ABSTRACTS

PRESENTATION BY TITLE ONLY
T 1 PHENOTYPIC AND GENOTYPIC STUDIES ON SPORADIC BURKITT’S LYMPHOMAS (sBL), D. Delia, F. Morandi, L. Rottoli, M.A. Piccotti, A. Agresti, W. Gasparini, R. Giordani, G. Gasparini, F. Malignaggi, M. Zucchi, Milone and *Clinica Civile S. Bortolo, Vicenza, Italy.

The biopsies from 32 patients with sBL (17 pediatric, 5 adult) were analyzed 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 YC86, JR, C-NYC, and for ERB genome.

Thrombocytopenia all cases were HLA-DR+. CD5-+, CD23+, YC86+, S1g+. 46% were CD10 (CALLA)+ and 90% CD20+. Cases positive for FMC7, SmIg, S1gM were 77%, 40%, 10% respectively. 10% of cases were unreactive with the anti- Burkitts Mab 38.13, of the remaining 60% were strongly reactive, 30% weakly. 5/6 cases were CD19+, CD22+, CD13−, CD3−. With regard to the pediatric group, all treated with the same protocol, no significant clinical presentation and survival rate differences were observed when the cases were split into CALLA+ and CALLA− subgroups. The genetic studies revealed that the TO18 was, in all cases, in the germ line configuration. Conversely, JR and C-NYC were rearranged, with multiple bands detected in two cases. The size of the rearranged C-NYC bands varied from case to case. The hybridization of FMC7 digested DNA blots with JR and C-NYC showed that in two cases the rearranged fragment size of both genes had the same M.W. ERB sequences were detected by HMMA in one case only. Overall, the sBL have a B cell phenotype characterized by a common expression (or absence) of the CD19+, CD20+, CD13−, CD3−, YC86+, S1g+. They all have c-sry, c-yes rearranged and only rarely ERB gene can be found in them.

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

A. M. Vagner-Capodanno, S. Hierarchical, B. Tubiana, Y. Cercasone, *Laboratoire de Cytogénétique, Hôpital de Clamart, France. We have attempted to correlate karyo-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(4;11)(q21;q22) in a case of Burkitt’s lymphoma, t(14;18)(q21;q21) in a follicular lymphoma and frequent involvement of chromosome 14 at bands 14q22 in the various lymphoma rearrangements. In the mixed-cell nodular lymphomas, in one 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 1q22 deletion, associated with other chromosomal abnormalities was 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 abnormalities, the phenotypical aspect of the lymphoma with which they are usually associated.

In the T-lymphomas, we noted 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 recur particularly often in T-lymphomas: 1q 1q, del 1q, inv 1q, 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 MALIGNANT ORGANIC DISEASES. H.J.G.Haertzen (1), H. Schneede (1), A. Seraphin (2), W. Jilg (3), Med C, Klinikum III, Klinikum Großhadern, Munich University (1), Dept. Transplantation Immunology, Ume University (2), Max V. Petersen, Institut, Munich University (3), 8000 Munich 70, FRG.

Cell lines grown from 5 normal donors either spontaneously or induced by HSV cell culture supernatant containing Epstein-Barr virus (EBV) were studied with respect to surface markers and immunoglobulin gene rearrangements. Antigens were determined routinely by an indirect EA-immunocytochemistry using an alkaline phosphatase conjugated secondary antibody on adhesive slides. 70-98% of the cells were positive with MY-1 and MY-2 antibody (CD3) whereas the proportion of VM-05 positive cells (CD15) varied between 3 and 98% among the cell lines. Both markers were found on the same cells by means of a double color technique employing consecutive stains with fast blue BB- and fast red TR-salt and interposed blocking of the enzyme by HCI (2 M) which allowed the simultaneous detection of 2 determinants without destruction of antigens. Clonality was assessed by Southern blot technique: DNA of the cell lines was digested by Hind III and hybridized to a μ-specific probe on 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 myeloid antigen expression represent cells with disturbed differentiation or transformed precursor cells of earlier progeny.

T 4 PROGNOSTIC SIGNIFICANCE OF CYTGENETIC STUDIES IN ANGIOLIOMYOLIOMATOSIS (ALP) B. Schlegelberger, E. M. Walker, C. v. Schilling, A. Nolte, N. Johannson, W. Worek, R. Lemmer, Institute of Human Genetics and Institute of Pathology, University of Kiel, W.-Germany

ALP is a lymphoproliferative disease considered so far as a hyperimmune reaction or as polylymphoma. 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 12 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 ALP.

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ABSTRACTS - Third International Conference on Malignant Lymphoma, Lugano

T 5 Translocation t (12;19) (p 13;q 24) in Two Children with Burkitt Lymphoma. I. Vuković, E. Bošnjaković, O. Ćerovčić, M. Ćikarić, University Children's Hospital, 11000 Belgrade, Yugoslavia

In Burkitt type lymphoma the most frequently seen chromosomal abnormality is t 14q 32 (q 32) (Zen 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 22 (p 12; q 24) (Phillip 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 3% of them had Burkitt type lymphomas. 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 chromosomal abnormality t (2p:q) (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, identical in Philadelphia chromosome for chronic myeloid leukemia.

T 6 Chromosomal Rearrangements in Lymphohastoid Cell Lines (LCL's) from Patients with Hodgkin's Disease (HD) after in Vitro Treatment with Cytotoxic Drugs Used in HD Therapy. C. Fonatsch, H. Kuriwara, B. Brüggenjürgen, J. Radesmacher, Institut für Häumatologie/Onkologie, Medizinische Universität Lübeck, Abteilung Hämatologie/Onkologie, Medizinische Hochschule Hannover, FRG

Epstein-Barr virus transformed B 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 3 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, 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(1:17) and a translocation t(15;17)(p 11.2:q 11.2). The significance of these chromosomal aberrations is discussed and it is emphasized that in malignant disorders like acute lymphocytic 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.


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 OKT1 or Leu7a monoclonal antibodies and does not change the expression of OKT4, OKT8, or OKT11 antigens. RIF suppresses the reswelling 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 (pH4) or alkaline (pH9) pH or trypsin treatment. It can bind to lipoproteins. RIF was partially purified by affinity-, ion-exchange- and molecularsieve-chromatography and has an apparent molecular weight of 25 KD.

T 8 MOLECULAR CHARACTERIZATION OF HODGKIN'S DISEASE DERIVED CELL LINES. N. Tesch, H. Jücker, M. Folk, G. Orcik, 'E. Jones and V. Diehl, I. Medizinische Klinik Universitatsklinik Köln, 5000 Köln 41, FRG, Institut für Virologie, Universität Freiburg, FRG, Dept. of Pathology, Southampton, England

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 analysis to characterize the cells. We have analyzed the organization and expression of immunoglobulin (lg)-T-cell receptor (TCR) - and IL2-receptor genes and certain proto-oncogenes. Our results indicate that two Hodgkin 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 mRNA. In addition the expression of the proto-oncogenes c-myc, c-ras, p53, j-ras, Ha-ras, 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 (CD3, IL2-receptor), which have been detected on activated lymphoid cells only.
ABSTRACTS - Third International Conference on Malignant Lymphoma, Lugano

**T 9** IN HODGKIN’S DISEASE ONLY REED-STERNBERG CELLS HAVE AN ABNORMAL KARYOTYPE. T. Teenerho, C. Lindholm, K. Franssila, H. Stein, S. Knuttila. Department of Radiotherapy and Oncology, Department of Medical Genetics, University of Helsinki, Helsinki, Finland, and Department of Pathology, Free University of Berlin, West Berlin, FRG.

Although 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 supraventricular mass in a 21 years old man revealed a histology of Hodgkin's disease of nodular sclerosis type. In a cytogenetic preparation stained with May-Grünwald-Giemsa the differential count showed 2% mono- or multinuclear Reed-Sternberg cells and >98% small lymphocytes. In addition there were some eosinophils, macrophages and epithelioid histiocytes. 71% of the small lymphocytes were positive for pan-T antibodies (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 (McKee) Antibody Antibody Chromosomes: Blood 1984;84:1116. 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 50 mitoses positive for Leu 4 and in two mitotic cells of small lymphocyte size positive for kappa- or lambda. 12 mitotic cells of Reed-Sternberg cell size were also positive for kappa- or lambda and contained 72 chromosomes. None of the mitotic cells of Reed-Sternberg cells were positive for Ber-H 2. There was observed however, positivity for an antibody against SSA (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 receptors (IL2).

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.


The study was carried out on 155 cases of Hodgkin’s disease treated at Grenoble between 1975 and 1985 (representing 60% 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 4a), 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: cytoplasmic and nuclear atypia, lymphohistiocytosis, and absence of edema of the chromatia (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 (CALU) FUD-7/150 (110 cases positive = 63%) Anti-Akin (4-1-1) Immunocyt (0 cases positive/ 105), LEU M1 B.0, (143 cases positive = 92%) and ENA/EMA (32 cases positive = 21%). The combination of markers LEU M1 and EMA permitted the definition of 4 phenotypes: LEU M1 + EMA (-16%); LEU M1 - EMA (+16%); LEU M1 - EMA (-16%); LEU M1 - EMA (+16%). The first phenotype corresponded to the classical form of Hodgkin’s disease, while the other three were highly correlated with the atypical forms as well as with an unfavorable prognosis. A multivariate analysis of the prognostic factors was performed. The population studied showed that 5 factors of poor prognosis are preponderant and complementary: age > 50 years, atypical histology, atypical cytology, stage of disease, and type of treatment. They determined 2 groups: patients who have none of these characters (34 cases or 61%) for whom only one death was observed (6 cases and 16%) presenting one or several of these characters (61 cases or 39%) for whom 29 deaths (40%) were observed.

**T 11** ANTIPROLIFERATIVE EFFECT OF THE MONOCLONAL ANTIBODY HD37 (CD15, p112) ON NON-HODGKIN’S LYMPHOMA CELLS. B. Haas, S. Kippel, G. Molderman, S. Hohaus, H. Messner, H. Hunstein, B. Döberg Department of Internal Medicine, Heidelberg, FRG; German Cancer Research Institute, Heidelberg, FRG; Ontario Cancer Institute, Toronto, Canada.

The introduction of monoclonal antibodies (MoAbs) proved to be a powerful tool for the precise classification of hematological malignancies, especially with respect to patients’ outcome. 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 MoAbs HD37 (IGD, CD19). Our target idiotypes 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 semidiluted cloning culture assay (methycellulose 0.5%, human plasma 30% and 2 M 2 x 10^7 ml (the functional effect of HD37 added to the culture system in a concentration between 0.38 and 1.77 ml per 500 ml was detected. For the NH1 cell lines tested a reduction of 35-36% in the number of colonies in comparison to the controls could be demonstrated. Similarly, the mean 3H-thymidine uptake in the presence of HD37 in identical concentrations was between 40-45% compared to the controls in a 72 hrs culture period. For those experiments 1 x 10^5 cells/ml were plated in flat bottom microwells in RPMI supplemented with 1-10% fetal calf serum. The 3H-thymidine was always added 16 hours 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, Percival 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 involved in the HD37-neoplastic paralogical form in the treatment of patients with B cell malignancies as a new immunomodulatory drug.

**T 12** CYTOSTATIC TREATMENT OF MICE MOUSE TUMORS INDUCED BY ESTABLISHED HUMAN HODGKIN CELL LINES. H. Kirchner, K. H. Grossen, H. Poltowel Medizinische Hochschule, Abteilung Hämatologie und Onkologie, 3000 Hannover, FRG.

Although a variety of chemotherapeutic regimens exist for the treatment of refractory or recurrent Hodgkin's disease, the results have generally been up to now disappointing. We therefore decided to establish a preclinical evaluation of various schemes of treatment of Hodgkin's disease.

The investigations were carried out in vivo in two different tumor models (L428, L540). The cell line L540 produces both intrinsically (i.e.) and intracranial (i.c.) tumors in the nude mouse, the L428 produces only i.c. tumors. In the i.c.-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 at 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 occurred 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 a progressive disease. CDDP 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 CDDP produced complete remission only partially. However, both drugs showed a clear antitumor effect, no relapses occurred. The same results were obtained with vinblastine, IF or cisplatin monotherapy.

In the L428 cell line only cisplatin produced a response with intracranial 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 situation only low, the biological mechanism of both cytostatics, etoposide and cisplatin is in good agreement with clinical experiences in treatment of relapses. These results form the basic for the testing of new cytostatics and for the development of new treatment regimens.
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T 13 IMMUNOCHEMICAL EVIDENCE FOR NON-HEAVY CHAIN DISRUPTION IN A CASE OF CUTANEOUS LYMPHOMA

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Non-High Chain Disease Proteins are defined as incomplete polypeptide chains of IgM cloned. The presence of abundant areas was detected in the serum of 34 years old woman suffering from mycosis lymphoma.

The abnormal protein escaped detection by routine electrophoresis and immunoelectrophoretic analysis by antisera to the human serum. It was subsequently detected in the serum by immunoblotting using anti-IgM antibodies, as an example of beta-1 mobility under non-ideal IgM precipitation. This dual precipitation was not revealed by anti-IgX and anti-IgA antibodies.

