ABSTRACTS

POSTER PRESENTATIONS

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P1

EBV-BURKITT'S LYMPHOMA ASSOCIATION OUTSIDE ENDEMIC AREAS: RESULTS OF A PILOT STUDY CARRIED OUT IN FRANCE

G.M. Lenoir [1], and T. Philip[2]

1. International Agency for Research on Cancer, 150, cours Albert Thomas, 69372 Lyon cédex 2, France
2. Centre Léon Bérard, Lyon, France

Burkitt's lymphoma (BL) is the most frequent childhood cancer in equatorial Africa, where 96% of the BL cases 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 cases having been virologically investigated and of the possible under-estimation of BL frequency in these areas (see: Philip et al., this Conference).

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

An extensive study conducted on most pediatric cases in a given area (Lyon, France), where both Caucasians and North-African lymphomas are treated, indicated that: - between 10 and 20% of BL occurring in Caucasian children are EBV-associated, whereas all the cases originating from North Africa (considered as a non-endemic area) were found to be associated with the virus. - Cytogenetic studies performed on 12 cases indicated that the three types of translocation observed (either t(8;14), or t(2;8), or t(8;22)), all showing rearrangement of chromosome 8, were independent of the association with EBV.

The comparative analysis of EBV-associated versus EBV-free BL which can be easily 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. Uchańska-Ziegler*, H.H. Kirchner+, H. Burrichter+ and P. Wernet*.
*Immunology Laboratory, Medical University Clinic, D-7400 Tübingen,
+Medizinische Hochschule Hannover, Abt. Hämatologie/Onkologie, Karl-Wiechert-Allee 9, D-3000 Hannover, FRG

The nature of the tumour cell in Hodgkin's disease has remained con versial, but the recent availability of cell lines derived from patients with Hodgkin's lymphoma (Schaadt et al., Int. J. Cancer 26, (1980)) has opened the possibility to study this subject in more de tail. The reactivity of one of these cell lines, L 428KS (a subclon of L 428), with over fifty monoclonal antibodies directed against v rious human lymphoid and myeloid antigens has been determined by us radioactive binding assays and indirect immunofluorescence tests. T results indicate that only a small number of the antibodies employe exhibit activity towards L 428KS cells. Reagents thought to be spec for mature or immature T cells like e.g. T033, T04 and NA1/34.HLK a well as OKT3 and OKT8 are unreactive, thereby excluding a relations of this Hodgkin's cell line to established T cell lines. L 428KS ce are unrelated to B cells as well, because they lack a number of mar kers characteristic for such cells like e.g. intracellular and surf immunoglobulin chains. Several monoclonal reagents 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 also not share number of antigens typically found on myeloblasts or later differen ation stages of granulopoiesis (detected e.g. by M1/70.HL or T03). the other hand, varying subpopulations (15-95%) of this cell line play antigens expressed also on different non-lymphoid hematopoiet cell lines as shown by reagents like T05, T06, T08 and T09. Antibo T02 and T020, which react with macrophages in several tissues, exh no reactivity towards L 428KS cells. Antigens controlled by the HL region are expressed very strongly on this cell line, while antibo directed against the heavy chains of HLA-A,B,C antigens do not rea In contrast, β_2-microglobulin, the small protein found in associat with HLA heavy chains, can easily be shown to be present on the su face of L 428KS cells. Surface marker studies with cloned sublines L 428KS cells and cultures treated with certain inducers of differ tiation are in progress to cast further light on the nature of thi tumour cell line. In conclusion, the L 428KS cell line is clearly ferent from other established human hematopoietic cell lines and t analysis of its surface antigens may indicate that the tumour cell Hodgkin's disease is most likely a cell type exhibiting characteri tics both of early myeloid and monocytoid cells.

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P3

IN VITRO DRUG SENSITIVITY OF BLAST CELLS FROM ACUTE LEUKEMIA AND MALIGNANT LYMPHOMAS.

J.D. Schwarzmeier, K. Mittermayer, E. Paietta. First Medical Clinic, University of Vienna, Vienna, Austria.

To detect resistance of tumor cells to anticancer drugs prior to chemotherapy, various in vitro test systems have been developed over the past few years. Most of these studies deal with cancer cells isolated from solid tumors. Only few attempts, however, have been made to apply these assays to acute leukemia and the leukemic phase of malignant lymphoma, 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 15:983, 1979), we studied the in vitro effect of cytostatic drugs on the incorporation of the RNA precursor ^{3}H-uridine into nucleic acids of the leukemic blasts. Since the success of chemotherapy is virtually dependent on the proliferative activity of the tumor cells, we additionally evaluated the rate of cellular ^{3}H-thymidine 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 leukemic phases of malignant lymphoma, and were incubated with the following drugs: adriamycin, cytosin arabinoside, methotrexate, 4-hydroperoxycyclophosphamide, 6-thioguanine, 6-mercaptopurine and prednisone. The effect of the cytostatic drugs on the ^{3}H-uridine incorporation by the tumor cells in vitro was expressed as percent inhibition of the ^{3}H-uridine uptake measured in cells not subjected to the cytostatic agents. Subsequently, the in vitro results were compared to the clinical response of the patient to chemotherapy. Our data indicate that in more than 90% of the patients drug resistance could be predicted by the assay. A positive correlation between inhibitory drug effect in vitro and response to chemotherapy in vivo existed in 50% of the cases tested so far. From these results we conclude that pretreatment sensitivity testing of leukemic cells is a reliable tool for the selection of effective chemotherapy in the individual patient.

P4

DRUG TRANSPORT AND CELLULAR SENSITIVITY TO ALKYLATING AGENTS IN BENIGN AND MALIGNANT HUMAN B AND T LYMPHOCYTES.

J.E. Byfield and Paula Calabro-Jones, Division of Radiation Oncology, University of California San Diego, 92103 USA

Lymphomas differ considerably in their sensitivity to chemotherapeutic regimens. In general, those with a greater rate of proliferation respond more rapidly and yield a higher CR rate than the more slowly growing tumors. In addition, non-cutaneous T cell lymphomas generally carry a poorer prognosis than many B cell types. We have examined the effects of both proliferation and B/T origin on the chemosensitivity of some human lymphoid cells. The proliferation-dependency of cytotoxicity was determined for mature peripheral human T cells by evaluating 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 cycling (18 hours post PHA). It was found that the sensitivity of T cells to killing increases with cycling for some alkylating agents (AA). These include Melphalan (Mel), nitrogen mustard (HN_2) and cis-dichlorodiammineplatinum (CDDP). Mel and HN_2 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 CDDP is taken up by an amino acid transport mechanism, perhaps explaining its nephrotoxicity. Remarkably neither active cyclophosphamide (phosphoramide mustard, PM) nor chlorozotocin appeared to penetrate mature T cells, although PM is active against B cell lymphoma lines. Regimens lacking cyclophosphamide may be more efficacious against T-lymphomas. Thus there appears to exist a histogenetic difference in lymphocyte sensitivity to some commonly applied AA. Another large group of lipophilic agents including nitrosoureas (BCNU, CCNU, Me-CCNU), AA (e.g. dimethylmyleran), and other agents (e.g. procarbazine) together with amphipathic drugs (Mitomycin-C, AQNU) show no proliferation-dependency of toxicity, i.e. both resting and cycling lymphocytes are equally sensitive. The data is consistent with the hypothesis that cell entry for these agents is dependent solely on solution for lipid soluble and amphipathic agents (carrier-independent drugs). This feature may explain their marrow recovery kinetics and cumulative marrow damage, together with their reduced tendency to induce tumor cell resistance. CD (lipid insoluble) agents probably all require specific membrane-transport mechanisms and are less toxic to resting cells (incl. marrow stem cells). This feature confers reduced cumulative marrow toxicity but a significantly greater tendency to develop tumor resistance based on membrane carrier mutations. The model predicts that many new AA probably can be synthesized based on membrane receptors. High growth fraction lymphomas should be more sensitive to such CD agents, especially on an alternating cyclical basis to inhibit resistance.

