50 CHROMOSOMAL ABERRATIONS IN LOW-GRADE MALIGNANT B-CELL LYMPHOPROLIFERATIVE NEOPLASIAS.

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Forty-seven patients with low-grade malignant B-cell lymphoproliferative neoplasia were studied. According to the Kiel classification 20 patients had classical CLL, 23 immunocytoma, 2 prolymphocytic leukemia (PLL) and 1 centroblastic-centrocytic lymphoma (CBCC). One patient could not be subclassified. Chromosome analysis was made after stimulation of separated peripheral blood lymphocytes and/or cells from lymph nodes with lipopolysaccharide from E. coli (LPS) or Epstein-Barr virus (EBV). The Q-banding technique was used for chromosome identification.

A sufficient number of metaphases, adequate for chromosome analysis, was found in 36 patients. Of these 24 had clonal aberrations, 14 had an extra chromosome 12, either alone or together with aberrations. Five patients had a 14q+ abnormality, and 3 patients had deletion of chromosome 11. Three patients had abnormalities of chromosome 6. Five patients had 3 or more clonal aberrations. Both patients with prolymphocytic leukemia had aberrations on chromosome 3. Other aberrations were found in all subgroups without clear differences in frequency.

One patient had a partial duplication of chromosome 12. An extra segment, q13 → q22, was attached to one chromosome 12. This abnormality had probably arisen through chromatide exchange.

Patients with 3 or more clonal aberrations had the shortest survival. Patients with +12 alone or together with other aberrations had a shorter probability of therapy-free survival than patients with a normal karyotype or than patients with too few metaphases for cytogenetic analysis. The shortest therapy-free survival was found in patients who had immunocytoma with +12.

In conclusion, chromosomal aberrations occur in more than 50% of patients with low-grade malignant B-cell lymphoproliferative neoplasias. More than 50% of patients with aberrations have an extra chromosome 12 which is the most specific abnormality. The genes that tend to be duplicated during leukemogenesis leading to these types of B-cell disorders characterised by trisomy of chromosome 12 are probably located on the segment q13 → q22. Multiple aberrations and an extra chromosome 12 signify a less favourable prognosis, particularly in the immunocytomas.

51 CHROMOSOME ABNORMALITIES IN BURKITT'S LYMPHOMA .

A. De La Chapelle, University of Helsinki, Helsinki, Finland

The breakpoints involved in recurrent structural chromosome abnormalities associated with Burkitt's lymphoma (BL) are close to the cellular myc oncogene on the one hand, and the structural genes for immunoglobulins on the other. Molecular studies have shown structural rearrangements in these genes that may alter their functions. These events may play a key role in the mechanisms leading to malignant transformation of B lymphocytes. It is believed that this may serve as a model for a better understanding of the mechanisms that lead to malignancy in other system as well. For this reason the current interest in chromosome abnormalities associated with BL goes well beyond the scope of BL itself.

In this presentation a critical review is given of chromosome abnormalities reported to occur in BL. It is shown that in addition to the 3 typical reciprocal translocations in each of which band 8q24 is involved, other structural abnormalities occur as well, whereas numerical abnormalities are rarer. The significance of these other abnormalities will be evaluated. Since many studies were made on established BL cell lines rather than on tumor material, an attempt is made to distinguish between primary and secondary abnormalities.

52 TLYM-1, A STAGE SPECIFIC TRANSFORMING GENE FROM T CELL LYMPHOMAS.

M.A. Lane, Chief, Laboratory of Molecular Immunobiology, Dana Farber Cancer Institute, Dep. of Pathology, Harvard Medical School

Transfection of NIH 3T3 cells with foreign DNA has facilitated the identification of a variety of activated cellular transforming genes from human and rodent neoplasms. Ras genes which are transcribed by every cell at every stage of differentiation have been found to be activated in 10-20 % of all tumors tested, while such genes as Blym-1 and T-lym1 are found to be activated only in cells of specific lineages at specific stages of differentiation.

TLym-1 has been found to be activated in 3 out of 4 human T-cell lymphomas and 7/8 rodent T-cell lymphomas. These neoplasms represent an intermediate stage of normal T-lymphocyte differentiation and the gene activated in these tumors differes by restriction endonuclease sensitivity from the gene activated in T-lymphoid neoplasms representative of a more mature stage of differentia - tion. TLym1 was isolated by molecular cloning and is about 2kb in size. The gene shares homology with genes encoded within the MHC1 region, and is somewhat novel in that it behaves as a secreted protein. Our current speculation is that TLym1 represents the transforming allele of a gene located within the TL/Qa region of the major histocompatibility locus and we further speculate that this may account for its highly stage specific expression in T-lymphoid tumors.

53 Prognostic Groups for Management of Clinical Stage (C.S.) I and II Hodgkin's Disease (H.D.) by Radiation Therapy.

S.B. Sutcliffe, M.K. Gospodarowicz, Teresa Chua, T.C. Brown, R.S. Bush

Radiation therapy for localised H.D. has conventionally been applied following staging laparotomy and with the use of prophylactic abdominal irradiation fields. Given increasing awareness of upper abdominal involvement despite supradiaphragmatic presentation, and the necessity for upper abdominal radiation despite negative laparotomy, an analysis has been undertaken to establish the circumstances whereby curative irradiation can be applied solely by resort to clinical parameters.

Two hundred fifty-two patients with C.S. I and II H.D. received radical radiotherapy between 1968-1977 at P.M.H. The actuarial overall survival, cause-specific survival (death from disease end point) and relapse-free rates at 10 years were 79%, 84% and 61% respectively.

A multivariate analysis to define prognostic factors indicated that age, stage and histology were of independent significance in determining survival and relapse. Disease bulk was predictive only of relapse.

Supra versus infradiaphragmatic presentation and mediastinal involvement were not of independent prognostic importance.

Radiation volume as a univariate determinant of relapse indicated higher relapse rates for "involved" or "mantle" fields compared with fields incorporating abdominal nodal sites of risk.

Three patient groups were defined retrospectively by relapse rate according to age, stage and histology.

<table>
<tr><th></th><th></th><th>IA</th><th>IA</th><th>IIA</th><th>IB&IIB</th></tr>
<tr><th>Age</th><th>Histology</th><th>Upper Cervical</th><th>Other Sites</th><th colspan="2"></th></tr>
<tr><td><50</td><td>LP/NS</td><td rowspan="3">Group I
Relapse
Rate 1/12 (8%)</td><td colspan="2" rowspan="2">Group II
Relapse Rate
63/187 (36%)</td><td rowspan="2">Group III</td></tr>
<tr><td></td><td>MC/LD</td></tr>
<tr><td>>50</td><td>LP/NS</td><td colspan="2">Relapse Rate 17/23 (74%)</td></tr>
<tr><td></td><td>MC/LD</td><td colspan="3"></td></tr>
</table>

Subsequent analysis of Groups I, II and III according to radiation volume indicated that the relapse rate for Group II could be reduced to approximately 25% by use of abdominal radiation.

Although mediastinal involvement was not of prognostic significance, those with massive mediastinal involvement (>10 cm T.D. on P.A. chest radiograph) had a significantly higher intrathoracic failure rate and a high resultant mortality.

A comparison of theoretical expectation of control for clinically staged patients with that achieved following surgical staging indicates that the proportion of patients cured by radiation alone is similar for both groups. In addition, categorisation by multiple clinical prognostic factors permits identification of patients with a similar expectation of control by radiation therapy as has been achieved following surgical definition of stage.

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CHEMOTHERAPY AND LOCALIZED IRRADIATION IN THE MANAGEMENT OF CLINICAL STAGES IA AND II2A HODGKIN'S DISEASE : F. Teillet, F. Teillet-Thiebaud, B. Asselain, Ch. Miot, G. Philippe, Ch. Fermé, J. Bernard. Groupe d'Etudes sur la maladie de Hodgkin -Hôpital Louis Mourier, 92700 Colombes, Hôpital Saint-Louis, 75010 Paris.

Between May 1977 and May 1980, 73 consecutive previously untreated patients, clinical supradiaphragmatic stages IA and II2A biopsy-prooved Hodgkin's disease, were included in a therapeutic trial. All patients received 3 cycles of MOPP. Then they were randomized into 2 series for irradiation 1) classical supradiaphragmatic extended-field irradiation (S), 2) localised irradiation of areas initialy involved (F). No spleno-lumbar irradiation was performed in any of the two series.

	(F)	(S)	
male	25	24	73
female	11	13	
IA	21	20	73
II2A	15	17	

The Complete Remission Rate was 98,5% (1/73). At 5 years, actuarial survival rate was : 98% in both series; disease-free survival rate was 85% in (F) and 80% in (S) series. In the (F) series, no patient relapsed in non-irradiated adjacent areas. 2 patients in (F) and 1 patient in (S) series relapsed in spleno-lumbar areas (4% of all patients). 2 of these 3 patients achieved a second complete remission. Up to now we have observed only one "second malignancy" in the (S) series : a cancer of the oesophagus, 3 years after completion of treatment in a 60 years-old patient. In order to reduce the therapeutic procedure in favorable clinical stages of Hodgkin's disease we evaluated the efficiency of a prior relatively slight chemotherapy in terms of prophylaxy by comparison betwen localised versus extended field irradiation. Thurthermore we evaluated the efficiency of such a chemotherapy on subdiaphragmatic occult disease from a clinical point of vue that is the incidence of relapses in infradiaphragmatic areas. From our data, it seems possible to assume that 1) when such a prior chemotherapy is used, reduction of irradiated field is possible, 2) the risk of infra-diaphragmatic relapses is low -less than 5%- and in such relapses salvage therapy is very efficient.