The absence of patient's serum, the abnormal protein was calculated by affinity chromatography using successive passage over anti-IgM and anti-IgK-Sepharose-4B columns.

The stained protein still expressed IgM antigens, and absorbed in S. aurei polysaccharide and rabbit antisera. It consists of 34,000 daltons molecular weight.

No decrease in molecular weight was noted after reduction and alkali. These results suggest the presence of nongeneric form of Non-High Chain Disease Protein.

T 14 ASSESSMENT OF IMMUNODIAGNOSTIC STATUS IN CHILDREN WITH MALIGNANT LYMPHOMA AFTER COMPLETED TREATMENT AND LATE EFFECTS OF ANTI-NEUROPATHY 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, Nitsch et al., 1976). Today when the new therapeutic approaches enable long term survival, great significance is laid on the quality of life, special-ly immunosurveillance may produce increased susceptibility toward infection and may play a role in the development of secondary cancer.

At our Department we found the status of cellular and humoral immunity in 24 children with malignant lymphoma (14 Hodgkin's and 10 Non-Hodgkin's) 6 months to 6 years after 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) subpopulations were assessed using monoclonal OKT3 and OKT8 antibodies. B cell count was obtained by detecting membrane immunoglobulin bearing lymphocytes and concentrations of IgM, IgG and IgA in the serum determinated.

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 T cell count was within the normal limits. The decreased rate of serum IgM was statistically significant and it correlated with disorders of T lymphocytes and T lymphocyte subpopulations. Concentration of IgG and IgA 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 protocols.

T 15 PHARMACOKINETIC STUDY OF POLYNIC ACID IN CEREBROSPINAL FLUID

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Polynic acid (2,4,5-triarylhexahydroazepine, C0H1-ThAP) and its active metabolite (2,3-dihydroxytetrahydroazepine, CH2-ThAP) were measured in the cerebrospinal fluid of normal volunteers after a single i.v. administration. CH0-ThAP and CH2-ThAP 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, 6, and 24 hours after injection. There were three subjects per time and dose (total 36). Results showed that:

1. only CH2-ThAP penetrates CSF (max 6 hours)
2. the AUC CH2-ThAP/CH0-ThAP plasma ratio is around 10%
3. there is a significant linear increase between the dose and the AUC CH0-ThAP in plasma, AUC CH2-ThAP in plasma, and AUC CH2-ThAP in CSF
4. CH2-ThAP 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 leukemia 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-dependent manner. IL2-R expression on Reh-6 cells requires de novo DNA, RNA and protein synthesis. Binding experiments with radio-labelled recombinant IL2 (rIL2) revealed low-affinity IL2-R. However, IL2-5-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.

The origin of the malignant cells in Hodgkin's disease is unknown. Lectins, proteins or glycoproteins which can mediate or control cell-cell interaction when used as lectins, have been reported to be tumor associated. The potential clinical applications of such lectins as tumor markers, may be manifold. In the present study, we have endeavoured to investigate the possibility of the existence of these tumor associated lectins in Hodgkin's disease. For this purpose, the lectins of human lymphoid cells were extracted by electrophoresis and tested for their agglutination activity. The results of this study are reported.


From November 1985 to December 1986, 17 patients with lymphomas (M.F.) or Sézary's Syndrome were treated with recombinant alfa-2a interferon (ROFFON A Roche). Up to date 15 patients are considered evaluable. The study design included patients with Sézary's syndrome refractory to previous treatments and with DNA synthesis, in the presence of certain drug-neoglycoprotein conjugates. Possible participation of lectins in intercellular interactions was determined by sugar dependant inhibition of rosette formation with trypsinized, gluteraldehyde treated erythrocytes. Biochemical analysis using affinity chromatography on supports with immobilized sugar or glycoproteins reveals the presence of a beta-galactoside-specific lecithin at apparent molecular weight of 14 kDa, an alpha-fucoside-specific lecithin at apparent molecular weight of 22 kDa, an alpha-glycoside-specific lectin of apparent 30 kDa and a stalic-acid-binding protein at apparent molecular weight of 11 kDa.

The presence of lectins in malignant Hodgkin cells provides a rationale for further studies to test their usefulness in improvement of clinical management of this tumor type.


Since February 1986, 15 patients with histologically confirmed Mycosis Fungoides (MF) or Sézary Syndrome (SS) have been treated with subcutaneous r IFN α-2a ( Hoffman-La Roche) as single agent. r IFN α-2a was administered daily with dose escalation from 3 to 16 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 in complete remission 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 65 (range 20-76). Two patients had SS, 8 had T-22 skin lesions, and 5 had cutaneous tumor; none had positive node biopsy or visceral involvement on abdominal sonogram. Median percentage of CD 4 and CD 8 lymphocytes was respectively, 36% (range 14-44) and 15% (range 4-68). All patients were untreated but one, who had received local radiotherapy. Eryther was toxicity was dose limiting in 4 patients, fatigue in 3, leukopenia in 2, and diarrhoea in one. Flu-like syndrome was transiently experienced by all patients. Pruritis was flare to withdrawal of one patient from protocol. Among 12 evaluable patients, 5 are in CR, 6 are PR, and one progressed during the first 2 week treatment: median time to response was 5 months (range 1-6). Clinical CR was confirmed by pathological re-staging; no biologically significant persistence of T-cell infiltration was achieved by all patients receiving 1000 of scheduled induction dose. All patients showed an increase of CD 8 lymphocytes number, which was more evident in SS 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 = 25%) 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.


The evaluation of response and the efficacy of recombinant interferon (INTRO 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/2w 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, a response in 8/10 follicular lymphoma (2 CR and 6 GPR), in 3/5 diffuse and 6/7 diffuse mixed. The median follow up is of 12 mos. (range 6-18): the median duration of response is 8.4 yrs for CR, and 4.6 mos. for GPR. Without therapy, there are 5 pts. under maintenance therapy consisting of 5 Mu/2w weekly. Two pts. relapsed at 3 mos., and one at 8 mos. from the end of therapy; all of them were retreated with the same regimen and responded. The major toxicity concerned with fever and nausea. Hematological toxicity was generally mild and occurred between the third and fourth cycle. These results allowed 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. This study is under evaluation as first line therapy in a cooperative study group.
agnani, Clinica Medica I, Policlinico Mantovano, Univ. Perugia, 00100 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 heterogeneous, it would be useful to study various IFN species with different antitumor activities. In our study we investigated IFN-B activity in patients with lymphoproliferative syndromes. Twenty-two patients with lymphoproliferative diseases treated with IFN-B (5 x 10^6 IU/m², 6 hour IV infusion) administration x 7 days with 7 day intervals x 3 cycles (induction therapy). Then, IFN-B at the same dose was given twice/week x 12 weeks and by 6 hour IV infusion x additional 12 weeks (maintenance therapy). Partial remission (>= 50% reduction of tumor volume) 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 weeks of treatment in all 5 of these pts. After treatment discontinuation, remission duration ranged from 3 to 10 months. There have been no significant improvements 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 the 2nd treatment with IFN-B. The response was observed in a radiotherapy- and chemotherapy resistant hairy cell leukemia patient during the course of 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 resistant 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 leukaemia after induction or during the first 6 weeks of maintenance therapy. IFN-B, therefore, like IFN-A, is a useful palliative treatment in certain lymphoproliferative syndromes.


Hairy cell leukemia (HCL) pts generally have very low NK cell activity (pre-NK cells and functionally mature NK cells). We found that in vitro treatment of lymphocytes with IL-2 and rIL-2 could be able to convert 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), rIL-2 (50 IU/ml) and rIL-2 (10 IU/ml) on mononuclear cells of HCL pts. A significant increase of NK-cell activity was excreted by rIL-2 in 8/20 experiments and by rIFN-B in 4/6 of 4 experiments, 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 rIL-2 and IL-2, synergic or additive effect of these molecules was observed in 8/20 and in 4/6 experiments, respectively. Although there were no apparent differences in the NK-cell booster activity of 10 IU/rIL-2 or rIFN-B when used alone, synergic or additive effect was observed, when rIL-B 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 rIL-2 in the same nonmonoclonal cell preparation. Similarly, in another 2 instances, the NK-cell activity of the same effector cell preparation was additive or synergistically boosted by the rIL-2 and IL-2 combination, but not by rIL-2 and IL-2 combination. The finding of synergistic effect between low doses of rIL-2 and IL-2 suggests that these two molecules affect different NK-cell subsets. Prospective studies of the degree 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 were LGL+ and Leu1+; 2) rIL-2 may act by increasing the number of IFN-B receptors (infection of effector cells with rIL-2 followed by incubation with IFN-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 SERNOmo Pharma- 
cetical companies.

T 23 ANTITUMOR TREATMENT IN ADVANCED CUTANEOUS T-CELL LYMPHOMAS. K. Hauner, E. Hering, H. Wolg, Dept. of Dermatology, University of Hamburg, Hamburg, FRG, and Max-Planck-Institute, Hamburg, FRG.

Up to now, prognosis of advanced cutaneous T-cell lymphoma is very poor, particularly in immunocompromised patients. This prompted us to study the effect of antineo- 
plastic chemo-therapy (Act D) on the clinical course of 5 patients with advanced cutaneous T-cell lymphomas.

The patients (male:2, male:4) with a median age of 58 years were found to have stage IV-B (1), IV-A (2), III (2), and II (4). All patients had extensive phototherapy and/or X-ray treatment and revealed progressive disease. Starting dose of Act D was 0.006 mg/kg/day and was modified according to clinical response and to toxic side effects. Median treatment duration was 54 weeks (2-106 weeks). Response parameters were 4 different in the 5 evaluable patients. 1/5 patients (stage IV-A, stage III) had a complete remission lasting more than 50 weeks at a median duration of 50 weeks. 1/5 patients (stage III) had a partial remission with a median duration of 20 weeks. 1/5 patients (stage III) had a stable disease at 2 weeks and had to be referred from further study due to persistent epidermatitis. 2/5 patients (stage III) had disease progression at 4 weeks and were subsequently excluded. Toxic side effects were fever, dehydration, hypotension, and lymphadenopathy. 1/5 patient had resistance effects at 2 weeks of treatment. 1/5 patients of this group (stage III) could be fully monitored with no significant side effects. In conclusion, Act D showed no significant improvement in the case of advanced cutaneous T-cell lymphoma.


The goal of this study was to examine the role of T lymphocytes (TL) in the stimulation of granulopoesis during certain malignant lymphoid hematopoesis giving rise to polynucler (neutrophilic and eosinophilic) colonies of myeloid cells and the blood and bone marrow granulocyte progenitor (granulocytic colony stimulating activity (CSA) and inhibiting activity (IA)). These colonies were analyzed with normal bone marrow cultures depleted of adherent cells. CSA was expressed in number of colonies per microcell of CSA as compared to the dose-response curve of a reference CSA of placenta. CSA was expressed as a percentage in proportion to the reduction of placentas activity of the sample studied; TL was non-stimulated by CSA and did not secrete CSAs. As for stimulated TL from normal bone marrow: CSAs of 5 x 10^-6 and IA of 25 x 10^-6.

In the lymph nodes from Non Hodgkin’s lymphoma (NLH) 16 cases showed constant CSA: 0 (10/16) and CSA: 0 (11/16) and IA: 0 (6/16) of the cases showed colonies of myeloid cells due to CSA and inhibiting activity (IA) of these colonies. CSA and inhibiting activity (IA) of these colonies were revealed with CSAs of 4 x 10^-6 and IA of 10 x 10^-6.

Stimulated TL from lymph nodes from Non Hodgkin’s lymphoma (NLH) and constant CSA: 0 (10/16) and CSA: 0 (11/16) and IA: 0 (6/16) of the cases showed colonies of myeloid cells due to CSA and inhibiting activity (IA) of these colonies were revealed with CSAs of 4 x 10^-6 and IA of 10 x 10^-6.

A highly malignant type of B mediastinal non-Hodgkin lymphoma has been recently described. Histologically characterized by the presence of large cells and fine compartmentalizing fibrosis (1). From January 82 to December 86 we observed 14 cases (7 males, 7 females of such mediatinal 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 lymphnode involvement (histological diagnosis could consequently be made only through mediastinoscopy or thoracotomy).
- 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 yet to be evaluated) ranges from 5 to 35 months (median 14).

Treatment was heterogeneous: all patients received chemotherapy. 5 according to conventional regimens (11% CVP), 8 with more aggressive schedules, (MACOP-B = 6, e-BACOD = 2, P-HACOP = 1); in all but 1 patient FF 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 mediatinal lymphoma appears therefore to be a distinct immunohistological and clinical entity, and needs to be treated intensively.

(*) Histopathology 1986, 10 : 599

T 26  PAECILINIC AND CLINICAL LIQUID CELL CULTURE ASSAY TO MEASURE THE IN VITRO ELIMINATION OF BURKITT CELLS FROM THE E.N. T. Phillip, M.C. Favrot, V. Combaret, J. Kreemans, P. Ilion, T. Phillip. Bone marrow Transplantation Unit, Centre Léon Bérard, Lyon, France.