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P5

INHIBITION OF MARROW CFU-c GROWTH IN PATIENTS WITH MALIGNANT LYMPHOMAS. P. Stryckmans, A. Delforge, M. Malarme, E. Rongé-Collard, T. Spiro, D. Bron, F. Vander Brugghen, Service de Médecine et Laboratoire d'Investigation Clinique H. Tagnon, Institut Jules Bordet, Brussels, Belgium.

Marrow cells from patients with malignant lymphoma have been shown to contain less CFU-c than marrow cells from normal controls (1). Using the CFU-c assay of Pike and Robinson, the clusters and colonies formation of nucleated bone marrow cells obtained from 29 patients with malignant lymphoma and from 27 normal subjects were compared before (D1) and after a 4 day stay at 4°C (D4). The median 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 more GM-CFU-c. The possible inhibition activity of PGE2, a known inhibitor of the CFU-c growth, was ruled out by adding Indomethacine at 10^{-6} M to the lymphoma marrow cells : the mean ratio of growth in presence of Indomethacine over the one observed without was 1.25. The normal and lymphoma blood lymphocytes inhibitory activith on 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 lymphomatous sera. Leukemia inhibitor activity (LIA) produced by leukemia cells has been described previously to inhibit the CFU-c growth, in our study LIA like inhibitory activity has been observed in one out of 3 patients; this LIA was obtained by a 4 day incubation of lymph node lymphocytes and inhibits by 50% a normal CFU-c growth. These results suggest an inhibition rather than a loss 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.

(1) Bull JM, De Vita VT, Carbone P. Blood 45:833, 1975.

P6

SPONTANEOUS (^{3}H)-THYMIDINE UPTAKE IN HISTOLOGICAL SUBGROUPS OF HUMAN B-CELL LYMPHOMAS

Kvaløy, S., Godal, T., Marton, P.F., Steen, H., Brennhovd, I.O., Abrahamsen, A.F. and Høst, H. The Norwegian Radium Hospital Montebello, Oslo 3, Norway.

Spontaneous (^{3}H)-TdR incorporation was studied in cell suspensions from 64 patients with monoclonal B-cell neoplasias. Among various incubation periods a long-term (20 h) assay with (^{3}H)-TdR had the greatest discriminatory power versus non-neoplastic lymph node cell suspensions. The (^{3}H)-TdR uptake correlated positively with cell volume, nuclear volume, and cells in S + G_2 + M phase of the cell cycle. A high degree of heterogeneity with regard to (^{3}H)-TdR incorporation was found within several histological groups of the Kiel classification, especially in low-grade malignant lymphomas of centroblastic/centrocytic origin and in the lymphoplasmacytoid groups. In highly malignant lymphomas (^{3}H)-TdR uptake was statistically, significantly higher than in lymphomas of low-grade malignancy.

Patients with localized disease (stages I and II) and those with "B"-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 (^{3}H)-TdR.

P7

MARKER ENZYME PROFILES IN PLASMA MEMBRANE OF CELLS ISOLATED FROM MALIGNANT LYMPHOMAS. G.Losa, P.Luscieti, G.Maestroni and E.Pedrinis. Laboratory of Cellular Pathology, Ticino Institute of Pathology, CH-6604 Locarno.

The activity profiles of marker enzymes bound to the plasma membrane were determined in cells isolated from lymph nodes of patients with malignant lymphomas. Most of the cases were histologically classified as non-Hodgkin lymphomas. Cells were collected in RPMI medium after teasing the fresh lymph nodes with a loose-fitting teflon pestle, washed twice in a saline solution and checked for viability by trypan blue exclusion. The composition of the population was assessed by testing cells for the presence of surface immunoglobulins using fluorescent anti-Ig polyvalent or anti single chain -F(ab')$_2$ antisera, of surface T antigens with fluorescent monoclonal antibodies and for non specific esterase with α-naphtylacetate. Activity levels of enzymes involved in purine metabolism, as 5'-nucleotidase (5'-AMPase) and nucleotide phosphodiesterase (PDAse), in ion transport as adenosine triphosphatase (Na-K)Mg-ATPase and alkaline phosphomonoesterase (PNPase), in aminoacid transport as γ-glutamyltranspeptidase (GLUPA) were assayed at saturating concentration of the substrate. Cells of the Hodgkin lymphomas were characterized by a high level of 5'-AMPase (> 90 nmole/hr/10^6 cells) and GLUPA (> 32 nmole). In non-Hodgkin lymphomas with a low proportion of lymphoid cells of both T and B origin, generally reduced enzymatic activities were recorded with the exception either of the (Na-K)Mg-ATPase (> 346 nmole/hr/10^6 cells)-only slightly inhibited by ouabain- or of the PDAase (> 80 nmole). In cases with an important proportion of lymphoid cells of both B and T type the 5'-AMPase displayed a high activity (> 54 nmole/hr/10^6 cells), whereas cases with a majority of cells bearing surface immunoglobulins (> 65 % of cells were positive to IgM/λ antisera) denoted a low activity level of each enzyme. Thus, it may be concluded that the morphological heterogeneity of non-Hodgkin lymphomas is also reflected by different enzymatic properties.

P8

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

B. VAN DEN HEULE, C. NICAISE, V. BIGIRIMANA, Institut J. Bordet, 1000 Brussels, BELGIUM.

Sequential occurence 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 mediastinal masses. Infiltrates 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 described in Hodgkin's disease and further aggravated by extensive combined modality treatment. Yet, considering the possible lymphocytic nature of the Sternberg cell, a "sarcomatous" 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.

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KINETICS OF THE INCIDENCE OF FUNCTIONALLY DOMINANT RING SHAPED NUCLEOLI (RN) IN LYMPHOCYTE NUCLEOLAR TEST IN HODGKIN'S DISEASE (HD). Z.Dienstbier, K.Smetana, S.Vasilu-ková, V.Foltýnová, M.Vohnoutová, M.Šámal. Charles University and Czechoslovak Academy of Sciences, Prague, Czechoslovakia.

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 desease. In contrast, the increased number of these cells shows a favourable prognosis of 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 are less influenced by the therapy but reacts with infectious complications.

	number of persons/examinations	absolute number of lymphocytes with dominant RN in mm^3	
		$\bar{x}$	S.E.M.
healthy controls	72/204	1 869	39
HD - untreated	19/ 31	1 260	17
HD - complete remission	12/ 73	900	6
HD - relapse	15/ 20	620	26

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 nucleolar test.

P10

ANGIO-IMMUNOBLASTIC LYMPHADENOPATHY: A MALIGNANT LYMPHOMA DUE TO NUCLEAR DNA CONTENT. H.H. Common and A. Böcking, Department of Int. Medicine and Department of Pathology, University of Freiburg, 7600 Freiburg, FRG

There is considerable controversy as to whether Angio-Immunoblastic Lymphadenopathy (AIL) is a benign, premalignant, or malignant disease. Lymph nodes from 10 previously untreated patients were studied. Imprints were made either from freshly cut lymph nodes immediat ly after surgical removal or from formalin-fixed lymph node biopsies. Feulgen microspectrophotometry was performed with an integrating microdensitometer (Vickers M 86) on individual cells. DNA-Histograms and malignancy grading revealed the following results: 1.) Within the mixed cell population there was one population of large cells with 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 und Sommerkamp, H: 32. Kongr. Deutsche Ges. Urol., 10.-13.9.1980, Berlin), AIL evolved to exist in different grades of malignancy. Two patients had grade I DNA-malignancy, 5 patients had grade II and 3 patients had grade III. 3.) Clinical courses correlate with the degree of aneuploiy, i.e. DNA-malignancy grading. Patients with grade I had the longest and those with grade III had the shortest survival times. These results support our earlier contentions, that AIL is in most cases a malignant lymphoma (Sandritter, W and Grim H: Beitr. Path. 160, 213-230, 1977; Common, HH: Verh. Deutsch Ges. Inn. Med. 86, 484-487, 1980).