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MOPP VS RADIOTHERAPY/MOPP FOR EARLY-STAGE HODGKINS DISEASE (HD)- A SIX YEAR FOLLOW-UP. Peter J. O'Dwyer, Michael B. Stewart, Peter H. Wiernik. Baltimore Cancer Research Center Investigational Drug Branch NCI and Albert Einstein Cancer Center, New York, NY 10461, USA.

Thirty-six patients (pts) with previously untreated HD stages IB to IIIA were randomized to treatment with extended field radiotherapy followed by MOPP (RT+C) or MOPP (C) alone. Distribution of histologic subtype, age and sex were similar in both groups. Two pts in each group were inevaluable: 1 died before treatment began, 1 had a non-Hodgkin's lymphoma, and 2 did not complete therapy. The 17 evaluable pts in the RT+C group included 1 stage IB, 7 IIA, 4 IIB, and 5 IIIA. Sixteen achieved complete remission (CR); one had a good partial remission (PR). Five pts relapsed from 18 to 66 months later, of whom 4 have died, 2 of progressive disease, 1 of sepsis, and 1 of squamous cell lung cancer. The median duration of CR is 63+ months, and of survival, 74+ months. Among the 15 evaluable pts in the C group, there were 8 stage IIA, 1 IIB, and 6 IIIA. There were 12 CR, 1PR and 2 non-responders (NR). The PR and 1 NR subsequently achieved CR with radiotherapy: neither has relapsed, though the former has now developed a secondary leukemia. Three pts relapsed 11-24 months later: one responded to and one failed subsequent radiotherapy, while one responded to retreatment with MOPP. The median duration of CR is 64.5+ months, and of survival 75+ months. The median follow-up for all evaluable pts is 75 months. There is no difference between the groups in terms of actuarial freedom from first relapse or actuarial survival. Late infectious disease morbidity was more prevalent in the RT+C group, and two pts are disabled by constrictive pericarditis following mantle radiation. Second neoplasms and hypothyroidism were observed in both groups. These results with chemotherapy alone in stage II and III patients are comparable to those of any previously-reported radiotherapy series. They continue to suggest that MOPP alone may be as effective and less toxic than combined modality therapy, and that restriction of radiation therapy for incomplete responders to chemotherapy may result in equal survival.

56 RANDOMIZED STUDY OF CHEMOTHERAPY ALONE VS CHEMOTHERAPY PLUS RADIOTHERAPY IN CLINICAL STAGE IA-IIA.

S. Pavlovsky, J. Dupont, E. Jiménez, F. Sackmann Muriel, C. Montero, G. Garay. From Grupo Argentino de Tratamiento de la Leucemia Aguda (GATLA) and Grupo Latinoamericano de Tratamiento de Hemopatías Malignas (GLATHEM), Buenos Aires, Argentina.

From September 1977 to December 1983 a total of 90 patients with previously untreated Hodgkin's Disease in clinical stage IA-IIA (without staging laparotomy) were randomly assigned to chemotherapy alone (CT) for 6 cycles or 3 cycles of the same chemotherapy followed by radiation therapy (3000 rads) to the involved area at diagnosis and with 3 more cycles of chemotherapy (CT-RT). Chemotherapy consisted of monthly cycles of cyclophosphamide 600mg/m^2/iv day 1; vinblastine 6mg/m^2/iv day 1; procarbazine 100mg/m^2/po day 1 to 14 and prednisone 40mg/m^2/po day 1 to 14 (CVPP). A total of 31 patients were $\leq$ 15 years old and 59 were older. Forty-seven were treated with CT and 43 with CT-RT.

The median time of treatment completion was 6 months for CT and 8 months for CT-RT. None of the patients received maintenance treatment.

The rate of complete remission (CR), duration of complete remission (DCR) and overall survival (OS) at 48 months are:

Treatment	No.Pts.	CR		DCR	OS
		No.	%		
CT	47	42	89	86%	94%
CT-RT	43	39	91	85%	84%

Five patients obtained partial remission with CT alone. All had mediastinal involvement, received further treatment with RT and remain alive. Of the four patients in CT-RT who failed to obtained CR one died of sepsis at 5 months and 3 died of progression of diseases at 9, 10 and 11 months.

Five patients relapsed in CT and 3 in CT-RT, while, among all the patients entered in the study, 2 and 6 died respectively.

We can concluded that combination chemotherapy CVPP produces a similar rate of CR, duration of CR and survival as CVPP plus radiation therapy in clinical stages IA-IIA of Hodgkin's Disease.

This study was supported in part by the Cooperative Cancer Treatment Research Program which is a project of the PAHO and NCI, Contract No. NO1-CM-27391.

57 COMBINED MODALITY THERAPY (CHEMOTHERAPY PLUS RADIOTHERAPY) IN HODGKIN'S DISEASE, CS IA TO IIIB.

II.- RESULTS OF THE H77 TRIAL (1977-1980). J.M. Andrieu*, Y. Coscas, P. Cramer, C. Julien, M.Weil, G. Tricot.

* Hematology, Hospital Laennec - 75340 Paris, France.

From january 1977 to april 1980, 173 patients (pts) with Hodgkin's disease (HD), clinical stages (CS) IA to IIIB were prospectively treated at hôpital Saint-Louis (Paris). Their initial characteristics were : - sex : males 102, females 71 ; - age : 5 to 65 years, median 28 ; - CS : IA 42, IIA 63, IB IIB 48, IIIA 9, IIIB 11 ; - histological type : I 28, II 71, III 55, IV 6, unclassif. 13). The 79 pts with CS IA and II_2A (only 2 areas involved on the same side of the diaphragm) followed the H 7701 trial which consisted in 3 MOPP cycles plus radiotherapy (40 Gy) which was randomized in 2 groups ; the first one received a focal irradiation only whereas the other one had a mantle, a mantle excluding mediastinium or an inverted Y plus spleen radiotherapy according to initial presentation. The 74 pts with CS_3II A (3 or more areas involved), IB, IIB followed the randomized H 7702 trial : the patients received at random 3 cycles of MOPP or CVPP (CCNU, Vinblastine, Procarbazine, Prednisone) ; partial and complete responders underwent a laparotomy with splenectomy followed by supradiaphragmatic irradiation (a lombo-aortic field was added in case of positive laparotomy). The 20 pts with CS III followed the H 7703 trial : 3 cycles of MOPP or CVPP (at random) were first given ; a splenectomy was then performed followed by total or subtotal nodal irradiation. At completion of therapy, 167 pts (96.5%) were in complete remission (CR). Twenty pts relapsed (in situ or marginal 3, non irradiated lymph nodes 14, visceral areas 3) after 3 to 60 months of CR (median 12) ; after individual retreatment 12 of them are alive (8 in second CR). Eighteen pts died (initial failures : 4 ; complications of chemotherapy : 2 ; relapsing pts : 8 ; deaths in first CR : 4 including 2 acute leukemias, 1 oesophagus cancer and 1 overwhelming infection). In january 1984 the median follow-up was 53 months (min 32, max 84). Actuarial probabilities (7 years) of survival (calculated from diagnosis) and disease free duration (calculated from completion of therapy) of the whole goup of patients are 87.5% and 85.2% respectively (IA:91.8% and 88%; IIA:92.1% and 89%; IB,IIB:82.6% and 78.7%; IIIA:88.9% and 88.9%; IIIB:76% and 88.9%. No differences were found between focal and more extended irradiations (trial H7701) and between 3 MOPP and 3CVPP (trials H7702 and H7703). Survival (but not disease free duration) is significantly lower in pts over 40 years of age ($P<0.05$).

58 COMBINED MODALITY TREATMENT OF HODGKIN'S DISEASE CONFINED TO LYMPH NODES. Janice P. Dutcher, MD and Peter H. Wiernik, MD
Albert Einstein Col of Med and Montefiore Med Cent, Bx, NY USA

Eighty-seven patients (pts) with newly diagnosed Hodgkin's disease (HD) pathologic stages IA, IIA, IIA_E, IIB, IIB_E, IIIA, $IIIA_E$, were randomized to receive either extended field radiotherapy alone (RT) or RT followed by 6 courses of MOPP chemotherapy (RT+C). All E Stage of lung patients had large mediastinal masses. Pts were entered into study from January 1970 to January 1974. 13 pts were excluded from long-term follow-up. Pts with stages IA, IIA, IIB were randomized and evaluated separately from pts with stage IIIA disease. Of 16 evaluable pts with less than stage IIIA, 29 received RT only and 17 received RT+C. Of 28 evaluable pts with stage IIIA, 12 received RT only and 16 received RT+C. After a minimum of 10 years follow-up, 55% of early stage pts treated with RT only are in continuous remission, compared to 90% of pts who received RT+C (p=0.053). 8 pts treated with RT only have relapsed: 2/2 pts with IIA_E lung (both dead of HD) and 2/2 pts with IIB_E (both dead of HD); 6/18 pts with stage IIA disease have relapsed (2 dead), including one at 94 months in nodes previously included in the RT port. One of 17 pts who received RT+C has relapsed and is alive at 113+ mos. Survival between groups is not statistically different (p=0.27). After a minimum of 10 years follow-up, 41% of pts with stage IIIA HD treated with RT only are in continuous remission, compared to 95% of pts treated with RT+C (p=0.006). Seven pts who received RT only have relapsed including 5 with IIIA (2 late relapses at 112 and 118 mos.) and 2/3 with $IIIA_E$ lung (both dead of HD). One pt treated with RT+C has relapsed and is alive at 118+ mo. If deaths due to all causes are included, there is no statistical difference in survival between groups (p=0.53). No deaths from HD have occurred in pts treated with RT+C. Deaths from other causes in pts with stage IIIA treated with RT+C include 3 cardiac, 2 lung Ca, and 1 early leukemia. No pts with IA, IIA, IIB treated with RT+C have died. 5 pts with IIIA treated with RT alone have relapsed and died of HD. 3 pts with early stage disease treated with RT only have died, 1 of fibrosarcoma in the RT port, 1 suicide, and 1 leukemia after relapse and re-treatment of HD. Combined modality therapy of pts with early HD may be superior to RT alone, especially in subgroups with large mediastinal masses and/or pulmonary extranodal extension, or generalized abdominal nodal involvement.

