involvement is found in 15-20% of high malignant non Hodgkin lymphomas. From 1981 through 1985, 44 previously untreated patients with primary non Hodgkin lymphoma of the Waldeyer's ring and the maxillary sinus were treated in our institution. Histopathological distribution based on the Kiel Classification. 29 cases were classified into high-malignant NHL, among them 16 centroblastic lymphomas, 15 cases into diffuse and follicular and diffuse subtypes of centroblastic-centrocytic lymphomas. 16 patients were allocated to stage I, 28 patients to stage II. Patients were treated with 60 Co-γ-ray (45 Gy), 26 of them with additional chemotherapy.
The survival rates at 50 months were 100% and 62% for stage I and II, respectively. The relapse-free survival rates were 72% and 52%. Patients in stage II treated with chemotherapy and irradiation had a substantially better prognosis than those without chemotherapy. The survival rates were 82% and 40%. There was no difference in stage I. While the value of additional chemotherapy for stage I is controversial, satisfactory results with CHOP-Bleo regimen were obtained for stage II. In advanced aged patients a less aggressive regimen (CVM) was favoured.

T 59

THE VALUE OF IMMUNOLOGICAL TESTS IN PROGNOSIS OF PATIENTS WITH HODGKIN DISEASE. M. Fidler Jenko, T. Šumi Križnik, J. Škrk, J. Červek, S. Plesničar, L. Tekavčič, The Institute of Oncology, Zaloška 2, 61105 Ljubljana, Yugoslavia

In 54 patients (40 males, 14 females, age 19-59 years) with Hodgkin disease absolute number of lymphocytes (ANL), transformation tests with PHA (TTL), skin tests with DNCB and PPD as well as conc. of serum gamma (G) and immunoglobulins (IG) were determined before primary treatment. The tests were correlated with known prognostic signs of the disease. Patients were followed from 1973-1986. Ann Arbor staging system was used, in half of the group determined surgically (patholgoical staging).
By the end of the observation period (Dec.1986), 28 patients were alive in remission, while 26 were dead.

According to survival, a group of patients remained alive longer (9-13 years) while the other group showed a shorter survival (3 months - 4 years).
Long-term survivors (30 patients) were younger, with earlier stages of disease and had more remissions following the treatment. Immunological tests showed normal ANL, over 40% TTL in 15 patients, DNCB reactive in 16, non-reactive in 7 patients, PPD positive in 10, negative in 20 patients. The serum conc. of G and IG was normal in all patients.
In the group (24 patients) with shorter survival (3 months - 4 years) the patients were older, with more advanced stages, B-symptoms and no remission following the treatment. Immunological tests showed low ANL in 15 patients, 30% and less TTL in nearly all patients, DNCB reactive in 10, non-reactive in 13, PPD positive in 6 and negative in 18; G and IG ser.concentrations were normal.

The study revealed that the initial immunological characteristics of patients with Hodgkin's disease are in positive correlation with already known prognostic signs of disease. The data will be statistically analysed.

T 60

NON HODGKIN'S LYMPHOMAS OF WALDEYER'S RING. S. Dal Fior, T. Chisesi, P. Coin, V. Stracca-Pansa, F. Pozza, E. Dini. Dpt. Radiotherapy & Hematology & Pathology, Ospedale S. Bortolo, 36100 Vicenza, Italy.

From 1973 to 1986, 50 consecutive patients with non Hodgkin's Lymphomas (NHL) of Waldeyer's ring (WR) were evaluated at S. Bortolo Hospital, Vicenza. The mean age was 66 (range 32-81), with a male to female ratio 1.38.1. Median observation was 60 months. The tonsil represented the most frequent site of involvement in 40 cases (in 19 patients both tonsils were involved); then, nasopharynx in 7 cases, base of tongue in 2 and soft palate in 1 patient. All pathology specimens were reviewed: 41 patients (82%) had an unfavourable histology according to the Rappaport classification; 28 (56%) low grade NHL were diagnosed according to the Kiel classification; Working Formulation grades were low in 9 patients (18%), intermediate in 26 patients (52%) and high in 14 cases (28%). One patient had an unclassifiable histology according to the Kiel and the Working Formulation. Lymphangiogram constituted a staging procedure in 24/50 cases and trephine bone marrow biopsy was performed in 42/50. According to the Ann Arbor staging system 12 patients were stage I, 17 stage II, 10 stage III, 11 stage IV. Three out of 24 (12.5%) clinical stages I-II were upgraded with lymphangiogram, and 1/22 (4.5%) shifted to stage IV by bone marrow biopsy. All stage I-II patients were treated as follows: radiotherapy alone, 14 patients (7 stage I); combined radiotherapy and chemotherapy, 18 patients (5 stage I). Chemotherapy constituted the treatment modality for all patients in stage III-IV. Complete remission was achieved in 12/12 stage I patients; 4/17 stage II patients; 6/10 stage III patients; and 6/11 stage IV patients. Our data allow for indicating as major prognostic factors the following: stage I vs stage II-III-IV (88% vs 18% - 66% - 30% 5-year survival; p = 0.01); low vs high grade histology according to the Working Formulation (81% vs 32% 5-year survival; p = 0.05); age less than 65 years vs more than 65 (75% vs 34% 5-year survival; p = 0.05). Radiotherapy is the treatment of choice for stage I, whereas chemotherapy could increase survival for patients in stage II. Gastrointestinal relapse is rare for I-II staged patients (1/29, 3.4%). We can conclude that WR involvement may be considered as a nodal region localization.

T 61 NHL IN A POPULATION BASED REGISTRY; ELDERLY PATIENTS INCLUDED.

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Population based registration of all new cases of NHL has been initiated by the Comprehensive Cancer Centre West (the Netherlands). From June 1, 1981, until December 31, 1984, 382 new NHL's patients were registered, representing at least the expected incidence (ALL, CLL, primary cutaneous lymphoma and myeloma were excluded).
A panel of pathologists ensured uniform immunohistological classification according to Lennert. Due to lack of frozen sections 25% of all cases were not classified. Of the remaining 271 classified NHL, 25% were of low-, 51% of intermediate- and 19% of high-malignancy grade (IWF 1982). All patients were staged according to the Ann-Arbor classification: 17% in stage I, 18% in II, 12% in III and 53% in IV. An unexpected high number of primary extranodal presentations (41%) was found.
Thirty-four percent of all cases were aged 70 or older (N=130).
Three years survival was significantly better in cases with stage I (p=0.0003), in cases with low-malignancy grade (p=0.002), in patients with follicular growthpattern (p=0.001), in cases younger than 70 (p=0.0001) and those who obtained a complete remission (p=0.0001).

Taking independant good prognostic factors on survival into consideration (stage I, low-malignancy grade, follicular growth pattern, complete remission), they were all less frequently represented in the elderly group.

Through this registration it became clear that 1/3 of the NHL's patients are aged 70 or older. Clinical trials should be designed in order to improve correct management of these elderly patients.

T 62 SOME EPIDEMIOLOGIC ASPECTS OF NON-HODGKIN'S LYMPHOMAS IN THE ISLAND OF SARDINIA IN THE YEARS 1974-1981.

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Through examination of registries of all pathology institutions and of all clinical departments of the island of Sardinia,with subsequent examination of the clinical documentations,all cases of hematological malignancies newly diagnosed in the years 1974-1981 in the resident population of the island(1.610.270 in 1978 census,almost constant in the considered years,also in age and sex distribution)have been collected.
Among them there were 531 cases of non-Hodgkin's lymphoma,histologically diagnosed.Histology was not revised.Knowledge of clinical documentation permitted exclusion of cases of leukemia.
-In 208 cases(39%) the disease was thought to have originated in extralymphonodal sites(gastric 36;intestinal 24;Waldeyer ring 39;cutaneous 36,of which Mycosis Fungoides 11;bone marrow 14;bone 8;salivary glands 8;other sites 43).
- Number of cases for year ranged 51-80(mean 66.7).
- Age adjusted incidence rate was 4.17 x 10^5 x year for males and 2.97 x 10^5 x year for females.Male-to-female ratio was 1.4.
- Age specific incidence curves demonstrated a first peak in age class 5-9 and then a progressive increment with peak in age class 65-74 (18 x 10^5 x year for males and 13 x 10^5 x year for females).
-Comparison of age adjusted incidence rates and of age specific incidence curves did not reveal any significant difference between urban and rural population.

This work was in part supported by a grant from Assessorato alla Sanità,Regione Sardegna.

T 63 BURKITT'S LYMPHOMA IN THE IVORY COAST

EVALUATION OF THE TREATMENT OF 194 CASES AND THE PROBLEM OF DURABLE REGRESSIONS.

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The authors present a study of 194 young patients treated in the Department of Stomatology and Maxillo-Facial Surgery of the University Teaching hospital, ABIDJAN

They place BURKITT'S LYMPHOMA in its position among all cancers in the IVORY COAST.

After a summary of the historical, clinical, radiological and histological aspects of the disease, they present a study of the management of 194 cases divided into 4 groups which correspond to four different chronological periods during which different treatments were tried.

They go through some particular aspects of the desease.

The results of their study are as follows :

108 complete clinical regression at discharge from hopital, but the majority are lost to follow-up.

The survival of patients seen at follow-up is from 4 months to 9 years.

Some associations or particular aspects constitute an aggravating factor.

Of all treatment, the association METHOTREXATE and ENDOXAN remains the most efficient.

Finally, contrary to English speaking authors, they are of the opinion that the prognosis of BURKITT'S LYMPHOMA still remains poor with few survival.

T 64 SOME EPIDEMIOLOGIC ASPECTS OF HODGKIN'S DIDEASE IN THE ISLAND OF SARDINIA IN THE YEARS 1974-1981.

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Through examination of registries of all pathology institutions and all clinical departments of the island of Sardinia,with subsequent examination of the clinical documentation,all cases of hematological malignancies newly diagnosed in the years 1974-1981 in the resident population of the island(1.610.270,1978 census)have been collected.
Among them there were 259 cases of Hodgkin's disease,histologically diagnosed.Histology was not revised.
-Number of cases for year ranged 20-48(mean 32.4).
-Age adjusted incidence rate was 2.0 x 10^5 x year(male 2.37 and female 1.65).Male-to-female ratio was 1.44.
This rate falls into the range reported for European countries,being lower than USA and higher than developing countries rates.
-Age specific incidence curves demonstrated,as in developed countries, low incidence in childhood and marked increase in young adulthood. They were bimodal in both sexes,with first peak in the third decade for both male and female,and second one,lower,in the sixth decade for male and in the seventh for female.Male-to-female ratio increased with age,reaching 4 in the seventh decade.
-Histological subtype pattern well compares with that reported in developed countries(NS 40.6%;MC 28.5%;LD 22.7%;LP 8.2%).
NS predominated in female,MC and LD in male.
-Age specific incidence curves by sex and by histologic subtype suggested that a great part of first peak was represented by NS(with female predominance)while second peak was mostly represented by MC and LD(with male predominance).
-Particularly in age classes from 0 to 40 years no difference in incidence emerged between urban and rural populations.