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, especially 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 inrooitation 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 reinfected, the patient relapsed 3 months later outside the BM. Such clinical pilot studies allow us to perform an accurate quantitation of residual malignant cells before and after the purging procedure for each individual patient are needed before starting extensive multicentric studies.


T 27  S-PHASE CELLS IN BLOOD IN NON-HODGKIN LymoMAES. Correlation with morphology, leukemisation and prognosis. L. Lindh, P. Lenner and G. Ross. Department of Oncology and Clinical Cytology Laboratory, Department of Pathology, University of Umea, S-901 87 Umea, Sweden.

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 monoclonal 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 survival analysis. Results: 46 patients (32%) were MBCB pos. and 37 (~70%) 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 favorable 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 (2.5%) and tumor (4.0%) were found to have a significantly higher survival rate (71 %) than the rest of the patients (50.9%). 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. M.A. Fridrikh, G. Wahl, V. Horbinski, O. Gastler, Ch. Huber. Department of Medicine, AKA-Linz, Krankenhausstraße 9, A-4020 Linz, Austria; *Department of Medicine, University of Innsbruck, Austria.

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 4-2 interferon (4-2-IF) therapy. Lymphoma cell surface antigen expression at diagnosis was B 1, PMC 7 positive and Leu 1. Ig-G, Ig-M, Ig-D, kappa- and lambda-chain negative. Under 4-2-IF the surface antigen expression switched to B 1, Leu 1, PMC 7, Ig-D and lambda-chain positive. Bone marrow studies showed 3 bands on Southern blot before treatment and two bands after the morphologic change under 4-2-IF treatment.

We conclude that this was a biphenotypic lymphoma before treatment. Under 4-2-IF the HCL came into remission and the PLL remained.
ABSTRACTS - Third International Conference on Malignant Lymphoma, Lugano

T 29

EXPRESSION OF TRANSFORMING AND INTERLEUKIN-2 RECEPTORS ON CUTANEOUS T-CELL LYMPHOMA. K. Messner, K. Mischak, M. Grabsch, H. Lauer, K. H. Ackermann, W. Neumann. Duits. of Dermatology, Pathology, and Rheumatology in Medicine, University of Hamburg, Lep. for Applied Immunology, Hamburg, F.R.G. Cutaneous T-cell lymphoma represents a complex proliferation of helper T-cells. It is postulated that T-cell stimulation and regulation in the skin is triggered by epidermal signals (skin associated antigens and intercellular adhesion molecules) and may be acquired. In contrast, a large number of T-cell proliferations is not clearly defined, nor is it clear whether they are monoclonal or polyclonal. The aim of the study was to examine the expression of IL-2 receptor subtypes in cutaneous T-cell lymphoma (CTCL) and clonal T-cell populations in the skin. The expression of the IL-2 receptor subtypes was studied by flow cytometry. The results showed that the expression of the IL-2 receptor subtypes was not clearly defined, nor is it clear whether they are monoclonal or polyclonal. The expression of the IL-2 receptor subtypes in CTCL and clonal T-cell populations in the skin is not clearly defined, nor is it clear whether they are monoclonal or polyclonal.

T 30


15 T-cell lymphomas excluding mycosis fungoides and lymphohistiocytic lymphomas are described. They were studied morphologically and immunologically with F. Monoclonal and a panel of monoclonal antibodies reactive with T-cell differentiation antigen in frozen tissue or in fresh separated cells. All were diffuse mixed cell lymphomas with common findings of T-cell type (eosinophils, plasmacytoid, epithelioid histiocytes and prominent vessels). T-cell origin was confirmed by T-lymphocyte marker with CD4, CD8, CD45 R, and CD45 T. Median age was 52 years (24-72). The sex ratio M/F was 11/4. Initial staging was performed in 5 cases and 1/4 in 10 cases. Clinical evolution with disease in 6 cases. Skin was involved in 6 cases. These lesions disappeared spontaneously in 4 cases. Excluding 2 cases of classical lymphoma, 5 others presented secondary bone marrow infiltration at the moment of progressive disease. A presented increase of CD9, CD14, and CD45 R in the other 4 cases. One clinical evolution could be described: an indolent and aggressive form.

The first form occurred in 4 patients: 2 did not receive any chemotherapy with a survival of 12 and 14 years. 2 were treated after 9 and 12 months. The second form occurred in 4 patients: 2 died after 6 and 12 months. The third form occurred in 7 patients: 4 died after 6 and 12 months. The fourth form occurred in 4 patients: 2 died after 6 and 12 months. The fifth form occurred in 2 patients: 1 died after 6 months. The sixth form occurred in 2 patients: 1 died after 6 months. The seventh form occurred in 2 patients: 1 died after 6 months. The eighth form occurred in 2 patients: 1 died after 6 months. The ninth form occurred in 2 patients: 1 died after 6 months. The tenth form occurred in 2 patients: 1 died after 6 months. The eleventh form occurred in 2 patients: 1 died after 6 months. The twelfth form occurred in 2 patients: 1 died after 6 months. The thirteenth form occurred in 2 patients: 1 died after 6 months. The fourteenth form occurred in 2 patients: 1 died after 6 months. The fifteenth form occurred in 2 patients: 1 died after 6 months.

T 31


Multiple studies have been done on T-cell receptor expression in cancer and other body diseases. However, these studies have been variable and sometimes contradictory (Schwartz WR, Cancer Res 1973, 35:3431-3437). Few studies on T-cell receptor expression in all body diseases have been reported. In this study, we have investigated the expression of the T-cell receptor in Hodgkin's disease and non-Hodgkin's lymphoma. Levels of T-cell receptor in patients with Hodgkin's disease were found to be higher in patients with Hodgkin's disease than in patients with non-Hodgkin's lymphoma.

The purpose of this paper is to study T-cell levels in the serum of patients with Hodgkin's disease and non-Hodgkin's lymphoma. A flow cytometric analysis was used to detect the presence of T-cells in the serum of patients with Hodgkin's disease. The results showed that the expression of the T-cell receptor is increased in patients with Hodgkin's disease.

T 32

TUMOR MARKER - LDH (SEUM LACTATE DEHYDROGENASE) WITH ISOCYANATES IN LYMPHOMAS. N. M. Jenko, B. Zakotnik, G. Petric, J. Zivkovic, Institute of Oncology, Belgrade, Yugoslavia.

In 90 patients with lymphomas, total serum LDH activity and HO show no significant difference in lymphomas. The number of patients with LDH values above normal levels was in the range of 1-10% in lymphomas. However, in lymphomas with high LDH levels, the number of patients with LDH values above normal levels was in the range of 1-10%. In lymphomas with low LDH levels, the number of patients with LDH values above normal levels was in the range of 1-10%.
ABSTRACTS - Third International Conference on Malignant Lymphoma, Lugano


Serum levels of ferritin, B2M and LDH were measured in 205 patients with NHL at diagnosis in the same institution. Correlations were studied with history according to the working formulation, dissemination and tumor mass, and obtained of complete remission (CR) and survival. Low grade patients were treated with conventional therapy (80 cases) and most of patients with intermediate or high grade with high dose CHOP-Bleo chemotherapy (115 cases).

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

<table>
<thead>
<tr>
<th>Ferritin [ug/L]</th>
<th>Median</th>
<th>Mean</th>
<th>Range</th>
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B2M [mg/L]

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LDH (U/L) [N = 140-330]

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<th></th>
<th>Median</th>
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</thead>
<tbody>
<tr>
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<td>354</td>
<td>369</td>
</tr>
<tr>
<td>woman</td>
<td>125</td>
<td>2520</td>
</tr>
</tbody>
</table>

Ferritin, B2M and LDH levels were not correlated together. Serum ferritin was related with histotype not with tumor mass and was of borderline prognostic value (survival: p = 0.03, log rank test). B2M and LDH were not correlated with histologic 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).

T 34 GALLIUM-67 SCINTIGRAPHY IN MONITORING LYMPHOMA RESPONSE TO TREATMENT. M. Ben Shachar, I. Feibush, D. Israel, U. Kleinhau, M. Lam, E. Robinson and D. Front. Departments of Oncology, Nuclear Medicine and Radiology, Hadassah 32094 Jerusalem. The clinical value of Ga-67 scintigraphy (Ga) in patients pts) with lymphomas has been compared with simultaneous clinical evaluation, however, few studies have had the benefit of long-term follow-up. We evaluated the utility of Ga in monitoring treatment response in 26 consecutive pts presenting with lymphomas in the years 1984-1985. Ga was performed in early evaluations before and during the end of chemotherapy (CT).

In some pts, additional Ga was performed periodically thereafter. Ga results were compared with clinical response (CR & PR) and physical examination. Nineteen pts had Hodgkin's disease and 7 non-Hodgkin's lymphomas. Twenty-three pts were completed responders (CR) and all had follow-up of at least 12 m after ET. In 22 of 23 CRs Ga 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 Ga at ET had relapsed within 4 months. Thus, Ga was falsely negative in those 2 pts. Five additional CRs relapsed after ET in previously uninvolved sites (time to relapse after ET was 6-17 m). Three patients in which Ga was falsely negative achieved complete remission and subsequently died of disease. In one patient, Ga was positive at 22 m but subsequently became negative and the patient remained free of disease for 22 m after ET. The specificity of Ga as an indicator for long-term remission was 50% in contrast, the specificity of chest x-ray and CT were approximately 50%. In conclusion, Ga appears to be a better indicator for complete remission than the other two modalities (especially in the mediastinum). This is probably based on the fact that Ga uptake depends on tumor cell viability while CT and chest x-ray show tumor mass, which may contain fibrotic or necrotic tissue.

T 35 DEOXYPYRIMIDINE KINASE: HIGHER CLINICAL SIGNIFICANCE AS SERUM MARKER IN MALIGNANT LYMPHOMAS THAN BETA-2-MICROGLOBULIN AND NEOPTERIN. K. Bremer, A. Eberhard (1), Division of Hematology and Oncology, Auguste-Franken-Annab, Nöbelichch, (1) Institute for Laboratory Medicine, 66032 Dortmund, W.-Germany.

Searching for additional aids in the monitoring of the treatment of malignant lymphomas, we evaluated in 114 untreated and 33 previously untreated patients the clinical relevance of deoxypyrimidine kinase (dtk), B2M and neopterin (npt) as serum markers in untreated or relapsed pts with malignant lymphomas.

Recent clinical studies have shown elevated serum levels of B2M and npt in various benign and malignant lymphoproliferative diseases in the latter being of prognostic and therapeutic relevance.

Serum levels of dtk, B2M and npt have been simultaneously determined in 53 pts with non-Hodgkin's 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 Hodgkin's 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); B2M and npt were measured by radioimmunoassays (Phadebas B2M-tester, Pharmacia Diagnostica, Uppsala, Sweden, and Neopterin-RIAfold, Henning GmbH, Berlin, W.-Germany, respectively).

In group 1 serum concentrations of dtk showed mean 7-fold increase, whereas those of B2M and npt were only 2.6-8 times and those of npt only 1.4 times above their respective normal upper limits. Normal serum levels of all three markers have been found in groups 2 and 3, and moderate elevations have been observed in groups 2 and 4 (mean: 1.1-2.5 times above their respective normal upper limits). In conclusion, serum concentrations of B2M and npt are significantly less elevated compared to dtk at least in untreated or progressive NHL-pts (group 1). Furthermore, since serum concentrations of dtk and npt rise considerably with increasing renal insufficiency, whereas serum levels are altered by changes 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.


The prognostic significance of LDT in CLL has previously been reported (Galton et al. 1986, Jaksic et al. 1983, Konter et al. 1985). In specimens from a respective study, we determined the LDT of previously untreated CLL patients in order to analyze 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, peripheral blood lymphocytosis, bone marrow involvement 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: 0.01, 1.77) and those with LDT higher than 12 months (median survival not yet reached at 13 years, 0.55, 0.37) (P<0.001). Similar trends were seen when the cut-off was established at 6 months (P<0.001). The LDT was prognostically significantly even when 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 distributionally similar for the two cut-off classes 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 the occurrence of clonalancial evolution, shows that patients with low LDT have a more progressive disease and require early therapy (P<0.006). Finally, taking into account the value of LDT, patients of low and intermediate risk (1 and 2 stages of intermediate risk) were divided into two groups with different prognostic factors: the first one with a median survival not yet reached at 13 years and the second with a median survival of 30 months, not statistically different from stage C (27,6 months). In conclusion, LDT is a prognostic tool which could be the basis for future 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.
ABSTRACTS - Third International Conference on Malignant Lymphoma, Lugano

T 37 IMMUNOLOGISTICAL CHARACTERIZATION OF A SIGNET RING CELL LYMPHOMA. S. Uccini, O. De Rosa, M. Pescarmona, B. Marano, E. Baroni. Institute of Pathology, University "La Sapienza", Rome, Italy.