59 CHEMOTHERAPY ALONE VS. COMBINED MODALITY THERAPY FOR STAGE III HODGKIN'S DISEASE: A FIVE-YEAR FOLLOW-UP OF SOUTHWEST ONCOLOGY GROUP (SWOG) STUDY #7518. P.N. Grozea, E.J. DePersio, C.A. Coltman, Jr., C.J. Fabian, F.S. Morrison, D.O. Dixon and S.E. Jones. University of Oklahoma Health Sciences Center, Oklahoma Medical Research Foundation, P.O. Box 26901, Oklahoma City, OK, 73190, and the Southwest Oncology Group, San Antonio, TX, 78229.

The SWOG initiated in October 1975 a clinical trial in pathological (laparotomy) stage III Hodgkin's disease with randomization to chemotherapy alone consisting of ten courses of MOPP plus low dose Bleomycin (LDB) vs. combined modality program of three courses of the same chemotherapy followed by total nodal irradiation (TNI). Systematic restaging has been performed with additional cycles of MOPP plus LDB administered for residual disease. All cases have been reviewed by the Lymphoma Pathology Panel. From the 137 patients registered until the closing date (April 1980) 117 are fully evaluable. With 59 months median time on the study of the surviving patients the results are as follows:

	MOPP + LDB	MOPP + LDB + TNI	P	
CR rate	89%	96%	0.27	(2 sided Chi square)
5-yr. relapse free survival	77%	81%	0.30	
5-yr. survival rate	86%	91%	0.48	Gehan test of significance

No statistically significant differences in CR rate by baseline characteristics or by A vs. B symptoms is detected (and not expected because of the large number of patients entering CR). Comparison of the relapse free survival (RFS) curves for the subset of nodular sclerosis shows a strong statistical trend (P = 0.051) in favor of the combined modality limb while the same comparison for the subset of mixed cellularity reveals only a trend to more relapses on the combined modality limb (P = 0.17). Toxicities of the two regimens were comparable with respect to immediate side effects and complications. Hematological toxicities, generally, allowed 59% of the patients on the chemotherapy alone limb to complete the ten cycles of MOPP + LDB and 66% of the patients on the combined modality limb to complete the full XRT (33% have low doses for the inverted Y). While survival curves are not statistically significantly different, more patients on the chemotherapy alone limb died of disease and more patients on the combined modality died of toxicities, including one AML and one late marrow failure. These results suggest that for the initial therapy of stage III Hodgkin's disease chemotherapy alone or combined modality could be similarly effective except for the histological type of nodular sclerosis for which combined modality treatment should be considered - presumably with reduced dose of TNI or involved field XRT to original sites of involvement (in order to decrease the risk of second malignancies while increasing the probability of relapse free survival).

60 A STUDY OF CHEMOTHERAPY (MVPP) FOR PATIENTS WITH STAGES IIIB AND IV HODGKIN'S DISEASE (HD) WITH AN ASSESSMENT OF PROGNOSTIC FACTORS.

W.P.Steward*, J.Wagstaff*, I.Todd# & D.Crowther,*Department of Medical Oncology, Christie Hospital, Manchester M20 9BX, #Department of Radiotherapy, Christie Hospital.

118 patients with previously untreated stages IIIB and IV HD were entered into a prospective study of treatment with chemotherapy, using Mustine, 6mg/m^2 i.v. days 1 & 8, Vinblastine, 6mg/m^2 i.v. days 1 & 8, Procarbazine, 100mg/m^2 orally daily, days 1-14 and Prednisolone, 40mgs. orally daily, days 1-14 (MVPP), repeated every six weeks to six courses beyond complete remission (CR) followed by radiotherapy to sites of previous bulk disease.

32 patients had stage IIIB, 20 patients, stage IVA and 66 patients, stage IVB disease. The bone marrow was involved in 16 patients (13%), the liver in 44 patients (37%) and lung parenchyma in 22 patients (19%). Median follow up was 62 months.

The overall CR rate was 74%, 71% of patients with stage IV disease achieved a CR. No factors predicted response. The overall relapse-free survival (RFS) was 86%. No factors predicted the duration of RFS.

Overall five year survival was 73%. Log rank analysis showed that survival was adversely affected by failure to achieve a CR ($p < 0.0001$), increasing age ($p = 0.0002$), high LDH ($p = 0.004$), stage IV disease ($p = 0.008$), high alkaline phosphatase ($p = 0.008$) and high AST ($p = 0.031$). A Cox's multivariate analysis was carried out and showed survival to be adversely affected by failure to achieve a CR ($p < 0.001$), increasing stage ($p < 0.001$), raised serum LDH ($p = 0.013$), increasing age ($p = 0.036$) and raised serum alkaline phosphatase levels ($p = 0.039$).

MVPP is a useful alternative to MOPP and is without associated neurotoxicity. Groups of patients have been identified with a poor prognosis using this regimen for whom alternative therapy should be considered in future.

61 STAGING AND TREATMENT WITH CYCLOPHOSPHAMIDE, VINCRISTINE AND PREDNISONE (CVP) IN ADVANCED CUTANEOUS T-CELL LYMPHOMAS(CTCL).

U.Tirelli,A.Carbone,A.Veronesi,E.Galligioni,M.Roncadin,M.G. Trovò,S.Tumolo,F.Brema,E.Grigoletto.Div. of Radiother.& Med. Oncology General Hospital, Pordenone;Centro di Riferimento Oncologico, Aviano, Pordenone, Italy.

The purposes of the study are to evaluate the staging of CTCL and the treatment with CVP of patients(pts) with advanced disease.Twenty-three consecutive pts with histologically confirmed CTCL underwent staging evaluation between Jan'75 and Nov'83.The routine staging procedures included chest x-ray,peripheral blood count and cytomorphology,bone marrow aspirate and biopsy,lymphangiogram,peritoneoscopy with multiple spleen and liver biopsies.Lymphnodal biopsy and/or cytology were performed in selected pts. After the staging was completed,pts were classified(most retrospectively) according to TNM system.Sixteen pts (7 males,9 females,median age 61 yrs,range 24-77)had advanced disease:2 pts had stage IIB for skin tumors;1 pt stage III for generalized erythroderma and 13 pts stage IV for lymphnodal histological involvement(9 pts) and/or visceral histological involvement(5 pts).Among pts with stage IV,6 pts had skin tumors and 7 pts generalized erythroderma. Bone marrow was involved in 3 pts,liver and spleen in 1 pt each.Peripheral blood involvement was present in 9 pts.All 16 pts but three were previously untreated with drugs.CVP was given for at least 3 cycles prior to the evaluation of response and for at least 6 cycles to CRs.Only 14 pts are evaluable for response,since 2 pts are still receiving their first cycles of CVP. CVP induced a 57% overall objective response rate with 4 CR of 43+,19,19,14+ mos duration.The overall median survival was 22.5 mos.Median survival for pts attaining CR vs PR and NR was 44+ vs 16 mos(p=.02).Five pts died of disease.Toxicity was quite acceptable.We conclude that:1)pts with CTCL,if properly staged,often present with advanced (stage IIB-III-IV)or extracutaneous (stage IV) disease(69% and 56% respectively in our series),in agreement with NCI data when only light microscopy was used (63% and 51%respectively in the 49 pts reported by Bunn Jr et al:Ann Int Med 1980; 93:223).In addition,bone marrow was involved in 13% of our pts compared to 2% of Bunn Jr et al series;2)The experience with combination chemotherapy alone in CTCL is limited(approximately 80 pts reported in the literature),the largest series reporting only 12 pts.CVP employed in 14 consecutive pts with advanced CTCL at our institution is an effective combination chemotherapy regimen.

62 TREATMENT OF CUTANEOUS T-CELL LYMPHOMAS (CTCL) WITH BIOLOGIC RESPONSE MODIFIERS: RECOMBINANT LEUKOCYTE A INTERFERON (IFL-rA) and T101 MONOCLONAL ANTIBODY. P.A. Bunn, K. Foon, D. Longo, D. Ihde R. Oldham, R. Schroff, J. Minna, E. Glatstein. National Cancer Institute Bethesda, MD.