This work was in part supported by a grant from Assessorato alla Sanità,Regione Sardegna.

ABSTRACTS - Third International Conference on Malignant Lymphoma, Lugano

T 65 NON-HODGKIN'S LYMPHOMA FOLLOWING THERAPY FOR HODGKIN'S DISEASE: DISEASE OR THERAPY RELATED?

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We have reviewed over 80 reported cases of non-Hodgkin's lymphoma (NHL) and other lymphoproliferative disorders occurring following the use of intensive chemotherapy and/or radiotherapy for the attempted cure of Hodgkin's disease (HD). To evaluate possible causative factors for this occurrence we have previously demonstrated (Cancer 50: 678-683, 1982) that the excessive incidence of acute non-lymphocytic leukemia as a second neoplasm in patients treated for HD is related to the type and amount of therapy administered. The relationship between the occurrence of NHL in patients intensively treated for HD and the treatment given for the HD is unclear. Five possible explanations for the development of NHL in patients with HD are considered: 1) the mutagenic and carcinogenic effects of radiation and/or alkylating agents and other cytotoxic drugs; 2) the immunosuppressive effect of radiation and/or cytotoxic drugs; 3) the immunologic defects caused by the HD itself; 4) misdiagnosis of HD as the primary neoplasm, especially in patients initially diagnosed to have the lymphocyte predominance form of HD; 5) combination of two or more of the above.

Based on the high frequency of occurrence of NHL in patients with immune defects due to congenital or acquired immunodeficiencies, and the natural history of presentation and behavior of reported cases of HD terminating in NHL, we postulate that NHL occurring in patients treated for HD is due to the immune deficiencies of such patients. Since most reported cases of NHL following HD provide no denominator for risk assessment, it is not possible at present to calculate the exact frequency of occurrence of this association. However, based on several reported series of patients, the figure may be as high as 4% at ten years.

T 66 CORRELATION BETWEEN AGE AND PROGNOSIS IN HODGKIN'S DISEASE (HD).

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The influence of age on presentation and cause of death was examined in 533 patients (pt) referred for initial treatment to the Netherlands Cancer Institute from 1966-1982. Factors analysed were age, sex, stage, histological subtype, disease-free survival (DFS), survival (S), and cause of death. A few subgroups were studied in more detail.
Below 40 yrs (<40) there were 194 males (♂) and 154 females (♀), and equal to or above 40 yrs (≥40) were 114 ♂ and 71 ♀.
The peak incidence for both sexes was from 20-30 yrs, there was no bimodal age curve. Male preponderance was not seen in stage II for both age groups. Nodular sclerosis (NS) occurred equally in both sexes, both < 40 and ≥40; the sex ratio for mixed cellularity (MC) was < 40:0.04 and ≥40:0.6 (n.s.).
Division over stage was equal: < 40:I:21%, II:49%, III:19%, IV:12%; ≥40: I:28%, II:39%, III:21%, IV:12%.
DFS was not affected by age in stage I, III and IV, but was worse >40 for stage II (p=0.03). Survival after relapse <40 was 80% and ≥40 47% (p=0.00).
Actuarial death at 10 yrs through HD was 13% up to 40 yrs, then increased to 22% (40-49 yrs, 77 pt), 42% (50-59 yrs, 47 pt) and 35% (60-69 yrs, 39 pt). Death through all causes was 17% up to 40 yrs and then started to increase: 42% (40-49 yrs), 62% (50-59 yrs) and 63% (60-69 yrs).
Cause of death <40 was 11% (40 pt) through HD and 5% (17 pt) from other causes (7: 2nd malignancy), ≥40 24% (44 pt) died from HD and 32% (60 pt) from other causes (40: 2nd malignancy).
We examined more closely 20 pt ≥40 who died within 12 months of diagnosis. Treatment was incomplete in 11 through chemotherapy complications (bone marrow depression and gastro-intestinal ulceration), in 4 because of incomplete staging, and in 1 through radiation pneumonitis.
Total nodal irradiation (TNI) was given to 14 pt ≥40 and 15 pt <40 with equal result.
Conclusion: distribution over stage and histology is not influenced by age in HD, nor is DFS. Survival decreases 40 yrs mainly through other causes of death and partly through bad tolerance of chemotherapy.

T 67 RESULTS OF INITIAL TREATMENT OF PATIENTS WITH HODGKIN'S DISEASE.

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Between January 1974 and March 1985 we followed 241 patients with Hodgkin's disease (HD) in all stages of disease: 28 (12%) cases were clinical stage (CS) I, 101 (42%) were CS II, 84 (35%) were CS III and 27 (11%) were CS IV. 173 (72%) of all patients had B symptoms of the disease. Patients in CS IA were treated with radiotherapy (RT) alone or RT combined with chemotherapy (CT). Patients in CS IB-IIB were treated with RT plus CT while those in CS IIIA-IVB were treated only with CT. We have used the following therapeutic regimens (in the descending order according to the number of treated patients): MOPP, COPP, CHlVPP and BCVPP. Cpmplete remission (CR) was achieved in 200 (83%) cases and according to clinical stages: CS I in 96%, CS II 88%, CS III 80% and CS IV in 52%. Complete remission was achieved in 95% of patients without symptoms (A) and 78% with B symptoms. 56% of all patients are in CR lasting for 5 years and longer. The most frequent histopathologic types were nodular sclerosis (36%) and mixed cellularity (33&). The influence of histopathologic type on the course of the disease was not statisticaly significant.

T 68 RADIOTHERAPY VS RADIOTHERAPY PLUS CHEMOTHERAPY IN HODGKIN'S LYMPHOMA STAGE I-II ABOVE THE DIAPHRAGM.

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From 1970 to 1984 231 pts affected by Hodgkin's lymphoma (LH) stage I-II above the diaphragm were observed. 104/231 pts (45%) received radiation therapy (RT) alone as total nodal irradiation (TNI) or sub-total nodal irradiation (sTNI) (mantle + paraaortic field), with a total dose of 40-44 Gy/4-5 wks. 127/231 pts (55%) received RT and 3-6 cycles of adjuvant chemotherapy (CT) as MOPP or ABVD. Results were analysed as survival (S) and disease free survival (DFS) vs the kind of therapy and vs mediastinal involvement. In the RT group DFS was 62%. 26/104 pts (25%) relapsed: 19/26 pts (73%) reached a complete remission (CR) again after 6 cycles of CT so the absolute survival of irradiated pts was 80%. In the RT + CT group DFS was 80%. 12/127 pts (10%) relapsed and only 3 of these pts got a CR again after CT. At last S is not significantly different in the two groups. After RT the DFS is 50% in pts with mediastinal involvement (M+) and 70% in pts without it (M-). The majority of relapsed M+ pts is now in CR after CT. After RT + CT the DFS is the same (80%) in pts with and without mediastinal involvement. The amount of drugs (3 vs 6 cycles) and "bulky" in the mediastinum did not significantly affect DFS. 3/10 irradiated pts died for severe lung fibrosis and 3/127 pts who received RT + CT died for infections.

ABSTRACTS - Third International Conference on Malignant Lymphoma, Lugano

T 69 THREE CYCLES OF MOPP PLUS RADIOTHERAPY (RT) FOR HODGKIN'S DISEASE (HD) CLINICAL STAGES (CS) IIIB AND IV. SEVEN-YEAR RESULTS OF THE PAF 80/34 TRIAL.

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From 10.80 to 12.85, 36 patients (pts) with CS IIIB and IVB (IIIB 18, IVB 18: Lung 5, lung + bone 1, bone 1, liver 6, bone marrow 3, bone marrow + liver 2 ; sex M 27, F 9 ; age range 8-62, median 28 ; histology LP 2, NS 15, MC 14, LD 4, unclass 1) were prospectively treated with the PAF 80/34 trial. Three cycle of MOPP (Mechlorethamine, Vincristine, Procarbazine, Prednisolone) were first given. Pts in complete remission (CR) and partial remission received total or subtotal nodal RT (40 Gy). Liver and/or lung(s) RT (20 Gy) were added when necessary. 10 pts did not enter in CR ; 8 of them died quickly (progressive disease under MOPP or RT 5, inadequate supportive care 3) ; the 2 others were salvaged by 3 courses of intensive chemotherapy and are alive in remission (3+ and 30+ months). Twenty six pts entered in CR.4 died after 2 to 33 months without having relapsed (viral hepatitis, post RT intestinal occlusion, secondary acute leukemia, unknown cause) and 22 pts remained in first CR. As of December 31, 1986, actuarial survival of the 36 pts (7 years) is 65.7%. That of the 28 pts who entered in CR with the PAF 80/34 protocol is 83.6% with a plateau since the 34th month of CR and no relapse so far.

T 70 CONBINED MODALITY TREATMENT FOR ADVANCED HODGIN'S DISEASE.

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Twenty patients (pt) with advanced Hodgkin's disease were treated by combination chemotherapy (M O P- B A P): Nitrogen mustard 6 mg/m i.v. day 1 , Vincrisine 1.4 mg/m i.v. days I and 8, Procarbazin 100 mg/m P.O. days 2-7 , 9-12 with Prednisone 40 mg/m cycle one and four, Adriamycin 30 mg/m i.v. day 8 and Bleomycin 2 mg/m i.v. days I and 8 . All pt. had received 6 cycles as induction therapy. The age ranged between 20-64 avr. 34.4 years. Clinical stages were : III A: 6 , III B: 6, IV B:8. Most of the pt. had bulky disease (75%), and 85% had more than three sites of involvement by the disease. Pathological types: Mixed cellularity 11, Nodular sclerosis 5 , and lymphocytic predominance 4 pt. Toxicity was observed as W B C less than 2000 in 5 patients, serious infection (fatal) in one pt., low voltage E.C.G. in one and all had alopecia . Gastrointestinal toxicity grade 3 in five. Two pt. were lost follow up. The 18 evaluble pt. were followed for 96 months. Complete remission (CR) was observed in 10/18 pt. four of them was proved by exploration for restaging. Partial remission (PR) in 6/18 pt. According to the studt protocol all pt. in PR had recived involved field radiotherapy. Three of them had achieved complete remission , two no change andthree pt. increased disease and death. Ten of the study group (56%) are still living after 96 months of initial therapy, eight of them (44%) are disease free. Noadditive toxicity was observed with radiotherapy . It is concluded from this study that M O P- B A P chemotherapy can produce prolonged disease survival in 44% of pt. with advanced Hodgkin's disease with bulky lesions and involved field radiotherapy can salvage 57% of pt. achieving partial remission after induction chemotherapy .

T 71 COMBINED MODALITY TREATMENT OF ADVANCED STAGES HODGKIN'S DISEASE WITH REDUCED CHEMOTHERAPY AND RADIOTHERAPY.

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In combined modality treatment protocols for advanced Hodgkin's disease radiotherapy (RT) has been mainly used as an adjuvant therapy at low dosages ($\leq$ 25 Gy). Since May 1981 we have been used higher dosages of RT ($\geq$30 Gy) in association with chemotherapy (CT) for CS IIB, III, IV patients (pts). The treatment protocol is outlined below.

