ABSTRACTS

POSTER PRESENTATIONS
ABSTRACTS - International Conference on Malignant Lymphoma, Lugano

P1

ENGLISH-LYMPHOMA ASSOCIATION OUTSIDE ENDEMIC AREAS: RESULTS OF A PILOT STUDY CARRIED OUT IN FRANCE

C. Lemort1 and T. Philip2
1. International Agency for Research on Cancer, 150, cours Albert Thomas, 69372 Lyon cedex 02, France
2. Centre Léon Bérard, Lyon, France

Burkitt's lymphoma (BL) is the most frequent childhood cancer in equatorial Africa, where high incidence rates are found to be associated with Epstein-Barr virus (EBV), as proven by the presence of viral markers within the tumour cells.

Outside endemic African regions, lymphomas having similar histopathological features, clinical presentation, and cytogenetic markers are reported on a sporadic basis. In these cases, the association with EBV is, however, considered as exceptional. In fact, this conclusion may be premature because of the limited number of studies having been ethically invasively investigated in EBV positive cases in these areas (see: Philip et al., this Conference).

In an attempt to evaluate more precisely the frequency of the EBV association outside endemic areas, a pilot study was implemented in France. The detection of 15 EBV-associated BL within the first year of study, seems the first indication that the association cannot be considered as exceptional and that EBV-associated cases are not found in children but also in adults.

An extensive study conducted on most pediatric cases in a given endemic area (Lyon, France), where both Caucasians and North American lymphomas are treated, indicates that: between 10 and 20% of BL occurring in Caucasian children are EBV-associated, whereas all the cases originating from North America (43 cases) were found to be associated with EBV. Cytogenetic studies performed on 12 cases indicated that the three types of translocation observed (either t(8,14), t(2,8), or t(8,12)), all showed rearrangements of chromosome 8, were independent of the association with EBV.

The comparative analysis of EBV-associated versus EBV-free BL which will be carried out in non-endemic areas, but which is not feasible in endemic areas, will help in evaluating the role of EBV in the aetiology of this type of tumour and may lead to new preventive and therapeutic measures.

P2

CELL SURFACE ANTIGENS AS DETECTED BY MONOCLONAL ANTIBODIES ON A HODGKIN'S-DISEASE-DERIVED CELL LINE, L 428Ks

A. Ziegler, V. Diehl*, B. Uchta-Les-Ziegler, H. H. Kirchner, H. Burrichter* and R. Burrichter*
*Immunology Laboratory, Medical University Clinic, D-7400 Tübingen, FRG
**Medizinische Hochschule Hannover, Abt. Hämatologie/Onkologie, Klinik V, 3000 Hannover, FRG

The nature of the tumour cell in Hodgkin's disease has remained controversial, but the recent availability of cell lines derived from patients with Hodgkin's lymphoma (Schaart et al., Int. J. Cancer 28: 239-247, 1982) has opened new perspectives for the investigation of these cells. The reactivity of one of these cell lines, L 428Ks (a subclonal of L 428), with over 50 monoclonal antibodies directed against various human lymphoid and non-lymphoid cell types was determined by using radio-binding assays and indirect immunofluorescence tests. The results indicate that only a small number of monoclonal antibodies react with Hodgkin's disease cells. Antigens thought to be specific for mature or immature T cells like e.g. T33, T40 and NAI/34HLK4 as well as OKT3 and OKT8 are unreactive, whereas a number of antibodies directed against B cells like OKT11, OKT8 and OKT14 in L 428Ks cells are unrelated to B cells as well, because they lack a number of markers characteristic for such cells. The lack of monoclonal antibodies reacting with Hodgkin's disease cells and the diversity in surface antigens of the T0-series e.g. T028 and T040, appear to exclude the possibility that L 428Ks cells are non-T, non-B lymphocytes. L 428Ks cells do not show any number of antigens found on myeloblasts or later differentiation steps of granulopoiesis (detected e.g. by T01/70 or T03). The other hand, several surface antigens (10-24) of this cell line react with T05, T06, T0B and T09 which react with macrophages in several tissues, e.g. lung, and reactivity towards L 428Ks cells. Antigens controlled by the HLA region are expressed very strongly on this cell line, while antigens not expressed in non-lymphoid hematopoietic cells like e.g. T05, T06, T0B and T09 are absent. In contrast, B2-microgobulin, the small protein found in association with HLA heavy chains, can easily be shown on L 428Ks cells and associated with cell lines of B type. In fact, 428Ks cells and cultures treated with certain inducers of differentiation are in progress to cast further light on the tumour cell line. In these the 428Ks cell line is clearly different from all established human lymphoblastic cell lines and analysis of its surface antigens may throw light on the Hodgkin's disease cell type exhibiting characteristics both of early myeloid and monocytic cells.


P3

IN VITRO DRUG SENSITIVITY OF BLAST CELLS FROM ACUTE LEUKEMIA AND MALIGNANT LYMPHOMAS. J. B. Sparkesmaier, E. Wittermayer, R. Paletti
First Medical Clinic, University of Vienna, Vienna, Austria.

To detect resistance of tumor cells to anticancer drugs prior to chemotherapy, variants in vitro test systems have been developed over the past few years. Most of these studies were carried out in solid tumors. Only few attempts, however, have been made to apply these assays to primary leukemias and lymphomas.

The leukemia phase of malignant lymphomas, even though in these diseases in vitro sensitivity testing is facilitated by the presence of more homogenous cell populations. - Using a modification of the short-term incubation method described by Volm et al. (Europ J Cancer 15: 833-840, 1979) we determined in vitro effect of cytocidal drugs on the incorporation of the DNA precursor J-uridine into nucleic acids of the leukemic blast. Since chemotherapy is virtually dependent on the proliferative activity of the tumor cells, we additionally evaluated the rate of cellular J-thymidin uptake as a DNA precursor. The cells were isolated from peripheral blood or bone marrow samples of 40 patients with various forms of leukemia including lymphoblastic J-thymidine uptake as a DNA precursor. The effect of the cytocidal drugs on the J-uridine incorporation into the tumor cells by the tumor cell line was determined by the percent inhibition of the J-uridine uptake measured in cells not subjected to the cytocidal agent. In control studies, we determined the extent to which the inhibition of the J-uridine uptake was dependent on the clinical response of the patient to chemotherapy. Our data indicate that in more than 90% of the patients the percentage of inhibition of the J-uridine uptake, measured by the cytocidal agent could be predicted by the assay. A positive correlation between inhibitory effect in vitro and response to chemotherapy was observed. These results support the conclusion that pretreatment sensitivity testing of leukemic cells is a reliable tool for the prediction of effective chemotherapy in the individual patient.

P4

DRUG TRANSPORT AND CELLULAR SENSITIVITY TO AXYLATING AGENTS IN RABIES AND MALIGNANT B AND T LYMPHOCYTES. J. E. Byfield and Pia Calabrò-Jones, Division of Radiation Oncology, University of California San Francisco, San Francisco, CA 94143 USA.

Lymphoblastic leukemia differs considerably in their sensitivity to cytotoxic chemotherapy. In general, those with a greater rate of proliferation respond better than other CR rate and the more slowly growing tumors. In addition, non-cytotoxic T cell lymphoblastic leukemia generally carry a poorer prognosis than many B cell types. We investigated the role of both chemosensitivity and T/B origin on the chemosensitivity of some human lymphoid cell lines.

The proliferation-dependency of cytotoxicity was determined for mature peripheral human T cells by measuring clonogenicity in soft agar when the cells were exposed to the drug (for 60 minutes) either prior to proliferation (pre-PHA) or following the induction of cell cycle (post-PHA).

It was found that the sensitivity of T cells to killing increases with cycling for some alkylating agents (melphalan, Mel). In contrast, many T cells were resistant to melphalan (Mel) and cis-dichlorodiaminoplatinum (DDP). Mel and HH2 are thought to be taken up by active transport. Thus, resting cells (both normal and lymphomatous) would be relatively spared by such carrier-dependent (CD) agents. The data also strongly suggests that CDPP is taken up by an amino acid transport mechanism, perhaps explaining its nephototoxicity. Remarkably, neither active cyclophosphamide (phosphoramide mustard, PM) nor chlorozotocin appeared to penetrate mature T cells, although PM is active against B cell lymphoma lines. Remaining lacking cyclophosphamide may be more efficacious against T-lymphomas. Thus there appears to exist a histogenesis that, at least in lymphoblastic leukemia, is more highly developed in lymphocytes than in T cells.

Another large group of lipophilic agents including nitrosoureas (BCNU, CCNU, Me-CCNU) and adriamycin (Adr) cause DNA damage. Antitumor drugs (Adr) are activated by cellular enzymes bound to the reaction products. By contrast, chemotherapy agents (cytoxan, Mel, DDP, etc.) cause DNA damage by binding to DNA strands. The problem is to determine the sequence of events involved in these mechanisms.

Histamine is one of the most important mediators of the inflammatory response. Tumor necrosis factor (TNF), a cytokine secreted by activated macrophages, has profound effects on the immune system, including promotion of tumour cell growth and inhibition of apoptosis. TNF has also been shown to induce IL-12 production by macrophages, which may be responsible for the induction of IL-12-dependent cytotoxic T lymphocytes (CTL). These results suggest that TNF may be a potential therapeutic target for the treatment of cancer.

The model predicts that many agents known to be useful based on mammalian studies. High growth fraction lymphomas should be more sensitive to such CD agents, especially on an antitumor normal basis in this disease setting.
P5


Marrow cells from patients with malignant lymphoma have been shown to contain less CFU-C than marrow cells from normal controls. Using the CFU-C assay of Pike and Robinson, the clusters and colonies formation of nucleated bone marrow cells obtained from 25 patients with malignant lymphoma (14 cases) and from 27 normal subjects were compared before (D1) and after a 4 day stay at 4°C (D4). The mean ratio between the CFU-C number at D4 and D1 (D4/D1) for lymphoma patients was 1.54; for normal this ratio was 0.9. This increased CFU-C growth at D4 was due to the proliferation of GM-CFU-C. The possible inhibition activity of PGE2, a known inhibitor of the CFU-C growth, was ruled out by adding Indomethacin at 10⁻⁴ M to the lymphoma marrow cells: the mean ratio of growth in presence of Indomethacin over the one observed without was 1.25. The normal and lymphoma blood lymphocytes inhibitory activity with normal CFU-C growth were compared: the lymphoma blood lymphocytes did not inhibit the normal CFU-C growth in a greater fashion than did normal lymphocytes. Normal or lymphoma sera were also added to normal CFU-C to evaluate their possible inhibitory effect; there was no significant change of the CFU-C growth in presence of normal or lymphoma sera.