CTCL (mycosis fungoides and Sezary syndrome) patients refractory to standard therapy were treated with $50X10^6$ units/m^2 of IFL-rA IM three times weekly (20 pts) or 1-100 mg of T101 monoclonal antibody 8 patients via an intravenous infusion over 2-24 hr to determine the effectiveness and toxicities of these therapies. The patients had advanced stages (13 with cutaneous tumors, 9 with erythoderma, 6 with generalized plaques; 13 with histologic lymph node involvement, 12 with peripheral blood involvement, and 5 with visceral organ involvement) and extensive prior therapy (topical HN_2 in 26, PUVA in 17, whole skin electron beam irradiation in 17, and systemic chemotherapy in 21). After IFL-rA there were partial responses in 9/17 evaluable patients (3 too early for response evaluation), minor or mixed responses in 3/17 patients, and no response in 5/17 patients. Partial responses lasted a median of 5+ mo with 5 continuing responses of 5+ to 19+ mo. duration. Toxicity consisted of a flu-like syndrome consisting of fatigue, anorexia, weight loss, malaise, and decreased performance status sometimes accompanied by mental confusion requiring dose reductions in all patients. All patients had transient fevers which became less pronounced with continued therapy. Reversible elevations in liver function tests (6 patients), nephrotic syndrome with renal failure, (1 patient) and modest decreases in WBC and platelet counts were noted. One patient previously treated with alkylating agents developed acute monocytic leukemia. T101 produced improvement in skin lesions in 2 patients, one of whom also had objective improvement in lymph nodes and peripheral blood. There were no complete or partial responses. Toxicity consisted of shortness of breath (3 patients given >10 mg over 2 hrs), mild fever (3 patients) and cutaneous purpura (1 patient). Shortness of breath was not observed with less rapid infusions. Lack of anti-tumor response may be due to absence of tumor localization with low doses, antigen modulation, inhomogeneous tissue uptake, development of anti-murine antibodies or lack of direct cytotoxicity. We conclude: IFL-rA has definite activity in CTCL, but new doses and schedules should be explored to reduce toxicity and achieve complete responses; T101 is relatively non-toxic but new approaches such as radio/drug-labeling are necessary to enhance cytotoxicity.

63 ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS): BASIC FINDINGS. Dan L. Longo, Ronald G. Steis, Anthony S. Fauci, H. Clifford Lane, Henry Masur, Edward P. Gelmann, National Institutes of Health, Bethesda, MD 20205

The AIDS syndrome is an almost uniformly fatal,transmissable new disease characterized by profoundly depressed cellular immunity and manifested clinically by serious, life-threatening opportunistic infections and neoplasms. Recently, a new strain of human retrovirus (HTLV-III) has been isolated as a putative etiologic agent. A variety of neoplasms have been noted among AIDS patients, particularly Kaposi's sarcoma (KS), an endothelial cell tumor, and a variety of lymphomas including diffuse large cell lymphoma, immunoblastic sarcoma, lymphoblastic lymphoma, and Hodgkin's disease. Neoplasms develop in about 40% of all AIDS patients; 36% develop KS and about 4% develop malignant lymphoma. The incidence of KS is nearly 50% in the male homosexual risk group and is less than 10% in the other major risk groups. Unlike the Kaposi's sarcoma endemic to Africa and most common in elderly Jewish and Italian men (which is localized to skin and curable by local irradiation in the vast majority), the KS in AIDS patients spreads to visceral organs, particularly the GI tract and lymph nodes, in nearly 3/4 of patients. Efforts to treat the KS in AIDS patients have included various preparations of interferons, interleukin-2, single agent and combination chemotherapy, and radiation (x-ray and electron beam). Trials of recombinant interferons (recombinant leukocyte A interferon; Hoffman-LaRoche used at Memorial-Sloan Kettering: recombinant alpha-2 interferon; Schering used at USCF) have yielded objective response rates of nearly 40%. Patients usually required at least 10 weeks of therapy and relapsed if interferon was discontinued. Responding patients tend to have disease limited to skin, no history of opportunistic infection, and T4/T8 ratios >0.5. We used 3 different doses of human lymphoblastoid interferon (Burroughs-Wellcome) in 29 AIDS patients with Kaposi's sarcoma. The response rate was 14%. During therapy most patients had a 30-50% decrease in lymphocyte count that returned to pre-therapy levels when treatment was stopped. Interleukin-2 has been used in about 15 patients without significant antitumor effect. X-radiation can quickly shrink masses in critical locations and election beam therapy is effective against skin lesions. Chemotherapy has the highest response rate (86%) and is effective at controlling life-threatening disease. However, the majority of patients die within a few months of opportunistic infection. No therapy has been shown to alter survival but selective use of radiation and chemotherapy can usually prevent death from KS. Patients who develop malignant lymphoma almost always die of lymphoma, therefore, attempts at remission induction with regimens effective in the individual histologic subtypes seem warranted. The ultimate success in controlling AIDS-associated neoplasia probably depends on reversing the underlying immune defect.

64 MALIGNANT LYMPHOMA IN HOMOSEXUAL MEN: CLINICAL FEATURES AND RELATIONSHIP TO ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS).

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Since the recognition of AIDS, the medical community has become increasingly aware of other medical conditions emerging among homosexual men. From March 1982 to March 1984, 18 homosexual males, ages 20-74, have been seen at NYU with lymphoma. Of these, 5 had epidemic Kaposi's sarcoma (EKS) and 4 had opportunistic infections (OI) 0-10 months (mos) prior to the diagnosis of lymphoma. In one patient with prior OI, EKS and lymphoma were both diagnosed on autopsy. Clinical data are summarized in the table.

Pathology	Stage/Site	Therapy	Outcome (Time From DX)	Associated Disease
DHL	IE(Thigh)	Local RT	Died(2mos)	No
DHL	IE(Small Bowel)	Resection	Relapse(3mos)	OI
		COPBLAM	Died(7mos)	
DHL	IV(Small Bowel)	None	Died(1week)	No
DHL	IV(Small Bowel)	CHOP	Died(10mos)	OI
DHL	IV(Lung)	None	DX on Autopsy	OI/EKS
Burkitt's	IV(CNS)	M-BACOD	Relapse(4mos)	No
		CHOP	Died(7mos)	
Burkitt's	IV	M-BACOD	Relapse(5mos)	No
			Died(7mos)	
Burkitt's	IV	Lost to follow up		
Burkitt's	IV	High dose CTX	PR(4mos)	No
PDL	IV	Local RT	Died(2mos)	No
PDL	IV	VP16/Bleo	Died(4mos)	EKS
PDL	IV	VP16/Bleo	PR(24mos)	EKS
Hodgkin's-NS	IIA	Total nodal RT	CR(2mos)	EKS
Hodgkin's-NS	IE(Tonsil)	Local RT	NED(5mos)	No
Hodgkin's-NS	IIIB	MOPP/ABVD	NED(11mos)	No
Hodgkin's-MC	IA(Axilla)	Local RT	Relapse(5mos)	No
Undifferentiated	IV	None	Died(2days)	EKS
Unclassified	1°CNS	Local RT	Died(2mos)	OI

The occurrence of 18 cases of lymphoma in male homosexuals in 24 mos in a single institution, and the association with EKS and OI suggest that lymphomas in this group may be a manifestation of AIDS. Unusual features of the non-Hodgkin's lymphomas are extra nodal presentation (14/14) and extremely poor prognosis (median survival = 4 mos) despite aggressive chemotherapy and a high initial response rate. In addition, 4 cases of Hodgkin's disease (1 with EKS) were seen. Interestingly, no cases of concomitant EKS and Burkitt's were seen. One patient presented with Burkitt's of the mandible with monoclonal markers showing IgG. Further characterization including mononuclear cell surface markers, other markers, such as Beta-2-microglobulin, cytogenetic evolution and serology is in progress.

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65 DIFFUSE LYMPHOMAS IN PATIENTS (PTS) AT HIGH RISK FOR ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS).

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Prisoners are a group well-recognized to be at high risk for AIDS. The incidence of AIDS in this population is approximately 120/100,000 per year and AIDS is now the leading cause of natural death in the New York State correctional system. Intravenous drug abuse has been identified as the most important risk factor for AIDS in this population. The Westchester County Medical Center (WCMC) serves as a referral center for approximately 10,000 New York State prisoners or one-third of the entire New York State prison population. Since November 1981, 36 prisoners have been diagnosed to have AIDS at this hospital. Although Kaposi's sarcoma is widely regarded as the most common malignancy associated with AIDS, this tumor was seen in only 2 (5%) of the 36 patients. Since patients who are immunosuppressed are known to be at increased risk for lymphomas, we retrospectively reviewed the pathology records of prisoners seen at WCMC over the same period of time. During the study interval, 6 prisoners were diagnosed to have diffuse non-Hodgkin's lymphoma (NHL), 1 had Hodgkin's disease and 1 had malignant histiocytosis. No patient with nodular lymphoma was seen. All patients with NHL met the criteria of the "Working Formulation" for high grade lymphomas. Among the 6 patients with NHL, only 1 was considered to have AIDS; this patient had a primary brain lymphoma. Our findings suggest that the incidence of NHL among prisoners is 30/100,000 per year, a 15-fold increase compared to the general population where the incidence has remained relatively constant at 2.2/100,000 per year. In addition, at least two other I.V. drug users who were not prisoners were diagnosed to have NHL over the same period. We conclude that diffuse lymphomas may represent yet another facet in the spectrum of the syndrome of acquired immune deficiency and may well be a more common expression of this syndrome among I.V. drug users/prisoners than Kaposi's sarcoma.

66 NON-HODGKIN'S LYMPHOMAS IN HOMOSEXUAL MALES. S. Riggs, S. Kalter, F. Cabanillas, F. Hagemeister, W. Velasquez, B. Barlogie, P. Salvador, P. Mansell, A. Rios, E. Hersh, J. Butler, M.D. Anderson Hospital & Tumor Institute, Houston, Tx. 77030.