Stage IIB 3MOPP+RT 30/40 Gy extended fields ± 3MOPP
Stage IIIA 3MOPP+RT 30/40 Gy total nodal
Stage IIIB-IV 6MOPP+RT 30 Gy on bulky disease

After five years, 82 pts have been enrolled and 64 (13 IIB, 22 IIIA, 29 IIIB-IV) are fully evaluable. The overall CR rate is 91% (58/64). CR rate for stages IIB and IIIA is 100% and for stages IIIB-IV is 79%. Seven pts relapsed (1 IIB, 1 IIIA and 5 IIIB-IV). After a median follow-up of 30 months, the actuarial disease free survival (DFS) at 60 months is 66%, and the overall survival is 75%. One pt died because of drug related pancytopenia. The treatment was stopped in one case for major cutaneous toxicity. One pt developed acute non lymphoblastic leukemia after salvage treatment (ABVD+RT). This protocol seems effective in achieving an high CR rate and a quite satisfactory DFS, particularly in intermediate stages. Acute toxicity is moderate and manageable. However, a longer follow-up is needed to evaluate late toxicity.

T 72 MOPP/ABVD OR MOPP/EBVD IN ADVANCED HODGKIN'S DISEASE. EXPERIENCE ON ONE HUNDRED PATIENTS.

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One hundred concecutive patients with advanced stages Hodgkin's disease were treated in our Unit with the alternating protocols of MOPP (mustargen, vincristine, procarbazine, prednisone)/ABVD (adriamycin, bleomycine, vinblastine, DTIC). Seventy six of them were newly diagnosed and 24 were in their first relapse. Of the newly diagnosed patients 56 received the MOPP/ABVD programme, while in the remaining 20 adriamycin was substituted with epirubicin (EBVD). The extent of the disease and the documentation of the complete remission (CR) were determined using well known criteria. Seventy patients were males and 30 females with a mean age of 38 years (15-67) and a mean follow up time from the diagnosis in the non-treated cases of 30 months (5-69). Seventeen patients were clinical stage IIB, 4 IIIA (bulky), 42 IIIB, 5 IVA and 32 IVB. Ten patients had the histologic subtype of lymphocyte predominance, 42 the nodular sclerosis, 38 the mixed cellularity and 10 the lymphocyte depletion. Our results obtained in the three groups were as follows:

	MOPP/ABVD	MOPP/EBVD %	MOPP/ABVD in first relapse
Complete remission	83	90	67
Mean follow up time of CRs in months (range)	26.5 (5-63)	6.2 (1-14)	27.7 (9-54)
Relapse rate	6.4	too early	12
Survival of CRs	96	"	82
Total survival	85	"	75

Of particular interest is our observation that epirubicin administered in the same dose with adriamycin (25mg/m^2), was equally effective. We concluded from our analysis that MOPP/ABVD in advanced Hodgkin's disease is very effective and that substitution of adriamycin in the ABVD programme by the less cardiotoxic epirobicin, is entirely justified.

ABSTRACTS - Third International Conference on Malignant Lymphoma, Lugano

T 73 THERAPEUTIC RESULTS IN STAGE III AND IV HODGKIN'S DISEASE.MULTICENTER PROTOCOL LMS-H-80.

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Between January 1, 1980, and December 31, 1984, a protocol of randomized prospective treatment was applied to 104 patients with Stage III or IV Hodgkin's disease. One of the goals of this study was to undertake therapy with minimal risks of secondary malignancy.
Stage III A patients were randomly divided into two treatment groups. One group (R1) received only supra -and sub- phrenic radiotherapy and the other (R2) underwent a series of 6 MOPP treatments followed by irradiation of the regions initially involved. First complete remission (RC1) was achieved in 93% : 100% in group R1 and 88% in group R2. Of the patients who achieved RC1 45% of those from group R1 and 92% from group R2 are still disease free at 5 years. Conversely acturial survival at 5 years is 100% for group R1 and 65% for group R2.
Stage III B patients were likewise randomly distributed into two groups. R1 received a total of 12 treatments alternating MOPP and CVPP, R2 received 3 MOPP treatments, supraphrenic radiotherapy, 3 more MOPP treatments and subphrenic radiotherapy. In all 83% achieved RC1 : 76,5% from group R1 and 89,5% from group R2. Of the patients who achieved RC1 80% of those from group R1 and 90% from group R2 are still disease free at 5 years. Conversely acturial survival at 5 years is 80% for group R1 and 38% for group R2.
For stage IV patients the therapies administered to the two randomly formed groups were 12 MOPP/CVPP treatments for R1 and 12 ABVPP (ADRIAMYCINE, BLEOMYCINE, VINBLASTINE, PROCARBAZINE, PREDNISOLONE) treatments for R2. In all 79% achieved RC1 : 74% from group R1 and 84% from R2. At 5 years 40% of R1 patients in RC1 were still disease free as opposed to 55% of R2 patients in RC1. Acturial survival at 5 years was 82% for group R1 and 45% for R2.
Overall, results were better for patients who achieved RC1 by the third month than for patients who did not achieve RC1 until the end of treatment. 3 patients presented a secondary malignancy (2,8%) : 2 AML and 1 high grade NHL.
In conclusion in this series radiotherapy alone was the best initial treatment for stage III A - relapses were readily reversed by chemotherapy with no special iatrogenic risk. For stage III B patients survival was better with chemotherapy alone. In stage IV, ABVPP chemotherapy was more effective than combined MOPP/CVPP treatment. Our experience shows that for advanced stage Hodgkin's disease radiotherapy or chemotherapy alone are more effective and less toxic than combined radio -and chemotherapy or two types of chemotherapy.

T 74 CHEMOTHERAPY OF ADVANCED STAGES HODGKIN'S DISEASE WITH ADRIAMYCIN, CYCLOPHOSPHAMIDE, ETOPOSIDE, DEXAMETHASONE AND VINCRISTINE (ACEDO).

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Despite excellent chemotherapy sensitivity of Hodgkin's disease advanced stages have only a moderate prognosis with conventional chemotherapy (MOPP; COPP - ABVD). More effective regimens including the most active agents are required. 21 patients (pts) have been treated with the following schedule: adriamycin 40 mg/m² i.v. day 1, cyclophosphamide 650 mg/m² i.v. day 1, etoposide 100 mg/m² i.v. day 3,4,5, dexamethasone p.o. 15 mg/m² day 1-4 and 8-11, vincristine 1,4 mg/m² i.v. day 1 and 8, q day 22, 4 - 6 cycles, with additional prophylactic selective oral decontamination.
Patients characteristics: 12 male, 9 female, mean age 36 (21 - 64) years, mean performance status (KI) 90%, clinical stage IIB (4), IIIAE (1), IIIB (5), IVA,B (11). 9/21 had bulky disease (EORTC criteria). 13 pts were untreated, 8 pretreated with CP (1), COPP (1), COPP/ABVD (2), COPP/ABVD/CEVD (1), COPP/ABVD + radiotherapy (3).
Results: 20 pts are evaluable for response (1 early toxic death). All pts responded: CR 55%, PR 45%.

	no prior treatment (n = 13)	pretreated (n = 7)
CR	8/13 (62%)	3/7 (43%)
PR	5/13 (38%)	4/7 (57%)

Median remission duration for CR was 7+ mos (4-11+) and for PR 10+ mos (2-12+); the median survival for all pts is 10,5+ mos (2-18+). Toxicity (21 pts, 100 cycles) was predominantly related to the bone marrow with leukopenia WHO °2 (19%), °3 (62%), °4 (19%), thrombocytopenia °4 (10%), neuropathy °1 and °2 (33%), fever and infection °1 (25%), °3 (5%), °4 (10%) including two lethal septicemias. 1 pretreated patient died from intracerebral hemorrhage due to uncorrected thrombocytopenia. Nausea/vomiting was common but tolerable with 33% °3 and no °4. 1 cardiomyopathy was observed in a pt with high anthracycline pretreatment.
Conclusion: This regimen is active in pretreated and untreated pts with advanced Hodgkin's disease. Though it is to early for final conclusions, the CR-rate in untreated pts appears not to be superior to standard chemotherapy regimens.

T 75 COMBINED CHEMOTHERAPY (CT) WITH ALTERNATING NON-CROSS RESISTANT REGIMENS (C-MOPP/ EBVD) AND RADIOTHERAPY (RT) IN PATIENTS WITH HODGKIN'S DISEASE (HD).

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Between March 1978 to June 1983, 49 consecutive untreated pts (32 males, 17 females, median age 36 years, range 13-72) with unfavourable stage II A (bulky mediastinum or E lesions in 9 pts) stage I-IIB (7), stage III (23) or stage IV (10) entered a prospective non randomized study with combined CT with alternating non-cross resistant regimens followed by RT. C MOPP/ABVD were given to all pts for 6 (IIA), 9 (I-IIB, IIIA) or 12 cycles (IIIB, IV) and in case of CR or PR 75% RT extended fields at doses between 3000 and 4000 rads was delivered in pts with stage II and III. In stage IV pts, RT was given at the same doses prevalently to areas of initial bulky disease. Two pts withdrew from therapy after the first ABVD (1 pt is alive at 26 mos, 1 is dead at 33 mos). The table reports the results in the 46 evaluable pts:

	NO (%) of pts with ---				Overall / Disease-free survival at 4 years (%)	
No of pts	CR after CT	PR after CT	CR after CT + RT	PR after CT + RT		
46	40 (87)	6 (13)	41 (89)	5 (11)	92	95

Median follow-up is 44 mos (range 21-69). 5 patients died with HD and they were all PRs. One of these pts died of bone marrow toxicity after ABVD. In 8 pts CT was stopped prior to the planned 9 or 12 cycles due to severe nausea and vomiting from ABVD. RT caused no severe toxicity. 1 pt developed right foot malignant melanoma and another a high-grade non-Hodgkin's lymphoma in an irradiated area. We conclude that after a median follow-up of 44 mos this combined treatment with alternating non-cross resistant regimens and RT was not associated to an increase in secondary leukaemia. However, taking into consideration the results of other long term studies, we suggest the use of smaller volume and lower doses of RT in association with CT.

T 76 ADVANCED HODGKIN'S DISEASE: COMBINED TREATMENT WITH ALTERNATING MOPP/ABVD CHEMOTHERAPY PLUS EXTENDED FIELD RADIOTHERAPY.