These results suggest an increased rate of proliferation for the decreased CFU-C in the marrow of patients with malignant lymphoma. At the present time, other inhibitory compounds as for example interferon were investigated.


P6

SPONTANEOUS ['3H]--THYMIDINE UPTAKE IN HISTOLOGICAL SUBGROUPS OF HUMAN B-CELL LYMPHOMAS


Spontaneous ['3H]--thymidine incorporation was studied in cell suspensions from 64 patients with monoclonal B-cell neoplasia. Among various incubation periods a 20-hour assay with ['3H]--thymidine had the greatest discriminatory power versus non-neoplastic lymph node cell suspensions. The ['3H]--thymidine uptake correlated positively with cell volume, nuclear volume, and cells in G + M + G phase of the cell cycle. A high degree of heterogeneity with regard to ['3H]--thymidine incorporation was found within several histological groups of the Kiel classification, expression of lymphoma cells of centroblastic/centrocytic origin and in the lymphoplasmacytoid groups. In highly malignant lymphomas ['3H]--thymidine uptake was statistically significantly higher than in lymphomas of low-grade malignancy.

Patients with localized disease (stages I and II) and those with 'HN symptoms showed increased incorporation of radioactive thymidine as compared to patients with disseminated disease (stage IV). Data suggest that there exists correlation between prognosis as determined by histopathology and spontaneous uptake of ['3H]--thymidine.

P7

MARKER ENZYMES PROFILES IN PLASMA MEMBRANE OF CELLS ISOLATED FROM MALIGNANT LYMPHOMAS. G. Losa, P. Lucchetti, G. Messeroni, and E. Pedrini, Laboratory of Cellular Pathology, Tiesco Institute of Pathology, Ch-6604 Locarno.

The activity profiles of several enzymes bound to the plasma membrane were determined in cells isolated from lymph node cells of patients with malignant lymphomas. Most of the cases were histologically classified as non-Hodgkin lymphomas. Cells were collected in RPMI-1640 medium after two washes with a cold Hanks' balanced salt solution, washed twice in a saline solution and checked for viability by trypan blue exclusion. The composition of the populations assessed was tested by cell-cell agglutination in the presence of fluorescein-labeled monoclonals using fluorescent anti-Ig polyclonal or anti single chain F(ab)2, antisera, of surface T antigens with fluorescein monoclonal antidodies and for non specific enzyme with alkaline phosphatase.

Activity levels of enzymes involved in purine metabolism, as 5'-nucleotidase ([5'-N]ase) and nucleotide phosphodiesterase ([NDPase]), in cell transport as deoxynucleoside triphosphate ([dNTPase]) and alkaline phosphomonoesterase ([PMase]), in aminoacid transport as glutamyltranspeptidase ([GluTP]) were assessed at saturating concentration of the substrate. Cells of the Hodgkin lymphoma were characterized by a high level of 5'-NDPase (> 90 nmol/hr/10⁶ cells) and GluTP (> 32 nmol). In non-Hodgkin lymphomas with a low proportion of lymphocytes, the cells of both B and T origin, generally examined enzymatic activities were recorded with the exception either of the [dNTPase] (> 346 nmol/hr/10⁶ cells) only slightly inhibited by ouabain- or of the [PMase] (> 60 nmol). In cases with an normal controls (1). Using the [dNTPase] assay of Pike and Robinson, the clusters and colonies formation of nucleated bone marrow cells obtained from 25 patients with malignant lymphoma (14 cases) and from 27 normal subjects were compared before (D1) and after a 4 day stay at 4°C (D4). The mean ratio between the CFU-C number at D4 and D1 (D4/D1) for lymphoma patients was 1.54; for normal this ratio was 0.9. This increased CFU-C growth at D4 was due to the proliferation of GM-CFU-C. The possible inhibition activity of PGE2, a known inhibitor of the CFU-C growth, was ruled out by adding Indomethacin at 10⁻⁴ M to the lymphoma marrow cells: the mean ratio of growth in presence of Indomethacin over the one observed without was 1.25. The normal and lymphoma blood lymphocytes inhibitory activity with normal CFU-C growth were compared: the lymphoma blood lymphocytes did not inhibit the normal CFU-C growth in a greater fashion than did normal lymphocytes. Normal or lymphoma sera were also added to normal CFU-C to evaluate their possible inhibitory effect; there was no significant change of the CFU-C growth in presence of normal or lymphoma sera.

These results suggest an increased rate of proliferation for the decreased CFU-C in the marrow of patients with malignant lymphoma. At the present time, other inhibitory compounds as for example interferon were investigated.


P8

HODGKIN'S DISEASE AND B-IMMUNOBLASTIC SARCOMA OR HODGKIN'S DISEASE EVOLVING INTO B-IMMUNOBLASTIC SARCOMA?


Sequential occurrence of Hodgkin's disease and B-immunoblastic sarcoma (B-IBS) has been occasionally reported but a possible relationship between these two entities remains to be clarified. This sequence was documented in a 17 years old male who initially presented with pathologic stage IIIb Hodgkin's disease. The patient had radiologically enlarged mediastinum and pathologically demonstrated cervical lymph node and splenic invasion of the nodular sclerosis subtype. A clinically complete remission was achieved for 12 months from initiation of therapy with 6 cycles of MOPP and sandwich mantle field radiotherapy. The patient massively relapsed in the mediastinum up to the retrosternal region but a biopsy revealed the presence of B-IBS only. A second remission could be obtained for nine months with ABVD. The patient subsequently developed a right lower lung mass which was found histologically to be nodular sclerosis Hodgkin's disease. He died rapidly thereafter and postmortem examination confirmed the simultaneous presence of two pathologically distinct lymphomatous infiltrates in both lungs and in the mediastinum. The picture of Hodgkin's disease was quite typical with numerous malignant mononuclear "reticular" cells. The other infiltrate was homogeneously formed of plasmacytoid cells. We also observed immunoblastic proliferation at the periphery of a number of Hodgkin's nodules in the lungs and in the mediastinal masses. Infiltretes were not clearly separated in these areas, suggesting a possible transitional state between the two types of malignant proliferation.

In addition, immunohistochemical studies demonstrated the presence of both light chains in malignant "reticular" cells as well as in malignant immunoblasts. B-IBS has been shown to arise selectively in immunodepressed patients. Accordingly, the development of a second neoplasm in this young patient could be related to the depression of cellular immunity commonly observed in Hodgkin's disease and further aggravated by extensive combined modality treatment. Yet, considering the possible lymphocytic nature of the Sternberg cell, a "sarcosomal" transformation of Hodgkin's disease with B immunoblastic morphology could conceivably result from a derepressed lymphocytic proliferation. Clinical, histological and immunohistochemical observations in our case report support this latter hypothesis.
P9


Functionally dominant RN are characteristic for lymphocytes with a reversible decrease of the nucleolar RNA synthesis. The number of these lymphocytes was studied in patients with HD depending on their clinical state. The results demonstrated that the significant decrease of lymphocytes with functionally dominant RN in number indicates the relapse of the disease. In contrast, the increased number of these cells shows a favorable prognosis and the complete remission. The changes of lymphocytes with functionally dominant RN in the peripheral blood of patients with HD precede several weeks the changes in their clinical state. The number of these lymphocytes is less influenced by the therapy but reacts with infectious complications.

number of persons/examinations absolute number of lymphocytes with functionally dominant RN in AB

<table>
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<tr>
<th>Health controls</th>
<th>HD - untreated</th>
<th>HD - complete regression</th>
<th>HD - relapse</th>
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<td>18/21</td>
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Differences between presented mean numbers are statistically significant (p < 0.05). Kinetics of the number of lymphocytes with dominant RN in the individual cases clearly demonstrate the clinical usefulness of lymphocyte nuclear test.

P10

ANGIO-IMMUNOBLASTIC LYMPHADENOPATHY: A MALIGNANT LYMPHOMA DUE TO NUCLEAR DNA CONTENT. H. H. Commen and A. Böcking, Department of Medicine and Department of Pathology, University of Freiburg, Freiburg.

There is considerable controversy as to whether angioimmunoblastic lymphadenopathy is a benign, pre-malignant, or malignant disease. Lymph node lymphocytes from previously untreated patients were studied. Imprints were made either from freshly cut lymph node sections immediately after surgical removal or from formalin-fixed lymph node biopsies. Feulgen microspectrophotometry was performed with a Leitz laser microspectrophotometer (VM-86) on individual cells. DNA-Histomorphometry and malignancy grading revealed the following results: 1.) Within the mixed cell population and normal lymph node biopsies all lymphocytes had a marked variability of nuclear DNA content and usually with a triploid or hyperdiploid stem line. 2.) Applying two formulas previously introduced for the DNA-malignancy grading of prostatic carcinoma (Böcking, A. & Sommerm, B., K. Kong. Deutsche Ges. Urol., 10, 179, 1980), all evaluable to exist in different grades of malignancy. Two patients had grade II and 3 patients had grade III. 3.) Clinical courses correlate with the degree of aneuploidy, i.e., DNA-malignancy grading. Patients with grade I had the longest and grade III had the shortest survival times. These results support our earlier contentions that ALL is in most cases a malignant lymphoma (Sandström, W. and Grim, H., Zeitschr. Path., 160, 101, 1997; Commen, H., Brit. J. Haematol., 86, 484-497, 1990).

P11

USE OF FINE NEEDLE ASPIRATION IN A LYMPHOMA CLINIC. A.R. Pontefex, M.D. & P. Klino, M.D. Cancer Control Agency of British Columbia, Vancouver, B.C., Canada.

Fine needle aspiration was utilized as a diagnostic aid in 19% patients in a central lymphoma clinic serving a large geographic area. The majority of the aspirates were taken from peripheral lymph nodes. However, subcutaneous, pelvic and abdominal masses and various organs were also sampled. Prior to this application to patients all the nodes removed for diagnostic purposes at a large teaching hospital had been aspirated following excision and comparisons made with the histologic sections.