P11

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

Fine needle aspiration was utilized as a diagnostic aid in 194 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 used 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 oncomplete information with the risk that this could be clinically misleading. This latter can be avoided or minimized in a clinic situation where the pathologists and clinicians cooperate as a closely funcioning team.

P12

ON THE NATURE OF BONE MARROW INVOLVEMENT IN AGGRESSIVE NON-HODGKINS LYMPHOMA. P. Klimo, H. Pontifex, C.C.A.B.C. Vancouver, B.C. V5Z 3J

Involvement of the bone marrow with non-Hodgkins' Lymphoma has be regarded as an ominous sign. Patients in this category are conside ed to have a poor prognosis, and as a result they tend to be treated aggressively. Yet the rates of complete remission have been disappointingly low. Many of these patients will never be disease free, 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 confir med, may substantially change the views on the nature of this phenomenon. This, in turn, may alter our views 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 lymphoma cells infiltrating bone marrow, and the lymphoma cells 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 distinct group of patients who, if treated to complete remission in the extramedullary sites, showed an unexpected long survival, even on r 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 corrobrated the following points in our hypothesis:

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

b) The compartment of well differentiated lymphoms cells may be reduced by aggressive therapy but it cannot be erradicated. This means that the patients are treatable but not curable.

c) Persistance of well differentiated cells in the marrow in otherwise asyptomatic patients does not necessitiate continuation of aggressive induction therapy. It may not require, at least temporarily, any therapy at all.

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[1,3], Nissim Haim[1], Ron Aplebaum[1], and Oren Zinder[2], the Department of Oncology[1] and Clinical Biochemistry[2], Rambam Medical Center, Haifa, Israel; and the Department of Radiation Oncology[3], Rhode Island Hospital, Providence, Rhode Island, U.S.A.

Serum Copper Levels (SCL) is a nonspecific 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 follow-up monitoring of patients with 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 150.3± 44.5. This was significantly (<0.0001) higher than 120.4±23.3 of the healthy controls (N=37). The SCL for the different subgroups: Stage I, II, III, IV, AD, and NED were respectively (N=16) 131.8±43.6, (N=14) 177.1±65.7, (N=12) 180.9±40, (N=13) 157.7±49.6, (N=16) 167±30.5, and (N=44) 132.±27.7. There was no significant difference between mean SCL of Stage I patients and either 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 II-IV or AD (P<0.0001). There were 62 males and 53 females. The mean SCL values were 138.4±36.2 and 164.1±49.4, respectively. This difference was significant at P=0.02. Of 71 untreated patients, there were 26 DLPD, 21 DH, and 10 NLPD patients. The SCL values are respectively 166.7±55.6, 154.9±45.2, and 185.8±43. The difference is not significant. One hundred and sixty-three determinations of SCL were done in patients with NED. 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 therapeutical results in 113 patients (pts) with NHL treated with chemotherapy alone or chemotherapy plus «iceberg» radiotherapy have been investigated.

43 pts were «well differentiated lymphocytic» (WDL), 48 «poorly differentiated lymphocytic» (PDL), 22 «hystiocytic» (H) type.

27 pts had stage II, 42 stage III and 44 stage IV.

Pts with active epatitis, recent myocardial infarction or clinically evident emolysis were excluded; no pt had received prior chemotherapy.

46% of all pts showed an initial extranodal (EN) tumour deposit (liver, bone marrow, G.I., lung, CNS).

LDH assay was performed employing the Technicon SMAC (normal values, 98-230 U/lt). Pretreatment LDH values were provisionally divided into 3 groups: 1) within normal range (<250 U/lt); 2) moderately increased (from 250 to 500 U/lt); 3) highly increased (>500 U/lt). Statistical analysis, however, did not show differences between groups 2) and 3).

LDH exceeded normal values at presentation in 46 pts (41%).

Increased LDH levels were associated with: a) a poor response to therapy: overall 15% complete responders versus 51% (WDL: P = .003; PDL: P = .001; H: P = .027) b) a significant reduction of survival: overall 31% surviving versus 89% at 36 months (WDL: P<.001; PDL: P<.001; H: P<.05).

EN pts had an overall shorter survival at 36 months: 48% surviving, versus 76% for the nodal cases (P<.005).

However, those EN who presented with an initially increased LDH, had survival shorter than similar cases presenting with normal LDH (overall 19% surviving versus 78% at 36 months; P<.001).

Conclusions: serum LDH behaves as a good prognostic index of therapeutic response and of survival in NHL. Besides, LDH still maintains this prognostic value within the cohort of pts with extranodal deposits.

P15

SERUM ISOFERRITINS IN HODGKIN'S DISEASE (HD). M. Cazzola, P. Arosio, P.G. Gobbi, G. Barosi, C. Iacobello, E. Ascari. Patologia Medica 1 and Clinica Medica 1, Pavia, Chimica Biologica V, Milan, and Istituto di Chimica, Brescia.

In a number of studies, elevated concentrations of serum ferritin were found in patients with HD independently of storage iron. Among the possible causes of ferritinaemia, abnormal ferritin production by the tumour has been suggested. However, determination of serum ferritin in HD has been always performed using assays for basic (liver or spleen) ferritin, while recent studies have indicated that malignant cells synthetize ferritin phenotypes with more acidic isoelectric points.

We raised in mice antibodies against acidic ferritin extracted from HeLa 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 reticulo-endothelial 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

THE PROGNOSTIC SIGNIFICANCE OF SERUM BETA 2 MICROGLOBULIN LEVELS IN THE MALIGNANT LYMPHOMAS

J.A.Child and E.H. Cooper, Department of Haematology, The General Infirmary, Leeds LS1 3EX and Unit for Cancer Research, University of Leeds, U.K.

Beta 2 microglobulin forms the light chain of HLA on the surface of all nucleated cells. Changes in serum β2m 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 β2m response may reflect important differences in cell biology, but the contribution of individual cell types is still uncertain. In a multicentre study of 254 patients with non-Hodgkin's lymphomas (NHL), serum β2m 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 β2m levels $>$ 3.5mg/l than in those with initial levels $<$ 3.5mg/l. These findings are compared and contrasted with those seen in related neoplasia: in Hodgkin's disease, the levels of β2m are raised less frequently and do not appear to have a direct relationship to prognosis; in chronic lymphocytic leukaemia the β2m levels correlate with tumour mass as assessed clinically by staging but give no indication as to prognosis over 2 years, whilst in myelomatosis there is a strong correlation between serum β2m, tumour load and prognosis.

Additional findings in NHL sub-sets based on longitudinal studies of up to 5 years will be presented.

Serum β2m may have a useful rôle in the stratification of patients with NHL and thereby aid therapeutic decision-making and clinical trial.

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P17

SERUM α1-ACID-GLYCOPROTEIN, HAPTOGLOBIN AND C3 IN HODGKIN'S DISEASE. A COMPARISON WITH OTHER ACUTE PHASE INDICATORS. P.G. Gobbi, G. Merlini, G. Attardo Parrinello, P. Cavalli, E. Ascari. Istituto di Patologia Medica I, University of Pavia, Pavia 27100, Italy.

Serum α1-acid-glycoprotein (α1S), haptoglobin (Hp) and complement fraction 3 (C3) were measured in 85 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 α1S 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 seric 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 α1S.

By a logistic discriminant analysis the ability of α1S, Hp and C3 to discriminate between disease activity and remission was compared with that shown by erythrocyte sedimentation rate (ESR), total α2-globulinaemia (α2), fibrinogenaemia (Fb), plasma copper (Cu) and iron (Fe), all data being collected at the same point in time in each patient. The well-known discrimination ability of combined Cu and Fe (75% of correct classifications) could be further improved by α1S much more than by Hp, C3, ESR, α2 and Fb singly computed. The number of correct classifications of patients made by combined Cu, Fe and α1S (81%) is very close to the maximum allowed by all the eight indexes together (82%). Such three laboratory tests can be considered the most reliable acute phase indicators for Hodgkin's disease out of the here evaluated ones.