Over the last two years, an increased incidence of lymphomas in homosexual males has been noted in several cities in the United States. During the period 1981-1983 we have evaluated & treated 14 homosexual males with advanced stage lymphomas. Ages ranged from 20 to 45 yrs. Five pts had diffuse large cell (DLCL), 5 had diffuse undifferentiated (DUL) of either Burkitt's (3) or non-Burkitt's (2) type, 2 had nodular poorly differentiated lymphocytic (NPDL), 1 had well differentiated lymphocytic (WDLL), & 1 had unclassifiable lymphoma. All were morphologically consistent with B cell neoplasms. All 5 pts with DLCL had focal brain lesions, with 2 of these presenting as primary CNS lymphoma. In contrast, only 1 of the DUL pts had CNS involvement, which was meningeal. Three of the DLCL pts had concomitant pulmonary lymphoma & extensive Kaposi's sarcoma. Pts with DUL tended to have the common abdominal & marrow involvement, but 1 also had bilateral tonsillar lesions. Only 1 of the DUL pts had Kaposi's sarcoma which was minimal. Three of the DUL pts had a history of fluctuating histologically proven reactive lymphadenopathy prior to the clinical onset of the lymphomas. B cell markers on the DUL tumor cells confirmed IgGK (3), IgGλ (1), & IgMK (1). All 3 DUL pts tested had the 8 to 14 chromosomal translocation in lymphoma tissue, & 2 of the 3 also had an XO abnormality in the malignant cells. A bizarre finding in the WDLL pt was extensive bilateral lymphoma of the earlobes. All pts tested had T lymphocyte helper/suppressor ratios less than 1 & decreased skin test delayed hypersensitivity, with the most marked abnormalities occurring in the DLCL pts. Antibody titers for cytomegalovirus & Epstein-Barr virus were positive in 10/11 & 11/11 pts tested, respectively. Antibodies to the human T leukemia-lymphoma virus were present in the sera of 2 DLCL & 1 DUL pt. Four of the 5 DLCL pts had severe prechemotherapy opportunistic infections, including Pneumocystis, Candida, & Toxoplasma. No pts had autoimmune hemolytic anemia or thrombocytopenia. Responses to treatment & survivals have been poor in all 5 DLCL pts, with 4 deaths & median survival of 3 mos. Four of the 5 DUL pts achieved a complete remission (CR), & 3 of these remain in CR at 7, 7, & 23 mos; none have died. The NPDL & WDLL pts all responded to treatment & are alive at >18 mos. In contrast to some earlier reports that immunosuppressed homosexual males cannot tolerate intensive chemotherapy, it continues to be our experience that the subsets of undifferentiated & indolent lymphoma pts may respond well to various adriamycin-containing regimens with minimal or no secondary infections. Increased awareness of the potential for development of CNS large cell lymphomas in homosexual males will hopefully lead to earlier diagnostic evaluations to distinguish these brain lesions from those caused by Toxoplasmosis & other opportunistic infections, & thus increased potential for successful treatment.

67 OVERVIEW ON CURRENT STRATEGY OF THE TREATMENT OF NON HODGKIN'S LYMPHOMAS. J.E. Ultmann, E.R. Gaynor, University of Chicago Cancer Research Center, 5841 S. Maryland Avenue, Chicago, IL 60637

Research of the past decade has provided substantial insight into the pathogenesis and treatment of the malignant lymphomas.

Using hybridoma technology, monoclonal antibodies have enabled us to probe the cell surface of both benign and malignant lymphocytes. What were previously known to be a group of diverse diseases from a clinical standpoint are now known to be diverse in their cellular origin and in their stage of differentiation. Probing into the nucleus of the cell, we now know that certain lymphomas are characterized by specific chromosomal abnormalities. Perhaps as in the case of chronic myelogenous leukemia and the acute leukemias, these chromosomal abnormalities will be found to correlate with and predict clinical characteristics including presentation, pathophysiology, and response to therapy. Further probing on a molecular level has begun to unravel abnormalities of the genetic code itself and has revealed the presence of oncogenes associated with specific chromosomal abnormalities suggesting a possible role for these DNA sequences in the neoplastic process. What the presence of the oncogene means and whether its presence is causal to the malignant process are questions of intense interest at the present time.

While we have made great strides in our understanding of the malignant lymphomas on a cellular and molecular basis, we continue to pursue effective therapy for these diseases. New drugs, new analogs of already available drugs, new combinations of drugs and new immunoregulatory approaches must be developed to improve on what has already been accomplished.

What then is the challenge which is before us? The challenge is threefold: to continue to expand our knowledge of the cellular and molecular nature of the malignant lymphomas, to synthesize these newly acquired insights into a meaningful model which will have prognostic and therapeutic significance, and to continue our search for ever more effective and ever less toxic treatment approaches to these malignant diseases.

68 UPDATE OF FAVORABLE (LOW GRADE) NON-HODGKIN'S LYMPHOMA.

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The favorable or low grade non-Hodgkin's lymphomas (NHL) include three major subtypes, small lymphocytic (SL), follicular, small cleaved cell type (FSC), and follicular, mixed small cleaved and large cell type (FM). The follicular subtypes are the most common type of NHL in major U.S. centers but is apparently less common in Europe and Japan. These lymphomas usually affect older indivi - duals (average age 55-60 yrs) and are usually widespread (stages III & IV) at the time of diagnosis.

Randomized trials of various treatment programs including combination chemotherapy, irradiation, combined modality therapy and single agent chemotherapy have revealed high response rates (65-80 % CR's), but also continuous high relapse rates without evident cure. Overall survival, however, is good with median of 6-10 years. A selected group of 83 asymptomatic patients with advanced low grade NHL have been followed without initial therapy (NIT) at Stanford. Median survival is 11 years. Median time to requiring therapy was 36 months, longer for FSC (48 months) than FM (16.5 months). Spontaneous regression occurred in 20 % of all patients, including 30 % of FSC group.

Histologic transformation tho higher grade NHL is a problem and occurs in treated and NIT groups equally, reaching 40-50 % at 10 years after diagnosis. These studies and interesting biologic observations will be reviewed.

69 WATCH AND WAIT VERSUS AGGRESSIVE COMBINED MODALITY THERAPY FOR ADVANCED FAVORABLE PROGNOSIS NON-HODGKIN'S LYMPHOMAS.

Dan L. Longo, Vincent T. DeVita, Jr., Eli Glatstein, Louis A. Matis, Richard I. Fisher, Robert C. Young. National Cancer Institute, Bethesda, MD 20205.

The management of advanced stage favorable prognosis non-Hodgkin's lymphomas, which generally include nodular poorly-differentiated lymphocytic (NPDL), nodular mixed (NML), diffuse well-differentiated lymphocytic (DWDL), diffuse intermediately differentiated lymphocytic (DIDL), and diffuse small cleaved cell lymphoma (DPDL-SC), is controversial. Until now the outcomes of the various treatment approaches have been roughly comparable. Randomized prospective clinical trials of single-agent chemotherapy, combination chemotherapy, systemic radiotherapy, and combined modality treatments have shown no significant differences in overall survival. In addition, with the possible exception of NML, the survival of favorable prognosis lymphoma patients treated to obtain complete response is not very different from the survival of a selected group of patients seen at Stanford who received no initial therapy. Therefore, it is not clear whether it is better to treat aggressively or conservatively. Another feature of the favorable lymphomas is their propensity to evolve into aggressive histologic subtypes, a conversion that may occur in 40% or more of patients. Treatment of the aggressive lymphomas has advanced to the point that a majority of such patients appear to be curable with combination chemotherapy. Thus, patients with favorable lymphomas may do best when they convert to aggressive lymphomas that may be cured with available therapies. To determine the best treatment approach to favorable lymphomas, we are randomizing patients with stages III and IV disease to receive no initial therapy or an aggressive attempt at remission induction with ProMACE-MOPP flexitherapy followed by low dose total lymphoid radiation. Patients randomized to no initial therapy may receive low dose palliative radiation to symptomatic masses, however, if they develop widespread symptomatic disease or disease in a site not adequately treatable with 2500 R, or if they undergo histologic conversion to an aggressive lymphoma subtype, they cross over to aggressive therapy. This study design allows us to address some of the unanswered questions in the treatment of favorable lymphomas. Are conservative and aggressive treatment approaches comparable in terms of survival? How frequent is histologic conversion in minimally treated patients? Are patients who convert to aggressive histology as responsive to therapy as patients with de novo aggressive lymphoma? Can an improvement in combination chemotherapy and the addition of total lymphoid radiation result in prolonged disease-free survival in favorable lymphoma patients? The answers to these questions are needed through the study of patients with favorable lymphoma. The consignment of such patients to palliative therapy outside a clinical trial setting delays the development of better treatment approaches.

70 TREATMENT OF DIFFUSE LARGE CELL NON-HODGKIN"S LYMPHOMAS.

Richard I. Fisher, Vincent T. DeVita, Dan L. Longo, Daniel C. Ihde, and Robert C. Young, National Cancer Institute, Bethesda, MD 20205.

Until the mid-1960's the advanced stage, high grade non-Hodgkin's lymphomas were rapidly progressive, fatal diseases with few patients remaining alive at 5 years. Studies conducted at the NCI then demonstrated that 47% of all patients with advanced stages of diffuse mixed, large cell, and undifferentiated non-Burkitt's lymphoma could achieve a complete remission documented by re-evaluation of all initially involved sites following treatment with either the C-MOPP or BACOP combination chemotherapy regimens. Furthermore, 70-80% of these complete responders had long-term disease-free survival tantamount to cure. Although histologic diagnosis did not determine the prognosis of these patients, clinical factors such as male sex, B symptoms, advanced stage, bone marrow disease, huge gastrointestinal masses, hepatic disease, low hemoglobin, and high LDH were all associated with a poor prognosis. By the mid-1970's, studies conducted at several institutions had also demonstrated that 30-40% of all these patients could be cured by combination chemotherapy. The third generation of NCI studies, termed the ProMACE-MOPP flexible induction program, significantly improved these results and has been recently published (Ann. Int. Med., 3/83). The ProMACE regimen includes cytoxan, adriamycin, VP-16, prednisone, and high dose methotrexate at 1.5 gm/m^2 followed by leucovorin rescue. This dose of methotrexate requires hospitalization for intravenous hydration, alkalinization, and monitoring of serum methotrexate levels. Patients received induction therapy with ProMACE, consolidation with MOPP, and late intensification with ProMACE. The duration of each phase of therapy was determined by the patient's rate of tumor response. Complete remissions were achieved in 74% of all patients and 73% of these complete remittors remain disease-free in excess of 3 years. Myelosuppression was dose limiting with a 10% septic death rate. Improved results were seen in all patient groups. The fourth generation of NCI studies randomizes patients to receive either the day 1 ProMACE drugs with the day 8 MOPP drugs and a lower methotrexate dose on day 15 vs. ProMACE on day 1 and CytaBOM on day 8 (cytarabine, bleomycin, oncovin, and methotrexate) (ASCO, 1984). Both of these regimens are given entirely in the outpatient clinic. Preliminary analysis suggests complete remission rates comparable to the original ProMACE-MOPP study although follow-up is still too short to know the durability of these complete remissions. There were no septic deaths. However, diffuse interstitial pneumonitis has been the major toxicity with an increased incidence of pneumocystis carinii pneumonia in the ProMACE-CytaBOM arm. All ProMACE-CytaBOM patients now receive prophylactic trimethoprim sulfamethoxazole. Further follow-up is required to determine whether these new regimens can provide durable complete remissions with less cost and toxicity.