Aspiration cytology was utilized as the sole morphologic diagnostic technique in the original diagnosis of lymphoma only when open biopsy was contraindicated for medical reasons or was otherwise impossible.

Aspiration cytology was utilized in the continuing care of patients with lymphoma in the following circumstances:
1. To confirm that a mass at another site or another time was still the patient's original disease.
2. To determine whether the patient's original lymphoma had evolved to a more aggressive histologic type.
3. As an aid in the patient with two separate malignancies.
4. As an aid in difficult diagnostic problems whether intrinsic to the disease or because of inadequate tissue sampling at the original surgery.
5. To furnish material for specialized diagnostic techniques.

The majority of recurrences of Hodgkin's disease could be confirmed with confidence as Reed-Sternberg cells were readily identified in aspirated specimens. Non-Hodgkin's lymphomas were assigned to three cytologic grades. The high grade, poorly differentiated tumours could be diagnosed with confidence. The better differentiated lesions could in most cases be distinguished from reactive states. Aspiration cytology was extremely useful in distinguishing anaplastic small cell carcinoma from lymphoma and also in the diagnosis of unexpected bacterial infections in lymphoma patients.

The advantages of the technique are speed, economy and minimal patient risk or discomfort. The disadvantage is the incomplete information which is particularly a clinical misleading. This latter can be avoided or minimized in a clinical situation where the pathologists and clinicians cooperate as a closely functioning team.

P12

ON THE NATURE OF BONE MARROW INVOLVEMENT IN AGGRESSIVE NON-HODGKIN'S LYMPHOMA. P. Klino, M.D., Pontefex, C.C.A.B.C., Vancouver, B.C., V5T 1J1.

Involvement of the bone marrow with non-Hodgkin's Lymphoma has been regarded as an indication that patients are consideread to have a poor prognosis, and as a result they tend to be treated aggressively. Yet the rates of complete remission have been disappointing and patients are still suffering from this disease, and will eventually succumb to their lymphoma. In contrast to the prevailing views on the significance of the bone marrow involvement, we have developed a hypothesis which, if confirmed, may substantially change the views on the nature of this phenomenon. In this, in turn, may alter our view on therapeutic approaches, as well as the prognosis. It may also help to elucidate some aspects of the pathogenesis of lymphomas.

We have repeatedly observed an apparent morphological discrepancy between the lymphomas infiltrating the bone marrow, and the lymphomas present in the extra medullary tissues, usually biopsied lymph nodes. We have also noted a significant difference in sensitivity of these two sub populations of cells to various therapeutic modalities. Lastly, we have taken notice of a distinctive group of patients, who, if treated to complete remission in the extramedullary sites, showed an unexpected long survival, even on no therapy, despite continued bone marrow involvement.

A retrospective analysis of 100 cases of non-Hodgkins' Lymphoma with biopsy confirmed bone marrow involvement, seems to have corroborated the following points in our hypothesis:

a) In the majority of patients with poorly differentiated non-Hodgkin's Lymphoma with bone marrow involvement, the marrow infiltrates are composed predominantly of well differentiated lymphoma cells. Therapy is in sharp contrast with the composition of extramedullary sites where immature lymphoma cells predominate.

b) The compartment of well differentiated lymphoma cells may be reduced by aggressive therapy but it cannot be eradicated, which means that the patients are treatable but not curable.

c) Persistence of well differentiated cells in the marrow in otherwise asymptomatic patients does not necessitate continuation of aggressive induction therapy. It may not require, at least.

d) The contingent of poorly differentiated lymphoma cells must be treated aggressively to ensure prolongation of survival.
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P13

THE VALUE OF SERUM COPPER LEVELS (SCL) IN NON-HODGKIN'S LYMPHOMA. Yoram Cohen,1,2 Nissim Haim,1 Ron Apelbaum,1 and Oren Zinder2, the Department of Oncology1 and Clinical Biochemistry2, Rambam Medical Center, Haifa, Israel; and the Department of Radiation Oncology3, Rhode Island Hospital, Providence, Rhode Island, U.S.A.

Copper is a specific indicator of disease activity in various malignant and nonmalignant conditions. Since about 20 years, SCL has been used in many centers for the initial evaluation and the follow-up staging of patients with Non-Hodgkin's Disease. However, its value in Non-Hodgkin's Lymphoma (NHL), as well as in various solid cancers, has not yet been established. SCL was studied in 115 patients with NHL using an atomic absorption technique. All patients were classified according to Rappaport's Classification, and were clinically staged. The patients were subdivided as follows: 55 initially untreated patients, Stages I-IV, 16 patients with active disease (AD) under treatment, and 44 patients were in a complete remission with no evidence of disease (NED) activity at the time of the SCL determination. The mean SCL (µg/100 ml) of all NHL patients (N=115) was 150±5.4. This was significantly (p<0.0001) higher than 120±4±3.0 of the healthy controls (N=57). The SCL for the different subgroups: Stage I, II, III, IV, AD, and NED were respectively (N=16) 131±6±4.6, (N=14) 177±65±7, (N=12) 180±94±0, (N=13) 157±74±9, (N=16) 167±3±0.5, and (N=44) 132±83±7. There was no significant difference between mean SCL of Stage I patients and other healthy controls or NED. But, NED patients had significantly higher SCL than the control (p<0.04) and significantly lower mean level than the combined mean values of Stages I-IV or AD (p<0.0001). There were 62 males and 53 females. The mean SCL values were 138±4±3±6 and 164±1±4±9, respectively. This difference was significant at p<0.02. Of 71 untreated patients, there were 26 SLPD, 21 DH, and 10 NLPD patients. The SCL values are respectively 166±75±5.6, 154±94±2.5, and 185±84±3. The difference is not significant. One hundred and sixty-three determinations of SCL were done in patients with NHL. These patients were followed-up for at least six months. Of 46 determinations >160, there were three relapses within six months. Of 117 determinations <160, there were seven relapses. Our study does not show return of SCL to normal values in complete responders nor a difference between histological subtypes in our experience. SCL seems to be useful for patients grouping into Stage I and NED as compared to Stage II, III, IV, but the value of SCL in the early prediction of relapse is as yet doubtful.

P14

SERUM LACTATE DEHYDROGENASE (LDH) AS A PROGNOSTIC INDEX IN NON-HODGKIN'S LYMPHOMAS (NHL). M.V. Fiorentino, L. Salvagno, L. Endrizzi, G. Pappagallo and V. Fosser, Medical Oncology Department, Padua General Hospital, Padua Italy 35100.

Relationships between pretreatment serum LDH levels and therapeutic results in 113 patients (pts) with NHL treated with chemotherapy alone or chemotherapy plus icebergs radiotherapy have been studied. Plasma LDH was measured by the Wako enzymatic method in 43 pts were ewell differentiated lymphocytoides (WDL), 48 poorly differentiated lymphocytoides (PDL), 22 histocytoides (H) type. 27 pts had stage II, 42 stage III and 44 stage IV.

P15


The serum number of the isoferritins, elevated in several concentrations of serum ferritin in the majority of patients with HD independently of storage iron, among the possible causes of ferritinemia, normal ferritin production by the tumour has been suggested. However, the determination of serum ferritin in a number of HD cases has been always performed using assays for basic (liver or spleen) ferritin, while recent studies have indicated that malignant cells synthesizes ferritin phenotypes with more acidic isoelectric points. We raised in mice antibodies against acidic ferritin extracted from HD and cells and used them to develop a radioimmunoassay (RIA) specific for acidic ferritin, which cross-reacted less than 5% with liver ferritin. Based on crystalline liver ferritin and rabbit antibodies another RIA specific for basic ferritin was developed.

Using these two specific RIAs we studied serum ferritin concentrations in patients with HD at presentation, during remission and in relapse. High concentrations of basic ferritin were found only in patients with systemic symptoms and were associated with low serum iron. These findings are compatible with the non-specific changes known to occur in the reticuloendothelial system of all cancer patients. Acidic ferritin was increased in about 95% of all untreated patients and its level was not related either to alterations of iron metabolism or indices of liver damage. Serum acidic ferritin in patients with HD may be derived from the malignant cells and/or lymphocytes. Its determination may provide a tool of potential diagnostic and prognostic importance in the management of HD.

P16


Beta 2 microglobulin forms the light chain of HLA on the surface of all nucleated cells. Changes in serum beta 2 microglobulin levels, which are independent of acute phase protein reactions, have previously been shown to reflect tumour load and/or disease activity in a wide range of lymphoproliferative disorders. This beta 2 microglobulin response may reflect important differences in cell biology, but the contribution of individual cell types is still uncertain. In a multivariate study of 254 patients with non-Hodgkin's lymphomas (NHL), serum beta 2 microglobulin levels were measured at diagnosis, prior to treatment. Levels >3.5mg/l were found in 17 of 67 patients with "good prognosis" histology compared with 44 of 87 patients with "poor prognosis" histology. Within the "poor prognosis" group mean survival was strikingly shorter in patients with initial serum beta 2 microglobulin levels >3.5mg/l than in those with initial levels <1.5mg/l. These findings are compared and contrasted with those seen in related neoplasia: in Hodgkin's disease, the levels of beta 2 microglobulin are raised less frequently and do not appear to have a direct relationship to prognosis. In chronic lymphocytic leukaemia the beta 2 microglobulin levels correlate with tumour mass as assessed clinically by staging but give no indication as to prognosis over 2 years, whilst in myeloma there is a strong correlation between serum beta 2 microglobulin, tumour load and prognosis. beta 2 microglobulin may be a useful marker in the stratification of patients with NHL and thereby aid therapeutic decision-making and clinical trial.
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P17
SERUM X-ACID-GLYCOPROTEIN, HAPTOGLOBIN AND C3 IN HODGKIN'S DISEASE, A COMPARISON WITH OTHER ACUTE PHASE INDICATORS. P.G. Gabbi, G. Merlini, G. Attardo Parmigiano, P. Cavalli, E. Ascari. Istituto di Patologia Medica I, University of Pavia, Pavia 27100, Italy.
Serum x-acid-glycoprotein (xMG), haptoglobin (Hp) and complement fraction 3 (C3) were measured in 83 consecutive patients with Hodgkin's disease by means of single radial immunodiffusion. 77 measurements concerned patients with active untreated disease, while 30 were made on patients in complete remission. Only xMG and Hp (this evaluated as deviation of each phenotype from its normal mean) showed much higher levels in untreated disease than in remission, whereas C3 had very similar values in both clinical conditions. Sex, histology, stage and general symptoms did not appear to influence the serum values of Hp and C3 in untreated patients; on the contrary, the advanced stages (III and IV) and less significantly the more severe histotypes (MC and LD) are statistically correlated to higher levels of xMG.