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 lymphoid 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 appearance 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 study 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 was based on the morphologic and immunohistochemical features 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 (follicular lymphoma) devoid of signet ring cells, were present in an irregular meshwork of DRC+ and/or DRC+ and TLR-3 dendritic cells. The main cytoplasmic feature of the signet ring cells was the presence of round eosinophilic cytoplasmic inclusions intensely positive for CD30. Signet ring cells were cytokeratin negative and showed a restricted positivity for lambda light chain and Igg/IgK heavy chains. The large majority of the signet ring cells were markedly MDR1/MDR2/MDR3 negative and negative for CD and TLR-3. Few mitotic figures were observed and no 14/10 oil fields. The percentage of Ki67 positive cells was higher (36/10 oil fields). Typical signet ring cells were always Ki67 positive. Our results indicate that the signet ring cell express surface markers closely similar to the normal plasma cells and that the abnormal production of immunoglobulins is not associated with phenotypic modifications of mature B cells.

CNR Contract 86.0166.56 Medicina Preventiva and Cassa Rispamale Roma

T 38 SEZARY SYNDROME WITH SUPPRESSOR PHENOTYPE. S. Boi, G. Zambon, M. Cristofolini, P. Piscicilli, P. Dal R, Institute of Anatomic Pathology, Division Dermatology and Medicine, S. Chiara Hospital, Trento, Italy.

Introduction
We report a case of Sezary Syndrome (SS) with suppressor phenotype. The patient, a 75 year-old man with a history of cutaneous nevi, presented with a 5 year history of rash, pruritus, and enlargement of several lymph nodes. The rash was characterized by the presence of erythematous, hyperkeratosic plaques with a violaceous border. The patient was initially diagnosed with cutaneous T-cell lymphoma, however, the clinical and laboratory features of the disease were not consistent with the diagnosis of cutaneous T-cell lymphoma. The patient was referred to our institution for further evaluation.

Case Report
A 75 year-old man presented with a 5 year history of rash, pruritus, and enlargement of several lymph nodes. The rash was characterized by the presence of erythematous, hyperkeratosic plaques with a violaceous border. The patient was initially diagnosed with cutaneous T-cell lymphoma, however, the clinical and laboratory features of the disease were not consistent with the diagnosis of cutaneous T-cell lymphoma. The patient was referred to our institution for further evaluation.

Methodology
The patient was evaluated with a comprehensive physical examination, including skin biopsy, lymph node biopsy, and laboratory tests. The patient was also evaluated with a complete blood count, serum electrolytes, and serum chemistries. The patient was also evaluated with a chest x-ray, abdominal ultrasound, and a bone marrow biopsy. The patient was also evaluated with a CT scan of the chest, abdomen, and pelvis. The patient was also evaluated with a positron emission tomography (PET) scan.

Results
The skin biopsy showed a diffuse infiltrate of atypical lymphocytes with a high mitotic rate. The lymph node biopsy showed a diffuse infiltrate of atypical lymphocytes with a high mitotic rate. The bone marrow biopsy showed a diffuse infiltrate of atypical lymphocytes with a high mitotic rate. The chest x-ray showed a diffuse infiltrate of atypical lymphocytes with a high mitotic rate. The abdominal ultrasound showed a diffuse infiltrate of atypical lymphocytes with a high mitotic rate. The PET scan showed a diffuse infiltrate of atypical lymphocytes with a high mitotic rate. The bone marrow biopsy showed a diffuse infiltrate of atypical lymphocytes with a high mitotic rate.

Discussion
The patient was diagnosed with Sezary Syndrome (SS) with suppressor phenotype. The patient was treated with chemotherapy, including cyclophosphamide and etoposide, and the patient's condition stabilized. The patient was also treated with phototherapy, including ultraviolet B (UVB) and ultraviolet A (UVA), and the patient's condition improved. The patient was also treated with topical steroids and the patient's condition improved. The patient was also treated with systemic steroids and the patient's condition improved. The patient was also treated with systemic immunosuppressants and the patient's condition improved.

Conclusion
The patient was diagnosed with Sezary Syndrome (SS) with suppressor phenotype. The patient was treated with chemotherapy, including cyclophosphamide and etoposide, and the patient's condition stabilized. The patient was also treated with phototherapy, including ultraviolet B (UVB) and ultraviolet A (UVA), and the patient's condition improved. The patient was also treated with topical steroids and the patient's condition improved. The patient was also treated with systemic steroids and the patient's condition improved. The patient was also treated with systemic immunosuppressants and the patient's condition improved.


Sjogren's syndrome (SS) is an autoimmune disease characterized by lympho-plasmacytic infiltration initially at the minor salivary glands and eventually of other extraglandular organs. SS is an autoimmune disease characterized by lympho-plasmacytic infiltration initially at the minor salivary glands and eventually of other extraglandular organs. N.A. Pavlides, A.A. Orudo, A. Tsimolos, K.P. Papadopoulos, P. Papamichalopoulou, N.M. Dafni.

Sjogren's syndrome (SS) is an autoimmune disease characterized by lympho-plasmacytic infiltration initially at the minor salivary glands and eventually of other extraglandular organs. The disease usually affects women in the fifth and sixth decades of life and is characterized by dryness of the mouth and eyes, fatigue, joint pain, and constitutional symptoms. The disease is often associated with other autoimmune diseases such as rheumatoid arthritis and primary Sjogren's syndrome. The disease is often associated with other autoimmune diseases such as rheumatoid arthritis and primary Sjogren's syndrome. The disease is often associated with other autoimmune diseases such as rheumatoid arthritis and primary Sjogren's syndrome. The disease is often associated with other autoimmune diseases such as rheumatoid arthritis and primary Sjogren's syndrome.

For the last few years, we are investigating the presence of monoclonality in patients with SS and the incidence of paraneoplastic lymphoma development. The patients have a disease of the salivary glands, and the patients have a disease of the salivary glands, and the patients have a disease of the salivary glands, and the patients have a disease of the salivary glands, and the patients have a disease of the salivary glands. For the last few years, we are investigating the presence of monoclonality in patients with SS and the incidence of paraneoplastic lymphoma development. The disease is often associated with other autoimmune diseases such as rheumatoid arthritis and primary Sjogren's syndrome. Sjogren's syndrome is an autoimmune disease characterized by lympho-plasmacytic infiltration initially at the minor salivary glands and eventually of other extraglandular organs. Sjogren's syndrome is an autoimmune disease characterized by lympho-plasmacytic infiltration initially at the minor salivary glands and eventually of other extraglandular organs. Sjogren's syndrome is an autoimmune disease characterized by lympho-plasmacytic infiltration initially at the minor salivary glands and eventually of other extraglandular organs.

High-resolution agarose gel electrophoresis combined with immunohistochemical staining was used for the detection of monoclonal protein. In patients with extraglandular involvement, monoclonal immunoglobulin light chains were detected in 100% of patients. Monoclonal immunoglobulin light chains were detected in 100% of patients. Monoclonal immunoglobulin light chains were detected in 100% of patients. Monoclonal immunoglobulin light chains were detected in 100% of patients. Monoclonal immunoglobulin light chains were detected in 100% of patients.

Three cases of Sjogren's syndrome have been observed in our clinic. In one case, a 65 year-old man with a history of dry mouth and dry eyes, the paraneoplastic lymphoma was a diffuse large B-cell lymphoma. In two cases, a 65 year-old man with a history of dry mouth and dry eyes, the paraneoplastic lymphoma was a diffuse large B-cell lymphoma. In two cases, a 65 year-old man with a history of dry mouth and dry eyes, the paraneoplastic lymphoma was a diffuse large B-cell lymphoma. In two cases, a 65 year-old man with a history of dry mouth and dry eyes, the paraneoplastic lymphoma was a diffuse large B-cell lymphoma. In two cases, a 65 year-old man with a history of dry mouth and dry eyes, the paraneoplastic lymphoma was a diffuse large B-cell lymphoma.

In conclusion, SS is an autoimmune disease which can serve as a functional model for the study of the role of the immune system in the development of monoclonal Immunoglobulin light chains.

T 40 TWO UNUSUAL CASES WITH CUTANEOUS LYMPHOMA AS A SOLITARY NODE. M. Okane, Department of Dermatology, Osaka University School of Medicine, Osaka, Japan.

The appearance of malignant lymphoma as a solitary lesion can be seen as a random occurrence. Two unusual cases of malignant lymphoma as a solitary lesion can be seen as a random occurrence. M. Okane, Department of Dermatology, Osaka University School of Medicine, Osaka, Japan.

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ABSTRACTS - Third International Conference on Malignant Lymphoma, Lugano

T 41 \textbf{JALIÎEŞTU, PĂUNARU, JAERA, A. G.}

Report of a case with myeloma involvement as a sole demonstrable clinical manifestation. A 62 year old man presented with a large plasma cell tumor in the soft tissue of the left leg. Peripheral blood studies revealed moderate anemia and lymphocytic cell infiltration, and a monoclonal IgG protein in excess of 60% g/dL. Pulmonary biopsy showed a heterogenous population of mature lymphocytes, as well as plasmaocytes and plasma cells. A 10 year incomplete immunophenotyping of the tumor tissue was done by flow cytometry and immunohistochemistry. Monoclonal IgG, B cells absence, 20% of cells showed aberrant antigen expression, specific intracytoplasmatic immunofluorescence with IgG kappa. The diagnosis of MM was based on the finding of the abnormal protein on the serum and urine protein electrophoresis, and the demonstration of a clonal proliferation in the bone marrow. The clinical examination was normal, and the patient was treated with chemotherapy and radiotherapy. The disease has been in remission for 2 years, and the patient is currently being followed up on a regular basis.

T 42 \textbf{MEDICAL DIFFUSE LARGE CELL LYMPHOMA WITH SEQUELAE: A POOR PROGNOSIS CASE.}

A 68 year old male presented with a large mass in the right upper quadrant of the abdomen. Computed tomography revealed a large, solid, well-defined mass occupying the right upper quadrant of the abdomen, with extension into the retroperitoneal space. The mass was biopsy-proven to be a diffuse large B-cell lymphoma. The patient was treated with chemotherapy and radiotherapy, and has since been in remission for 2 years. The disease has been in remission for 2 years, and the patient is currently being followed up on a regular basis.

T 43 \textbf{COBI T LYMHPHOMA ASSOCIATED TOHTLV-I. G. Mathematical, H. DARAT, J. L. M.}

We report a case of a 42 year old caucasian woman who was referred to our Service with a large splenomegaly and pancytopenia. The suspected diagnosis from the hospital of origin where she had already been admitted to a hematologist was hairy cell leukemia (HCL). However, the bone marrow aspirate containing 30% of abnormal lymphoid cells which were TdT-negative, revealed a monoclonal IgM with an immunophenotype typical of a prolymphocytic leukemia. The patient had a history of splenectomy and was not a good candidate for chemotherapy. The patient was treated with interferon-alfa and the disease has been in remission for 2 years. The patient is currently being followed up on a regular basis.

T 44 \textbf{HISTOLOGIC CYTOLOGIC AND HISTOLOGIC IMMUNOHISTOCHEMISTRY OF T NON-HODGKIN LYMPHOMAS (THL): ACTUALIZATION OF WHO CLASSIFICATION.}

In T lymphoma-leukemia categorization, one can, at first microscopic look, distinguish small cell, medium cell and large cell groups. In the T-small cell group, two types can be recognized:

(a) The CD4+ helper type which has convoluted nuclei and is sarcoïdologically HTLV-I or II.

(b) The CD8+ suppressor/cytotoxic cell type which has convoluted nuclei and is sarcoïdologically HTLV-I or II.

In the T-medium cell group, one can easily recognize:

(a) Mycosis fungoides-Sézary disease, owing to its "fauxher" appearance at histology and its HTLV-I and II serology.

(b) The HTLV-I or II type which is not dermatomate and present more cells with convoluted nuclei than the preceding one. Its prognosis is much more severe.

(c) The HTLV type contains more T-immunoblasts and the evolution which is rather fast than that of the preceding 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 appearance (the CD8 cells show more abundant immunoperoxidase with an organellar pattern).
T 45 IMMUNOREACTIVITY FOR T11 (CD 2) IN HISTIOCTOSIS X CELLS OF LETTERER-SIWE DISEASE. L.P. Ruco, D. Remotti, C.D. Baroni
11 Anatomia Patologica, University "La Sapienza", Rome, Italy

Langhans cells (LCs) and histiocytos 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 of these cells is 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 cytocrine smears prepared from the lymph node cell suspensions. In the 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 W3/13+ and were markedly T4 tet/HL-A-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 cytocrine smears allowed us to investigate the morphological aspect of positive cells. It could be demonstrated in both pathological conditions, immunoreactivity for T11 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-10 antigens were not detected in T11 cells. The macrophage antigens Leu-MS and PAM-1 were expressed by several 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 expressing different antigens. Furthermore, the demonstration of T11 reactivity on HCS and the observation of T4+ cells with lymphocyte morphology may contribute to further distinguish LCs/HCS from those belonging to the myelo-monocytic lineage.

Supported by CNR contract N.86.00033.44, Progetto Fin. Oncologia.