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Between 1981 and 1985, 29 consecutive, untreated patients with stage III B-IV Hodgkin's disease have been referred to our Institution. Median age was 31 yrs (range 17-54 years). The treatment consisted of alternating MOPP/ABVD chemotherapy combined with extended field radiotherapy (40-44 Gy) as follows: 20 patients received sequential therapy (6 CT + RT), 9 patients were treated with "ping pong" modality (2 CT + Mantle + 2 CT + Spade field + 2 CT + Iliac and inguinal nodes) 28 out of 29 achieved complete remission (96.5 %); one patient died from progression of disease. The median observation time is 42 months, median FFR is 27 months. To date no relapse has been observed. Toxicity was evaluated in terms of dose rate reduction. 12 patients needed a delay in treatment schedule (41.3 %): 8 of them experienced a reduction of drugs or radiation dose of about 50% and 30% respectively. No one was dropped out of therapy because of general toxicity. No pulmonary, cardiac or hepatic toxicity was noticed. 11 cases (37.9 %) of HZV infection were recorded.
These results represent a major improvement compared with the historical groups treated in our Institution. Further follow-up is needed to validate these data, in order to clarify the role of conventional versus more aggressive approaches (ABMT) in these "high-risk" patients.

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T 77 PRELIMINARY EXPERIENCE WITH CYCLOSPORINE IN HEAVILY PRE-TREATED HODGKIN'S DISEASE.

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Hodgkin's disease (HD) may be regarded as a proliferative disorder of the immune system, and a weak immune reactivity in remission may well represent the goal of the treatment, rather than its side effect. These assumptions led to a trial of cyclosporine A (CsA) for advanced HD with no standard treatment left. Ten patients were included in the study, all with B symptoms and with a biopsy-proven extranodal relapse after at least two combinations of chemotherapy. CsA was taken orally at the initial daily dose of 7.5 mg/kg. Whole blood CsA levels were regularly followed using the RIA method. The optimal therapeutic dose was then determined individually and was found to vary from 4-13 mg/kg for the desired blood CsA levels in the range 400-800 ng/mL. Seven patients experienced a relief of B symptoms. Three partial remissions and two minor responses (25-50%) were recorded, lasting for 3 to 6 months. Renal toxicity with an increase of creatinine to 150-200 µmol/L was seen in five patients, usually associated to dehydration and/or high blood CsA levels. Renal function always returned to normal after lowering the CsA dose and adequate hydration. Slight hypertrychosis in two female patients, gingival hyperplasia in another two, and two cases of Grade 1 peripheral neurotoxicity were the only other side effect. It is concluded that: 1. CsA may be moderately effective even in advanced recurrent HD; 2. good gastric tolerance, oral route of drug administration, and lack of myelotoxicity are its important characteristics; 3. regular monitoring of kidney function and of blood CsA levels are mandatory for the optimal therapeutic ratio; 4. CsA should only be considered within a carefully planned trial and limited to patients with no standard treatment left.

PREVIOUS THERAPY SITES OF RELAPSE CYCLOSPORINE TREATMENT

#	MOPP RT	MOPP ABVD	Other ABVD	Lung Nodes	Marrow Liver	Individual Dose, mg/kg	Renal Toxicity §	Remission/ Response
1		*	*	*	* *	13	1	partial
2	*	*	* *	* *	* *	6	1	minor
3	*	*	* *	*	*	10.3	0	progression
4	*	*	*	* *	*	9	1	partial
5	*	*	*	*		4.3	1	minimal
6	*	*	* *	* *	*	6	1	progression
7			* *	*	*	6	1	stable
8	*	*	* *		*	5	0	progression
9	*		* *	* *	*	7.5	0	progression
10	*	*	*	* *	*	5	0	partial

§ Renal toxicity, Grade 1: rise of creatinine to 150-200 µmol/L, reversible

T 78 FAST ALTERNATING CHEMOTHERAPY WITH COP/ABV/IMEP IN PATIENT'S WITH HODGKIN'S DISEASE.

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The German Hodgkin Study Group started a pilot study of a fast alternating chemotherapy consisting of 3 non-cross-resistant combinations: COP (Cyclophosphamide 800 mg/m^2 d1, Vincristin 1.4 mg/m^2 d1, Prednisone 40 mg/m^2 d1-15), ABV (Doxorubicin 40 mg/m^2 d15, Bleomycin 10 mg/m^2 d15, Vinblastin 6 mg/m^2 d15), and IMEP (Ifosfamide 1000 mg/m^2 d29-33, Etoposid 100 mg/m^2 d29-31, Methotrexate 30 mg/m^2 d31, Prednisone 40 mg/m^2 d29-35) in order to improve results and patients' compliance. Each part of the therapy was given two weeks after the preceding part or as soon as leucocytes recovered to 2.5 x 10^3 / mm^3 and platelets to 80 x 10^3 / mm^3. Dose was not reduced unless therapy had to be delayed more than 2 weeks.

30 patients with Hodgkin's disease stages II - IIIA with risk factors (large mediastinal mass, 3 or more involved lymph node areas, extranodal disease, and / or high ESR) and IIIB/IV have so far started COP/ABV/IMEP therapy. To date, 22 are evaluable for response. 14 pts. had no prior therapy, 8 pts. had been previously treated. 16/22 (73%) pts. achieved complete remission (CR) after 2-4 cycles of chemotherapy. With additional radiotherapy, 2 more pts. achieved CR, so that after the end of therapy 18/22 (81%) of pts. are in CR. COP/ABV/IEMP was extremely well tolerated by the pts. The main toxicities were leukopenia, slight nausea and vomiting as well as alopecia. Leukopenia caused delay of therapy of less than one week in 50% of pts. (mostly after IMEP), however dose reduction was rarely necessary. Even though therapy was continued as soon as leucocytes were > 2.5 x 10^3 / mm^3, no serious infections were observed. COP/ABV/IMEP is an effective and well tolerated chemotherapy protocol which should be tested against standard protocols in a prospective randomized trial.

The recruitment continues and updated results will be presented. Supported by BMFT 01ZP550A

T 79 FIRST RESISTANCE TO CHEMOTHERAPY IN HODGKIN'S DISEASE (HD).

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Patients (Pts) treated for HD who failed to respond to initial combination chemotherapy (CT) or relapse soon after achieving CR are considered CT-resistant Pts. In our experience we define first resistance to CT as Pts with tumor regression of less than 50% after initial CT. Pts who have disease progression under CT or within 6 months of completing CT plus radiotherapy (RT). From 10.80 to 12.85, 240 previously untreated Pts with clinical stage IA-IVB HD received MOPP, ABVD or MOPP alternating with ABVD, followed by RT. 16 Pts were characterized as CT-resistant and have been followed over a period of 6 to 52 months. There were 8 males, 8 females ; mean age was 29 y (16-41). Pathology included NS-8, MC-7, unclassified-1. Stage distribution was IEA 1, IIA 2, IIB 5, IIIEB 2, IIIEA 1, IIIB 1, IIIEB 1, IVB 3. Mediastinum was involved in 15 Pts, 5 of whom had bulky mediastinum disease. Treatment before failure consisted of 2 to 6 cycles of CT, MOPP 7 Pts, ABVD 2 pts, MOPP alternating with ABVD 7 Pts, followed by RT in 3/16 Pts. Resistance to CT occured in 13 Pts while receiving CT and 3 Pts within 4 months of completing CT + RT, and was observed on sites initially involved (nodal 9 Pts, extranodal 2 Pts, both 5 Pts). 10 Pts (5 stages I-II, 3 stages III, 2 stages IV) underwent surgical restaging with splenectomy after CT, no HD was found in 4 stages I-II and one stage IIIA, but was pathologic in 5 other Pts. Salvage treatment consisted of RT + CT in 11 Pts (1 autograft bone marrow), CT alone 2 Pts. 10 Pts died with progressive disease, 6 to 30 months from beginning of treatment. 4 of 6 Pts are still alive and remain limited stages. We conclude that first resistance to CT can occured in advanced and localized HD, can be early detected according the tumor response. The management of Pts who fail to respond to initial CT is poorly defined, salvage treatment is dependent on the extension of the disease at restaging.

T 80 CHEMOTHERAPY OF HODGKIN'S DISEASE RESISTANT TO COPP/ABVD WITH CCNU, VINDESINE, ETOPOSIDE AND DEXAMETHASONE (CEVD).

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The management of patients with advanced Hodkgin's disease who fail to respond to primary treatment or relapse early after achieving complete remission (CR) remains a problem. To improve the prognosis of these patients, the German Hodkgin Study Group initiated a prospective trial with CEVD in patients resistant to both COPP and ABVD therapy. The CEVD protocol consists of CCNU (80 mg/m^2 p.o. d1), Etoposid (120 mg/m^2 p.o. d1-5, d22-26), Vindesine (3 mg/m^2 i.v. d1, d22), and Dexamethasone (3 mg/m^2 p.o. d1-8; 1.5 mg/m^2 d9-26). To date, 32 pts. are evaluable for response. 13/32 (41%) achieved CR, 5/32 (16%) achieved PR with an overall response rate of 56%. 3 pts. showed stable disease and 11 progressed. The median duration of CR was 8 months (range 2 to 34+). The main side effects were leukopenia, thrombocytopenia, Cushing's syndrome including the manifestation of latent diabetes mellitus and alopecia. The regimen was well tolerated with only minimal nausea and vomiting. The observed response rate as well as the fact that long-term responses could be achieved is very encouraging. The efficacy of the CEVD regimen suggests that the incorparation of this regimens or parts of it into primary chemotherapy of Hodgkin's disease might be advantageous.

The recruitment continues and updated results will be presented. Supported by BMFT 01ZP550A.

ABSTRACTS - Third International Conference on Malignant Lymphoma, Lugano

T 81 EBV/C-MOPP REGIMEN AGAINST HODGKIN'S DISEASE (HD).

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Initial studies with ABV versus ABVD combinations in advanced malignant lymphomas showed equiactivity and reduced gastrointestinal toxicity for ABV regimen in Hodgkin disease (2nd Int.Conf. on Mal. Lymph., Lugano 1984). From February 1984, we have incorporated epirubicin instead of adriamycin in the new EBV polychemotherapy.
Our combined approach program for HD consisted of: 2 courses of EBV (E=Epirubicin 30 mg/mq/i.v. + B=Bleomycin 10 mg/mq/i.m. + V=Vinblastine 6 mg/mq/i.v.; all drugs given on days 1 & 15 q. 4 weeks) alternated with 2 courses of C-MOPP regimen (doses as in MOPP with Cyclophosphamide 650 mg/mq instead of Mechloretamine on days 1 & 8) ± standard radiotherapy. In all stage IV patients alternating chemotherapy was given till CR + 2 consolidation courses (+ selected radiotherapy in sites of initial bulky disease). In 38 patients so far entered in this pilot study, therapeutic results (WHO criteria, Cancer 47:207-214, 1981) are as follows:

Trial evaluation	No.Eval.	CR	PR	Comment
After 2 courses	33•	18%	79%	• 4 early; 1 lost to f.up
After 4 courses	28°°	39%	57%	°° 2 early; 1 lost to f.up; 2 deaths for other reasons
Completing treatment	21*	86%	14%	* 6 early; 1 lost to f.up.

Of the initial 38 patients, 55% has yet completed the treatment program: at present 15 patients are CR continuously free of disease from 6^{+}-24^{+} months.