P18
THE CLINICAL USEFULNESS OF ACUTE PHASE PROTEIN FACTORS IN THE COMBINED CYTOSTATIC TREATMENT OF PATIENTS WITH MALIGNANT LYMPHOMA
I. TOTH, M. Osvath, S. Eckhardt
National Institute of Oncology, Budapest, Hungary.
Our aim was to study the changes of two acute phase protein factors: haptoglobin (Hp) and complement fraction 3 (C3) in patients with Hodgkin and non-Hodgkin lymphoma in order to evaluate their usefulness as prognostic indicators of the therapeutic results.
Fifty patients with Hodgkin's disease and 45 with non-Hodgkin lymphoma were studied. Patients were treated with polychemotherapy using COPP or ABVD combination in Hodgkin disease and CHOP or COPP-R in non-Hodgkin lymphoma. Examined parameters were determined before each cycle of cytostatic treatment and following it at the time of control examinations.
A rapid and early fall of serum Hp and especially of C3 already after the initial cycle of treatment with COPP and ABVD was followed in every case by complete remission in stage III and IV Hodgkin lymphomas. Only a decrease in Hp levels frequently not reaching the norm range was observed in partial remissions. Interestingly, in stage II partial remission was not accompanied by a decrease of Hp and C3 levels. The increase of Hp was a reliable indicator of therapeutic failure.
It is concluded, that simultaneous examination of the above parameters in Hodgkin's disease is a valuable help in the prediction of the effect of chemotherapy.

P19
111 children from 16 institutions with all varieties of NHL entered the BFM study 1976/80. In addition to local chemotherapy and radiation the slight acute phase induction and continuation therapy as used by the BFM-study group for acute lymphoblastic leukemia (Henze et al. Klin. Pädiat. 193 (1981)). In the risk group (widely spread abdominal and or CNS disease) more chemotherapy (therapy B2) than in the standard group (therapy A) was given. Several subgroup were defined based on clinical staging (MOLLER), histology (KILO-classification) and/or immunological typing. Sufficient information in NHL of O-, T- or B-cell origin was obtained in 95/111 patients. Probability of continuous complete remission (p-CRR after 3 to 5 years was calculated by life table analysis, including non-responders and deaths from various reasons after initiation of therapy.

P20
EVALUATION OF PROGNOSTIC FACTORS IN NON-HODGKIN'S LYMPHOMA: AN APPLICATION OF THE "MULTIPLE CORRESPONDENCE ANALYSIS" TECHNIQUE.
M. Van Glabbeke, M. Buyse, P. Carde, M. Burgers, E. Somers, M. Qa M. Bayat; E.O.R.T.C. Data Center, Brussels, Belgium; Statistiques, Institut d'Éducation Physique et de Kinésithérapie, Université Libre de Bruxelles; E.O.R.T.C. Radio-chemotherapy Coop erative Group.
As the prognostic of patients with non Hodgkin's lymphoma is influenced by several factors, correlated between them in a complex way and requiring large samples of patients. The "multiple correspondence analysis" allows to visualise these factors, their correlations and their prognostic value for survival and response to therapy.
"Factorial axes" are first calculated, taking the pattern of correlation between all factors into account: "factorial axes" can be taken two by two to constitute a successive "factorial planes". All levels of all prognostic factors can be projected on these "factorial planes" and response and survival categories superimposed. All correlations can be estimated from the distances in the "factorial axes" system and visualised on the factorial plans.
This method has been applied to a sample of 162 patients with primary stage III or IV non Hodgkin's lymphomas, entered in the study E20751 of the EORTC radio-chemotherapy cooperative group, between 1975 and 1980.
Induction and maintenance therapy were allocated by randomization between two standardised treatments. Potential prognostic factors taken into account are pathology (cell pattern, Rappaport, Kiel and Luke's classification), presentation the disease (involved sites and Ann Arbor stage) age, sex and treatments.
The successive computed factorial axes correspond to "cell pattern" (Kiel's classification being the best one), "liver, bone marrow, mediastinal and hilar nodes involvement" and "other nodes involvement". Short term survival is correlated with initial cell pattern; overall survival is correlated with cell type. Response is correlated with liver, spleen, bone marrow, mediastinal and hilar nodes involvement. Response is slightly correlated with cell pattern and cell type, the best responses being observed in the worst histologies.
All these conclusions have been further investigated by classical statistical methods.
ABSTRACTS - International Conference on Malignant Lymphoma, Lugano

P21
SURVIVAL AND REMISSION DURATION CHARACTERISTICS OF ADVANCED STAGE LYMPHOMAS. Maurice Barcos, Richard Herrmann, Leon Stutzman, German Gomez, and Edward S. Henderson. Roswell Park Memorial Institute, Buffalo, N.Y. 14263.

In a group of 227 cases of non-Hodgkin's lymphomas admitted without previous therapy from 1971 to 1975, there were 152 cases with advanced (Stage III and IV) disease. These included 41 cases with follicular cleaved cell lymphomas, 14 cases with follicular mixed cleaved and non-cleaved cell lymphomas, and 40 cases with diffuse large non-cleaved cell lymphomas. Their corresponding rates of complete remission (CR) were 76%, 79%, and 45%, respectively. Although the corresponding overall median survivals for the three groups of patients were 64 months, not reached (NR), and 9 months, respectively, the corresponding median survivals of those who achieved CR were 70 months, NR and NR, respectively. Among the latter, the corresponding median durations of CR were 34 months, 11 months and 11 months, respectively. The results confirm the importance of achieving CR in patients with advanced stage lymphomas of both favorable and unfavorable histologic subtypes.

P22
RISK OF LEUKEMIA IN PATIENTS TREATED FOR HODGKIN DISEASE.
D'Alonzo, P.M., Barr, P., Castelli, L., Pauker, S., Fefer, A., and Caselgren, Divisione di Ematologia Policlinico & Matteo Pavie.

We reviewed 281 consecutive adult patients with Hodgkin disease treated at Division of Hematology of Policlinico & Matto Pavie from January 1970 through December 1979, to assess the risk of development of acute leukemia. The median time of follow-up was 8.6 years. Eighty-nine patients (31%) were treated with intensive radiotherapy alone (STNfor TN), 70 (26%) with chemotherapy alone (MOPP or MOPP4004), and 163 (65%) with both radiotherapy (ST or TN) and combination chemotherapy (MOPP or MOPP4004). For relapses, the patients received further chemotherapy. The cumulative incidence of leukemia was calculated for the series (170 person-years), or separately for each group of treatment (RT:ST), CT:RT(T:RT:778 person-years). No leukemias occurred in 88 patients treated with RT or CT alone. Six cases of acute leukemia in the group of patients treated with RT:CT (crude rate of 7.5 per 1000 person-years at risk). Five patients belonged to TN+MOPP treatment group and a single one was given RT after polycythemia vera as adjuvant for 24 months. The sequence of treatment was RT followed by CT in two cases, CT followed by RT in four cases with systemic symptoms. No salvage MOPP has been administered after RT. All cases were in clinical remission and off all treatment; the latency time from initiation of therapy to bone marrow involvement was 12-48 months. The actuarial probability of leukemia at five years was 2.4% and 4.7% for the entire group of patients, 3.8% and 5.3% for the combination therapy group. All leukemias, except one, had a preleukemia phase lasting 1-6 months. Only two patients had myelodysplasia or myeloproliferative disease. The morphology of overt leukemia was myeloid or myelomonocytic in four cases, prolymphocytic and undifferentiated in the other two cases. The response to therapy was poor in all cases, with a median time of therapy failure from the onset of leukemia of 4 months (range: 4-9 months). In conclusion: a) the observed risk of developing subsequent leukemia in patients with Hodgkin disease treated with combined modalities could be carefully considered in planning the future therapeutic approach, especially with new drugs limited to one side of the diaphragm and with systemic symptoms (RT alone) without adjuvant chemotherapy, or, conversely, in patients with systemic symptoms without bulky disease (CT alone); b) acute leukemia developing after Hodgkin dis., has distinct clinicopathological features.

P23
MENSTRUAL CYCLE, PREGNANCIES AND OFFSPRING AFTER MOPP THERAPY FOR HODGKIN'S DISEASE. JM André, NE Ochoa-Holín, Institut de Recherches sur les Maladies du Sang, Hôpital Saint-Louis, Paris 75010.

By means of a questionnaire, the menstrual cycle, pregnancies and offspring were studied before and after MOPP therapy (3 or 6 cycles) in 68 women treated for Hodgkin's disease between 1972 and 1976 (trials 7201, 7202, 7202CZ). All were between 16 and 45 years old at diagnosis; none received subdiaphragmatic irradiation. All were in persistent complete remission. Before treatment, all had regular menses; 70 pregnancies occurred; the median age of the 36 primigravidae was 25; 61 chil- dren were born, 2 with minor abnormalities. After therapy, oligo or amenorrhea occurred in 26.4% of the patients, this percentage being different according to the age at therapy: 4.8% before 30, 61.5% after 30 (p<0.001); 50 women (73.6%) kept regular periods; 30 pregnancies occurred in 22 women; the median age of the 14 primigravidae was 27; 22 children were born, with minor abnormalities; all children born after therapy have normal physical and intellectual development.

We conclude that for women (73.6%) who kept regular periods, MOPP therapy has no impact on fertility, pregnancies and offspring.