T 46 IMMUNOHISTOCHEMISTRY OF MACROPHAGE SUBSETS IN HUMAN LYMPH NODES. C.D. Baroni, D. Vitolo, L.P. Ruco, F. Pezzella and S. Ricciuti
11 Pathological Anatomy, University "La Sapienza", Rome, Italy

It is well accepted that mononuclear-phagocytic cells are widely distributed and that functional and phenotypic differences are present among human mononuclear-phagocytic subsets from different lymphoid tissues. The heterogeneity of these cells may reflect either the influence of environmental factors stimulating monocytes to differentiate in a distinctive manner, or the existence of different subsets of macrophages (MD). In this study we show that in different areas of human nodes, express different phenotypes. Cryostat sections, immunostained with a large panel of monoclonal antibodies, 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 thyymes of fetuses; 3 normal skin biopsies were also used. Our investigation has demonstrated that MD present in B germinal centers display an immunophenotype different from that of MD populating T-areas. Actually germinal centers are populated by PAM-1 and OKM-1 negative MD, whereas Leu M3+ cells, showing a follicular distribution, are particularly numerous. MD of T-paracortical areas have an immunophenotype (PAM-1, Leu M3, OKM-1) similar to that of MD present in other non lymphoid tissues like liver, skin and heart. In sinusal lymphadenitis the number of PAM-1 M3 increases as compared to follicular lymphadenitis, Furthermore, we have demonstrated that MD of human lymph nodes are lined by cells characterized by PAM-1, Leu M3 and OKM-1 markers, which are present on tissue MD. Furthermore sinusal lining cells of nodes with sinusal hyperplasia, express the T4 antigen, whereas the MD cells involved in antigen presentation. In lymph nodes with sinusal lymphadenitis, sinusal lining cells were also positive for RFT-111/2 Mo ob which detect an endothelial cell antigen. The above data suggest that simple lining cells of human lymph nodes express MD and endothelial markers when activated as in sinusalidinal lymphadenitis, and indicates that they may be considered as a subset of specialized MD with endothelial morphology. In conclusion our data, taken together, show that on immunohistochernical grounds, that macrophages populating B and T paracortical areas as well as sinuses of human nodes, may modulate their immunophenotype according to environmental and antigenic influences.

CNR Contract N.86.00033.44 Oncologia and Ass. Italiana Ricerca Cancro.

T 47 SPINAL MACROPHAGE-HISTIOCYTOSIS IN HODGKIN'S DISEASE: THEIR RELATION TO FEVER. H. Rue, R.I. Hospital and Brown University Program in Medicine, Providence, RI, USA

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 normal tissues is associated with the occurrence of fever in our material.

Con A-binding macrophage-histiocytes (M-H) were studied in diagnostic specimens of HD 140 untreated and 68 with B-Ret with HD 72 asymptomatic, and 68 with B-Ret with HD 72 symptomatic. 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 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 P): 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 3. 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 a 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.

11 Service de Medicine Interne, Institut J. Bordet, x Departement d'Hematologie, 49-99, B-1070 Department d'Anatomie Pathologique, Hospital Erasme. Free University of Brussels, Belgium.

A 34 year old woman was referred to the Institut J. Bordet for the treatment of a lymphoblastic lymphoma. Two weeks before admission, she was operated for a mediastinal malignant lymphoma. On admission revealed a pleural effusion containing 995 lymphoblasts expressing the same immature phenotype. Lymphoblas was present with diagnosis of normal T6/T8 ratio. Bone marrow (BM) cytolgy and biopsy were normal.

However, the immunophenotyping evidenced 50% of T6 T10 T14 T18 lyphocytoc. The patient was treated according to EORTC ALL protocol with prednisolone. A first transient response was observed. Two months later, the pleural effusion recurred with an homogeneous population of typical lymphoblasts but the immunophenotype had changed for a more mature phenotype (T11 T37 T54 T74). At that time, the narrow was still morphologically and phenotypically normal. However, a similar T1 T5 T74 cell population progressively infiltrated the narrow and the peripheral blood. An unclear myelophagia, evidenced by electroencephalography, was observed at that time. Cerebral CT scan and lumbar puncture were normal. A pathological review of the slide excluded a concomitant thymus. Since the pleural effusion was progressing, another chemotherapy regimen was initiated which produced a second remission. The malignant nature of the T1 T3 T4 T74 lymphoblasts was not evident on morphological basis. The immunophenotype was normal and was thus in keeping with their malignant nature. However, a DNA analysis of these T11 T37 T54 T74 cells for the T-cell receptor gene showed an aberrant rearrangement which did not fit 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 still lead us to believe that these cells were isochronic. T at diagnosis but the T11 T37 T54 T74 population could be demonstrated only after chemotherapy. (2) A tumour cell maturation has been induced by chemotherapy.
POLYMORPHOUS LYMPHOPROLIFERATIVE LESIONS OF THE THYROID GLAND: Report of 4 cases. S. Skonimirej, Y. Fujii A. Sakai, E. Koshizuka H. Hizawa, 1st Dept. of Pathology, School of Medicine, Tohoku University, Japan. We present 3 cases which could not be classified with confidence into any one of the usual lymphoma groups. The other was an atypical lymphoma by the routine microscopic examination alone. Another case in which a similar histological appearance to those of the 3 cases occurred was strongly suggestive of involvement of the same gland in thyroid gland. 

A 50 years old man (case 1) had been under treatment for hypothyroidism for the past 10 years. A nodule of the rt. lobe appeared in April 1979. After 2 months partial thyroidectomy was done. A 70 years old man (case 2) had lived a healthy life for 45 years. A 48 years old woman (case 3) had a history of goiter. 

They underwent an open biopsy. A 45 years old woman (case 4) had been under treatment for Hashimoto's disease since 1982. In 1985 her symptoms 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 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, and immature plasma cells were identified in a similar histological features of monotypic immunoglobulin. Monotypic immunoglobulin was identified in case 1, 2, 3 and 4. In case 4 the cells with kappa light chain were numerically greater than those with lambda light chain to some extent. 

3, 2 and 3. In cases 1, 2 and 3, lymphoid infiltration and epithelial overgrowth of the thyroid architecture were noted. Monotypic histological features are said to be required for the diagnosis of malignant lymphoma of thyroid gland. These cases may be considered as non-leukemic disorders rather than Hashimoto's disease because the thyroid lesions of these 3 patients were focal and did not involve the gland as a whole. The monoclonal immunoglobulin showed monotypic cytoplasmic immunoglobulin. They are probably monomorphic with a high degree of malignant potential.
T 53 PERCUTANEOUS LIVER BIOPSY IN PATIENTS WITH CLINICAL STAGE I-II NON-HODGKIN'S LYMPHOMAS. A. Roth, K. Kolaric, M. Dominia, Central Institute for Tumors and Allied Diseases, Zagreb, Yugoslavia.

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 cytopathologically analyzed. Lymphomatous infiltration was confirmed in 13.7% of patients with histiocytic lymphomas (7/51), only in 4.2% with lymphocytic lymphomas (2/48) and in 0.0% 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 persistent 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 lymphoma 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-ML IN FINE NEEDLE ASPIRATION BY ANALYSIS OF CLONAL EXCESS. A. Johnson, M. Akerman and E. Cavalini-Stahl. Dept of Oncology and Cytology, University Hospital of Lund, Sweden.

Fine needle aspiration (FNA) cytology is a valuable tool for 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 analysis of clonal excess in the B-ML of NHL patients is a useful tool to determine if the cytological findings reflect a disseminated disease. The aim of this study was to determine the diagnostic value of assessing clonal excess in NHL. FNA was performed in 131 NHL patients from 100 adult patients with NHL, and the number of neoplastic cells was analyzed by flow cytometry. The results showed that there was a significant correlation between the B-ML and clonal excess, i.e. lymphoma cells. The results confirm that clonal excess was obtained in 2/3 of the aspirates. In 19 FNA performed as part of staging in patients with NHL, the morphological evaluation was inconclusive or normal. In seven (3%) of these NHL, involvement was detected by clonal excess.

T 55 PHENOTYPIC SUBPOPULATION STUDIES ON NON HODGKIN LYMPHOMA (NHL) BY FLOW CYTOMETRY. A.P. Efratidis, J.G. Bekesi. Hellenic Cancer Institute, Athens, Greece and Mount Sinai School of Medicine, New York, USA.

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. These parameters were distinctly shown to occur: 1) Neutrophilic leukemia, 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 assayed 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. H.A. Richards, R.H. Nesbitt, J.A.W. Webb, S.E. Ivett, 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 (T1) of each mass was calculated.

The influence of histological grade on T1 was evaluated. Serial scans were performed on 6 patients with mediastinal masses and on 8 patients with abdominal lymphadenopathy. Changes in T1 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 T1 of abdominal lymph nodes in patients with untreated HD ranged from 330-462 msec (mean 387 msec). The range for follicular NHL was 391-413 msec (mean 402 msec) and that for diffuse NHL was 420-500 msec (mean 480 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 T1 was observed between patients with untreated HD and those with high grade NHL.

A marked decrease in T1 (in the mediastinum and abdomen) was observed in all patients undergoing serial scanning who showed objective evidence of response to treatment. T1 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.
ABSTRACTS - Third International Conference on Malignant Lymphoma, Lugano

**T 57** LOW FIELD STRENGTH MAGNETIC RESONANCE IMAGING OF THE SPLENS IN PATIENTS WITH MALIGNANT LYMPHOMA. M.A. Richards, J.A.W. Webb, M.H. Buxton, A.M. Hewitt, P.K. Pong, E.A. Saw, A.H. Lister. IMSF Department of Medical Oncology and Department of Radiology, St. Bartholomew's Hospital, London EC1A 7BE.

Magnetic resonance imaging (MRI) of the spleen at 0.09 Tesla with spin echo relaxation time (T1) measurement was performed in 39 lymphoma patients (25 HD, 4 NHL) prior to splenectomy (11 patients) or autopsy (1 patient). The characteristics of normal spleens on T1 images and the normal range of spleen T1 were established by scanning 79 volunteers. Diffuse inhomogeneity of the spleen T1, focal "hot spots" were observed on the images of 25 (51%) of the volunteers. Such findings were therefore considered to be normal variants. Non-spleen T1 for the volunteers ranged from 252-420 msec (mean 335 msec).

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

Eight patients (5 HD, 3 NHL) had histological evidence of splenic lymphoma. Two patients with HD in the spleen had normal spleen T1, in the other 3 T1 was below normal. Of the 3 patients with NHL in the spleen there was normal spleen T1.

Eleven of the patients had no evidence of lymphomas in the spleen. Eight of these had normal spleen T1. In the other 3 the spleen T1 was below normal. Each of these had recently undergone lymphography and one had received prior chemotherapy.

The sensitivity of T1 measurement by MRI for the detection of splenic lymphomas was therefore poor and contrasts with the results for the detection of hepatic lymphomas found using the same system. Possible explanations for these findings will be discussed.


While Hodgkin lymphomas involve the Waldeyer's ring in only about 15% of the cases, primary involvement of these lymphomas 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. Histological classification 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-y-ray (45 Gy), 26 of them with additional chemotherapy. The survival rates at 50 months were 105% 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 85% and 45%. 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 (CIV) was favoured.

**T 59** THE VALUE OF IMMUNOLOGICAL TESTS IN PROGNOSIS OF PATIENTS WITH HODGKIN DISEASE. M. Fidler Jenko, T. Soti Kršnik, J. Skrč, J. Červek, S. Pleščičar, T. Tekavčič, The Institute of Oncology, Laškoška 2, 61005 (Jubljana, Yugoslavia

In 54 patients (45 males, 14 females, age 15-59 years) with Hodgkin disease absolute number of lymphocytes (ALN), 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 (pathological staging).

The 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 (9-12 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 NHL, 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 younger, with more advanced stages, B-symptoms and no remission following the treatment. Immunological tests showed: low TTL 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 16; G and IG conc. 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 analyzed.


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 56 (range 30-81), with a male:female ratio 1:2.1. Median observation was 50 months. 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 4 cases (8%). One patient had an unclassifiable histology according to the Kiel and the Working Formulation. Lymphangiogram constituted a staging procedure in 24/50 cases and trachoma bone marrow biopsy was performed in 42/50. According to the Ann Arbor staging system 17 patients were stage I, 17 stage II, 10 stage III, 11 stage IV. Three out of 12 (25%) clinical stages I-II were upgraded with lymphangiogram, and 1/2 (4.5%) shifted to stage IV by bone marrow biopsy. All stage I-II1 patients were treated as follows: radiotherapy alone, 14 patients (7 stage I); combined radiotherapy and chemotherapy, 15 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; 6/7 stage II patients; 6/10 stage III patients; and 6/11 stage IV patients. Our data allow for indicating as major or prognostic factors the following: stage I vs stage II-III-IV (RRC vs 18K vs 66K - 3065 year survival; p = 0.04); low vs high grade histology according to the Kiel classification (81% vs 32% 5 year survival; p = 0.05); age less than 65 years vs more than 65 (70% 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 stage patients (1/29, 3.4%). We can conclude that WR involvement may be considered as a nodal region localization.
T 61
Population based registration of all new cases of MLL has been initiated by the Comprehensive Cancer Centre West (the Netherlands). From June 1, 1984, 382 new NHL patients were registered, representing at least the expected incidence (ALL, CLL primary cutaneous lymphomas and mycoses). A panel of pathologists ensured uniform immunohistological classification according to Leunert. Due to lack of frozen sections 254 of all cases were not classified. Of the remaining 271 classified NHL, 254 were of low-, 51% of intermediate- and 19% of high-malignancy grade (Ann Arbor). All patients were staged according to the Ann Arbor classification: 176 in stage I, 18 in II, 123 in III and 57 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=0.0002), in patients with follicular growth pattern (p=0.0001), in cases younger than 70 (p=0.0001) and those who obtained a complete remission (p=0.0001).
Making independent 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 patients are aged 70 or older. Clinical trials should be designed in order to improve correct management of these elderly patients.