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THE CLINICAL USEFULNESS OF ACUTE PHASE PROTEIN FRACTIO IN THE COMBINED CYTOSTATIC TREATMENT OF PATIENTS WITH MALIGNANT LYMPHOMA

I. TÓTH, M. OSVÁTH, S. ECKHARDT
National Institute of Oncology, Budapest, Hungary

Our aim was to study the changes of two acute phase protein fractions: ceruloplasmin /Cp/ and haptoglobin /Hp/ 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 i Hodgkin's disease and CVP or CHOP-Bleo. in non-Hodgkin lymphoma. Examined parameters were determined before e cycle of cytostatic treatment and following it at the time of control examinations.

A rapid and early fall of serum Hp and especially of C already after the initial cycle of treatment with COPP and ABVD was followed in every case by complete remiss in stage III and IV Hodgkin lymphomas. Only a decreasi trend of these values frequently not reaching the norm range was observed in partial remissions. Interestingl in stage II partial remission was not accompanied by a decrease of Cp and Hp 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 he in the prediction of the effect of chemotherapy.

In patients with non-Hodgkin lymphoma treated by CVP o CHOP-Bleo. only the changes of serum Hp has prognostic and therapeutic value.

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THE BFM STUDY 1976/80 ON CHILDHOOD NON-HODGKIN'S LYMPHOMA (NHL): PROGNOSTIC RELEVANCE OF CLINICAL STAGE AND HISTOLOGY/IMMUNOLOGY. St.Müller-Weihrich, G.Henze, B.Kornhuber, H.-J.Langermann, R.Ludwig, D.Niethammer, J.Ritter, H.Riehm. Dept.of Pediatrics, Universities of Berlin-West, Frankfurt/M., Freiburg, Heidelberg, München-Schwabing, MÜnster/Westf., Tübingen, Federal Republic of Germany.

111 children from 16 institutions with all varieties of NHL entered the NHL study BFM 1976/80. In addition to local therapy all patients received the slightly modified 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 (widespread abdominal and/or CNS disease) more chemotherapy (therapy B2) than in the standard group (therapy A) was given. Several subgroups were defined based on clinical staging (WOLLNER), histology (Kiel-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-CCR after 3 to 5 years was calculated by life table analysis, including non-responders and deaths from various reasons after initiation of therapy.

	n	p-CCR after (mths)
All patients, stages I-IV	111	0.62 +/- 0.06 (73)
All patients, stages I and II	40	0.84 +/- 0.06 (73)
All patients, stages III and IV	71	0.50 +/- 0.08 (64)
O-NHL/T-NHL, stages I-IV	46	0.70 +/- 0.12 (64)
O-NHL/T-NHL, stages I and II	9	0.72 +/- 0.17 (35)
O-NHL/T-NHL, stages III and IV	37	0.72 +/- 0.12 (64)
B-NHL, stages I-IV	49	0.56 +/- 0.07 (62)
B-NHL, stages I and II	25	0.83 +/- 0.08 (62)
B-NHL, stages III and IV	24	0.29 +/- 0.09 (33)
NHL of unknown type	16	0.59 +/- 0.13 (73)

Conclusions: 1) Origin of NHL from lymphocyte subsets and clinical stage are the most important prognostic factors. 2) Chemotherapy used in this study is highly efficient in O-NHL and T-NHL, but not in disseminated B-NHL. For these patients a new therapeutical concept has to be developed.

(Supported by the Stiftung Volkswagenwerk)

P20

EVALUATION OF PROGNOSTIC FACTORS IN NON HODGKIN'S LYMPHOMA: AN APPLICATION OF THE "MULTIPLE CORRESPONDANCE ANALYSIS" TECHNIQUE. M. Van Glabbeke, M. Buyse, P. Carde, M. Burgers, R. Somers, M. Qa M. Hayat; E.O.R.T.C. Data Center, Brussels, Belgium; Séminaire de statistique, Institut d'Education 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 lym oma is influenced by several factors, correlated between themselv analyses by classical statistical methods may be complex and requ large samples of patients. The "multiple correspondance analysis" allows to visualize these factors, their correlations and their prognostic value for survival and response to therapy.

"Factorial axes" are first calculated, taking the pattern of corr ation between all factors into account; "factorial axes" can be taken two by two to constitute successive "factorial plans"; all levels of all prognostic factors can be projected on these "facto ial plans" and response and survival categories superimposed.

All correlations can be estimated from the distances in the facto ial axes system, and visualized on the factorial plans.

This method has been applied to a sample of 162 patients with pri ary stage III or IV non Hodgkin's lymphoma, entered in the study RC20751 of the EORTC radio-chemotherapy cooperative group, betwe 1975 and 1980.

Induction and maintenance therapy were allocated by randomization between two standardized treatments.

Potential prognostic factors taken into account are pathology (ce pattern, Rappaport, Kiel and Luke's classification), presentation the disease (involved sites and Ann Arbor stage) age, sex and trea ments.

The successive computed factorial axes correspond to "cell patter "cell type" (Kiel classification being the best one), "liver, sple bone marrow, mediastinal and hilar nodes involvement" and "other nodes involvement".

Short term survival is correlated with initial cell pattern; over- all survival is correlated with cell type.

Response is correlated with liver, spleen, bone marrow, mediastina 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.

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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, 41 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
E. Brusamolino, M. Lazzarino, G. Castelli, G. Pagnucco, P. Isernia and C. Bernasconi. Divisione di Ematologia Policlinico S. Matteo Pavia

We reviewed 251 consecutive adult patients with Hodgkin disease treated at Division of Hematology of Policlinico S. Matteo of Pavia from January 1970 through December 1979, to assess the risk of development of acute leukemia. The median time of follow-up was of 48 months (range:6-135 mos.). Eighteen patients (7%) were treated with intensive radiotherapy alone (STNIor TNI), 70 (28%) with chemotherapy alone (MOPP or MOPP+ABVD) and 163 (65%) with both radiotherapy (STNI or TNI) and combination chemotherapy (MOPP or MOPP+ABVD for relapses). The cumulative time-risk of developing leukemia was definied as person-years at risk, calculated for the whole series (1073 person-years), or separately for each group of treatment (RT:50,CT:236,RT+CT:787 person-years). No leukemias occurred in 88 patients treated with RT or CT alone. Six cases of acute leukemia were observed in the group of patients treated with RT+CT (crude rate of 7.5 per 1000 person-years at risk). Five patients belonged to TNI+MOPP treatment group and a single was given inverted Y RT followed by procarbazine 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 sistemic simptoms. 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 onset of leukemia ranged between 32 and 90 months. The actuarial probability of leukemia at five ans seven years was 2.9% and 4.7% for the entire group of patients, 3.8% and 5.3% for the combination therapy group. All leukemia,except one, had a preleukemic phase lasting 1to 6 months with pancytopenia, basophilic stippling in erythrocytes, circulating erythroblasts and dysplastic marrow (atypical erythroblasts and magakaryocytes, excess of blasts). The morphology of overt leukemia was myeloid or myelomonocytic in four cases, promyelocytic and unclassifiable in the other two cases. The response to therapy was poor in all cases with a median time of survival from the onset of leukemia of 4 months (range:1-9+ mos.). In conclusion: a)the observed risk of developing subsequent leukemia in patients with Hodgkin disease treated with combined modalities should be carefully considered in planning the future therapeutical protocols, particularly in patients with disease limited to one side of the diaphragm and without sistemic simptoms (RT alone without adjuvant chemotherapy),or, conversely, in patients with sistemic simptoms 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 Andrieu,ME Ochoa-Molina, 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, 7201 P2, 7202C2). All were between 16 and 45 years old at diagnosis ; none received subdiaphragmatic irradiation; allwere in persistent complete remission. Before treatment, all had regular menses ;70 pregnancies occured ; the median age of the 36 primigravide was 25 ; 61 children were born, 2 with minor abnormalities. After therapy, oligo or amenorrhea occured 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 occured in 22 women ; the median age of the 14 primigravida was 27 ; 22 children were born , 1 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