71 THE USE OF CHEMOTHERAPY FOR LOCALIZED LARGE CELL LYMPHOMA; UPDATED RESULTS FROM THE UNIVERSITY OF ARIZONA.

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Historically, radiotherapy alone has been used to treat lymphoma of unfavorable histology with limited spread (stages I, IE, II, IIE) but this has proven curative in only carefully selected patients with the most limited disease (stages I or IE). The majority of patients with stage II or IIE disease recur after radiotherapy and many succumb to their disease. Because current multi-drug chemotherapy programs, particularly those containing doxorubicin, are curative for patients with large cell ("histiocytic") lymphoma of more advanced stage (III or IV) we have been evaluating the use of initial chemotherapy alone (CT) or with adjuvant involved field radiotherapy (CT + RT) after achievement of complete response (CR). Early results have been published (Lancet 1:358, 1979; Blood 62:413, 1983). In this presentation we will update our experience. Forty-nine patients have received CT alone (30 patients) or CT + RT (19 patients). Histologic subtypes include diffuse large cell (47 patients) and follicular large cell (2 patients). Chemotherapy consisted of the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) in 48 patients and C-MOPP in another patient with heart disease. Potentially adverse patient characteristics included stage II or IIE disease in 63%, age > 65 years in 33%, gastrointestinal tract involvement in 14%, and bulky disease in 35% of patients. The CR rate is 98% (48 of 49). At a median follow-up time of 41 months, 84% of all patients remain continuously free of disease. Eight relapses have occurred: 6 of 30 receiving CT and 2 of 19 receiving CT + RT. Five of 8 patients with recurrence have achieved a second CR. Forty-five patients (92%) remain alive. None of the potential adverse prognostic factors listed above affected outcome of therapy including age > 65 (2 relapses in 14 patients). Our experience with rapid clinical staging and immediate combination chemotherapy for apparently localized lymphomas of unfavorable histology appears to be a valid strategy. The optimal amount of chemotherapy and the role for involved field radiotherapy remain to be defined.

72 CELL OF ORIGIN OF HODGKIN'S DISEASE.
C.W. Berard, Div. of Pathology, St. Jude Children's Hospital, Memphis, USA

A historical review of the evaluation of treatment concepts will be presented.

73 **Reactive Lymphadenopathy Simulating Malignant Lymphoma**
R.F. Dorfman, Stanford University, Stanford, California

This presentation will comprise a discussion of certain lesions/disorders frequently referred to me in consultation, in addition to others recently described. Reference will be made to the importance of avoiding technical errors in the preparation of lymph node biopsies which unquestionably lead to many of the problems encountered in their evaluation. The method of evaluation is based on an assessment of both architectural and cytologic features. The discussion on follicular lesions will include distinction between follicular hyperplasia and follicular lymphoma; Castleman's disease with emphasis on the recently described multicentric form and its association with lymphomas and Kaposi's sarcoma; progressive transformation of germinal centers and the provocative proposal that this phenomenon is histogenetically related to the nodular form of Hodgkin's disease; and persistent lymphadenopathy in homosexual males characterized mainly by florid follicular hyperplasia with "folliculysis".

Histiocytic lesions/disorders include histiocytosis X (Langerhans cell granulomatosis) and its distinction from sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease). Criteria for the distinction of these disorders from malignant histiocytosis and from sinusoidal large cell lymphoma will be presented. Immunoblastic proliferations and disorders include consideration of angioimmunoblastic lymphadenopathy and its distinction from "abnormal immune reactions" and from peripheral T cell lymphomas. Finally mention will be made of the newly described disorder, "Kikuchi's necrotizing lymphadenitis" and its distinction from other necrotizing lesions of lymph nodes.

The presentation will conclude with a discussion of the place of frozen sectioning in the evaluation of lymph node biopsies.

74 LYMPHOCYTE DEPLETED HODGKIN'S DISEASE - DOES IT EXIST?

Elaine S. Jaffe, M.D., Jeffrey A. Kant, M.D., Ph.D., Susan M. Hubbard, B.S., Dan L. Longo, M.D., Richard M. Simon, Ph.D., and Vincent T. DeVita Jr., M.D. National Cancer Institute, Bethesda, Md., USA.

Lymphocyte depleted Hodgkin's disease (LDHD) has been regarded by many as the poorest prognostic group of patients with Hodgkin's disease. Others have suggested that LDHD may be a distinct clinicopathologic entity and have questioned its relationship to Hodgkin's disease. Of 198 patients who received MOPP treatment at the NCI for Hodgkin's disease between 1964 and 1976, 43 (22%) were originally classified as LDHD. The initial diagnostic biopsies from 39 of these patients were rereviewed and revealed 10 with non-Hodgkin's lymphomas, 9 with LDHD, 13 with nodular sclerosing Hodgkin's disease, lymphocyte depleted subtype (NSLD), and 7 with Hodgkin's disease lacking a lymphocyte depleted component. The non-Hodgkin's lymphoma patients were further subclassified as diffuse, large cell (2 cases) and large cell, immunoblastic (8 cases). In many cases the pleomorphic character of the neoplastic infiltrate and/or inflammatory background was suggestive of peripheral T-cell lymphoma, but due to the retrospective nature of the study, no immunologic phenotyping could be performed. The pathologic review was done without knowledge of clinical features which were examined after review in the three major subgroups. Of 10 patients with non-Hodgkin's lymphoma only 3 had a complete remission (30%), and median survival was 7 months. A number of these patients presented with clinical features unusual in Hodgkin's disease such as bulky abdominal disease, epitrochlear lymphadenopathy and hypercalcemia. In contrast to the non-Hodgkin's lymphomas, complete remissions were attained by 67% and 85% of patients in the LDHD and NSLD groups, respectively; median survival had not been reached in either group with a minimum of 81 months followup. Mediastinal masses greater than one-third of the chest diameter were seen in three of these patients; none were observed in the non-Hodgkin's lymphoma group. The median age of patients was 46.5 years in the non-Hodgkin's lymphoma group compared with 23 and 29 years in the LDHD and NSLD groups. Lymphocyte depleted Hodgkin's disease, adequately treated, is in our experience no worse than other histopathologic subtypes of Hodgkin's disease. The erroneous inclusion of patients with high grade non-Hodgkin's lymphomas into this subtype of Hodgkin's disease may be one reason for literature reports of its more aggressive nature. The diagnosis of LDHD should be made cautiously, particularly in patients with clinical features unusual for Hodgkin's disease at presentation.

75 IMMUNO-ELECTRON MICROSCOPIC STUDY OF IMMUNOGLOBULIN PRODUCTION BY NON-HODGKIN'S MALIGNANT LYMPHOMAS.

L. Lombardi, G. Della Torre, R. Giardini, F. Rilke, Istituto Nazionale Tumori, 20133 Milan, Italy.

Sixteen selected cases of non-Hodgkin's lymphomas (NHL), representing different steps of B-cell morphofunctional modulation, were studied by an avidin-biotin complex technique modified for electron microscopy. Mechanically isolated tumor cells were fixed with 0.4% glutaraldehyde in 0.01 M hypotonic buffer, incubated with biotinyl goat anti-human IgG heavy and light chains and with avidin-peroxidase conjugates in saponin-containing solutions, fixed again with 2.5% glutaraldehyde, treated with diaminobenzidine and H_2O_2, and processed for electron microscopy. Control cells were incubated with biotinyl goat anti-mouse IgG. Unstained ultrathin sections were observed. A large number of cells of those lymphomas which reflect the early stages of modulation toward plasma cells, namely chronic lymphocytic leukemia (2 cases) and centrocytic (2 cases) and centroblastic (1 case) NHL, showed labelling of immunoglobulins on the membranes of the perinuclear and rough endoplasmic reticulum cisternae with scarce immunoglobulin accumulation within the cisternae. Only a few centrocytes of centroblastic-centrocytic NHL (3 cases) showed a weak labelling of intracytoplasmic membranes. The cells with an evident plasmablastic differentiation of lymphoplasmacytoid NHL (3 cases) and of 2 cases of immunoblastic NHL showed immunoglobulins on the membranes and within the cisternae of the rough endoplasmic reticulum. However, the centrocytes of one of the cases of lymphoplasmacytoid NHL, which revealed features of a follicular center cell lymphoma with plasmacytic differentiation, showed immunostaining of intracytoplasmic membranes without immunoglobulin accumulation. The third case of immunoblastic NHL showed labelling of the intracytoplasmic membranes and of the periphery of Russell bodies, whereas diffuse intracisternal immunoglobulin accumulation was not observed. As regards Burkitt's lymphoma (2 cases), most cells of one case showed labelling of intracytoplasmic membranes, whereas a few cells with a large central nucleolus accumulated immunoglobulins in the rough endoplasmic reticulum cisternae. Numerous cells of the second case showed immunoglobulins within vesicles of a large Golgi complex.