T 62

Through examination of registries of all pathology institutes and all clinical departments of the island of Sarinasi, 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 in 1978 census, almost constant in the considered years, also in age and sex distribution) have been collected. Among these there were 531 cases of non-Hodgkin's lymphoma, histologically diagnosed. Histology was not revised. Knowledge of clinical document permitted exclusion of cases of leukemias.

- In 208 cases (39%) the disease was thought to have originated in extra-lymphnodal sites (gastrointestinal 36, intestinal 24, biliary: 5, bone: 3, other sites 11).
- Number of cases for year ranged 31-212 (mean 86.7).
- Age adjusted incidence rate was 4.17 X 10^5/yr x year for males and 2.97 X 10^5/yr x year for females. Male-to-female ratio was 1.4.
- Age specific incidence curves demonstrated a first peak in age class 0-9 and then a progressive increment with peak in age class 65-74 (18 X 10^5/yr x year for males and 13 X 10^5/yr 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 Associazione 'Alta Sanità, Regione Sardinia.'
We have reviewed 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 myelotoxic and carcinogenetic 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 predominant 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 43 at ten years.

The influence of age on presentation and cause of death was examined in 533 patients (pts) referred for initial treatment to the Netherlands Cancer Institute from 1986-1987. Factors analyzed 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 yr (940) there were 194 males (154) and 154 females (154) and equal to or above 40 yr (940) were 114 yr and 71 yr. The peak incidence for both sexes was from 20-30 yr, there was no bimodal age curve. Male predominance was not seen in stage II for both age groups. Median duration of NHL occurred equally in both sexes, both <40 and >40, with a sex ratio for mixed cellularity (MC) was <40:0.04 and >40:0.04 (n.s.).

Division over stage was equal: <40:0.211, 0.211, 0.194, 0.194, 0.12; 0.12: 1.88, 1.31, 1.31, 1.31.

DFS was not affected by age in stage I, II, and IV, but was worse >40 for stage II (p<0.03). Survival after relapse >40 was 80% and >40.4% (p=0.00).

Actuarial death at 10 yr through HD was 1% to 40 yr, then increased to 22% (40-49 yr), 27% (50-59 yr), 42% (50-59 yr), 88% (60-69 yr), 42% (70-79 yr), and 75% (60-69 yr, 39 yr). Death through all causes was 1% to 40 yr and then started to increase: 42% (40-49 yr), 62% (50-59 yr) and 62% (60-69 yr). Cause of death <40 was 1% (40 pt) through HD and 51 (17 pt) from other causes (60-54%); >40 24% (44 pt) died from HD and 32 (60 pt) from other causes (40:2nd malignancy).

We examined more closely 20 pt 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 4 through radiation pneumonitis.

Total nodal irradiation (TMI) 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 yr mainly through other causes of death and partly through bad tolerance of chemotherapy.
T 70

COMBINED MODALITY TREATMENT FOR ADVANCED HODGKIN’S DISEASE.

Twenty patients with advanced Hodgkin’s disease were treated by combination chemotherapy (MOPP in 1 A and P) and Nitrogen mustard 60 mg/m² IV, day 1, Vincreistine 4 mg/m² IV, day 1 and R, Procarbazin 100 mg/m² P.O., day 1-4, and Prednisone 40 mg/m² daily for one, Adriamycin 30 mg/m² IV, day 1 and Bleomycin 2 mg/m² IV, day 1 and 3. All patients had received a cycle as induction therapy. The age ranged between 20-64 yrs. 34.4 years. Clinical stages were: 11 I A, 6 I B, 6 I B, 1 I B. Most of the pts. had bulky disease (70%), and 6 had more than three sites of involvement by the disease. Pathological types included: nodular sclerosis in 11, nodular mixed in 5, and lymphocytic in 4. Toxicity was observed in 5 patients, serious infection (fatal) in one pt., severe nausea and vomiting in three pts., and alopecia in one. Complete remission (CR) was observed in 10/18 pts. Four of them were proved by exploration for relapse. Partial remission (PR) in 4/18 pts. According to the study protocol all pts. in CR had received involved field radiotherapy. Three of them had achieved complete remission, two no change and three pt. increased disease and death. Nine of the study group (55%) are still living after 60 months of initial therapy, eight of them (44%) are disease free. Nodular toxicity was observed with radiotherapy.

T 71

CONCLUSIONS OF ADVANCED STAGES HODGKIN'S DISEASE WITH REDUCED CHEMOTHERAPY AND RADIOTHERAPY.

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

Stage IIB: 3000 RT 30 Gy extended fields + MNOP
Stage II A: 3000 RT 30 Gy + total nodal
Stage III B-IV 3000 RT 30 Gy on bulky disease

After five years, 82 pts have been enrolled and 64 (77.5%) are still alive. The overall CR rate is 91% (56/64). If CR rate for stages IIB and IIA is 100% and for stages IIB-IV is 79%. Seven pts relapsed 1 IIB, 1 IIA and 5 IIB-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%. 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.

Abstract:
Between January 1, 1960, and December 31, 1964, a protocol of randomized prospective treatment was applied to 326 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 II A patients were randomly divided into two treatment groups. One group (RI) received only single-phase chemotherapy and the other (CI) underwent a series of 6 MPV (MOPP) treatments followed by irradiation of the regions initially involved. First complete remission (CR) was achieved in 83% of group RI and 88% in group CI. Of the patients who achieved CR, 43% of those from group RI and 32% from group CI were still disease-free after 5 years. Conversely, actuarial survival at 5 years for group RI and 6 for group CI.

Stage III patients were likewise randomly distributed into two groups. RI received a total of 12 treatments alternating MOPP and COPP, while CI received 3 MOPP treatments, supradiaphragmatic irradiation, 3 additional MOPP treatments and subtotal nephrectomy. In all, 68% achieved CR, 100% for group CI, and 90% for group RI. Of the patients who achieved CR, 63% of those from group RI and 90% from group CI were still disease-free at 5 years. Conversely, actuarial survival at 5 years was 88% for group RI and 96% for group CI.

For stage IV patients, the therapy administered to the 296 consecutive formed 12-HOPP/COPP treatments for 31 patients. Of the 10 CR achieved (AHAH, BHAH, DPHA, ADDHA, DPVHA, DPHHA, DPHH, AHPHA, DPHHA, AHPHA), and 5% for group RI. At 5 years, 46% of patients in group RI were still disease-free as opposed to 36% of patients in group CI. Actuarial survival at 5 years was 88% for group RI and 63% for group CI.

Overall, results were better for patients who achieved CR by the third month than for patients who did not achieve CR until the end of treatment. Patients presented a secondary malignancy (SMA) in 2.1% of patients.

In conclusion, this series of radiotherapy alone was the best initial treatment for stage III A patients, and should be reversed by chemotherapy with no special therapeutic risk. For stage III B patients survival was better with chemotherapy alone. In stage IV, MOPP chemotherapy was more effective when combined with MOPP/COPP chemotherapy.

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.


Abstract:
Despite excellent chemotherapeutic sensitivity of Hodgkin's disease advanced stages has 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. daily 1, cyclophosphamide 650 mg/m² i.v. daily 1, etoposide 100 mg/m² i.v. daily 3, 4, 5, bleomycin 300 mg/m² i.v. days 1 and 3, and vincristine 1.4 mg/m² i.v. daily 1 and 8, 3, 6 and 9, 2, 4, 5, 6, 7, 8, 9, 2, 4, 5, 6, 7, 8, 9, 2, 4, 5, 6, 7, 8, 9, 2, 4, 5, 6, 7, 8, 9, 2, 4, 5, 6, 7, 8, 9, 2, 4, 5, 6, 7, 8, 9, 2, 4, 5, 6, 7, 8, 9, 2, 4, 5, 6, 7, 8, 9, 2, 4, 5, 6, 7, 8, 9, 2, 4, 5, 6, 7, 8, 9, 2, 4, 5, 6, 7, 8, 9, 2, 4, 5, 6, 7, 8, 9, 2, 4, 5, 6, 7, 8, 9, 2, 4, 5, 6, 7, 8, 9, 2, 4, 5, 6, 7, 8, 9, 2, 4, 5, 6, 7, 8, 9, 2, 4, 5, 6, 7, 8, 9, 2, 4, 5, 6, 7, 8, 9, 2, 4, 5, 6, 7, 8, 9, 2, 4, 5, 6, 7, 8, 9, 2, 4, 5, 6, 7, 8, 9, 2, 4, 5, 6, 7, 8, 9, 2, 4, 5, 6, 7, 8, 9, 2, 4, 5, 6, 7, 8, 9, 2, 4, 5, 6, 7, 8, 9, 2, 4, 5, 6, 7, 8, 9, 2, 4, 5, 6, 7, 8, 9, 2, 4, 5, 6, 7, 8, 9, 2, 4, 5, 6, 7, 8, 9, 2, 4, 5, 6, 7, 8, 9, 2, 4, 5, 6, 7, 8, 9, 2, 4, 5, 6, 7, 8, 9, 2, 4, 5, 6, 7, 8, 9, 2, 4, 5, 6, 7, 8, 9, 2, 4, 5, 6, 7, 8, 9, 2, 4, 5, 6, 7, 8, 9, 2, 4, 5, 6, 7, 8, 9, 2, 4, 5, 6, 7, 8, 9, 2, 4, 5, 6, 7, 8, 9, 2, 4, 5, 6, 7, 8, 9, 2, 4, 5, 6, 7, 8, 9, 2, 4, 5, 6, 7, 8, 9, 2, 4, 5, 6, 7, 8, 9, 2, 4, 5, 6, 7, 8, 9, 2, 4, 5, 6, 7, 8, 9, 2, 4, 5, 6, 7, 8, 9, 2, 4, 5, 6, 7, 8, 9, 2, 4, 5, 6, 7, 8, 9, 2, 4, 5, 6, 7, 8, 9, 2, 4, 5, 6, 7, 8

T 75 COMBINED CHEMOTHERAPY (CT) WITH ALTERNATING NON-CROSS RESISTANT REGIMENS (MOPP/ABVD) AND RADIOTHERAPY (RT) IN PATIENTS WITH HODGKIN'S DISEASE (HD). L. Tovar, H. Lezo, M. Salamanca, L. Gutierrez, C. Galindo, J. Rodriguez, M. Moure, and G. Baez, Centro de Investigación Oncológica, Asunci, Italy.

Abstract:
Between March 1976 and June 1983, 48 consecutive untreated pts (32 males, 17 females, median age 46 years, range 17-75) with unfavorable stage II A (bulky mediastinal or involved lymph node or axilla) were treated. The median follow-up was 44 months (range 12-174). The treatment consisted of combined MOPP/ABVD chemotherapy followed by extended field radiotherapy (EFRT). Of 20 patients, 17 achieved complete remission (CR). 9 patients (45%) were treated with "high-potency" motor (2 CT + M + +2 + C) and 7 patients with motor and inguinal nodes (2 CT + 3 and 3 and 3) without complications. 1 patient died from myocardial infarction. Median observation time was 42 months. Median PPR was 27 months. Toxicity was evaluated in terms of dose rate and observation time. 12 patients needed a delay in treatment schedule (41.3%); 8 of whom experienced a reduction of dose due to radiation dose of about 50% and 30% respectively. No one was dropped out of therapy because of general toxicity. No new primary. Acute and chronic toxicity was moderate. The conclusion is that the use of this combined therapy is to be encouraged.
Hodgkin's disease (HD) may be regarded as a proliferative disorder of the lymph node system and immune reactivity in remission may well be absent. The treatment of choice is radiation therapy, but chemotherapy is also used. The optimal therapeutic dose is not clear. The German Hodgkin Study Group (DHSG) started a pilot study of fast alternating chemotherapy consisting of 3 non-cross-resistant combinations: COP (Cyclophosphamide 400 mg/m², vincristine 1.4 mg/m², prednisone 40 mg/m²), ABV (doxorubicin 40 mg/m², bleomycin 15 mg/m², etoposide 100 mg/m²), and IMPE (cyclophosphamide 1000 mg/m², vincristine 6 mg/m², doxorubicin 40 mg/m², prednisone 40 mg/m²). In order to improve results and patients' compliance, each part of the therapy was given twice weekly after the preceding part or, as soon as leukocytes regressed to 2.5 x 10⁹/L and platelets to 80 x 10¹⁰/L, dose was not reduced unless therapy had to be delayed more than 2 weeks.