RESULTS OF TREATMENT AND COMPLICATIONS ENCOUNTERED IN HODGKIN'S DISEASE LONG-TERM SURVIVORS. V.Vecchi,P.Rosito,L.Serra,A.Pession,M.P.Villa,A. Cascio,A.Balsamo. Department of Pediatrics, Bologna University (ITALY)

Twenty children,15 ♂ and 5 ♀ ages 2 through 13 years,with pathological stages I,II,III Hodgkin's disease were treated with chemotherapy plus radiotherapy from 1969 to 1978. Pathologic stages I and II disease were 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 III are now off-therapy. The other 5 patients stage III disease 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 follows: -growth and development:a modest retardation of height and crown-rump length occurred particulary in boys who received at least mantle or abdominal radiotherapy 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 showed significant increased peak GH response. At present time the interpretation of these interesting data is difficult. All patients were clinically euthyroid. Thyroid function studies done in 13 patients showed significant increased TSH values and normal levels of T_3,T_4.The basal gonadotrophins,testosterone, estradiol serum levels and the peak responses 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 serum gonadotrophins 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,had a severe paramediastinal fibrosis with restrictive ventilation disorder and left ventricular function disorder. Besides he showed a decreased crown-lung length, a significant scoliosis,a thin neck and narrow interscapular distance. Of the 13 patients receiving mantle radiation 4 had scoliosis. No evident psycological difficulties were seen. -immunological status:all patients were found to have marked depression of their lymphocytes blastogenic response to mitogen phytohemoagglutinin (PHA). Skin-test reactivity to intradermal antigen (PPD,Candida Albicans,Streptokinase-Streptodornase) was normal but there was high percentage of subjects with skin anergy to PHA. No abnormality of serum immunoglobulins was found. B-cells were not significantly decreased in our series. No increased susceptibility of serious infections was observed. Splenectomy did not increase the incidence of infection (all patients received penicillin prophylaxis).

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

J.Z. Fuks, J. Aisner, P.H. Wiernik.
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 lymphoma appears similar regardless of the level of clinical response achieved (complete or partial response). The clinical course of 100 patients with non-Hodgkin's lymphoma treated on a randomized study (CAVP vs. CVP) were reviewed to determine the accuracy 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, ^{67}gallium scans, 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%) fatty infiltration, fibrosis or benign hyperplasia of lymph nodes were found. Among the 17 pre-operative lymphangiograms there were 13 (78%) false positive, no false negatives, 2 (11%) true positive, 1 (5.5%) true negative, and one equivocal results. Among the 18 pre-operative ^{67}gallium scans there were 5 (27.5%) false positive, 2 (11%) false negative, 1 (5.5%) true positive, 8 (45%) true negative and 2 equivocal results. Among 5 patients who 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 found to be in histological complete response, 12 remain alive, (10 continue in complete response), 1 died as a complication of surgery, and 2 died without residual disease. The median survival for the 16 patients is 35+ months (range 0-80+ months) after laparotomy. Restaging procedures such as lymphangiograms and ^{67}gallium scan are inaccurate and second look operations are needed for appraisal and correlation of response and survival.

P26

STAGING LAPAROTOMY IN HODGKIN'S DISEASE: A BRITISH NATIONAL LYMPHOMA INVESTIGATION STUDY. T. S. Worthy, Regional Radiotherapy Centre, Leeds, LS16 6QB, England.

This study, begun in 1970, comprised patients with Clinical Stage I & IIA (upper half) Hodgkin's Disease (HD) included in a randomised trial comparing local field with extended field radiotherapy (Clin. Rad, 1981, in the press). Staging laparotomy was not mandatory but 400 of 610 patients were staged pathologically (PS). 88 (22%) became Pathological Stage III, in 61 (15%) the spleen was involved, 6 (1.5%) had liver involvement. Laparotomy patients were significantly younger (P 0.001) and had a higher proportion of Stage I (P 0.001). Actuarial survivals to 10 years were: laparotomy 88%, no-laparotomy 72% (P 0.01); PS Stage I & II 90%, PS Stage III & IV 81%. Comparison of sub-groups showed a significantly worse prognosis only in males over 45 years (P 0.03). DFS were 53% for laparotomy, 37% for no-laparotomy (P 0.04); 57% and 44% when adjusted for adjacent area recurrence in the local radiotherapy group. Following laparotomy, initial recurrence in the abdomen was 6% compared with 30% without laparotomy. In Stage III the spleen was involved in 70%. Splenic involvement produced no difference in survival (S + 67%, S - 78%, P 0.50) but DFS was significantly worse (S + 23%, S - 70% P 0.02). Laparotomy mortality was 0.5%, major morbidity 1%. Our experience over 10 years indicates that increased selectivity is required in advising laparotomy in females as this produces no increase in survival - a result of the high response rate to chemotherapy or radiotherapy for recurrence. For those males over 45 years who are unsuitable for laparotomy, radiotherapy should be supplemented by chemotherapy.

P27

Malignant lymphomas involving the gastrointestinal tract
(A report on 38 cases)

H.Huber, C.Gattringer, M.Aufschnaiter, Ch.Huber,
E.Steiner, G.Leitner and G.Weiser.

Department of Medicine, Department of Surgery,
Department of Pathology, University of Innsbruck, Austria

Thirty eight patients with lymphomas of the gastrointestinal tract were included in this retrospective study. Localisation of the lymphomas, staging, histology and response to therapy were investigated.
The stomach was involved in 30 cases (79 %), the small bowel in 5 and the colon in 1 case. In 2 cases involvement of the stomach plus ileum and ileum plus colon were found, respectively. At the time of diagnosis 15 patients were stage I_E, 14 stage II_E, 2 stage III_E, and 7 stage IV_E. The histological examination according to the Kiel classification revealed 14 low malignant lymphomas (including 7 centroblastic/centrocytic) and 22 high malignant lymphomas (including 16 immunoblastic). One M.Hodgkin (stage II_E) was seen in addition. 16 out of the 22 high malignant lymphomas (73 %) were stage I or stage II.
The exact clinical course could be evaluated in 28 patients. The principle therapeutic approach was a surgical resection of the tumor burden. A complete tumor resection was possible in 13 patients (of total 27 undergoing surgery). A cytotoxic and/or radiotherapeutic treatment was applied to 20 patients. The cytotoxic regimen for low malignant lymphomas consisted of a monotherapy (chlorambucil) or CVP. In high malignant lymphomas the C-MOPP regimen was usually employed.
Fifty percent (14/28) achieved a long time complete remission. The observation time is 28 months (median). The median survival (according to the life table method) has not been reached at 5 years. The probability of a 5-year survival was 62 %.
The therapeutic strategy emerging from this study is finally discussed.

P28

Malignant extra nodal non-Hodgkin lymphoma (NHL) in the head and neck region.

J.Th.P. Janssen, D.J.Th. Wagener, V. Duurkens, P. van den Broek, M.J.J.T. Bogman, I. Kazem; St Radboud Hospital, University of Nijmegen, Nijmegen, The Netherlands.

Eighty five patients with primary extra nodal NHL of the head and neck region were treated in the periode 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 I and II towards stage IV.
Staging laparotomy with splenectomy performed on 7 of 54 patients with stage I and II disease and with a diffuse histologic 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 lymphohistiocytic 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%, 66% and 89% CR resp., whereas the treatment of patients in stage IV resulted in 36% CR.
The 5-years actuarial survival of patients in a CR was 53% and 10-years survival 46%. All patients who did not respond to treatmer died within a year.
The prognosis of stage II patients in a CR was worse than that of patients in stage III and IV. Patients with stage IV who survived longer than one year seemed to be apparently cured.
Patients with lymphocytic type of lymphoma had higher tendency for relapse. The survival of patients with nodular lymphoma is better than with diffuse lymphoma.