Toxicity after EBV or C-MOPP was moderate and always reversible:

WHO grade	1	2	3
Myelosuppression	42%	-	8%
Nausea & Vomiting	54%	22%	-
Mucositis	21%	13%	-
Hair loss	29%	13%	-
Neurotoxicity	17%	8%	-

Our results seem to indicate a favourable impact of this new EBV/C-MOPP regimen against Hodgkin disease, even in advanced stages. The separate effects of EBV versus C-MOPP in the induction phase (initial 2 courses) are also being prospectively evaluated.

T 82 ABLETOP, A NEW EFFECTIVE REGIME FOR HODGKIN'S DISEASE.

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Decreased patient and doctor compliance due to poor tolerance of ABVD is impairing the therapeutic usefulness of this widely used salvage regime. A less toxic alternative, consisting in ADM 30 mg/m2 i.v., day 1, BLEO 5 mg/m2 i.m., days 1-3, and VP16 100 mg/m2 i.v., day 1-3, every three weeks, was tested in a collaborative phase II trial. In 16 patients evaluable for toxicity, doses had to be reduced in 16/87 cycles due to leukopenia (7) or BLEO lung toxicity (9) and were increased in 4/87 cycles. Therapy was delayed for more than 1 week in 6 cycles. Median leukocyte nadir was 3100/mm3 and no grade 4 leukopenia occurred. Grade 0-2 nausea and vomiting only were seen in 14/16 patients, but grade 3-4 alopecia in 13/16. A mean dose of 52 mg ADM, 24 mg BLEO and 484 mg VP16 was administered during these cycles. 15 patients were evaluable for response. Overall, 7 CR, 5 PR, 2 NC and 1 PD for an 80% remission rate (95% confidence limits: 52 - 96%) were found. In 12 pretreated patients (12 had one, 7 two and 3 three prior chemotherapy regimes, 6 were previously irradiated), 5 CR and 5 PR (83% remission rate) were obtained. We conclude that ABLETOP is an active regime in Hodgkin's disease, is well tolerated even in heavily pretreated patients and deserves further evaluation.

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T 83 ABVC-SALVAGE CHEMOTHERAPY FOR RELAPSING OR RESISTANT HODGKIN'S DISEASE

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Salvage chemotherapy for patients with relapsing or primary resistant Hodgkin's disease (HD) is an on-going challenge in clinical oncology. From 1979 to 1986 we treated patients (pts.) with primary or secondary resistant HD. Patients characteristics were as follows: N= 27, 22 male, 5 female. Age 16 - 56 years ($\bar{X}$= 34,9 ± 10,5 years), median age 36 years. Classification according to histological subtypes: 1/27 lymphocytic predominance (LP), 18/27 mixed cellularity (MC),5/27 nodular sclerosis (NS), 3/27 lymphocytic depletion (LD).
The treatment regimen consisted of Adriamycin 60 mg/m², day 1; Bleomycin 15 IU, day 1 and 15; Vinblastine 6 mg/m², day 1; CCNU 100 mg/m² day 1 (max. single dose 160 mg). Each treatment cycle was repeated on day 28 or after hematological recovery.
The following results were achieved: complete remission (CR) in 13/27 pts. (48,15%), partial remission (PR) in 6/27 pts. (22,25%) and no change (NC) in 4/27 pts. (14,8%). Progressive disease (PD) was observed in 4/27 pts. (14,8%).
Response rates (CR + PR) by histology are: 1/1 LD, 14/18 MC, 4/5 NS, 0/3 LD.
Pretreatment characteristics of responders (19 pts.) were: COPP (10), combined modality (3), COPP (4) and BVC (2) at time of relapse, and of non-responders including NC: COPP (6) and combined modality (2).
The overall response rate (CR + PR) was 70,4% of patients. Duration of CR was 4+ to 66+ months ($\bar{X}$= 30,9 ± 22,4 months, median 20 months). After an observation period of more than 5 years, 5 pts. are in continuing complete remission.
Toxicity consisted mainly of nausea and vomiting in nearly all pts. Hematologic toxicity in the form of leucocytopenia and thrombocytopenia was moderate in general, however, considerable for heavily pretreated patients. Therefore, a prolongation of therapy free intervals became neccessary in 33/133 treatment cycles. No treatment related deaths or episodes of bleeding occurred.
In conclusion, ABVC therapy in relapsing or primary resistant HD is effective and results in a considerable number of complete and long term remissions.

T 84 LAENNEC INTENSIVE SALVAGE CHEMOTHERAPY (LISC) REGIMEN FOR REFRACTORY HODGKIN'S DISEASE : RESULTS AT 2 YEARS.

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Between Oct 84 and Dec 86, 13 patients (pts) with refractory Hodgkin's disease (HD) received the LISC regimen. Their initial characteristics were : sex M10, F3 ; age mean 27 years, min 10, max 53 ; clinical stage (CS) IIB 4, IIIB 4, IVB 5 ; histology LP 1, NS 8, MC 4. 10 pts had refractory HD to MOPP + ABVD (3 to 7 cycles) ; 2 had refractory HD to 3 MOPP cycles + Radiotherapy (RT) ; 1 pt had an early relapse 10 months after 3 ABVD cycles + RT. At the time of the LISC, CS of the 13 pts were IIB 4, IIIB 5, IVB 4. The LISC regimen consisted in 3 monthly courses of Vindesine (continuous infusion) 1mg/m2/day, day1 to 5 ; Adriamycine (continuous infusion) 40 mg/m2/day, day 1 to 3 ; BCNU 140 mg/m2/day, day 3 ; VP 16 200 mg/m2/day, day 3 to 5 ; Methylprednisolone 200 mg/day, day 1 to 5. Mean duration of the 3 courses of this LISC was 99 days (min 90, max 105). 3 to 11 days (mean 8) of pancytopenia (<500 PMN/ul and <50,000 platelets/ul) occurred after each cycle. Overall, a mean of 9 units (5 to 20) of packed red cells and a mean of 92 units of platelets (40 to 200) were transfused to each patient. Documented infections occurred during pancytopenia in 11/13 pts. At completion of the LISC, 11/13 pts were in complete remission (CR). 2 pts (III B, IV B) did not enter in CR ; one died after 16 months of survival (since the first day of LISC) ; the other survives since 9.5 months. 7 pts in CR received prophylactic low dose RT (20 Gy). 1 of them (CS II B) relapsed 4 months later and died after 12 months of survival. As of December 30, 1986, 10 pts are alive in CR with 3.5 to 26 months of survival (since LISC). The 2-year acturial survival of the 13 pts is 72.7%. The relapse free duration of the 11 pts who entered in CR is 81%. LISC regimen compares favorably to salvage ABVD or equivalent chemotherapy with its low CR rate and low 2-year survival and to massive chemotherapy followed by autologous bone marrow transplantation with its high toxicity and risk of HD reinfusion.

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T 85 PROGNOSTIC AND THERAPEUTIC ANALYSIS OF NON-HODGKIN'S LYMPHOMAS WITH FAVOURABLE HISTOLOGY.

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Two hundred patients with favourable histology lymphoma consecutively observed from 1978 to 1985 were retrospectively rewieved in an effort to elucidate factors affecting the prognosis. The induction therapy of stages II, III,IV non randomly assigned consisted of cyclic combination chemotherapy (125 pts.), radiotherapy followed by chemotherapy (23 pts) and Chlorambucil alone (26 pts). The therapy of stage I consisted of radiotherapy alone (26 pts). The overall remission rate was 58%: 20% among patients treated with Chlorambucil, 47% among those treated with combination chemotherapy and 85% among those treated with chemo-radiotherapy ($p < 0.005$). Radiotherapy alone produced 92% CR in patient with localized disease with 13% relapse rate. No differences in remission rate, survival and relapse-free survival were recorded between patients treated with combination CVP chemotherapy (89 pts)and those treated with combination chemotherapy containing Adriamycin (59 pts). Differences in survival and relapse-free survival were recorded between patients treated with combination chemotherapy-radiotherapy and those treated with only combination chemotherapy ($P<0,005$). Prognosis was strongly correlated with the response with 93% probability of survival at 9 years of patients who obtained CR and 36% of patients who did not. The prognostic analysis performed taking into account age (>60 y versus <60 y), stage (I,II versus III, IV), symptoms (yes versus not), bone marrow involvement (yes versus not), leukemic syndrome (yes versus not) and histologic subtype (follicular center cell lymphoma versus diffuse center cell lymphoma, versus lymphocytic and lymphoplasmacytoid lymphoma) showed as relevant factors stage ($p < 0,005$) and bone marrow involvement ($p < 0,005$). Maintenance therapy with Chlorambucil after combination chemotherapy in patients with stage IV and bone marrow involvement (27 pts) did not produce any enhancement of survival with respect to the same category of patients treated without maintenance therapy (52 pts).
In summary, our analysis shows that prognosis of lymphomas with favourable histology is dependent on the dissemination of disease and response to therapy. The combined use of chemotherapy and radiotherapy seems to be the best choice of treatment for patients with disseminated disease. Finally radiotherapy alone seems to ensure a good control in patients with localized disease.

T 86 THE ACTIVATION ASSOCIATED ANTIGEN 4F2 PREDICTS PATIENT SURVIVAL IN LOW GRADE NON-HODGKIN LYMPHOMAS

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Expression of the activation associated 4F2 antigen, transferrin receptor and interleukin-2 receptor on suspended cells from 75 biopsied low grade non-Hodgkin's lymphomas (L-NHL) of B cell origin was correlated to patient survival, clinical prognostic parameters and estimated DNA synthesis. 4F2 antigen expression correlated significantly with poor patient survival, with high DNA synthesis and treatment response, but not with patient survival. On the other hand, the interleukin-2 receptor was neither correlated to patient survival nor to other studied markers for cell activation, but seemed to be expressed on certain subsets of lymphomas. We suggest that the monoclonal antibody against the activation associated 4F2 antigen could be used to select patients with L-NHL for aggressive chemotherapy.

T 87 TREATMENT RELATED TOXICITY IN ELDERLY PATIENTS WITH MALIGNANT LYMPHOMA: AN E.O.R.I.C. LYMPHOMA GROUP STUDY.