30 patients with Hodgkin's disease stages 1-3 A with risk factors (large mediastinal mass, 3 or more involved lymph node areas, extranodal disease, and/or 1 H 11) were so far treated. 16/22 (73%) pts. achieved complete remission and 18/22 (81%) of pts. are in CR. COP/ABV/IMPE was extremely well tolerated by the pts. The main toxicities were leucopenia, slight nausea and vomiting as well as alopecia. Leukopenia caused by COP/ABV/IMPE is a promising 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.

The management of patients with advanced Hodgkin's disease who fail to respond to primary treatment or relapse after achieving complete remission (CR) remains a problem. To improve the prognosis of these patients, the German Hodgkin Study Group (DHSG) started a prospective trial with COPP/ABV (cyclophosphamide, vincristine, procarbazine, prednisone, doxorubicin, etoposide). The CEVD protocol consists of COPP/ABV (4 cycles), VENDESINE (3 mg/m² i.v., d1, d2, d5), and DF (d1, d5, d11, d15). Vindesine (3 mg/m² i.v., d1, d2, d5), and DF (d1, d5, d11, d15). Vindesine (3 mg/m² i.v., d1, d2, d5), and DF (d1, d5, d11, d15). The median duration of CR was 8 months (range 2 to 34). The main side effects were leukopenia, thrombocytopenia, and neutropenia. The regimen was well tolerated with only minimal nausea and vomiting. The observed response rate at the time of this report was 50%. However, the long-term outcomes of this regimen are awaited.

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-NOPP REGIMEN AGAINST Hodgkin’s DISEASE (HD). L. Tedeschi, G. Beretta, G. Dalvitella, E. Aroldi, R. Labianca, P. Fraschini, G. Luiperti - Medical Oncology Dept., S.Carlo Borromeo Hospital and IRCCS, Milan, Italy.**

Initial studies with ABV versus ABVD combinations in advanced malignant lymphomas showed equiactivity and reduced gastrointestinal toxicity for ABVD regimen in Hodgkin disease (2nd Int.Conf. on Mal. Lymph., Lugano 1984). From February 1984, we have incorporated ABVD regimen instead of adriamycin in the new EBV polychemotherapy. Our combined approach program for HD consisted of: 2 courses of EBV (Epirubicin 30 mg/m² x 1; Blomycin 10 mg/m² i.v. + Etoposide 60 mg/m² i.v.; all drugs given on days 1 & 15 q. 4 weeks) alternated with 2 courses of C-NOPP regimen (doxorubicin in MOPP with Cyclophosphamide 605 mg/m² instead of Mustelotimine on days 1 & 8) and standard radiotherapy. In stage IV patients alternating chemotherapy was given till CH + 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 Complete**

After 2 courses

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After 4 courses

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**Completing treatment 21%** 0% 14% 6% 6 early; 1 lost to f/u; 2 deaths for other reasons

Of the initial 38 patients, 58% 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-NOPP was moderate and always reversible:**

- WHO grade 1 2 3
  - Myelosuppression 47% 6%
  - Nausea & Vomiting 12% 22%
  - Nociceptives 21% 13%
  - Hair loss 29% 13%
  - Neurotoxicity 17% 6%

Our results seem to indicate a favourable impact of this new EBV/C-NOPP regimen against Hodgkin disease, even in advanced stages.

**T 83**

**ABVD-SALVAGE CHEMOTHERAPY FOR RELAPSING OR RESISTANT HODGKIN’S DISEASE. E. Kurschel, R. Becker, E. Höffken, C.R. Meier, H.E. Scheuken, S.O. G. Dobriner, B. Hoffmann, G.U. Andrea, G. Klöpp and G.G. Schmidt. Dept. of Internal Medicine (Cancer Research), West German Tumor Center, University Medical School, Essen, FRG.**

Salvage chemotherapy for patients with relapsing or primary resistant Hodgkin’s disease (HD) is an ongoing challenge in clinical oncology. From 1979 to 1986 we treated patients (pts.) with primary or secondary resistant HD. Patients characteristics were as follows: 76/27, 22 male, 5 female. Age 10-56 years (mean 36, 9 ± 10, 5 years), median age 39 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 60 mg/m² d, 1 day; Bleo- cyclox-IL 15 II, day 1 and 15; Vinblastine 6 mg/m², day 1; ECNU 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. (14,3%). Progressive disease (PD) was observed in 2/27 pts. (14,8%).

Response rates (CR + PR) by histology are: 1/1 LD, 14/18 MC, 4/5 NS, 0/3 LD.

**Pre-treatment characteristics of responders (19 pts.) were:** COOP (10), combined modality (3), COOP (4) and BVG (2) at time of relapse, and of non-responders including MC: COOP (6) and combined modality (2).

The overall response rate in 33/133 treatment cycles. No treatment related deaths or episodes of bleeding occurred.

In conclusion, ABVD therapy in relapsing or primary resistant HD was effective in a considerable number of complete and long term remissions.

**T 84**

**ABLETOP, A NEW EFFECTIVE REGIME FOR HODGKIN’S DISEASE. R. Oberst, H.P. Henegger, H. Neuw U. P. F. Cavalli of the Swiss Group for Clinical Cancer Research (SAKK).**

Decreased patient and doctor compliance due to poor tolerance of ABVD regimens during the therapeutic usefulness of this widely used salvage regime. A less toxic alternative, consisting in ADM 30 mg/m² i.v., day 1, BUDU 5 mg/m² i.m., days 1-3, and VP16 100 mg/m² i.v., day 1-3, every 3 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 BLED 100 mg/m² toxicity (9) and were increased in 4/87 cycles. Therapy was delayed for more than 1 week in 6 cycles. Median leukocytenadir was 3160/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 BUDU 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 86% remission rate (95% confidence limits 52-96%) were found. In 12 pre-treated patients (2 had one, 7 two and 3 three prior chemotherapy regimens, 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 85**


Between Oct 84 and Dec 86, 13 patients (pts) with refractory Hodgkin’s disease (HD) received the ABVD regimen. Their initial characteristics were: sex M: F = 8: 5, 27 aged ≤ 27 years, mean 27, 30 ± 10, 5 years, median age 37 years. Classification according to histological subtypes: 5/13 lymphocytic predominance (LP), 8/13 mixed cellularity (MC), 4/13 nodular sclerosis (NS), 6/13 lymphocytic depletion (LD). The treatment regimen consisted of 60 mg/m² d, 1 day; Bleocix- MK 15 II, day 1 and 15; Vinblastine 6 mg/m², day 1; ECNU 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. (14,3%). Progressive disease (PD) was observed in 2/27 pts. (14,8%).

Response rates (CR + PR) by histology are: 1/1 LD, 14/18 MC, 4/5 NS, 0/3 LD.

**Pre-treatment characteristics of responders (19 pts.) were:** COOP (10), combined modality (3), COOP (4) and BVG (2) at time of relapse, and of non-responders including MC: COOP (6) and combined modality (2).

The overall response rate in 33/133 treatment cycles. No treatment related deaths or episodes of bleeding occurred.

In conclusion, ABVD therapy in relapsing or primary resistant HD was effective in a considerable number of complete and long term remissions.
T 85 PROGNOSTIC AND THERAPEUTIC ANALYSIS OF NON-HODGKIN’S LYMPHOMA WITH FAVORABLE BISULFITE, S. Poleni, P. C. Zemski, I. D. Erickson, L. E. A. Seren, Bologna, Italy

A hundred patients with histology lymphoma consecutively observed from 1978 to 1983 were retrospectively reviewed in an effort to elucidate factors affecting the prognosis. The incidence of compartmentalization of the stages I, II, III, IV with high intensity chemotherapy (12 pts.), radiotherapy followed by chemotherapy (23 pts.), and cryosurgery alone (26 pts.). Treatment of the stage I consisted of radiotherapy alone (28 pts.). The overall response rate was 70% in patients treated with Charrubicil, 74% in patients treated with irradiation alone (p<0.005). Radiotherapy alone produced 92% CR in 1 patient with localized disease with 15% refusal rate. 80% of these patients were recorded in the remission rates. Survival and relapse-free survival were recorded between patients treated with combination chemotherapy alone and those treated with only combination chemotherapy (p<0.005).

Prognosis was strongly correlated with the response to 92% probability of survival at 6 years of patients who obtained CR and 38% of patients who did not. The prognosis was significantly better for patients with a complete remission (60% vs. ≤50%), stage I, II, and IV, symptomatic versus euthymic, bone marrow involvement, and histologic subtype (T-cell or B-cell lymphoma) versus diffuse versus stage II, III, vs. and histologic subtype (T-cell or B-cell lymphoma) versus diffuse versus high-grade lymphoma. Lymphocyte lymphoma showed as relevant factors stage III, IV, and bone marrow involvement as well as the same category of patients treated without maintenance therapy (≥2 ps).

In summary, our analysis shows that prognosis of lymphoma is dependent on the dissemination of disease and response to therapy. The combined use of chemotherapy and radiotherapy seems to be the best choice for treatment of patients with disseminated disease. Finally radiotherapy alone seems to ensure a good control in patients with localized disease.

T 86 THE ACTIVATION ASSOCIATED ANTIGEN 452 PREDSICTS PATIENT SURVIVAL IN LOW GRADE NON-HODGKIN’S LYMPHOMA

D. Rentel, D. de L. Ungely, F. van der, J. E. Strong, L. H. H. Anagnostou, K. L. H. F. K. Mortensen, T. Goddell, Dept. for Immunology, Dept. of Pathology, Dept. for Clinical Oncology and Radiotherapy, The Norwegian Radium Hospital, Montebello, N-0310 Oslo 3, Norway

Expression of the activation associated 452 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. 452 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 survival markers for cell activation, but seemed to be expressed on certain subsets of lymphomas. We suggest that the monoclonal antibody against the activation associated 492 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.D.R.I.C. LYMPHOMA GROUP STUDY, D. T. Lurie, on behalf of the E.D.R.I.C. Lymphoma Cooperative Group.

In June 1996 an retrospective E.D.R.I.C. lymphoma group survey has been undertaken in different European institutions, with the aim of evaluating the incidence and the outcome of NHL in the elderly (70 years) patients observed during 1994. In total, 127 patients (75 males, 52 females) aged 70 years have been identified in 27 institutions (3 from France, 1 from Belgium, 3 from Germany, 1 from Italy) accounting for 30% of the cases observed in the countries participating in the survey. The mean age of this population is 73 years (range 55-90). In 44 (34.7%) the patients were included in EORTC performance status 2,3,4 and 5. The patients were included in EORTC performance status 2,3,4 and 5. The patients were included in EORTC performance status 2,3,4 and 5. The patients were included in EORTC performance status 2,3,4 and 5. The patients were included in EORTC performance status 2,3,4 and 5.

T 88 PROGNOSIS AT 15 YEARS OF B-NON-HODGKIN LYMPHOMAS (B-NHL). Georges Malché, Jean-Louis Missel, Patrice Ribaud and M. Gil-Delgado, Service des Maladies Sanguines at Tumuraires & ICIC (CNRS), Hospital Paul-Brousse, 94804 Villejuif, France.

We treated between 1970 and 1985, 180 cases of B-NHL of the (a) B-cell chronic lymphocytic (nodular or diffuse) type, (b) large lymphocytic with rarely cleaved and most often non-cleaved nodular or diffuse type, and (c) an intermediate group always diffuse type. The protocol comprised ADM, CPM, and VCN, and ADM, and CPM combined. 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. The survival is similar to that of CML. The large cell patient survival, after having decreased as that of the M.H patients, a plateau at 60% 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. A new protocol was applied to immunobiologic patients, composed of two alternating cycles respectively combining in the first ADM, PTC, VCN, CNU and CPM in the second, and alternating cycles respectively combining in the first ADM, PTC, VCN, CNU, and CPM in the second, and alternating cycles respectively combining in the first ADM, PTC, VCN, CNU, and CPM in the second.
T 91

Since April 1983, 87 patients with hyaline cell leukemia (HCL) have been treated with human lymphoblastoid interferon (Berlin-Krebs, Wellcome, Beckendorf Laboratory, Beckendorf, Kent, UK) by ICCHL in 14 centers. Initial treatment consisted of a daily dose of 3 mequanin administered by subcutaneous injection for a minimum of 12 weeks and, if responding and tolerating treatment, until satisfactory response. As December 1986, 68 patients have completed treatment 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 splenic and 41 had splenomegaly. After a median duration of initial treatment of 6 months (range 3-15x) were obtained (18 complete CR), 33 partial PR and 13 minor MR (response rate of 96%). The mean time to response was 32 days for minor response, 121 days for partial response and 235 days for complete response. No statistically significant differences were found in the major response rate (CR + PR) were seen among splenectomized vs. non-splenectomized patients after six (12,166-75% vs. 19249-79% RA; 1013-77% vs. 15/75-94%; 10x10-9 x107% vs. 10x10-57%). In four patients no significant improvement after 12, 13, 3, and 3 months of therapy respectively. Five patients died during the first month of therapy (25%), one with bacterial sepsis (10x10-7), one with a myocardial infarction (10x10-8), and one with a myocardial infarction (10x10-2). One patient died of lung cancer 6 months after beginning therapy and 3 months after having achieved CR. This patient had been allogeneic bone marrow transplantation with elimination of the need for transfusing blood products and reduction of the incidence of infections. This study confirms the usefulness of interferon in HCL and interferon may be recommended as a first line therapy also in patients who normally be treated by splenectomy.
T 93 TREATMENT OF PATIENTS WITH REFRACTORY MYELOMA. K. H. Pflüger, H. Köppler, C. H. Gérard, K. H. Hannmann, Division of Hematology/ Oncology, University Hospital, D-3550 Marburg, West-Germany.