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HIGH INCIDENCE OF ECHOCARDIOGRAPHIC PERICARDIAL EFFUSION IN NON-HODGKIN'S LYMPHOMA.

G.C. Acquatella, E.T. Roura, 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/IV and 6 (19%) were in stage I/II.
Echocardiographic examination of the heart revealed that 17 patients (65%) 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. Pericardiocentesis in 5 patients disclosed lymphoblasts by cytocentrifuge 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 78% 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 neoplasic infiltration, except in patients with lymphoblastic lymphoma where it may be a useful tool for diagnosis.
Patients with neoplasic cells in the pericardial fluid were treated as the whole group with sistemic 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 IN CHILDHOOD ACUTE LYMPHOCYTIC LEUCEMIA AND LYMPHOMA.

O. Metz, W. Stoll and W. Plenert. Department of Pediatrics (Carl-Zeiss-Stiftung) and Department of Nuclear Medicine, Friedrich-Schiller-University, 6900 Jena, GDR

Since January 1,1972, 86 children who,between the ages of 7 months and 16 8/12 years,developed an ALL or a non Hodgkin-Lymphoma(NHL), have been given i.th. injections of 198Au-colloid and methotrexate. Depending on their ages, the children received a single i.th. injection of radiogold activity between 1.24 and4.89 mCi (45.88-181MBq) instead of telecobalt irradiation. Since May 1980 such patients as were treated according to the LSA_2L_2-protocoll have, trough 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 arachnoidea,The tumoricide effect (beta rays) extends selectively over the distribution space of the latent meningosis leucaemia. The brain parenchyma is spared by the betarays, which extend only for 3,6mm. The weak gamma radiation make scintigraphic control possible.Patients: ALL=76 children(41boys and 35 girls) and NHL=10 children(8boys and 2 girls). Results: 6o out of the 86 children are still alive.As per March 31,1981, the average period of remission was 30 months.The following relapses occured:20 children developed a marrow relapse(23.3%), 2 children a simultaneous marrow-meninges relapse(2.3%), 8 children a primary meningosis leucemia(9.3%), and one child a retrc bulbar nervus opticus infiltrate.After a cytostatic therapy of about 36 months the treatment of 36 out of the 86 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 meningosis leucemia. Side effects: After radiogold injections 9 children had headaches, nausea and vomiting (10.5%), and 5 children ran a fever (5.8%). These complaints did not last longer than 24 hours. Later complications such as apathy syndrom or leukencephalopathy were not found in any of the patients. Reexamination by means of coputertomography revealed no radiogenic brain parenchyma lesions after 198Au-colloid.

P31

Primary Non-Hodgkin's lymphoma of the CNS. Results of radiotherapy in 15 cases. D. GONZALEZ GONZALEZ, DEPART. OF RADIOTHERAPY, UNIVERSITY HOSPITAL, WILHELMINA GASTHUIS, 1054 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; negative lymphography; normal bone marrow aspirates; 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 badly demarcated 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 5 years after treatment. The other patients died within 2 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.
Our cases will be compared with other reported series in the literature and implications for the treatment of this disease will be discussed.

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PRIMARY CNS-LYMPHOMAS: CLINICO-PATHOLOGICAL FINDINGS, CSF-CYTOLOGY AND IMMUNOLOGY.

U. Bogdahn, D. Dommasch, P. Wünsch, H. Krüger, K. Pflughaupt, R. Wodarz, R. Rohkamm. Neurologische Universitätsklinik Würzburg, 8700 Würzburg, Germany.

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 unspecific 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 unspecific reactive changes from typical lymphomatous disease is discussed. Combination of CT-findings, cytological and immunological examination of CSF make an early clinical diagnosis possible.

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F. Lauria , M. Fiacchini, P. Mazza and S. Tura
Istituto di Ematologia "Lorenzo e Ariosto Seràgnoli", 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) have been 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 I A, 8 as stage II A, 3 as stage II B and 1 as stage II_EB. 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 rads) ,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 disappearence 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 neurotoxicity) 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 Olweny, who treated Ugandan children with early stage HD with MOPP chemotherapy and suggest of CR and survival rates comparable with, perhaps better than, those achieved with radiotehrapy alone. Thus 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.

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

Peter H. Wiernik, 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 yields superior response rate, response duration, and survival compared to treatment with MOPP alone for patients with advanced Hodgkin's disease. Twenty patients received MOPP alone (12 currently evaluable) and 21 received MOPP-SCAB (15 currently evaluable). 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 30 years (range 17-63) and 11 of the 15 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 has died. Another MOPP patient died in CR from infection during drug-induced granulocytopenia. The other MOPP CR patients remain in CR from 1+ to 22 + months. Fourteen of 15 (93%) evaluable MOPP-SCAB patients achieved CR and 3 have 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 nonresponder (stage IV A, MC histology, age 63 years) died of Hodgkin's disease

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, 14 % of MOPP alone courses were delayed because of pancytopenia compared to 4 % of MOPP-SCAB courses. Two epsiodes of bacteremia, 3 of Herpes zoster, and 4 of fever of unknown origin occured with MOPP alone whereas only 2 episodes of fever of unknown origin occured 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 accure patients.

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TREATMENT OF MOPP-RESISTANT HODGKIN'S DISEASE WITH ADRIAMYCIN, BLEOMYCIN, VINBLASTINE AND IMIDAZOLE CARBOXAMIDE (ABVD). F. Mandelli; C. Biagini; A.P. Anselmo; R. Maurizi-Enrici; A.M. Testi; F. Mauro; A.M. De Luca; S. Amadori and G. Papa. Institute of Hematology, University of Rome, 00161 Roma, and Institute of Radiology University of Rome, 00161 Roma, ITALY.

Twenty patients (pts) with advanced Hodgkin's disease resistant to MOPP were treated with the chemotherapy combination ABVD (adriamycin, bleomycin, vinblastine and imidazole carboxamide).
Complete response (C.R.) 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 15 pts. showing progressive disease during primary therapy with MOPP. Eight of ten complete responders have remained continously 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.

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COMBINATION TREATMENT FOR ADVANCED HODGKIN'S DISEASE (HD), V. Fosser, L. Salvagno, L. Endrizzi, A. Paccagnella, P. Sperandio, O. Vinante, 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 (pts) with advanced HD, entered into 3 programs.

- Program 1 (for stages (sts) IIAS+, IIIAS-): Total Nodal Radiation (TNR) + 6 MOPP.
- Program 2 (sts IIBS-, IIIAS+, IIIBS-): TNR + 6 MOPP + 12 ABVD doses.
- Program 3 (sts IIBS+, IIIBS+, IVA, IVB): 6 MOPP + 12 ABVD + Radiation Therapy (RDT) 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 IVB) having extranodal involvement as follows: liver 15 pts, lung 8, bone 5, bone marrow only 1, multiple sites including bone marrow 2).
85 overall pts (81%) obtained a complete remission (94% in IIIAS- pts, 95% in IIIAS+, 70% in IIIB, 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 now 7 relapses and 4 deaths (possibly treatment related).
Tolerance of treatment has been good in programs 1 and 3, while for program 2 the long duration of treatment and the haematological depletion, required in a majority of pts to stop tratment just after completion of RDT.
In stage IV the same survival (and DFS) has been obtained as in stage IIIB and IIIBS+; we would stress that 5/8 pts resistant to MOPP, obtained full remission after ABVD and 3 further pts after iceberg RDT.
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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REMISSION AND FAILURE IN STAGE III AND IV HODGKIN'DISEASE TREATED BY MOPP.