P24

Twenty children, 15 5-5 5 ages 2 through 13 years, with pathologic stages I, II, III Hodgkin's disease were treated with chemotherapy plus radiotherapy from 1969 to 1978. Pathologic stages I and II disease was found in 18 patients. Their disease-free survival is 100% and all 18 patients are off-therapy with a median observation time of 5 years. In our series 2 of 7 patients with pathologic stage IIIB disease are on-therapy. The other 5 patients are in therapy all in first complete remission. All 20 patients off-therapy were investigated with regard to long-term side effects. The results obtained are as follow -growth and development; a modest retardation of height and crown-rump length occurred particularly in boys who at least maintain or even show normal pharmacy during the early years of rapid growth. Almost all patients had a decrease in their height percentile from the time of diagnosis to the present. -hormonal status: preliminary results show a significant increased peak GH response. At present the interpretation of these interesting data is difficult. All patients were clinically euthyroid. Thyroid function studies done in 11 patients showed significant increased TSH values and normal levels of T4,T3. The basal gonadal function, testosteroni levels and relative somatotropin response to LHRH were normal in all boys. Of 5 females patients, 3 girls had normal levels of FSH, LH and estradiol in serum, and 2 girls, who received inverted Y-fields radiotherapy, had elevated circulating levels of sera gonadotropins suggesting some disturbance of hypothalamic-pituitary interaction. -other organs and systems: no patient developed at present time second tumors. One patient who received a mantle radiotherapy with tumor dose of 4500 rad, bad a severe paramedialastinal fibrosis with re- sulting post-radiotherapy lung damage. The patient's pulmonary function besides he showed a decreased crown-length, a significant scolio- sis, a thin neck and narrow intercostal distance. Of the 13 patients receiving mantle radiation 4 had scoliosis. No evident psychological difficulties were seen. -immunological parameters were normal. All patients were found to have marked depression of their lymphocytes blastogenic response to mitogen phytohemagglutinin (PHA). Skin-test reactivity to intradermal antigens (PPD, Candida albicans, Streptococci-Streptococci) was normal but there was high percentage of subjects with skin energy response. No abnormality of serum immunoglobulins was found. B-cells were not significantly decreased in our series. No increased susceptibility of se- rious infections was observed. Splenomegaly did not increase the inci- dence of infection (all patients received penicillin prophylaxis).
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P25

THE VALUE OF NON-INVASIVE RESTAGING PROCEDURES IN THE NON-HODGKIN'S LYMPHOMAS

Baltimore Cancer Research Program, DCT, NCI, Baltimore, Maryland 21201 U.S.A.

The intensity and duration of treatment for the non-Hodgkin's lymphomas remains controversial since survival for some patients with non-Hodgkin's lymphomas appears similar regardless of the level of clinical response achieved (complete or partial response). The clinical course of 160 patients with non-Hodgkin's lymphoma treated on a randomized study (CAMP vs. CVP) were reviewed, permitting determination of the efficacy of non-invasive restaging procedures and correlate the non-invasive restaging results with histopathology obtained on restaging laparotomy. After maximal clinical response to treatment, physical examination, lymphangiograms, 87 gallium scan, sonograms, CT scans and intravenous pyelography yielded 33 complete responses and 38 partial responses. Among the 38 patients with partial response, 20 had normalization of physical examination and laboratory tests but were judged to have residual disease on the basis of the non-invasive restaging procedures. Exploratory laparotomy was performed in these 20 patients after a mean of 2 additional courses of chemotherapy and a repeat of all the positive non-invasive restaging procedures. Laparotomy showed residual disease in 4 of 20 (20%). In 16 (80%) patients 87-gallium scan there were 5 (31.3%) false positive, 2 (11%) true positive, 7 (55.8%) true negative, and one equivocal results. Among the 18 pre-operative 87-gallium scans there were 13 (72%) false positive, no false negative, 2 (11%) true positive, 1 (5.5%) true negative, and one equivocal result. Among the 18 pre-operative 87-gallium scans 7 patients had either positive CT scans (3 patients), abdominal sonograms (2 patients) or intravenous pyelography (1 patient) none had residual tumor at laparotomy. Among the 16 patients treated in the period 1961 through 1979, Seventy percent of the cases had an involvement of Waldeyer's ring. Improved staging procedures in recent years resulted in a shift in the percentage of patients from stage 1 and 2 towards stage IV. Staging laparotomy with splenectomy performed on 7 of 54 patients with stage I and II disease and with a diffuse histiocytic type of the lymphoma did not yield additional information about abdominal involvement. In 55 (64%) of the patients complete remission (CR) was achieved, 15 (18%) of the patients had partial remission (PR) and there was a treatment failure in 15 patients (18%). Patients with a lymphocytic cell type achieved a CR in a slightly higher percentage (71%), than the histiocytic (64%) and lympho-histiocytic type (58%). The incidence of CR in patients with a nodular cell pattern of the lymphoma was 91% and 56% in patients with diffuse cell pattern. The treatment of patients in stage I, II and III resulted in 76.5%, 66.5% and 53% CR res., whereas the treatment of patients in stage IV resulted in 36% CR. The 5-years actuarial survival of patients in a CR was 52% and 10-years survival 46%. All patients did not respond to treatment died within: a year. The prognosis of stage II patients in a CR was worse than that of patients in stage I and IV. Patients with stage IV who survived longer than one year seemed to be accurately cured. Patients with lymphocytic type had a higher tendency for relapse, whereas patients with nodular lymphomas is better than with diffuse lymphoma.
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P29
HIGH INCIDENCE OF ECHOCARDIOGRAPHIC PERICARDIAL EFUSION IN NON-HODGKIN'S LYMPHOMA.
G.C. Acquatella, E.T. Roure, A. Maury, R. Stern, H. Acquatella
Lymphoma Clinic and Echo Laboratory, Hospital Universitario de Caracas, Venezuela.

Thirty-two patients 16 male, age 15-65 years mean 44 years, with non-Hodgkin's lymphoma were studied, 26 (81%) were in stage III/IIV and 6 (19%) were in stage I/II.
Echocardiographic examination of the heart revealed that 17 patients (55%) had pericardial effusion (P.E.) including 4 with cardiac tamponade.
In 8 patients with large P.E. there was radiographic evidence of a mediastinal mass or a hilar adenopathy, but only 2 with moderate or small P.E. had this association. Pericardiocongestion in 5 patients disclosed lymphoblasts by cyt centrifuge smears, cell block and cytochemistry (positive acid phosphatase). In 3 patients the diagnosis was established previously by lymph node biopsy but in 1 the diagnosis was made by the pericardial tap; the fifth patient had increased numbers of mesothelial cells in the pericardial fluid.
The total remission rate was 83% in the group with P.E. and 76% in the group without P.E., no significant statistic difference between the groups was found.
The survival at 24 months was 50% there was no survival difference between the patients with or without P.E.
No patient required surgical or intracavitary chemotherapy; large P.E. should undergo cytological screening since it does not always imply neoplastic infiltration, except in patients with lymphoblastic lymphoma where it may be a useful tool for diagnosis.
Patients with neoplastic cells in the pericardial fluid were treated as the whole group with systemic chemotherapy Cyclophosphamide, Vincristine, Adriamycin, Prednisone (C.H.O.P) plus palliative mediastinal radiation (2000 Rads) with significant improvement.
3/17 patients had persistent P.E. after 2 months of therapy and had not entered in remission.

P30
MENINGOSIS-PROPHYLAXIS WITH INTRATHECAL 198AU-COLLOID AND METHOTREXATE TREATMENT IN CHILDHOOD ACUTE LYMPHOCYTIC LEUKEMIA and LYMPHOMA
D. Metz, U. Stoll and W. Planet, Department of Pediatrics (Carl- Zeiss-Stiftung) and Department of Nuclear Medicine, Friedrich Schiller-university, Jena, Germany.

Since January 1, 1972, 86 children who, between the ages of 7 months and 168/12 years, developed an ALL or a non Hodgkin's Lymphoma (NHL), have been given 1-th. injections of 198Au-colloid and methotrexate. Depending on their ages, the children received a single 1-th. injection of radiogold activity between 1.24 and 0.89 mCi (45,80-181MBq) instead of telecobalt irradiation. Since May 1980 much patients as were treated according to the LSA-L protocols have, though lumbar puncture and with two weeks in between, been given two indentical applications of 198Au activity for meningosis-prophylaxis. Radiogold spreads in the subarachnoidal spaces and is phagocytized by the arachnoides. The tumoricidal effect (beta rays) extends selectively over the distribution space of the latent meningosis-1edema. The brain parenchyma is spared by the betarays, which extend only for 3,6mm. The weak gamma radiation make actigraphy control possible. Patients: ALL:76 children(41boys and 35 girls) and NHL:10 children(6boys and 2 girls). Results: 60 out of the 86 children are still alive. As per March 31, 1981, the average period of remission was 30 months.
The following relapses occurred: 20 children developed a marrow relapse(23.5%), 2 children a simultaneous marrow-meninges relapse(2.3%), 8 children a primary etiologic lesion, 3 children a retrobulbar optic neuropathy infiltrate. After a cytostatic therapy of about 36 months the treatment of 36 out of the 65 children(41.9%) has so far been concluded. 30 of these patients are still in uninterrupted remission.
5 patients developed a marrow relapse and one child a meningeal leucomias. Side effects: After radiogold injections 9 children had headaches, nausea and vomiting (10%). 5 of them had a fever (5.8%). This complaints did not last longer than 24 hours. Later complications such as apathy syndrome or leukencephalopathy were not found in any of the patients. Reexamination by means of computer tomography revealed no radio- genic brain parenchyma lesions after 198Au-colloid.

P31
Primary Non-Hodgkin's lymphoma of the CNS. Results of radiotherapy in 15 cases.
G. Ghirlanda, Generali, Department of Radiotherapy, University Hospital, Wilhelmina Gasthuis, 1013 EG Amsterdam, the Netherlands.

Primary Non-Hodgkin's lymphoma of the CNS is a rare condition. The number of cases reported in the literature does not exceed 200 patients. The present series comprises 15 cases of primary Non-Hodgkin's lymphoma of the CNS. The pathology was reviewed and the cases were classified according to the Lukes/Collins criteria. The patients included in the study satisfied the following criteria: confirmed pathology; no other clinical evidence of NHL localization apart from the CNS; normal chest x-rays; normal radiological brain scans; normal bone marrow aspirations; normal liver and kidney biochemical tests.

The duration of the symptoms up to the time of diagnosis was, in all cases, no more than 4 months. The mean age was 55 years. There was a predominance of male cases. At surgery, the tumor presented as infiltrating with edematous borders so that a total removal of the tumor was never possible.

Postoperative radiotherapy was given with a Cobalt-60 unit to the whole brain, by means of two opposite fields, aiming a total dose of 40 Gy in 4 weeks. Only three patients are alive at present, 2, 3 and 27 years after treatment. The other patients died between 3 years following surgery and radiotherapy. The cause of death was, in all cases, a relapse in the irradiated areas. No case showed signs of dissemination outside the CNS. A radiation dose of 40 Gy in 4 weeks is sufficient to control NHL in other localizations in the body. However, this does not seem to be the case in CNS localizations. One similar case was compared with other reported series in the literature and implications for the treatment of this disease will be discussed.