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In June 1986 a retrospective E.O.R.I.C. lymphoma group survey has been undertaken in 50 different European institutions, with the aim of evaluating the incidence and the outcome of NHL in the elderly (70 years) patients observed during 1984. Thus far, 127 patients (57 males,68 females) aged 70 years have been identified in 12 institutions (6 from Holland, 3 from France, 1 from Belgium, 1 from West Germany and 1 from Italy) making up 27% of the overall cases of NHL seen in the same period of time.The median age of this population is 77years (range 70-90); 34%, 27% and 25% of the patients are included in ECOG performance status 2,1 and 0 respectively.Low grade histology according to Working Formulation was observed in 20% of the patients, whereas intermediate and high grades in 46% and 34% of the patients respectively. Stages III and IV according to Ann Arbor were recorded in 39% of the patients, whereas B symptoms in only 19% of the patients.We have arbitrarily defined surgery, local radiotherapy or chemotherapy regimens with ≤ 2 drugs as conservative therapy (CI); whereas extended radiotherapy, chemotherapy regimens with ≥ 3 drugs or combined treatments as aggressive therapy (AT).Among the 64 patients treated with AI, treatment related deaths occurred in 9 (14%) patients and severe toxicity (grades 3-4 according to WHO) in additional 16 (25%) patients.On the other hand, among the 57 patients treated with CI, there was no lethal toxicity and severe toxicity was observed in only 3 (6%) patients.This difference is highly significant ($p < 0.001$).Infection was the cause of toxic death in 7 patients treated with regimens ≥ 3 drugs, including PROMACE-MOPP,BACOP, COP;whereas intestinal perforation after abdominal radiotherapy and gastric ulcer perforation after a regimen including prednisone were the cause of toxic death in one patient each.Among patients with stage II,III, and IV high-intermediate grade NHL, complete response was obtained in 14/16 (30%) patients treated with AI and in 5/15 (33%) patients treated with CI.Follow-up is too short to evaluate the duration of response and survival.Our data show: 1) a significant proportion of NHL, mostly with high-intermediate grades,occurs in patients aged ≥ 70 years; 2) aggressive treatments, in particular chemotherapy regimens with ≥ 3 drugs, administrated to elderly patients (≥ 70 years,median age of 77 years), are associated with significant lethal and severe toxicity; 3) prospective randomized studies are clearly needed in order to evaluate the activity and toxicity of intensive chemotherapy regimens,specifically devised for patients aged ≥ 70 years with unfavourable NHL.

T 88 *PROGNOSIS AT 15 YEARS OF B-NON HODGKIN LYMPHOMAS (NHL).*

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We treated between 1970 and 1985, 180 cases of B-NHL: of the (a) B-cleaved nucleus small lymphocyte (nodular or diffuse) type, (b) B-large lymphocyte with rarely cleaved and most often non cleaved nuclei, nodular or diffuse type, and (c) 13 B-medium cell always diffuse type. The protocol was the same: (a) the 6-month remission induction chemotherapy comprised ADM, VCR, CPM and PDN; (b) the one-year adjuvant maintenance chemotherapy only included VCR, CPM and PDN.
The small cell patient survival has decreased according to a straight line which went down at 15 years to 10%, with a 50% survival at 15 years. This survival is similar to that of CLL.
The large cell patient survival, after having presented as that of De Vita patients, a plateau at 40% between 3 and 5 years, decreased again to go down to 0% at 15 years.
The medium cell type patient survival is at 65% at 3 and a half years. The immunoblastic type similarly treated patient curve went down at 15% at one year and a half.
A new protocol was applied to immunoblastic patients, composed of two alternated cycles respectively combining in the first ADM, PTC, VDS, CCNU, PCZ and PN, and in the second N_2, ARC, VCR, ASP, BLM and PN. The survival obtained with this protocol presents, at the third year and half, a plateau at 50% starting at 6 months and still persisting at 3 years and a half.
In conclusion, the small cell cleaved NHL patients seem to statistically gain nothing with an intensive treatment and our to day treatment with only chlorambucil, PDN chemotherapy followed by bestatin + zinc active immunotherapy seems as good or better; the immunoblastic type needs, on the contrary, a very intensive chemotherapy, and the large cell type reinforced chemotherapy with or without autologous bone marrow retransfusion between 3 and 5 years, followed by bestatin and zinc active imunotherapy.

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T 89 PREDICTION OF SYMPTOM-FREE SURVIVAL AND TOTAL SURVIVAL IN ADVANCED LOW-GRADE NON-HODGKIN LYMPHOMA

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The prognostic relevance of histopathology according to the Kiel-classification, stage, presence or absence of initial symptoms and four different serum markers (Deoxythymidine kinase, S-TK, Lactic dehydrogenase, S-LDH, S-haptoglobin and S-orosomucoid) were prospectively investigated in 185 consecutive cases of low-grade non-Hodgkin lymphoma. All parameters gave prognostic information concerning total survival. The best information regarding the probability of survival was obtained from the presence or absence of symptoms from lymphoma manifestations other than those caused by a local tumour mass. Primarily asymptomatic patients had a median survival exceeding 6 years, whereas it was 2.5 years for patients with general symptoms. Patients with local symptoms only had an almost as favourable survival as those without any symptoms. Within the group of patients initially symptomatic, additional prognostic information was provided by S-TK. Total survival was significantly superior for patients with lymphocytic (LC) lymphomas and follicular centroblastic/centrocytic (CB/CC) lymphomas (median not reached after 6 years) than for those with immunocytic (IC), centrocytic or mixed follicular and diffuse CB/CC lymphomas (median 3 years), respectively. Seventy-seven patients were initially asymptomatic; in these patients treatment was postponed until symptoms occurred. The two serum markers S-TK and S-LDH, in particular, but also S-orosomucoid and histopathology predicted the length of symptom-free survival. Patients with S-TK below 10 units/l (upper normal value 5 units/l) or S-LDH below 8.0 ukatal/l (normal below 6.7) had a median symptom-free survival of about 4 years. In contrast, it was less than 1 year for those with values above these levels. The median symptom-free time for patients with foll CB/CC lymphoma was 5 years, for those with LC lymphomas 2.5 years and for those with foll/diff CB/CC and IC lymphomas, respectively, about 1 year. Using the information from S-TK and/or from S-LDH, possibly in combination with histopathology, it is possible to properly select patients for primary expectancy or immediate therapy.

T 90 RECOMBINANT LEUKOCYTE A INTERFERON THERAPY FOR PREVIOUSLY UNTREATED ADVANCED LOW GRADE NON HODGKIN'S LYMPHOMA

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Eleven consecutive patients (pts) with previously untreated non Hodgkin's lymphoma (NHL) with favourable histology and advanced stages have been treated with low/moderate doses of recombinant leucocyte A interferon (r-IFN αA) at the Hematology Department of the University of Rome, since December 1985.
Clinical characteristics were: male-8; median age-52 years (24-68); Ann Arbor stage III-4, IV-7; histology (Rappaport classification) N-MLL = 8, N-PDLL = 3.
Treatment consisted of r-IFN αA at the dose of 6 MU/mq given i.m. 3 times a week for 12 weeks, followed by weekly maintenance therapy for an additional 12 weeks in pts responding to therapy. Pts with stable disease at 4 weeks, in absence of severe toxicity, received 8 additional weeks of treatment at an escalated dose (12 MU/mq 3 times a week).
Eight pts were evaluable for clinical response. Objective tumor response were seen in 5/8 pts: complete remission = 1 pt (12,5%), partial remission = 4 pts (50%), stable disease = 2 pts (25%), progressive disease = 1 pt (12,5%).
Interferon treatment was tolerated without severe toxicity by most pts. Flu-like symptoms and fatigue occurred in all pts, but was not dose limiting. Therapy was discontinued prematurely in two pts due to side effects.
Our clinical phase III-trial has clearly showed effectiveness of low and moderate doses of IFN in previously untreated favourable histology NHL.
Toxicity of this treatment appears to be generally mild and fully reversible after discontinuation of r-IFN αA in all cases.
The use of maintenance therapy should be explored in responders. Further studies should be also directed towards the combined use of IFN and chemotherapic agents as initial therapy for pts with low grade NHL.

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T 91 TREATMENT OF HAIRY CELL LEUKEMIA WITH HUMAN LYMPHOBLASTOID INTERFERON: A MULTICENTER STUDY FROM THE ITALIAN COOPERATIVE GROUP FOR HAIRY CELL LEUKEMIA (ICGHCL)

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Since April 1985, 87 patients with hairy cell leukemia (HCL) have been treated with human lymphoblastoid interferon (Wellferon, Wellcome Research Laboratories, Beckenham, Kent UK) by ICGHCL in 14 centers. Initial treatment consisted of a daily dose of 3 megaunits administered by subcutaneous injection on an outpatient basis. Patients were treated for a minimum of twelve weeks and, if responding and tolerating treatment, until satisfactory response. As December 1986, 68 patients have completed at least three months of therapy, and are evaluable according to the criteria for evaluation of response to treatment in HCL, proposed at the International Workshop of HCL held in Leeds Castle, 22-24 September 1986. Of the 68 evaluable study patients, 20 had been previously splenectomized, 7 had non palpable spleen and 41 had splenomegaly. At the time of initiation of interferon, 40/68 patients were neutropenic (neutrophils < 1,000), 39/68 were thrombocytopenic (platelets < 100,000), 26/68 were severly anemic (Hb < 10), 21 had the leukemic phase (wbc > 10,000 and 50% or more hairy cells). After a median duration of initial treatment of 6 months (range 3-15+) were obtained 18 complete (CR), 33 partial (PR) and 13 minor (MR) responses, for a total response rate of 94%. The mean time to esponse was 52 days for minor response, 121 days for partial response and 255 days for complete response. No statistically significant differences in the major response rate (CR + PR) were seen among splenectomized vs. splenomegalic patients after six (12/16 = 75% vs. 19/24 = 79%) and nine (10/13 = 77% vs. 15/19 = 79%) months of treatment. Four patients had no significant response after 12, 12, 3 and 3 months of therapy respectively. Five patients died during the first month of therapy (3 of sepsis, 2 of myocardial infarction) and one within the second month (of sepsis). One patient died of lung carcinoma 6 months after beginning therapy and 3 months after having achieved CR. This outpatient selfadministered regimen was well tolerated, with mild fever, fatigue, myalgias usually resolving within one month. Only in two patients treatment had to be withdrawn because of major toxicity: severe thrombocytopenia (one case) and toxic hepatitis (one case). In most patients, tumor remissions resulted in an improved quality of life with substantial improvement of performance status, elimination of the need for transfusing blood products and reduction of the incidence of infections. This study confirms the responsiveness of HCL to interferon also in nonsplenectomized patients with high tumor burdens. Interferon may be recommended as a first line therapy also in patients who would normally be treated by splenectomy.

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T 92 VAD AS SALVAGE THERAPY IN LOW GRADE NON HODGKIN'S LYMPHOMAS (NHL).

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The VAD regimen combines continous infusion of vincristine 0.4mg and doxorubicin 9mg/m² per day x 4 with pulses of dexamethasone (40mg/day on day 1-4, 9-12, 17-20) repeated on day 28 (Barlogie et al (1984) NEJM 310: 1353-56).

Since March 1985 19 patients (pts) aged 32 to 75 years (median 55) with relapsing or refractory lymphomas: 5 immunocytomas and 14 cb/cc mL were treated with 1-10 VAD courses. All pts were intensively pretreated with multi drug chemotherapy. Several of the following regimens were applied in most pts: chlorambucil + prednisone, COP, COPP, CHOP, IMVP16 and ProMACE-CytaBOM. 7 patients received additionally radiotherapy.

From 17 pts who are evaluable for response, 13 pts (76%) achieved a partial remission (PR) with a duration of 6 to 48 weeks (median 25). 4 pts show no further disease progression lasting 6 to 32+ weeks. 3 relapsing pts responded again with a PR when they were treated secondly with VAD.