Cl.JACQUILLAT, G.AUCLERC, M.F.AUCLERC, M.WEIL
Hôpital Salpétrière Service d'Oncologie Médicale, 47 Boulevard de l'Hopital 75651 PARIS Cedex 13 FRANCE

224 patients with stage III and IV Hodgkin'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 received Vinblastin maintenance combined to "reinduction" courses of MOPP (68 patients) or to irradiation (57 patients).
At twelve years remission curves are "plateauing" at 75 % for those patients who achieved C.R. and 48 % 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 lymphoma" heralding an unfavorable prognosis.
The lymphogram picture should thus been included as parameter of initial classification and treatment active in "non Hodgkin lymphoma" such as CHOP should be tried in these high risk patients.

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

In a phase II trial of DVA in a dose of 2-4 mg/M^2/week I.V., 4/26 Hodgkin's disease (HD) 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/M^2 I.V. on days 1 and 8 was combined with CCNU (100 mg/M^2 p.o. day 1) and melphalan (6 mg/M^2 p.o. day 1-4)-CAD. Since 9/79 13 patients heavily prior treated with MOPP and or ABVD have been treated with CAD. Among these patients there has been 1 complete remission (CR), 4 PR, 2 minor responses (MR) and 6 who failed to respond. Our 8 drug trial in which MOPP was alternated with ABVD in combination with low dose radiotherapy (RT) resulted in a CR in 50/57 (88%) and a PR in 7/57 (12%) previously-untreated patients with advanced HD with only a 16% relapse rate at 36 mo. (Clin. Bull. 10:138-143, 1981). In an attempt to improve upon these results, CAD was added as a third non-cross resistant combination. Dacarbazine was dropped from ABVD to reduce nausea and vomiting. CAD in alternating sequence with MOPP and ABV combined with low dose RT was randomized versus MOPP/ABVD/low dose RT for untreated patients with stages IIB, IIIB and IV HD. Since 2/79, 21 patients have received CAD/MOPP/ABV/RT and 21 MOPP/ABVD/RT. Among patients evaluable for response on CAD/MOPP/ABV/RT 12/15 (80%) are in CR and 3/15 (20%) in PR. For MOPP/ABVD/RT 13/18 (72%) are CR, 3/18 (17%) in PR and 2/18 (11%) failed to respond. Thus far remission rates with CAD/MOPP/ABV/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$_2$-L$_2$ PROTOCOL.

V.Vecchi,P.Rosito,F.Vivarelli,A.F.Mancini,A.Pession,L.Serra,G.Paolucci
Division of Hematology-Oncology; Department of Pediatrics, Bologna University (ITALY).

From 1976 to 1980, 28 previously untreated children with non-Hodgkin's lymphoma were staged and treated with a modified version of the LSA$_2$-L$_2$ protocol proposed by Wollner: stage III and IV had, in addition, prophylactic treatment of the central nervous system (CNS) with cranial irradiation (2400 or 1800 rad) plus intrathecal methotrexate. Twenty-seven of twenty-eight patients achieved complete remission (96,42%). The disease-free actuarial survival is 73%. The median remission duration is 28+ months (range 3+ to 56+ months). The disease-free actuarial is 100% for 6 children with stage I-II disease and 64% for 22 stage III-IV children after a median observation times respectively of 25+ and 24+ months. None of the 21 high-risk patients that achieved a complete remission developed CNS-disease after prophylactic treatment. There were 6 relapses, all on therapy;of these 6 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 times range from 38+ to 57+ months from diagnosis. No drug-related or infectious death occured but 70% of these patients suffered serious toxicity in the consolidation phase. Mielotoxicity 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$_2$-L$_2$ coupled with CNS prophylaxis had considerably improved the prognosis of non-Hodgkin's lymphoma in children, even if further modification of this treatment (chemotherapy, surgery and radiotherapy) or alternative therapeutic approaches are required for increasing disease-free survival of patients with ominous 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 LYMPHOBLASTIC LEUKEMIA (T-ALL)

G.Henze, H.-J.Langermann, W.Brandeis, A.Jobke, U.Lasson, S.Müller-Weihrich, G.Schellong, J.Treuner, H.Riehm. Dept. of Pediatrics, Universities of Berlin-West, Freiburg, Heidelberg, Kiel, München-Schwabing, Münster/Westf., Tübingen, Federal Republic of Germany.

From October, 1970, to December, 1980, 72 children and adolescents were treated for T-NHL and T-ALL in BFM 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 IV pts was < 25 %, i.e. no cases of ALL included. T-ALL was diagnosed by either the presence of an anterior mediastinal mass (THY) and/or positive immunology (E+). All patients were given the West-Berlin 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/mm^3) 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 diagnostic criteria and therapeutic regimens is given in the table.

	n	Treatment A/B	p-CCR after (mths
T-NHL/T-ALL	72	48 / 24	0.67 +/- 0.07 (127
T-NHL 75	35	30 / 5	0.68 +/- 0.14 (64
T-ALL 70 - 79	37	18 / 19	0.64 +/- 0.08 (127
ALL 70/76 THY	15	15 / 0	0.47 +/- 0.13 (127
ALL 76/79 THY	14	1 / 13	0.79 +/- 0.11 (52
ALL 76/79 E+	15	3 / 12	0.73 +/- 0.11 (53
ALL 76/79 E+/THY	22	3 / 19	0.77 +/- 0.09 (53

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 BFM 76/79.

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EXPERIENCES WITH 76 CHILDREN WITH NON-HODGKIN'S LYMPHOMA (NHL).
H.P. Wagner, C. Baumgartner, E.A. Bleher, A. Feldges, A. Hirt, P. Imbach, A. Lüthy, H.J. Plüss, J. Sartorius, E. Signer, M. Wyss.
Swiss Pediatric Oncology Group (SPOG, a member of SAKK).
Since 1975 a modified LSA_2-L_2 protocol (Schweiz med Wschr 109, 797, 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 since 1975 (group II). Only children with histologically or cyto- and immunologically proven extraosseous NHL presenting with <1 % blast cells in peripheral blood and <25 % blast cells in the bone marrow and excreting 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

	I	II	III	IV	all
group I	4/4/13	3/3/10	13/17/55	7/7/22	27/31/100
group II	2/8/18	0/6/13	12/24/53	2/7/16	16/45/100

Localization of primary

	Tonsils + Epi-pharynx	Extranodular + nodular but not mediastinal	Mediastinum ± nodular	Abdomen
group I	3/3/10	6/7/22	7/8/26	11/13/42
group II	0/7/16	3/10/22	7/15/33	6/13/29

The 2-yrs-disease-free survival was 19 % (6/31) in group I and 58 % (14/24) in group II.
In group II 29 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: 0/3/10; T: 3/6/21; 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 intraabdominal Murphy stage III and IV disease.

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COMBINATION CHEMOTHERAPY IN NON-HODGKIN'S LYMPHOMA: RESULTS OF 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 35 24 Israel.

During the years 1970-1975, 100 patients with non-Hodgkin's lymphoma (NHL) were treated by combination chemotherapy of the COP/P regime. All patients were in advanced stages (III & IV) or after radiotherapy failed. Thirteen patients were children (under 16 years of age). The chemotherapy consisted of Cyclophosphamide: 650 mg/m^2 I.V., days 1 & 8, Vincristine: 1.4 mg/m^2 I.V., days 1 & 8, Prednisone 40 mg/m^2 P.O., days 1-14. Thirty-seven patients received in addition to the above, Procarbazine: 100 mg/m^2 P.O., days 1-14. The treatment was repeated every 28 days. After complete remission (CR) was achieved, consolidation and maintenance was given during one year. Fourty seven (54%) of the adult patients responded (CR+PR). CR was obtained in 34 (39%) of the patients. Seven (26%) of 27 patients with histiocytic lymphoma (HL) and 24/55 (44%) with lymphocytic lymphoma (LL) achieved CR. Relapse occurred in 13/34 (38%) of those who obtained CR. None of the patients with HL has yet had a relapse.

The actuarial survival of all adult patients is 35% for 8 years. However, patients not responding or partially responding died within one year or 3.5 years respectively. The 8 years actuarial survival (minimum follow-up is 5 years) and the relapse free survival of CR patients is 80% and 50% respectively. For those with LL type the survival is 70% and relapse free survival 45%. Only 3/13 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 sub-groups of NHL but has only a small effect on children with NHL.