P32
PRIMARY CNS-LYMPHOMAS: CLINICO-PATHOLOGICAL FINDINGS, CSF-CYTOL OGY AND IMMUNOLOGY.

Primary CNS-lymphomas constitute about 1% of intracerebral tumors since 1978 eleven patients were treated in our hospital because of tumors classified as primary intracerebral T-cell derived (3), B-cell derived (6) and unclassified (2) Non-Hodgkin lymphomas. Ten patients had infiltrations in cerebral hemispheres, cerebellum,pons and periventricular ependyma; one patient presented with an epidural spinal manifestation. Appearance in CT-findings was either as hypo- or hyperdense round infiltrations with varying contrast enhancement. Diagnosis was made in three patients with CSF-cytology and immunology, in seven patients with neurosurgical intervention, and in one patient at autopsy. Cytological methods comprised PAPPENHEIM staining, examination for unspecified esterase, acid phosphatase and PAS-staining. Besides immunofluorescence, E-rosetting, quantitative immunoglobulin determination, isoelectric focussing, CSF tumor cell stimulation and examination of cultured CSF-cells are presented. The advantage of immunological methods to exclude un speific reactive changes from typical lymphoma-findings is discussed. Combination of CT-findings, cytological and immunological examination of CSF make early clinical diagnosis possible.
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P33
F. Laura, M. Fiacchini, P. Mazza and S. Turra
Istituto di Ematologia "Lorenzo e Ariosto Seragnoli", Policlinico S.Orsola, Bologna.

COMBINATION CHEMOTHERAPY IN STAGES I AND II HODGKIN'S DISEASE

Between 1971 and 1978, 15 adult patients (9 M; 6 F) with stage I or II Hodgkin's disease (HD) were treated with MOPP alone.

Eleven patients had Nodular Sclerosis (NS) and 4 Mixed Cellularity (MC) histological subtype. The extent of the disease was established by physical examination, radiography of the chest, lymphangiography and bone marrow biopsy. Laparotomy and splenectomy were performed in only 4 patients. Three patients were classified as stage IA, 8 as stage II A, 3 as stage II B and 1 as stage II A. All but one received 6 courses of MOPP chemotherapy, which was chosen in preference to radiotherapy for the following reasons: 3 patients had severe concurrent disease, 2 patients presented with wide mediastinal enlargement (1 with adjacent lung involvement) thought to carry a high risk for interstitial pneumonitis after radiotherapy, 1 patients refused further radiotherapy after the first two doses (300 rad), which caused persistent nausea and vomiting. Chemotherapy was preferred because of the advanced age or personal circumstances of the other patients. Complete Remission (CR) was defined as a complete disappearance of all clinical and radiological evidence of the disease.

Fourteen of the 15 patients achieved a CR (92%) and 12 are still in CR 28-109 months after completion of chemotherapy. Six patients have been relapse-free for over 3 years and 6 for more than 5 years (one patient died after two months). Mild clinical toxicity (e.g. nausea and vomiting and neutropenia) was recorded in all patients. Haematological toxicity was negligible and never interrupted or delayed therapy.

Our results, though from a small number of patients, are in agreement with those reported by Olwey, who treated Ugandan children with early stage HD with MOPP chemotherapy and support of CR and survival rates comparable with, perhaps better than, those achieved with radiotherapy. HD chemotherapy may be a valid alternative to radiotherapy as primary treatment for some patients with early stage HD, e.g. those with symptomatic disease, histologically poor prognosis, or at high risk of respiratory complications after radiotherapy.

P34
MOPP ALONE COMPARED WITH MOPP ALTERNATING WITH STREPTOZOTOCIN, CCNU, ADRIAMYCIN AND BLEOMYCIN (SCAB) FOR ADVANCED HODGKIN'S DISEASE.

Peter H. Wierink, Dan Longo, Patricia Duffey, Robert C. Young, Vincent T. DeVita, Jr., Division of Cancer Treatment, NCI, Baltimore and Bethesda MD.

To date, 41 patients have entered this study which is designed to determine whether a treatment program employing a new effective drug combination (SCAB) alternating with standard MOPP is superior to MOPP alone for patients with advanced Hodgkin's disease. Twenty patients received MOPP alone (12 currently evaluable) and 21 received MOPP-SCAB. The evaluable MOPP patients had a median age of 31 years (range 15-58) and 7 of the 12 were males. The median age of the MOPP-SCAB evaluable patients is 36 years (range 17-63) and 11 of the 17 were males. Nine of 12 MOPP patients had B symptoms as did 11/15 MOPP-SCAB patients. Five of 12 MOPP and 6/15 MOPP-SCAB patients had MC or LD histology. Thus, the groups are comparable, but more males and more older patients were randomly allocated to MOPP-SCAB.

Eleven of 12 (92%) MOPP patients achieved CR. 2 CR patients relapsed at 2 and 10 months, both stage IV B and 1 had died. Another MOPP patient died in CR from infection due to drug-induced granulocytopenia. The other MOPP CR patients remain in CR from 1 to 22 months. Fourteen of 13 (92%) evaluable MOPP-SCAB patients achieved CR and 1 has relapsed at 4, 8, and 18 months (all had stage III B). The other MOPP-SCAB CR patients remain in CR from 1 to 29 months. The MOPP-SCAB patients have a median age of 63 years died of Hodgkin's disease II A, II B.

Life table analysis shows no difference in disease-free survival between the 2 treatment regimens at 30 months. Nausea and vomiting were more severe with MOPP-SCAB compared to MOPP alone. However, 44% of MOPP alone courses were delayed because of pancytopenia compared to 4% of MOPP-SCAB courses. Two episodes of pneumonia, 3 of Herpes zoster, and 4 of fever of unknown origin occurred with MOPP alone whereas only 2 episodes of fever of unknown origin occurred with MOPP-SCAB.

Patients with advanced Hodgkin's disease had a 90% CR rate on this study. No significant differences in outcome between MOPP alone and MOPP - SCAB treatment have emerged from this early evaluation of the study, which continues to accrue patients.

P35
TREATMENT OF MOPP-RESISTANT HODGKIN'S DISEASE WITH ADRIAMYCIN, BLEMICIN, VINCBLASTINE AND IMIDAZOLE CARBOXYLIDE (ABVD). F. Mandelli; C. Biagioni; A.P. Arselmo; R. Mariuzzi;Enrico A.M. Testi; F. Mauro; A.M. De Luca; S. Messori and G. Papa. Institute of Hematology. University of Rome, O0161 Roma, and Institute of Radiology University of Rome, O0161 Roma, ITALY.

Twenty patients (pts) with advanced Hodgkin's disease resistant to MOPP were treated with the chemotherapy combination ABVD (adriamycin, bleomicin, vincristine and imidazole carboxylide). Complete response (CR) was achieved in 55% of patients. The observed response rate was not related to age, sex, histological subgroups or extent of disease. It is also noteworthy that ABVD induced CR in 7 of 16 pts. showing progressive disease during primary therapy with MOPP. Eight of ten complete responders have remained continuously free of disease from a minimum of 12+ to a maximum of 48+ months after they had achieved CR. Median survival for the entire group is 36 months. Survival of complete responders is significantly longer than that of non-responders. Toxic manifestations caused by ABVD were well tolerated and reversible. The results indicate that ABVD appears to be a useful tolerable and simple multiple-drug chemotherapy for use in MOPP-resistant patients with Hodgkin's disease.

P36
COMBINATION TREATMENT FOR ADVANCED HODGKIN'S DISEASE (IHD), V. Fossar, L. Salvagno, L. Endrizzi, A. Pacagnella, P. Borsandino, V. G. Cartei, P. De Besi and M.V. Fiorentino, Medical Oncology Department, Padua General Hospital, Padua Italy 35100.

From 1.1.1975 to 12.31.1980 105 consecutive, previously untreated patients IHD with advanced HD, entered into 3 programs.

Program 1 (for stages (st) IIA+, IIB+): Total Nodal Radiation (TNR) + 6 MOPP.

Program 2 (st IIBs, IIBs+, IIBs+: TNR + 6 MOPP + 12 ABVD)

Program 3 (st s IIBs+, IIBs+, IVA, IVB): 6 MOPP + 12 ABVD + Radiation Therapy (RTD) on residual bulky tumour.

Histological subtypes were: lymphocytic predominance in 8, nodular sclerosis in 36, mixed cellularity in 54, lymphocytic depletion in 3; 4 pts were non subclassified.

The number of pts per group was respectively: 19, 37, 49.

31/49 pts in program 3 were stage IV (of which 23 pts IVA) having extranodal involvement as follows: liver 15 pts, lung 8, bone 5, bone marrow only 1, multiple sites including bone marrow 21.

85 overall pts (81%) obtained a complete remission (94% in IIA+ pts, 95% in IIBs+ 70% in IIB, 77% in stage IV pts). Actuarial survival at 5 years in program 1 is 85%, in program 2 65% and in program 3 59%.

Disease Free Survival (DFS) in the three programs is 85%, 45% and 40%.

There have been up to 7 relapses and 4 deaths (possibly treatment related).

Tolerance of treatment has been good in programs 1 and 2, while for program 2 the long duration of treatment and the haematological depletion, required in a majority of pts to stop treatment just after completion of RTD.

In stage IV the same survival (and DFS) has been obtained as in stage IIB and IIBs+; we would stress that 5/8 pts resistant to MOPP, obtained full remission after ABVD and 3 further pts after iceberg RTD.

Results for pts included in our programs 1 and 3 are acceptable according to international standards, while analysis of program 2 suggests the following change in policy: second line treatments should be reserved for relapse, instead of being administered to patients already in remission.
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P37

REMISION AND FAILURE IN STAGE III AND IV HODGKIN'S DISEASE TREATED BY MOPP.
C.1. JACQUILLAT, G. AUCLERC, M.F. AUCLERC, H. NEIL
Hôpital Salpêtrière Service d'Oncologie Médicale, 47 Boulevard de l'Hôpital 75651 PARIS Cedex 13 FRANCE

224 patients with stage III and IV Hodgkin's disease (H.D.) have been treated by 6 monthly MOPP courses. 190 patients achieved remission and among them there were 109 complete remission (C.R.). All patients involved Vinblastin maintenance combined to "reinduction" courses of MOPP (68 patients) or to irradiation (57 patients).