Toxicity observed in 94 VAD courses included congestive heart Failure (ECOG grade 1-2) in 2 pts, aseptic hip necrosis in 1 pt, psychosis (grade 2) in 1 pt, polyneuropathia (grade 1) in 1 pt, urosepsis in 1 pt, skin necrosis due to a paravasate in 1 pt without central catheder and mild intermittent hyperglycemia in 8 pts.

VAD regimen is an effective salvage treatment for low-grade NHL with acceptable toxicity and should be evaluated in previously untreated patients. VAD seems to be not cross resistent to COP. The quality and duration of remission may be to improve by prolonging and intensifying this treatment regimen.

ABSTRACTS - Third International Conference on Malignant Lymphoma, Lugano

T 93 TREATMENT OF PATIENTS WITH REFRACTORY MYELOMA.

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Only few treatment programs have been effective in patients with multiple myeloma resistant to alkylating agent and prednison combinations. Patients who fail to primary chemotherapy or suffering from renal insufficiency are known to have low response rate and short survival after subsequent salvage chemotherapy.

In this investigation the results of salvage therapy in 21 patients with multiple myeloma refractory to prior chemotherapy and in 5 patients with primary treatment because of severe renal insufficiency are demonstrated. Three different chemotherapy protocols were employed: 1st VP-mono (etoposide monotherapy; 2nd VCPVP (vincristine, cyclophosphamide, prednison, etoposide); 3rd VAP (dexamethaxone with vincristine and doxorubicin) by continous infusion. Several patients received successively more than onle of these regimens. Treatment with VAD revealed good responses in 19 out of 21 patients. Median remission duration was found to be 11 months. The probability of survival according to Kaplan-Meier after onset of salvage therapy has not reached the median at 30 months. The median time of observation is 15 months. Patients with renal insufficiency showed a high remission rate, too. In these cases the regimen needs no dose modifications. Infections and therapy induced cushing's syndrome represented the most important side effects. Six patients out of 21 died 5, 8, 13, 14, 21 and 26 months after onset of VAD therapy. Three patients with resistant multiple myeloma, 1 from septicemia, and 2 from acute leukemia. The response rates for etoposide monotherapy and VCPVP were significantly lower. Nevertheless, two VAD non-responders showed remissions with VP-mono and VCPVP respectively suggesting that VP16-monotherapy or VCPVP are effective treatment modalities in these patients with a poor prognosis. Therefore it seems rational to apply these drugs before employing more aggressive regimens as high dose melphalan with or without autologous bone marrow transplantation. The study is still in progress.

T 94 FIRST RESULTS OF THE CHRONIC LYMPHOCYTIC LEUKEMIA TREATMENT WITH EXTRACORPOREAL PHOTOPHERESIS

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As several studies show the progress of chronic lymphocytic leukemia of B-cell type (B-CLL; stage II-III according to Rai) can not be influenced by ordinary leukapheresis. During the last years extracorporeal photopheresis therapy was successfully applied in patients, suffering from cutaneous T-cell-lymphomas, i.e. a similar lymphocyte related malignancy. Therefore, we tested this method in patients with B-CLL, using the effect of UVA activated 8-methoxypsoralen (8-MOP) which leads to irreversible bridgings of the pyrimidine bases of mitotic cells.

2 hours before inserting a venous canula, all patients received 0.6 mg/kg body weight 8-MOP to achieve plasma levels of 50 ng/ml or above. Then, 240 ml of leukocytes obtained by leukapheresis where suspended in 300 ml of patient's plasma and thereafter extracorporeally exposed to UVA light with a total dose of approx. 200 J/cm^2. After this photochemotherapy the so treated cells were retransfused. This regimen was executed on 2 successive days monthly. Approx. 65 % of the irradiated cells were not vital until the end of the following week as assessed by means of in vitro tests. The whole procedure was well tolerated by the patients, and no side effects were observed.

In peripheral blood cell counts a sustained cell reduction with diminution of the pan B$^+$ lymphocytes could be seen as well as reappearance of granulocytes and CD 3$^+$ lymphocytes. The counts of platelets and red blood cells were unchanged or slightly increasing.

Additionally to the effect of cytoreduction photopheresis therapy caused the appearance of normal peripheral blood cells. Therefore, the results suggest the superiority of extracorporeal photopheresis, compared with leukapheresis alone. The underlying mechanism remains not yet clear.

T 95 MITOXANTHRONE IN PATIENTS WITH NEWLY DIAGNOSED LOW-GRADE NON-HODGKIN LYMPHOMAS, HIGH ACTIVITY OF A DAILY SCHEDULE.

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Twentyone consecutive previously untreated patients with low-grade non-Hodgkin lymphomas were treated with Mitoxanthrone 5 mg/m^2 daily for 3 days q 3 weeks. A cumulative dose of 165 mg/m^2 was not exceeded. According to the International Working Formulation 7 patients had small lymphocytic lymphomas, 10 patients had folicular small cleaved cell lymphomas and 4 patients had follicular, mixed small and large cell lymphomas. Eighteen patients are now evaluable for response and toxicity and all 18 obtained remission, 5 CR and 13 PR. 17/18 patients are still in remission but duration of remission and survival cannot yet be evaluated due to short follow-up (0-12 months). Non-hematologic toxicity was modest. No alopecia was seen and only 4 patients had nausea and vomiting (WHO grade 1-2). No cardiac toxicity was seen. White blood cell count da, 12 was median 2,0 x 10^9/l (range 0,7-3,4 x 10^9/l). Platelet counts below 100 x 10^9/l was only observed in 5 patients. Cumulative toxicity which required dose reduction was observed in 13/18 patients, 72%, and in 6 patients delay of treatment was necessary.

In conclusion Mitoxanthrone is a highly active and well tolerated drug in this subset of patients.

T 96 PHASE II TRIAL OF FLUDARABINE (FAMP): AN ACTIVE AGENT IN LOW GRADE LYMPHOMA.

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Fludarabine phosphate (9-β-D-arabinofuranosyl-2-fluoro-adenine 5' phosphate or 2-fluoro-ara-AMP) is a new purine nucleoside which is a derivative of Ara-A, fluorinated to resist adenosine deaminase. We investigated this agent in hematologic malignancies at a dose of 25 mg/m2/day for five days (every 3 weeks) to determine effectiveness and toxicity. Of 78 patients entered, 70 were evaluable. Median age was 56 years (range 20 to 77) and 40% were female. All patients had received prior chemotherapy, 93% had previously received ≥ 4 drugs, 60% had received ≥ 3 combination chemotherapy regimens. Half of the patients had received prior radiation therapy. Response rates were 67% for follicular small cleaved cell lymphoma (FSCCL) (N=15), 75% for follicular mixed lymphoma (FML) (N=4), 100% for follicular large cell lymphoma (N=1), 50% for transformed lymphoma (N =4), 33% for small lymphocytic lymphoma (SLL) (N=9), 71% for chronic lymphocytic leukemia (CLL) (N=7), 67% for mycosis fungoides (N=3), 25% for Hodgkin's disease (N=8), 6% for diffuse large cell lymphoma (N=18) and 0% for unclassified lymphoma (N=1). All responses were partial except for 2 patients with follicular small cleaved lymphoma who had complete responses. For responding patients the median time to response was two months and median duration of response was five months (1 to 17+ months). A total of 254 courses of fludarabine were administered (median = 2, range 1 to 12). Hematologic toxicity included median nadirs of 1200 granulocytes/µl and 137x10^3 platelets/µl. Cumulative myelotoxicity limited the duration of treatment in five patients. Treatment was well tolerated and the only severe complications were infections (5 patients). In contrast to the higher doses of fludarabine used in acute leukemia, no central nervous system toxicity was seen at this dose level. We conclude that fludarabine is an active new agent in low grade lymphoma (FSCCL, FML, SLL), CLL and mycosis fungoides with an overall response rate of 60% and deserves further investigation in these diseases.

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T 97 PHASE III STUDY OF EPIRUBICIN, VINCRISTINE AND PREDNISONE (EOP) VS CYCLOPHOSPHAMIDE, VINCRISTINE AND PREDNISONE (COP) IN FAVORABLE NON-HODGKIN'S LYMPHOMA.

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To study the potential efficacy and toxicity of a new anthracycline in treating low-grade, non-Hodgkin's lymphoma, a comparative trial was developed treating previously untreated and treated pts. Eligible pts received either epirubicin 75 mg/M^2 IV or cyclophosphamide 800 mg/M^2 IV day 1, along with vincristine 1 mg/M^2 IV day 1 and prednisone 100 mg PO x5 days, every 21 days for 12 cycles. To date, 73 pts have been entered with med. age of 61 yrs (range 28-86) and med. PS 1 (range 0-2) and med. Stage IV (range II-IV). Two-thirds of the pts are previously untreated. Interim response rates are comparable: 85% (EOP) and 89% (COP), with most of the responses PR at this analysis. Med. nadir WBC (granulocytes) for the EOP is 3,000/mm^3 (800) and 4,300/mm^3 (2,100) for COP. Nausea/vomiting was infrequent: 18% (EOP) and 11% (COP). Alopecia was almost universal for EOP but only seen in 35% for COP. Med. change in ejection fraction (EF) for pts receiving EOP was 0.65 (pretherapy) and 0.57 (post-therapy). Three pts were taken off study for cardiac effects: One pt with baseline 0.45 because of drop in EF to 0.39 after 3 doses of EOP; and two pts because of development of clinical CHF. Interim results suggest that EOP produces comparable results to COP in low-grade, non-Hodgkin's lymphoma. Duration of response and differential toxicity will be monitored.

T 98 HIGH DOSE CYTOSINE ARABINOSIDE (ARA-C) IN THE TREATMENT OF CHRONIC LYMPHOCYTIC LEUKEMIA (CLL).

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Peripheral blood cells of patients with CLL have high levels of nucleotide kinases responsible for the intracellular activation of Ara-C. We investigated the activity of high dose Ara-C with or without high dose decadron in patients with CLL and small lymphocytic lymphoma (SLL). Patients received 3 grams/m^2 Ara-C intravenously over 2 hours for 2-4 doses at 12 hour intervals. Treatment was generally continued until disease progression occurred. Twenty-four patients were studied (20 with CLL, 4 with SLL). Median age at the time of treatment was 60 years (range 48-72). Twenty-one patients had previous treatment. Twelve patients with CLL had Rai Stage III or IV and the 4 patients with SLL had Ann Arbor Stage III or IV. One patient had an early death and was inevaluable for response. The remaining 23 patients were not all evaluable for all categories of response (bone marrow [BM], peripheral blood [PB], peripheral adenopathy [PA], abdominal and pelvic disease [AP]). The following table shows the response rate as the percentage of evaluable patients in each category:

	PB	BM	PA	AP	All Sites
CR	3/19 (16)	4/14 (29)	6/17 (35)	0/13 (0)	0/11 (0)
PR	5/19 (26)	2/14 (14)	4/17 (24)	4/13 (31)	1/11 (9)
TR	8/19 (42)	6/14 (43)	10/17 (59)	4/13 (31)	1/11 (9)

The median duration of the complete responses was 11 months (range 5-16) and of the partial responses was 8 months (range 2-18). Of 7 factors analyzed, only the total white count (WBC) prior to treatment predicted for peripheral blood response. Six of eight patients with a WBC of $\leq$ 50,000 responded. Of the 11 patients with a WBC of $>$ 50,000 only 2 responded ($p<.05$). Seven of the nine patients who also received high dose decadron achieved a response. Two patients with stage IV CLL expired 10 and 18 days following their first treatment. In 87 courses of Ara-C, 6 cases of pneumonia, 2 episodes of sepsis, and 1 case of pseudomenbranous colitis were documented. We conclude that although high dose Ara-C produces a significant number of responses, as a single agent given as an intermittent infusion it is not adequate for the management of patients with CLL. High dose decadron may contribute to the efficacy of Ara-C.