76 FLOW-CYTOFLUOROMETRIC DNA ANALYSIS IN NON-HODGKIN'S LYMPHOMAS.

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209 lymphomas were analyzed with respect to proliferative activity (S-phase frequency) and ploidy (DNA content) in relation to histopathological classification according to the Kiel and Rappaport classifications. Low grade malignant lymphomas according to the Kiel as well as the Rappaport classifications had significantly lower proliferative activity than the high grade malignant lymphomas. However, there was a marked variation in the proliferative activity between individual cases, especially among follicle centre cell derived and high grade malignant lymphomas. Approximately 30 per cent of the lymphomas were considered aneuploid (according to DNA content). Aneuploid lymphomas were most frequent among CB/CC and lB lymphomas. Interestingly, a considerable proportion of the aneuploid CB/CC lymphomas had a DNA content in the near tetraploid range, while most of the other aneuploid lymphoma types had relatively small variations in the DNA content. There was no significant difference in the proliferative activity between aneuploid and "diploid" non-Hodgkin's lymphomas (NHL) with the same diagnosis. By stepwise discriminant analysis, S-phase frequency, not DNA content, was found to significantly discriminate between low and high grade malignant lymphomas, both according to the Kiel and the Rappaport classifications. Discriminant analysis showed that 94 per cent of the low grade malignant lymphomas could be identified as such on the basis of their proliferative activity, whereas only 63 per cent of the high grade malignant lymphomas could be identified as malignant according to the proliferative activity. Very similar results were obtained with respect to proliferative activity using the Kiel and the Rappaport classifications as the basis for the division of lymphomas into high and low grade malignancy groups. These results indicate that the Kiel and Rappaport classifications equally well identify highly proliferative lymphomas and that proliferative activity analyzed by flow-cytofluorometry seems to be a marker of malignancy partly independet of the histopathological classification.

77 THE PROGNOSTIC SIGNIFICANCE OF CYTOLOGICAL SUBDIVISION OF NODULAR SCLEROSING HODGKIN'S DISEASE: ANALYSIS OF 1156 PATIENTS.

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We have histologically reviewed 1156 cases of nodular sclerosing Hodgkin's disease which were entered into the clinical trials of the British National Lymphoma Investigation during the period between 1970 and 1980. Cases have been categorised according to the cytological appearances of the cellular nodules into the low and high grade malignancy groups which have been termed Grade 1 and 2 respectively. 71.6% were histologically classified as Grade 1 and 28.4% as Grade 2. When patients presenting at all stages are analysed together, there is a large difference between the survivals of the Grade 1 (84.3% five year survival) and Grade 2 (59.9% five year survival) types of nodular sclerosing Hodgkin's disease. This difference is statistically highly significant ($X^2 = 73.79; p<0.001$). 884 patients either underwent a staging laparotomy or had evidence of stage IV disease. Within this group, large differences in survival are present between the two grades when patients with stage I and II disease are examined ($X^2 = 44.41; p<0.001$) and when patients with stage III and IV disease are studied ($X^2 = 39.82; p<0.001$). Stage is an important prognostic factor in the Grade 1 histological group, patients presenting at stages I and II having a superior survival (93.5% five year survival) to those presenting at a more advanced stage (79.6% five year survival) and this difference is statistically highly significant ($X^2 = 26.0; p<0.001$). The prognostic significance of stage is less marked in the Grade 2 histological group ($X^2 = 5.55; p<0.025$). It therefore appears that cytological subdivision is of great value in predicting prognosis.

78 BURKITT'S LYMPHOMAS: MORPHOMETRIC ANALYSIS OF 55 CELL LINES WITH GEOGRAPHICAL, VIRAL, IMMUNOLOGIC, AND CYTOGENETIC CORRELATIONS.

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Fifty five cell lines derived from endemic and non-endemic Burkitt's tumors (established by G. LENOIR, IRCC, LYON) were characterized by morphometric means using a Leitz ASM semi-automatic quantitative analysis system on plastic embedded cell suspension pellets. Nuclear parametric discriminators computed on line were: size (with 13 Log nuclear area classes previously defined), shape, area dispersion. General characteristics including geographical origin, EBNA status and caryotype were available for the great majority of the cell lines.

The Burkitt's lymphomas are usually mapped in a discrimination zone defined by classes 3 and 4, with a low value for shape & area dispersion discriminator. The histomorphometrical classification emphasizes the cytological polymorphism of Burkitt's cell lines, in the size, shape, and shape & area dispersion of the nuclei. 24 cell lines are mapped in the zone of large cell lymphomas (size class $\geq$ 5). Nuclear shapes differed from case to case, with frequently irregular nuclei. Finally, a morphological continuum seems to extend from typical small noncleaved cell lines to polymorphous large cell lines.

Simultaneously, a cytological and cytomorphometric study was done on cytospin preps with analysis of the following parameters: (1) cytology : chromatin pattern, size and number of nucleoli, mitosis number, plasmacytic transformation, (2) cytomorphometry : nuclear area, whole cell area, cytoplasm to nucleus ratio, shape. A linear relationship exists between histomorphometrical and cytomorphometrical results, especially for nuclear areas.

The comparison of the morphometric data with immunological, viral, geographical data shows some interesting points: EBV + cell lines are significantly larger than EBV - ones, a pre-B phenotype ($c\mu$ +) and an East African origin are significantly associated with largest cells; there is a strong relationship between African origin, pre-B phenotype, EBV + character, and large cells. Moreover, we were able to compare in some cases the cytologic and morphometric findings in the cell lines with morphology and morphometry of the original tumors.

Finally, this study points out (1) the transforming role of EBV, especially in the cases of massive contamination, (2) the possibly different target cell in Burkitt's lymphomas, (3) the large spectrum of morphological pictures from small noncleaved to large cleaved, noncleaved and immunoblastic types.

79 NON-HODGKIN LYMPHOMA WITH MULTILOBATED NUCLEI; A DISTINCT PATHOLOGIC ENTITY?

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We previously documented cutaneous T-cell lymphoma, multilobated type, and subsequently found lymphoid cells with multilobated nuclei (MC) in Non-Hodgkin Lymphoma (NHL) of lymph node. This prompted us to evaluate whether NHL with MC is a specific morphologic and immunologic entity, or is part of a spectrum of various subtypes of NHL. NHL with a conspicuous component of MC and in which a full-scheme immunological, enzymehistochemical and electronmicroscopical analysis was possible were investigated. Apart from two cases of cutaneous T-cell lymphoma, one case of atypical Sezary's Syndrome with early immunoblastic transformation with large and small MC was found. A wide spectrum of B-NHL contained MC. It included one case of B-CLL with small MC, and four cases of ML Centroblastic Centrocytic (ML CbCc). Much more (21/48) cases of ML Polymorphic Immunocytoma (ML Pl) and ML CbCc contained low numbers of MC. Even more, we observed MC in follicle centres of several benign reactive lymph nodes. Five extranodal B-NHL (maxilla, mandible, elbow, retroperitoneum) contained MC and were classified as ML CbCc or ML Cb. One mediastinal NHL, diffuse undifferentiated large cell (DUL), which lacked immunological markers for B or T lymphocytes contained numerous very large MC. However, MC are not specific for NHL as we encountered one case of undifferentiated carcinoma and of myelomonocytic leukemia, both disseminated into lymph nodes, with this nuclear feature. We concluded that the occurrence of MC does not warrant a T lymphocytic origin or even a lymphoid origin of tumour cells.

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80 TREATMENT OF AGGRESSIVE LYMPHOMA IN JAPAN

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A total of 100 patients with advanced non-Hodgkin's lymphoma (NHL) were treated with a combination chemotherapy consisting of vincristine, cyclophosphamide, prednisolone and adriamycin (VEPA) in a cooperative study group involving 5 major institutions. Of 41 patients with T-cell lymphoma, there were 15 complete remissions (36.6%); however, only 3 (16.7%) of 18 patients either with adult-T-cell leukemia or with pleomorphic T-cell lymphoma obtained complete remission.

On the other hand, VEPA produced complete remission rates of 58.5% and 72.2% in 41 patients with B-cell lymphoma and in 18 patients with surface markers undetermined but defined to be B-cell lymphoma by morphology, respectively.

Median durations of complete remissions were 4 months for T-cell and 16 months for B-cell type, while 10 of 13 patients with cell lineage-undetermined are still in remission of more than 2 years.

Thus, the result has indicated that cell-lineage is an important prognostic factor for HNL and T-cell lymphoma; especialy, ATL and pleomorphic type are the worst histology, because none of conventional drugs used in the treatment of NHL appears to be sufficiently active for these two tumors.

In several new drugs tested recently, Human Lymphoblastoid Interferon and VP-16 seem to have some activity against T-cell lymphoma.