At twelve years remission curves are "plateauling" at 75 % for these patients who achieved C.R. and 68 % for those who had partial remission, and for all patients the ten years survival rate is 55 %. The parameters which influence C.R. achievement are age, fever, histology, but the best predictive parameter seems to be the lymphogram: diffuse involvement and aspects of cystic storage pattern as seen in "non Hodgkin lymphomas" heralding an unfavorable prognosis.

The lymphogram picture should thus been included as parameter of initial classification and treatment active in "non Hodgkin lymphomas" such as CHOP should be tried in these high risk patients.

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P38

DESACETIL VINBLASTINE AMIDE SULFATE (DVA, VINDESTINE) IN THE TREATMENT OF HODGKIN'S DISEASE. B. S. Strauss, B. Kostner, J. B. Lee, C. W. Young, B. D. Clarkson.
Memorial Sloan-Kettering Cancer Center, New York, NY 10021, U.S.A.

4 In a phase II trial of DVA in a dose of 2-4 mg/m²/week (peak 4/6 Hodgkin's disease (H.D.) patients heavily pretreated with vincristine and vinblastine achieved a partial remission (PR) (Cancer Treat. Rep. 63:793-794, 1979) In an attempt to devise a non-cross resistant drug combination with MOPP and ABVD, DVA in a dose of 3 mg/m²/IV. on days 1 and 8 was combined with CSRT (100 mg/m² p.o. day 1) and melphalan (6 mg/m² p.o day 1-4) and CAD. Since 979 13 patients heavily prior treated with MOPP and/or ABVD have been treated with CAD. Among these patients there has been 5 complete remission (CR), 4 PR, 2 minor responses (MM) and 2 who failed to respond. Our 8 drug trial in which MOPP was alternated with ABVD in combination with low dose radiotherapy (RT) (RT) resulted in a CR in 55 (583) and a PR in 7/5 (62) previously untreated patients with advanced HD with only a 167 relapse rate at 36 months.

In an attempt to improve upon these results, CAD was added as a third non-cross resistant combination. Macarbazine was dropped from ABVD to reduce nausea and vomiting. CAD in alternating sequence with MOPP and ABVD combined with low dose RT was randomized versus MOPP/ABVD/low dose RT for untreated patients with stages IIIB/IV and/IV HD. Since 2/1/79, 21 patients have received CAD/ MOPP/ABVD/RT and 21 MOPP/ABVD/RT. Among patients evaluable for response on CAD/MOPP/ABVD/RT 15/10 (80) are in CR and 3/15 (20) are in PR. For MOPP/ABVD/RT 13/18 (72) are in CR, 3/18 (17) in PR and 2/15 (13) failed to respond. Thus far remission rates with CAD/MOPP/ABVD/RT are at least as good as those with MOPP/ABVD/RT, and patient acceptance has been greatly increased by reduced nausea and vomiting.

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NON-HODGKIN'S LYMPHOMA IN CHILDREN: RESULTS OF TREATMENT WITH THE MODIFIED LSA-T² PROTOCOL.
Division of Hematology-Oncology; Department of Pediatrics, University of Pavia ITALY.

From 1976 to 1980, 26 previously untreated children with non-Hodgkin lymphomas were staged and treated with a modified version of the LSA-T² protocol proposed by Wollner: stage III and IV had, in addition, prophylactic treatment of the central nervous system (CNS) with cranial irradiation (CRI) or 1000 rad plus intraventricular methotrexate. Twenty-seven of twenty-eight patients achieved complete remission (96,42%). The disease-free actuarial survival is 73%. The median remission duration is 24 months (range: 1 to 66 months). The disease-free actuarial survival is 100% for children with stage I-II disease and 64% for stage III-IV children after a median observation time, respectively of 25 and 24 months. None of the 21 high-risk patients who achieved a complete remission developed CNS-disease after prophylactic treatment. There were 6 relapses, all on therapy of these failures 5 died: the median time for recurrence is 7 months and the median survival time is 12 months. The latest relapse was on therapy at 31 months; this patient, surviving with disease, had bone marrow and peripheral nodal involvement at diagnosis. Of 22 patients in first complete remission 9 are off-therapy and have shown no evidence of recurrence with a median observation time of 48 months; their survival time range from 38 to 57 months from diagnosis. No drug-related or infectious death occurred but 70% of these patients suffered serious toxicity in the consolidation phase. This toxicity was reversible and covered with appropriate blood products. In our experience the mediastinal involvement and leukemic conversion at diagnosis were not unfavourable prognostic factors. It is concluded that this multimodal and multiple drug regimen like the LSA-T² coupled with CNS prophylaxis had considerably improved the prognosis of non-Hodgkin's lymphomas in children, even if further modification of this treatment (chemotherapy, surgery and radiotherapy) or alternative therapeutic approaches are required for increasing the disease-free survival of patients with special features: primary skeletal or subcutaneous disease and Burkitt-type histology.

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TREATMENT RESULTS IN CHILDHOOD T-CELL NON-HODGKIN'S LYMPHOMA (T-NHL) AND ACUTE LYMPHOCYTIC LEUKEMIA (T-ALL).

From October, 1970, to December, 1980, 72 children and adolescents were treated for T-NHL and T-ALL in BPM studies: NHL-BFM 75, ALL-BFM 70/76 and ALL-BFM 76/79. In NHL diagnosis of T-cell disease was based on morphological (Kiel-classification: convoluted type) and/or immunological criteria (E-rosette test). 30/35 NHL pts presented with a typical anterior mediastinal mass. Clinical stage distribution according to the WOLLNER classification was 1, 5, 20, 9 pts with stages I, II, III, IV. Bone marrow infiltration in stage I/IV was present in no case and ALL included. T-ALL was diagnosed by either the presence of an anterior mediastinal mass (THM) and/or positive immunology (+). All patients were given the West-Berli ALL protocol for remission induction (treatment A). Additionally, since 1976, pts with increased risk for relapse (NHL: initial CNS involvement and/or massive intraabdominal disease, ALL: usually WBC > 25000/mm³) received an intensive reinduction protocol early in remission (treatment B). The probability of continuous complete remission (p-CCR) obtained by life table analysis with respect to treatment criteria was given in the table.

<table>
<thead>
<tr>
<th>n. Treatment</th>
<th>p-CCR after (mths)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-NHL/T-ALL</td>
<td>72</td>
</tr>
<tr>
<td>T-NHL 75</td>
<td>35</td>
</tr>
<tr>
<td>T-ALL 90-79</td>
<td>35</td>
</tr>
<tr>
<td>ALL 70/76</td>
<td>15</td>
</tr>
<tr>
<td>ALL 76/79</td>
<td>15</td>
</tr>
<tr>
<td>ALL 76/79 E+</td>
<td>15</td>
</tr>
<tr>
<td>ALL 76/79 E+ 22</td>
<td>3/19</td>
</tr>
</tbody>
</table>

For a comparable cure expectancy patients with T-ALL need more intensive therapy than those with T-NHL as demonstrated by the results in all study BPM 76/79.
(Supported by the Stiftung Volkswagenwerk)
ABSTRACTS - International Conference on Malignant Lymphoma, Lugano

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EXPERIENCES WITH 76 CHILDREN WITH NON-HODGKIN'S LYMPHOMA (NHL).
Swiss Pediatric Oncology Group (SPOG, a member of SAKK).

Since 1975 a modified LSA-L protocol (Schwartzman, Wachter 1987, 1979) was used for the treatment of children with NHL in Switzerland. Clinical data and survival of 31 pts seen by one of the authors up to 1975 (group I) were compared to those of 45 children treated by members of SPOG from 1975 (group II). Only children with histologically or cyto- and immunologically proven extranodal NHL presenting with $<$1% blast cells in peripheral blood and $<$5% blast cells in the bone marrow and excluding normal amounts of catecholamine metabolites were included. Since one of the main goals of SPOG is to administer optimum therapy to all children with cancer in Switzerland, no pts were excluded for any reasons in both groups. Clinical data and treatment results were compared as follows: x/y/z + x: number of pts dead; y: total number of pts in stratum; z: relative importance of stratum in %:

Staging according to Murphy

<table>
<thead>
<tr>
<th>Group</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>group I</td>
<td>4/4/13</td>
<td>3/3/10</td>
<td>13/11/55</td>
<td>7/12/22</td>
<td>7/23/1/100</td>
</tr>
<tr>
<td>group II</td>
<td>2/8/18</td>
<td>0/6/13</td>
<td>12/24/53</td>
<td>7/27/16</td>
<td>16/45/100</td>
</tr>
</tbody>
</table>

Localisation of primary

<table>
<thead>
<tr>
<th>Tonsils</th>
<th>Extramedullary +</th>
<th>Mediastinum</th>
<th>Abdomen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>7/13/10</td>
<td>13/7/22</td>
<td>7/8/26</td>
</tr>
<tr>
<td>Group II</td>
<td>10/3/16</td>
<td>21/7/22</td>
<td>7/15/33</td>
</tr>
</tbody>
</table>

The 2-yr disease-free survival was 19% (6/31) in group I and 58% (14/24) in group II.

In group II 19 pts had immunological cell marker studies: at a median follow-up of almost 1 yr the results were as follows (x/y/z defined as above): Non-T non-B: 1/3/10; T 1/6/21; B (non-Burkitt-like): 2/10/34.5; B (Burkitt-like): 7/10/34.5.

Autologous bone marrow transplantation after intensive chemotherapy and total body irradiation is now used for intrabdominal Murphy stage III and IV disease.

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COMBINATION CHEMOTHERAPY IN NON-HODGKIN'S LYMPHOMA: RESULTS OF A LONG TERM FOLLOW-UP. M. Ben-Shachar, Y. Cohen, E. Robinson.
The Northern Israel Oncology Center, RAMBAM Medical Center, Faculty of Medicine, Technion - Israel Institute of Technology, Haifa 31905, Israel.

During the years 1970-1975, 100 patients with non-Hodgkin's lymphoma (NHL) were treated by combination chemotherapy of the COP/P protocol. The patients with intermediate stages (IIA & IIB) or stage II were treated by pulse therapy of those with a complete remission and with maintenance chemotherapy. Chemotherapy consisted of Cyclophosphamide 60 mg/m² i.v. days 1 & 8, Vinca Alkaloid 0.1 mg/m² i.v. days 1 & 8, Prednisolone 40 mg/m² P.O., days 1-4. Thirty-seven patients received in addition Rituxan (7 ons). Twenty of the 37 had NHL of the B cell type.