T 99 NOVANTRONE IN COMBINATION WITH STERECYT (NOSTE) IN LOW-GRADE NON-HODGKIN LYMPHOMA (LGNHL).

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Novantrone® (mitoxantrone, dihydroxyanthracenedione) and Sterecyt® (prednimustine, a chlorambucil ester of prednisolone) has shown therapeutic activity in non-Hodgkin lymphoma. In order to evaluate the efficacy and toxicity of NOSTE, 22 patients with LGNHL stage III-IV were entered into the study between September 1984 and June 1986. Eligibility criteria included: a) histopathologically proven disease as determined by Kiel classification; b) at least one measurable lesion; c) WHO performance status $\leq$3; d) previous therapy discontinued at least 4 weeks ago.
Median age was 61 years, range 40-78. Sixteen patients were previously treated.

Novantrone was administered at a dose of 8 mg/m^2 IV in 100 ml of 0.9 mg/ml NaCl solution for 30 min on days 1 and 2 and Sterecyt 100 mg/$\leq$1.6 m^2 - 150 mg/$>$1.6 m^2 orally on days 1 to 5. The regimen was repeated every 4th week.
The number of courses per patient ranged from 2 to 10.

Objective response was obtained in 16 of 22 patients: CR in 15/22 (68%) and PR in 1/22 (4.5%). No response occured in 6 previously treated patients (27.5%). The median duration of response was 17 months, range 5 - 26. The crude survival was 14/22 (63%) and the tumor-free survival was 11/22 (50%) at the time of the last analysis on December 1st, 1986. No serious side-effects were noted.

The data indicate that NOSTE is effective in LGNHL. The advantages include: mild hematological toxicity, infrequent non-hematological toxicity and good tolerance especially in elderly patients.

T 100 AN EVALUATION OF TWO SCHEDULES OF CYCLOPHOSPHAMIDE AND PREDNISONE AS SECONDARY THERAPY IN MULTIPLE MYELOMA; NATIONAL CANCER INSTITUTE OF CANADA EXPERIENCE.

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Cyclophosphamide has been given in 2 schedules to 97 myeloma patients in 3 National Cancer Institute of Canada studies. Oral cyclophosphamide 325 mg/m^2 and prednisone 100 mg on 4 consecutive days every 4 weeks produced 3 responses in 37 patients who never achieved a stable response (primary resistance) to melphalan and prednisone (MP) and no responses in 3 patients relapsing after a stable response (secondary resistance). Intravenous or oral cyclophosphamide 150-250 mg/m^2 once per week with alternate day oral prednisone 100 mg produced 7 responses in 28 primary resistant patients and 10 responses in 29 secondary resistant patients. While the escalated dose of prednisone probably contributed to the responses seen with weekly cyclophosphamide, responses were also seen in patients who did not receive the escalated prednisone suggesting that the schedule of cyclophosphamide may be important. Previous response to MP was not a significant factor in predicting response to weekly cyclophosphamide and alternate day prednisone. One patient died with neutropenic sepsis after declining antibiotic therapy. Three patients developed acute myeloblastic leukemia after receiving both alkylating agents. The results suggest that the regimen of weekly cyclophosphamide and alternate day prednisone may be as effective as more aggressive regimens in the treatment of patients with myeloma who have failed MP therapy.

ABSTRACTS - Third International Conference on Malignant Lymphoma, Lugano

T 101 NON HODGKIN'S LYMPHOMA WITH FAVOURABLE HISTOLOGY:CLINICAL FINDINGS AND PROGNOSIS IN 142 CASES.

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The present study was carried out to investigate the clinico-pathologic features of non-Hodgkin's disease in patients with favourable histologic subtype. Over the period from July 1974 to June 1986, 142 consecutive cases were diagnosed (80 males, 62 females; median age 56). The Rappaport histologic subgroups were: LLWDd = 48%; LLPDn/n-d = 48%; LHn = 3.5%; 108 patients (76%) were in stage III or IV.

Eight patients had extranodal presentation (gastrointestinal tract = 5; conjunctiva = 2; skin = 1). Mediastinal involvement was observed in 11.2% of cases, bulky disease in 11.9%. Fourteen patients (9.8%) has documented B-symptoms. Polychemotherapy combinations with doxorubicin were used in 73.3% (N=61) of patients aged under 60 years and in 32.2% (N=19) of patients aged over 60 years.

Overall, complete remission (CR) was achieved in 78 pts (58.7%). The percentage of CR in various subgroups was the following: Stage I or II = 79.4% (27/34); Stage III or IV = 51.5% (51/98); age less than 60 yrs = 66% (51/77); age over 60 yrs = 48% (27/56); LLWDd histologic subtype = 46.9% (31/66); LLPDn/n-d = 72.6% (45/62); LHn = 40% (2/5). The achievement of CR was strongly influenced by the number of involved lymphnodal sites: in fact, CR was observed in 88.5% of pts with 5 or less involved sites and only in 11.5% of pts with more than 5 involved sites.

Overall, 5-yr survival was 78% while 10-yr survival was 45%. These data correspond to a median survival of 9.8 yrs. In patients who achieved CR, 5-yr and 10-yr survival was 90% and 58%, respectively (median survival over 10 yrs) while these two percentages were 58% and 18% in the remaining patients (median survival = 6.3 yrs). The log-rank test showed a significant difference in survival between these two groups (p 0.001). Survival was also influenced significantly by the presence of systemic symptoms (p 0.01).

T 102 Primary Gastric Lymphoma: our experience.

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Primary lymphoma (PGL) is the most frequent not epitelial gastric malignant neoplasia. We observed 13 cases of non-Hodgkin PGL between 1979 end 1985.

Patients and methods: 7 patients were female and 6 were male; median age was 54 years (range 31-80). Minimum follow-up period was 24 months. Preoperative endoscopic diagnosis was undifferentiated carcinoma (4 cases), moderately differentiated carcinoma (3 cases), gastric ulcer (2 cases), atrophic chronic gastritis (2 cases), enteroid metaplasia (1 case), pseudopiloric metaplasia (1 case).

Treatment: 12 patients had subtotal gastrectomy and 1 total gastrectomy. Histological Classification (Working Formulation): 3 patients had low grade, 7 were intermediate grade and 3 high grade malignant lymphoma. Staging (Musshoff): 4 patients were Ie and 9 IIe. There were 2 postoperative deaths, caused respectively by sepsis (Ie), and by myocardial necrosis (IIe). A patient died from myocardial necrosis after one month after surgery.

Results: to date 10 patients are evaluable for recurrences and survival (3 stage Ie and 7 stage IIe). 3 patients (stage IIe) received nº 8 cycles of CHOP after surgery as "adjuvant" chemotherapy. Overall survival at 36 months for the 10 evaluable patients is 70% (7/10), while disease free survival is 50% (5/10). 5 of 7 patients treated with only surgery relapsed (2/3 stage Ie and 3/4 stage IIe). Two of these patients were subsequently treated by chemotherapy and are in complete remission. All the patients who received "adjuvant" CHOP had no recurrences.

Conclusions: diagnosis of PGL before surgery remains very difficult. Our limited experience does not allow us conclusive remarks on the relationship between histology and prognosis. The role of adjuvant chemotherapy in the treatment strategy for stage Ie needs more extensive studies. Chemotherapy seems to prevent recurrences of the disease in stage IIe. Despite of the treatment, PGL survival remains higher than gastric adenocarcinoma.

T 103 MANAGEMENT OF PRIMARY LYMPHOMAS OF THE CENTRAL NERVOUS SYSTEM.

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From 1956 to 1986 seventeen patients with primary lymphoma of the central nervous system were seen at the University of Kansas Medical Center. There were 11 male and 6 female patients and the median age was 63 years. Most of the tumours were located supratentorially (12/17 patients). Histologically the tumours were diffuse with the 9 being Histiocytic; 3 mixed histiocytic-lymphocytic; 1 lymphocytic and 4 unclassified. Involvement of the craniospinal axis was seen in 4/14 (28.5%) cases. Patients treated with surgery only had a median survival of 3 months as compared to 7 months when treated with biopsy followed by Radiation therapy. Patients who had resection of the tumour followed by Radiation therapy had the best median survival (17.5 months). Recommendations will be made regarding management of these tumours.

T 104 SURGERY AND CHEMOTHERAPY IN GASTRIC NON - HODGKIN LYMPHOMA.

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We have retrospectively examined 31 cases of gastric non-Hodgkin lymphoma treated at our Division from 1981 to 1986. 17 pts. were males, 14 were females (M/F =1.21); their ages ranged from 16 to 74 years with a median age of 40. 10 pts. (32.3%) presented with stage IE 9 (29%) with stage II-E and 12 (38.8%) with stage IV. According to the Working Formulation classification histologic subtypes of intermediate malignancy were prevalent: 17 pts. (54.8%). 9 pts. had tumors of high grade malignancy (29%) and 3 pts. had low grade NHL (9.7%). 2 pts. were unclassified. 28 of these pts. have completed induction therapy (median follow-up 21.6 months). 14/16 pts. with stage I-E and II-E underwent partial or total resection; after surgery all pts. received chemotherapy, using the CHOP (5 pts.) or the CVP (9 pts.) regimen. 11 pts. (78.6%) achieved complete remission (7 pts. with stage I-E and 4 pts. with stage II-E): they all are in continous first complete remission with a median follow-up of 29.6 months (range 16 to 55 months). 2 pts. achieved partial remission and then underwent abdominal progression of their disease. 1 pt. died early because of infection during chemotherapy induced aplasia. The 2 pts. treated with chemotherapy alone (at reduced doses because of age) had progressive disease and died 8 and 9 months thereafter. 10/12 pts. with stage IV were treated with chemotherapy (8 with CVP, 1 with CHOP, 1 with PROMACE), achieving 6 complete remission and 2 partial remissions; 2 pts. had progressive disease. 2 pts. died before chemotherapy. Only 3 of these pts. underwent surgery: 1 of them,who had only partial resection of tumor, died after 8months; 2 pts. achieved CR: 1 of them is in 1st CCR after 31 months, the other one died after 61 months for unrelated cause (alcoholic cirrosis), without evidence of lymphoma at autopsy.