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

Johnsson A, Cavallin-Ståhl E, Landberg T and Möller T for the Swedish Lymphoma Study Group
Dept of Oncology, University Hospital, S-221 85 Lund, Sweden

To assess the value of adjuvant chemotherapy after radical radiotherapy in localized 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 laparotomy. Histologic typing is performed according to Rappaport.

Histologic type	Therapy
NLWD DLWD	Individual therapy
NLPD DLPD NM DM NH DH	X R T — R A N D → CVP → No adjuvant therapy

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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F-MACHOP: A NEW COMBINATION CHEMOTHERAPY PROGRAM FOR HIGH-RISK NON-HODGKIN'S LYMPHOMAS (HR-NHL).
S.Amadori, A.P. Anselmo, Cimino, A.M. De Luca, P. Fidani, C. Guglielmi, G. Papa, C. Biagini F. Mandelli. Cattedra di Ematologia e Istituto di Radiologia, Università di Roma, Italy.

This study was designed to test the effectiveness of a sequential combination 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 Kiel classification). The F-MACHOP regimen consists of vincristine (0.5 mg/m^2 i.v. hr 0 and 12), cyclophosphamide (800 mg/m^2 i.v. hr. 24), 5-fluorouracil (15 mg/kg c.i. hr. 24-30), cytarabine (1000 mg/m^2 c.i. hr. 30-36), adriamycin (60 mg/m^2 i.v. hr.36), methotrexate (500 mg/m^2 c.i. hr. 48-54), and prednisone (60 mg/m^2 p.o. days 1-14). Folinic acid rescue (20 mg/m^2 i.v. q.12 hr. x 4) was started 24 hr. after MTX. 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, lymphoblastic or immunoblastic histology) received monthly intrathecal prophylaxis (methotrexate + cytarabine) x 6 doses followed upon achievement of complete remission (CR) by cranial irradiation. Of 30 pts. on study, 9 have completed therapy with 7 CR and 1 PR rested 1 mo. after 6 courses of F-MACHOP. Five pts. died during treatment because of gram negative sepsis (4 pts., 3>45 years of age) or progressive disease (1 pt.). Six of the 7 complete responders are in continuous CR after 1-9 + mos.; 1 pt. relapsed in the marrow at 2 mos. Toxicity included neutropenia, thrombocytopenia, nausea and vomiting. These preliminary results indicate that F-MACHOP is an active regimen for HR-NHL; pts. older than 45 years of age appear unable to tolerate this regimen.

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REFRACTORY MALIGNANT LYMPHOMA: PHASE II STUDY OF CIS-PLATINUM (DDP), VP 16-213 AND PREDNISONE.
Th.Kroner, W.F.Jungi, J.P.Obrecht. Divisions of Oncology: Kantonsspital CH-8401 Winterthur, Kantonsspital CH-9007 St.Gallen, Kantonsspital CH-4000 Basel; for Swiss Group for Cancer Research (SAKK).

From Dec 79 to Feb 81 22 patients (pts) with advanced malignant lymphomas refractory to conventional chemotherapy were treated with cis-platinum (DDP) (60 mg/m^2 iv, d 1), VP 16-213 (120 mg/m^2 po, d 3-5) and prednisone (60 mg/m^2 po, d 1-5). Courses were repeated every 3 weeks. DDP was administered as follows: 30 min after prehydration with 500 mls iv fluid DDP was infused for 15 min, followed by 2000 mls iv fluid for 4 hours. Diuretics were not given. Treatment was usually ambulatory.

20 pts were evaluable for response and toxicity: 7 with Hodgkin's disease (HD) and 13 with Non-Hodgkin's lymphoma (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/µl and platelet nadir < 75'000/µl with median WCB nadir on day 20 (range 6-40) and median platelet nadir on day 15 (range 7-35). One pt died of agranulocytosis with septicemia after the first course, prior to treatment cholestatic liver damage due to tumour infiltration was present. Due to haematologic toxicity drug dosage was reduced in 27% of all cycles, the intervals were prolonged to 4 or more weeks in 55% of all cycles. Nephrotoxicity was minimal, not necessitating any dosage modifications.

We conclude that the combination of DDP, 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-HODGKINS LYMPHOMA . D.P. Derman.Univ.of the Witwatersrand,Johannesburg, S.A.

Seventeen patients with non-Hodgkins Lymphoma were treated with a regimen including Cyclophosphamide, Oncovi Prednisolone and V.P.16. Long term follow up 15 reported Seventeen patients who had no prior chemotherapy are available for analysis. Most patients were suffering fro diffuse large cell lymphoma of clinical stage III or IV. Response to chemotherapy was seen in 10 (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 lymphoma treated with C.O.P. without V.P.16. In particular neurotoxicity did not appear to be enhanced by the combination of Vincristine and V.P.16. In addition 13 patients with Non-Hodgkins lymphoma and Hodgkins disease, refractory to treatment with MOPP or COP were also treate with this regimen. Responses were seen in 5/13 of these patients. It is concluded that V.P.16 is an active drug in the lymphomas and can be used on combination with the vinca alkaloids without excessive toxicity.

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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 Onehundred and sixtyfour patients with a diagnosis of non-Hodgkin's Lymphoma were randomised to receive 3 weekly cycles of chemotherapy comprising either the epiposophyllotoxin Teniposide (VM 26) (100 mgm/m^2 IV x 1), Cyclophosphamide (400 mgm/m^2 p.o. x 5), Prednisolone (100 mgm p.o. x 5) designated PEP or Vincristine (1.4 mgm/m^2 x 1, max 2 mgm) with the same doses of Cyclophosphamide and Prednisolone designated COP. Results were analysed 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 20% and Stage IV 71%). For each histological sub-group, the results were similar using either regime, in respect of remission incidence and survival. In favourable histology NHL, PEP produced 57% complete remission (CR) and 29% partial remission (PR) compared with 54% CR and 19% PR for COP. Survival in these patients was also similar for the two regimens, the relative death rates being 1.13 for PEP-treated patients and 0.88 for COP-treated patients (P = .75). In patients with unfavourable histology NHL, PEP 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 = .49).

Neurotoxicity was the only long term adverse side effect and this was significantly less marked in patients who received Teniposide in place of Vincristine. All other 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 recognised during the early phase of the Study that an Anthracycline appears to increase the remission rate in the unfavourable histology disease. Thus since March 1979 - 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 histology disease with Adriamycin added to PEP and COP. To date 215 patients have been randomised into these three arms.

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PREDNIMUSTINE IN THE TREATMENT OF NON-HODGKIN'S LYMPHOMAS. T. Möller, L. Håkansson, I. Könyves and T. Landberg. Dept. of Oncology, University Hospital, Lund and LEO AB Research Laboratories, Helsingborg, Sweden.

Prednimustine (Sterecyt^R), a chlorambucil-ester of prednisolone synthezised at Leo Research Laboratories, Sweden, has been used in the treatment of non-Hodgkin's malignant lymphomas at the Dept. of Oncology, University Hospital, Lund, since 1972.
The drug was found to be effective at an oral daily dose of 40 - 60 mg. The results of this single drug study in 37 patients have been reported previously, and will be updated with regard to remission duration and presented.
Later, in a randomized clinical trial, Prednimustine was given either as a continuous regimen (40 - 60 mg daily) or as an intermittent regimen (200 mg daily for 5 consecutive days, repeated every 2 weeks). A total number of 43 patients entered this study. No difference in response rates were noted between these two regimens. In all patients the treatment could be given ambulatory. The results of this trial will be presented.
Based on the remission rate of this single drug regimen, it was decided to compare Prednimustine treatment with COP in a randomized Swedish national trial in non-Hodgkin's malignant lymphomas, stages III - IV of favourable histologies. This study was started in 1979, and some preliminary data will be reported at the conference.