The achievement of a complete response (CR) was achieved in 14 of the 37 patients. Sixty-nine of the 37 patients were treated with a combination of two different drugs: COP/P plus Rituxan. The treatment was repeated every 28 days. After complete remission (CR) was achieved, consolidation and maintenance was given during one year. Forty-seven patients (74%) of the patients achieved a complete remission (CR) and received four courses of low-dose CY after CR. The three patients with histocytic lymphoma (HL) and six patients with lymphocytic lymphoma (LL) achieved CR. Relapse occurred in 13/36 (38%) of those who obtained CR. All of the patients with HL had NHL relapse, but none of the patients with HL had a relapse. The actuarial survival of all adult patients is 95% for 8 years.

The correlation of the survival of all adult patients is 35% for 8 years. However, patients not responding to chemotherapy or who had partial remission died within the first year. The 8 years actuarial survival (minimum follow-up is 5 years) and the relapse-free survival of CR patients is 90% and 50% respectively. For those with HL the survival is 70% and relapse-free survival 45%. Only 15/31 children are still alive and with no evidence of disease. The remainder of the patients failed to respond and died within several months. COP/P regime is an effective treatment in some subgroups of NHL but has no significant effect on children with NHL.

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CVP-REMISSION MAINTENANCE IN STAGE I - II NON-HODGKIN'S LYMPHOMAS

Dept of Oncology, University Hospital, S-221 85 Lund, Sweden.

To assess the value of adjuvant chemotherapy after radical roddiography in localised non-Hodgkin's lymphomas a prospective randomized study is going on in Sweden since 1975. The staging procedure is based on the Ann Arbor concept, but does not include isotope examination. Histologic typing is performed according to Rappoport.

<table>
<thead>
<tr>
<th>Histologic type</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>NLWD</td>
<td>DLLD</td>
</tr>
<tr>
<td>NLPD</td>
<td>DLPD</td>
</tr>
<tr>
<td>NM</td>
<td>DM</td>
</tr>
<tr>
<td>NH</td>
<td>DM</td>
</tr>
</tbody>
</table>

Patients in stage I and II are given locally extended radiotherapy to a total target absorbed dose of 40 Gy in 20 fractions. Patients in complete remission 6 weeks after the conclusion of radiotherapy are then randomized to receive 9 cycles of CVP (length of cycle 21 days) or no further therapy. One hundred and twenty patients have entered the study. The median follow-up time is 36 months. There is a significant difference between the two arms in respect to relapse-free survival but so far no difference in overall survival. The results in respect to histologic type and nodal versus extranodal disease will be shown.

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This study was designed to test the effectiveness of a sequence of seven cycle active cytotoxic drugs for HR-NHL (pts<15 years of age: all stages and histologies; pts>15 years of age: all stages, unfavourable histology only by the IELL classification). The F-MACHOP regimen included novebeine (0.5 mg/m² i.v. on the 0th and 12th day), cyclophosphamide (400 mg/m² i.v. hr. 24), 5-fluorouracil (15 mg/kg c.i. hr. 24-30), cytarabine (1000 mg/m² c.i. hr. 30-36), Adriamycin (60 mg/m² i.v. hr. 36), methotrexate (500 mg/m² c.i. hr. 40-54), and piperazone (60 mg/m² p.o. days 1-14). Folic acid rescue (20 mg/m² i.v. q.12 hr. x 4) was started 24 hr after the last cycle. Courses of therapy were administered every 3-4 weeks for a total of 6 courses. All pts<15 years of age and those at high risk for meningeal localization (bone marrow involvement, lympho- or proctological or intracranial histology) received monthly intrathecal prophylaxis (methotrexate + cytarabine) x 6 doses followed upon achievement of complete remission (CR) by cranial irradiation. On day 30 pts. on study, 9 have completed therapy with 7 CR and 1 PR response.

F-MACHOP is the only regimen tested in children $<$15 years of age for HR-NHL. This study was designed to test F-MACHOP by RCT. Fifty pts. died during treatment because of grade negative sepsis (4 pts. $>$35 years of age) or progressive disease (1 pt.). Six of the 7 complete responders are in continuous CR after 1-9 mos. 1 pt. died after 6 mos. due to neutropenic pneumonia, sepsis and septic shock. These preliminary results indicate that F-MACHOP is an active regimen for HR-NHL; pts. older than 45 years of age appear to tolerate this regimen.
ABSTRACTS - International Conference on Malignant Lymphoma, Lugano

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REFRACTORY MALIGNANT LYMPHOMA: PHASE II STUDY OF CIS-PLATINUM (DEP), VP 16-213 AND PREDNISONE.
From Dec 79 to Feb 81 22 patients (pts) with advanced malignant lymphomas refractory to conventional chemotherapy were treated with cis-platinum (DEP) (60 mg/m² iv, d 1), VP 16-213 (120 mg/m² po, d 3-5) and prednisone (60 mg/m² po, d 1-5). Courses were repeated every 3 weeks. DEP was given after 30 min of prehydration with 500 ml iv fluid DEP was infused for 15 min, followed by 2000 ml iv fluid for 4 hours. Diuretics were not given. Treatment was usually ablative.
20 pts were evaluable for response and toxicity: 7 with Hodgkin’s disease (HD) and 13 with Non-Hodgkin’s lymphomas (NHL). All pts were heavily pretreated with a median of 5 different cytotoxic agents (range 3-9) in various combinations. 12/20 had also had radiotherapy. A total of 67 treatment courses were given (median 3 courses/pt, range 1-9). 5/7 pts with HD and 5/13 pts with NHL achieved a partial response. No complete response was observed. Median duration of response was 10 weeks (range 2-17). All responses occurred within the first cycle.
Vomiting and myelosuppression were the most prominent side effects. In 8/20 pts WBC nadir was <2000/m³ and platelet nadir 75’000/m³ with median WBC nadir on day 20 (range 6-40) and median platelet nadir on day 15 (range 7-15). One pt died with sepsis, and one with neutropenic fever after the first course, prior to therapy startcholestatic liver damage due to tumour infiltration was present. Due to haematological toxicity drug dosage was reduced in 2/3 of all cycles, the intervals were prolonged to 4 or more weeks in 5/6 of all cycles. Nephrotoxicity was minimal, no necessitating any dosage modifications.
We conclude that the combination of DEP, VP 16-213 and prednisone is effective and tolerable in advanced malignant lymphomas and lacks cross-resistance to commonly used first-line drug combinations.

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COMBINATION CHEMOTHERAPY WITH COP + VP 16 IN NON-HODGKIN’S LYMPHOMA. D.P. Derman. Univ.of the Witwatersrand, Johannesburg, S.A.
Seventeen patients with non-Hodgkin’s Lymphomas were treated with a regimen including Cyclophosphamide, Oncovin Prednisolone and VP-16. Long term follow up is reported. Seventeen patients who had no prior chemotherapy were available for analysis. Most patients were suffering from diffuse large cell lymphomas of clinical stage III or IV. Response to chemotherapy was seen in 19 (60 per cent). Median duration of survival was 10.5 months. Three patients were disease free for periods exceeding 4 years. The toxicity of the regimen was not significant greater than that found in a concurrent series of patients with lymphomas treated with COP without VP-16. In particular, neutropenia did not appear to be enhanced by the combination of vincristine and VP-16. In addition 13 patients with Non-Hodgkin’s lymphomas and Hodgkin’s disease, refractory to treatment with MOPP or COP were also treated with this regimen. Responses were seen in 3/11 of these patients. It is concluded that VP-16 is an active drug in the lymphomas and can be used in combination with the vincra alkaloids without excessive toxicity.

P47
A COMPARISON OF TENIPOSIDE (VM 26) AND VINCristINE IN THE MANAGEMENT OF NON-HODGKIN’S LYMPHOMA - A RANDOMIZED STUDY OF 164 PATIENTS.
I.A. Cooper. Cancer Institute, Melbourne, Victoria, Australia 3000.
Australian and New Zealand non-Hodgkin’s lymphoma multicentre Co-operative Chemotherapy Study Group.
From nine institutions between July 1974 and December 1977, over 1,600 patients were enrolled in a phase III comparison of VM 26 and vincristine. The criteria for entry were: histologically proven non-Hodgkin’s lymphomas (VM 26) (100 mg/m² IV x 2,15 days after each course of VM 26 and vincristine; Prednisolone (100 mg/m² P.O. x 5) designated PEP or vincristine (1.4 mg/m² IV x 1) designated PEP in an attempt to reduce the weekly dose of VM 26 and prednisolone designated COP. Results were analyzed according to whether the disease was of favourable (47 patients) or unfavourable (117 patients) histology. The great majority of patients in each group had clinically advanced disease (Stage III in 204 and Stage IV 714). For each histological sub-group, the results were similar whether the patients were treated with VM 26 or vincristine. In patients with unfavourable histology, VM 26 produced 57% complete remission (CR) and 24% partial remission (PR) compared with 34% CR and 35% PR for COP. Survival in these patients was also similar for the two regimens, the relative death rates being 1.11 for PEP-treated patients and 0.86 for COP-treated patients (p = 0.75). In patients with unfavourable histology, VM 26 produced 38% CR and 28% PR compared with 43% CR and 35% PR for COP, the relative death rates being 1.10 for PEP-treated patients and 0.90 for COP-treated patients (p = 0.49).
Neutropenia was the only long term adverse side effect and this was significantly lower in patients who received Teniposide in all of the toxic effects occurred with equal frequency. The results of this study show that Teniposide (VM 26) can be used in place of vincristine in combination with Cyclophosphamide and Prednisolone in the treatment of non-Hodgkin’s lymphoma. This agent carries no significant neurotoxicity.
The group recognized during the early phase of the study that an Anthracycline appears to increase the remission rate in the unfavourable histologic disease. A second Study has been activated to study the effect of combining Teniposide and Vincristine with an Anthracycline (Adriamycin). Cyclophosphamide and Prednisolone and comparing its efficacy in unfavourable histologic disease with Adriamycin added to PEP and COP. To date 215 patients have been randomized into these three arms.