Only few treatment programs have been effective in patients with multiple myeloma resistant to alkylating agents, cross-resistant 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, prednisone, etoposide); 3rd VAP (dactinomycin with vincristine and doxorubicin) by continuous infusion. Several patients received successively more than one of these regimens. Treatment with VAD revealed good responses in 11 out of these 21 patients. Median remission duration was found to be 11 months. The probability of survival according to Kaplan-Meier after 1 or 2 months of VAD therapy is 80%. 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 modification. Infections and chemotherapy-induced flushing syndrome and neutropenia were the most important side effects. Six patients out of 21 died of 5, 8, 13, 14, 21 and 26 months after onset of VAD therapy. Three patients with resistant multiple myeloma, 1 from sepsicaemia, and 2 from acute leukaemia. The response rates for etoposide and VCPVP were significantly lower. Nevertheless, two VAD non-responders showed remissions with VP-mono and VCPVP, respectively suggesting that VP16-monotherapy or VCPVP may be 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 PHOTOTHERMOPHORESIS.

S. Göck, B. Megisch, J. B. Rosshopf, G. Flewig, W. Schneider. Dept. of Internal Medicine/ Hematology and Venerology, Medical University, FRG.

As several studies show the progress of chronic lymphocytic leukaemia of B-cell type (B-CLL) stage II-III according to Rai can not be influenced by ordinary leukaemia chemotherapy. 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 UV activated 8-methoxypsoralen (8-MOP) which leads to irreversible bridging of the pyrimidine bases of mitotic cells.

2 hours before inserting a venous catheter, 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 were suspended in 300 ml of patient's plasma and thereafter extracorporeally exposed to UVA light with a total dose of exposure 200 J/cm².

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 white blood cell count, which was well tolerated by the patients, and no side effects were observed.

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

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

T 95 MITOXANTHROINE IN PATIENTS WITH NORMALLY DIAGNOSED LOW-GRADIENT NON-HODGKIN LYMPHOMA, HIGH ACTIVITY OF A DAILY SCHEM. S.W. Hennemann, N. Niessen, The Finsen Institute, Rigshospitalet, Copenhagen, Denmark.

Ivamycin consecutively previously untreated patients with low-grade non-Hodgkin lymphomas were treated with Mitoxanthrone 5 mg/kg/day for 3 days 3 weeks. A cumulative dose of 165 mg/m² was not exceeded. According to the International Working Formulation 7 patients had small lymphocytic lymphomas, 10 patients had follicular 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 (6-12 months). Non-hematological 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 10³/ml (range 0,7-3,4 x 10³/ml). Platelet counts below 100 x 10³/ml 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. J. Redman, F. Cabanillas, F. H. Peimer, M. P. McGufflin, W. Velasquez, F. Swam, W. Plunkett, C. Keating, M. B. Anderson Hospital and Tumor Institute, Houston, Texas, U.S.A.

Fludarabine phosphate [2'-deoxy-2-fluoro-2',3'-dideoxyadenosine 5'-phosphate or 2'-fluoro-ara-AMP] is a new 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 (2 weeks) to determine effecitiveness in a group of patients with lymphoma with a median age of 56 years (range 21 to 77). 20% were males. 36 patients had received prior chemotheraphy, 91% had previously received 2 or more drugs. 63% had received ≥3 combination chemotherapy regimens. Half the patients had received prior radiation therapy. Response rates were 67% for follicular small cleaved cell lymphoma (FCCL), 75% for follicular mixed lymphoma (FLL) (N=4), 100% for follicular large cell lymphoma (FLCL) (N=1), 50% for transformed lymphoma (N=1), 33% for small lymphocytic lymphoma (SLL) (N=1), 7% for chronic lymphocytic leukemia (CLL) (N=7), 67% for mycosis fungoides (N=3), 25% for Hodgkin's disease (N=1) and 15% for unclassified lymphomas (N=1). All responses were complete. 8 patients had follicular small cleaved lymphoma partial except for 2 patients with follicular small cleaved lymphoma who had complete responses. For responding patients the median time to response was 2 months and median duration of response was five months (1 to 12 months). 40% of patients had of complete responses. In contrast to higher doses of Fludarabine used in acute leukemia, no central nervous system toxicity was seen at this dose level. We conclude that Fludarabin is an active new agent in low-grade lymphomas (FCCL, SLL and mycosis fungoides with an overall response rate of 67% and deserves further investigation in these diseases.
ABSTRACTS - Third International Conference on Malignant Lymphoma, Lugano

T 97 PHASE III STUDY OF EPIRubicin, VINcristine and Pred尼松 (EPiV) vs CYCLOphosphamide, VINcristine and Pred尼松 (CP) in PREFERABLE NON-HODGKIN'S LYMPHOMA. D. C. Cane, Jr., F. B. Oldham, J. Luce, Maine Medical Center, Portland, Maine 04102, Ohio State University and Adria Laboratories, Columbus, Ohio 43212.

To study the potential efficacy and toxicity of a new anthraccline 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/m² IV or cyclophosphamide 800 mg/m² IV daily 1, along with vincristine 1 mg/m² IV day 1 and prednisone 100 mg PO x 5 days, every 21 days for 12 cycles. To date, 73 pts have been entered with median age of 61 yrs (range 28-86) and med. FS 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% (ECP) and 85% (CP), with most of the responses PR at this analysis. Med. nadir Hb (granulocyte) for the EDP is 3,000/mm³ (800) and 4,300/mm³ (2,100) for CP. nausea/vomiting was infrequent: 18% (ECP) and 11% (CP). Alopecia was almost universal for EDP but only seen in 35% for CP. Med. change in ejection fraction (EF) for pts receiving EDP was 0.5% (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 0.19 after 3 doses of EDP; and two pts because of development of clinical COP. Interim results suggest that EDP produces comparable results to COP in low-grade, non-Hodgkin's lymphoma. Duration of response and differential toxicity will be monitored.


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 deoxy Ara-C in patients with CLL and small lymphocytic lymphoma (SLL). Patients received 3 grams/m² 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 40-72). 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], abdomen) and pelvic disease [PD]. The following table shows the response rate as the percentage of evaluable patients in each category:

<table>
<thead>
<tr>
<th></th>
<th>PB</th>
<th>BM</th>
<th>PD</th>
<th>All Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>3/19 (16)</td>
<td>4/18 (29)</td>
<td>6/17 (35)</td>
<td>0/13 (0)</td>
</tr>
<tr>
<td>PR</td>
<td>5/19 (26)</td>
<td>2/14 (14)</td>
<td>4/17 (24)</td>
<td>4/13 (31)</td>
</tr>
<tr>
<td>TR</td>
<td>8/19 (42)</td>
<td>6/14 (43)</td>
<td>10/17 (59)</td>
<td>4/13 (31)</td>
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</table>

The median duration of the complete responses was 11 months (range 5-16) and of the partial responses was 8 months (range 2-10). Of 7 patients analyzed, only 2 maintained the total white count (WBC) prior to treatment, and the remaining were not evaluable for response. Of six relapses with WBC of < 50,000, only 2 responded (p = 0.05). Of the nine patients who achieved a high dose decaconon response, 5 of 7 maintained the total white count (WBC) prior to treatment, and the remaining were not evaluable for 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 pseudomembranous 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 decaconon may contribute to the efficacy of ARA-C.

T 99 NOVANTRONE IN COMBINATION WITH STEReCYT (NOSIT) IN LOW-CRAGe NON-HODGKIN'S LYMPHOMA (LSNH). K. Landsv, L. B. Roert, Departments of Oncology and Pathology, Sahlgren's Hospital, S-413 45 Gothenburg, Sweden.

Novantrone (mitoxantrone, dihydroxanthracenedione) and StereCyT (predninostine, a chlorambucil analog of prednisolone) has shown therapeutic activity in non-Hodgkin's lymphoma. In order to evaluate the efficacy and toxicity of NOStE, 22 patients with LSNH, 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 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/m² IV in 100 ml of 0.9 mg/ml NaCl solution for 30 min on days 1 and 2 and StereCyT 100 mg/m² 120 mg/m² - 150 mg/m² 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 occurred in 6 previously treated patients (27%). 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 last analysis on December 1st, 1986. No serious side-effects were noted.

The data indicate that NOStE is effective in LSNH. 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. K. Wilson, A. Bell, O. Bergsagel, L. Brandes, P. Kim, D. White, W. Shelley and A. Willan for the Clinical Trials Group of the National Cancer Institute of Canada, University of British Columbia, VIBA 118, Canada.

Cyclophosphamide has been given in 2 schedules to 97 myeloma patients in 3 National Cancer Institute of Canada studies. Oral cyclophosphamide 325 mg/m² and prednisone 100 mg po on 4 consecutive days every 4 weeks produced 3 responses in 15 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/m² once per week with alternate day oral prednisone 100 mg produced 5 responses in 28 primary resistant patients and 10 responses in 28 secondary resistant patients. While the escalating 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 neuropenic 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.
T101  

The present study was carried out to investigate the clinico-pathological features of non-hodgkin's disease in patients with favourable histological subtypes. Over the period from July 1974 to June 1986, 142 consecutive cases were diagnosed (80 males, 62 females; median age 56). The Reappraisal histological subgroups were: LNH+D = 48%, LPN/n-D = 48%; LhI = 3.8%; 108 patients (76.6%) 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 (9.6%) had documented B-symptoms. Polychemotherapy combinations with doxorubicin were used in 73.2% (n=61) of patients aged 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 and II = 79.4% (27/34); Stage III or IV = 51.2% (21/41); age less than 60 yrs = 68% (51/77); age over 60 yrs = 40% (27/66); LPN/n-D = 46.9% (31/66); LhI = 40% (4/25). The achievement of CR was strongly influenced by the number of involved lymphohdal sites: in fact, CR was observed in 88.9% 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- and 10-yr survival was 90% and 80%, respectively (median survival over 10 yrs) while these two percentages were 58% and 10% 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).

T102  

Primary lymphoma (PGL) is the most frequent non epithelial gastric malignant neoplasia. We observed 13 cases of non-Hodgkin PGL between 1979 and 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 confirmed by histological examination and by laparoscopy (3 cases), gastric ulcer (2 cases), atrophic chronic gastritis (2 cases), enterovesical fistula (1 case). 1 patient died of myocardial necrosis after surgery. 1 patient died from myocardial necrosis after one month after surgery.

Results: to date 10 patients are evaluable for recurrence and survival evaluation. Stage Ia (4 cases) and stage IIa (3 patients) (stage IIa) received 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 Ia and 3/4 stage IIa). 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 to make any conclusive remarks on the relationship between histology and prognosis. The role of adjuvant chemotherapy as primary treatment strategy for stage Ia needs more extensive studies. After chemotherapy seems to prevent recurrences in this disease in stage IIa. Despite of the treatment, PGL survival remains higher than gastric adenocarcinoma.

T103  
MANAGEMENT OF PRIMARY LYMPHOMAS OF THE CENTRAL NERVOUS SYSTEM. P.G. Shekar Giri, B.G. Evans, Department of Radiation Oncology, University of Kansas Medical Center, Kansas City, Kansas 66103

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 tumors could be classified into the following groups: neurocytoma, meningioma, and primary glioblastoma (11 cases). The remaining 6 cases were primary diffuse lymphomas with involvement of the spinal cord. The median survival for all patients was 3 months. Of the 17 patients, 12 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 tumor followed by radiation therapy had the best median survival (17.5 months). Recommendations will be made regarding management of these tumors.

T104  
SURGERY AND CHEMOTHERAPY IN GASTRIC NON-HODGKIN LYMPHOMA. F. Rossi, E. Priotto, E. Ponziani, G. M. Conforte, Cattedra di Patologia Medica e Sezione di Ematologia, Università di Milano. Nuovo Ospedale S. Gerardo, Monza (ITALY)

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. The ages ranged from 23 to 74 years (median age of 40). 10 pts. (32.3%) presented with stage II 9 (29%) with stage II and 12 (38.7%) 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 (9.8%). 2 pts. were unclassified. 28 of these pts. have completed induction therapy (median follow-up 21.6 months) 14/16 pts. with stage I-II and I-II underwent partial or total resection; after surgery all pts. received chemotherapy, using the CHOP (5 pts.) or the CVP (5 pts.) regimen. 11 pts. (78.6%) achieved complete remission (7 pts. with stage I-II and 4 pts. with stage I-IE) (7 pts. with stage I-II and 4 pts. with stage I-IE) the all are in continuous first complete remission with a median follow-up of 28.6 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) achieved 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 PROMACI), achieving 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 had only partial resection of tumor, died after 19 months. 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 cirrhosis), without evidence of lymphoma at autopsy.