81 MODERATE DOSE METHOTREXATE (m) COMBINED WITH BLEOMYCIN (B), ADRIAMYCIN (A), CYCLOPHOSPHAMIDE (C), ONCOVIN (O) AND DEXAMETHASONE (D), m-BACOD, IN ADVANCED DIFFUSE HISTIOCYTIC LYMPHOMA (DHL). A.T. Skarin, G.P. Canellos, D.S. Rosenthal, D.C. Case and J.M. MacIntyre. Dana-Farber Cancer Institute, Brigham and Women's Hospital and Harvard Medical School, Boston, MA. 02115. The use of high dose methotrexate (M=3g/m^2) requires critically important urinary alkalinization and hydration to avoid serious renal and other complications. In addition, assay of blood MTX levels must be measured and the drug expense can be prohibitive. The M-BACOD program (Skarin et al, J. Clin. Oncol. 1:91-98, 1983) was therefore modified by employing moderate dose MTX (m) at 200mg/m^2 IV on days 8 and 15 of each 3-week cycle. Leucovorin factor rescue, 10mg/m^2 was given at 24 hrs q 6h x 6 to prevent toxicity; B (4mg/m^2 IV), A (45mg /m^2 IV), C (600mg/m^2 IV) and O (1.0mg/m^2 IV) were given on day 1 along with D (6mg/m^2 qd x 5) for a total of 10 cycles. The m-BACOD program has been completed in 53 evaluable patients (median age 43, range 17-73 yrs), with Stage I, II, II_E (10 pts), III (9 pts) or IV (34 pts) DHL. Only 4 patients had prior therapy, while 29 patients (55%) had B-symptoms. Sites of extranodal disease included marrow - 7 patients (13%); effusion - 7 patients; bone, GI - 6 patients each; lung, liver - 6 patients each; soft tissue - 3 patients; skin - 2 patients; other - 10 patients. A CR was achieved in 40 patients (75%): Stage I, II, II_E 7/10 (70%), Stage III 7/9 (78%), and Stage IV 26/34 (76%); a PR in 8 patients (15%), while 5 patients (10%) had NR. The median follow-up time in CR patients is 13 mo. (range 5-27 mo.) from time of CR. 9 patients (23%) have relapsed (8/26 Stage IV) all within 1 year except for 2 (15 and 16 mo.). All PR patients relapsed within 3-9 mo. While m-BACOD was not designed for CNS prophylaxis, CNS relapse occurred in 1 CR and 1 PR patient. All 5 NR patients and 5/8 PR patients died from progressive disease, compared to only 3 CR patients (7.5%). The median follow-up of the remaining CR patients is 17^+ mo. after start of therapy (range 7^+ - 28^+ mo.). Of the entire study group, 40 patients (75%) are alive with 31 (58%) are relapse-free. Toxicity included mucositis mainly after day 8 MTX in 21 patients, representing 6% of courses, but no significant renal complications occurred. Leucopenia with fever occurred in 13 patients (24%) but was fatal in only 1 patient (2%). Bleomycin was discontinued due to fever/chills in 3 patients and reversible pulmonary infiltrates in 6 patients (11%). Moderate dose MTX in the m-BACOD program results in a CR rate and durability comparable to high dose MTX (M-BACOD) but use of m on day 8 and 15 results in increased mucositis. The latter may be improved by increased hydration. Before recommending m-BACOD for general use, further patient accrual and longer follow-up are required, to determine whether a relapse-free survival comparable to M-BACOD ($\sim$ 65%) can be achieved.

82 A RANDOMISED COMPARISON OF ADJUVANT VAP + M vs CMOPP IN RADIOTHERAPY TREATED CLINICAL STAGES I & II HIGH GRADE LYMPHOMA (NHL).

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Sixty patients with histologically confirmed (centrally reviewed) clinically staged (including bone marrow aspirate and trephine; CAT scanning of the abdomen and pelvis) high grade NHL (DPDL, DH, DM, DU) were treated with involved field radiotherapy (XRT). Post-XRT randomisation was to either six weeks VAP (Vincristine, 2 mgs.i.v. wkly x 6; Adriamycin, 50mgs/m² i.v. every 2 wks x 3; Prednisolone, 40mgs p.o. daily for 6 wks) followed by two years oral maintenance(M) (6MP, 50mgs/m² p.o. daily; Methotrexate, 10mgs/m² p.o.wkly and Cyclophosphamide, 200mgs/m² p.o.wkly: all for 2 years) or six cycles of CMOPP (Cyclophosphamide, 650mgs/m² i.v. days 1 & 8; Vincristine, 2 mgs i.v. days 1 & 8; Procarbazine, 100mgs/m² p.o. days 1-14; Prednisolone, 40mgs p.o. days 1-14) at three weekly intervals.

Two patients failed to achieve CR (3%). Both developed disease outside the irradiated field, either before or shortly after starting adjuvant chemotherapy. The overall CR rate was 97% (VAP = 96%; CMOPP = 97%). The six week VAP programme was much better tolerated than CMOPP.

	RFS%		Survival %	
	2yrs	5yrs	2yrs	5 yrs
XRT + VAP + M	83	74	80	68
	No signif.diff.		No signif.diff.	
XRT + CMOPP	90	82	89	89

Ten deaths have occurred (VAP = 7, CMOPP = 3), five of these from intercurrent causes (Ca.ovary (VAP), melanoma (CMOPP), astrocytoma (VAP), coronary artery disease (VAP) and pneumocystis carinii (VAP)). A further patient died from respiratory failure with pulmonary shadowing (CMOPP) but no postmortem was performed (?lymphoma/infection). Two patients died with CNS lymphoma and two with generalised disease. One patient relapsed in an XRT field and achieved a CR with further XRT and remains disease-free at six years.

Histology and age did not affect RFS or overall survival.

Seven patients with bulky disease (>5cm) have died versus three without it, but the RFS is the same for both groups.

We conclude that six weeks of VAP + M is well tolerated and produces as good results as the more intensive CMOPP, but that chemotherapy might be more appropriate alone or prior to XRT.

83 A RANDOMIZED TRIAL OF C-MOPP vs BACOP FOR THE TREATMENT OF DIFFUSE MIXED AND HISTIOCYTIC (DHL) LYMPHOMAS.

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There is enough evidence that combination of cyclophosphamide, vincristine, procarbazine and prednisone (C-MOPP) and bleomycin, adriamycin, cyclophosphamide, vincristine and prednisone (BACOP) can each produce long-term complete remission (CR) in patients with DHL. We have assessed the relative efficacy of these regimens in a randomized trial. As of November 1983, 102 patients have been entered and 88 are evaluable (BACOP 48, C-MOPP 40). Both groups are comparable in age, stage and distribution of histology. Seventy six percent were stages III and IV. There were 25/48 (52%) with BACOP and 19/40 (48%) in C-MOPP that achieved CR (P=N.S.). At 48 months, 60% of BACOP patients and 35% of C-MOPP patients who achieved CR are expected to continue in first CR ($P < 0.05$). No relapse has been observed after 18 months. The percent remaining in CR at 48 months of patients treated with BACOP and C-MOPP according to stages are: I-II: 71% and 66% (P:N.S.), III-IV: 58% and 24% ($P < 0.05$). There have been 25 deaths in each group, with 32% in BACOP and 25% in C-MOPP alive at 48 months. Complete responders have 53% of possibility of continuining alive at 48 months, compared to 12 and 6 months of median survival of partial and null responders ($P < 0.005$). Pattern of relapse was the original site of disease in 72% of patients; 19% of relapses were in CNS but only 7% were isolated CNS first relapses. Toxicity of BACOP has not been markedly greater in terms of myelosupression or clinically evident cardiac or lung toxicity. BACOP showed a higher duration of CR than C-MOPP only in stages III-IV, although this difference does not have a significant impact in overall survival. More intensive combinations and schedules are needed for the treatment of this aggressive disease. (Supported by the Collaborative Cancer Treatment Research Program, a project of the Pan American Health Organization and US National Cancer Institute, Contract NO1-CM-27391).

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84 LYMPHOBLASTIC LYMPHOMA IN ADULTS: A STUDY ON 30 PATIENTS TREATED WITH TWO DIFFERENT PROGRAMS ACCORDING TO BONE MARROW FINDINGS. C. Bernasconi, E. Brusamolino, M. Lazzarino, L. Salvaneschi, P. Isernia. Divisione di Ematologia, Ospedale Policlinico San Matteo, Istituto di Ricovero e Cura a Carattere Scientifico, 27100 Pavia, Italy.

A study was done on thirty previously untreated adult patients affected with lymphoblastic lymphoma with two different therapy programs according to bone marrow findings. The pathologic diagnosis was done on lymph node biopsies (24 cases), on bone marrow biopsies (3 cases), on tonsil, skin and testis in one case, respectively. The classification criteria were according to the Working Formulation for clinical usage (NCI, 1982). The median time of follow-up was of 18 months (range 6-65+ mos). Patients with bone marrow involvement were given an ALL-like program, consisting of vincristine 1.4 mg/m^2, daunorubicin 60 mg/m^2, cyclophosphamide 600 mg/m^2, i.v., once a week for 6 weeks, and prednisone 40 mg/m^2 per os, a day, during all the induction time. Patients in complete remission after 6 cycles had CNS prophylaxis, with cranial irradiation with ^{60}Co (24 Gy) and five doses of intrathecal methotrexate (12 mg/m^2). Maintenance therapy consisted of 6-mercaptopurine 50 mg/m^2 per os, daily and of methotrexate 15 mg/m^2, i.v. once a week for three weeks a month. The fourth week was covered by a reinduction course with vincristine 1.4 mg/m^2 and prednisone 40 mg/m^2. Every three courses, daunorubicin was added, up to the total dose of 450 mg/m^2. Chemotherapy was withheld after 3 years of continuous disease-free survival. Bone marrow negative patients were given a program consisting of cyclical polychemotherapy and radiotherapy on bulky mediastinum (lymphoma program). The regimen was CHOP-Bleo for 6 cycles of induction therapy every 4 weeks and 2 adjunctive cycles of consolidation without further maintenance regimen or CNS prophylaxis. Bulky mediastinum was delivered an involved field high-energy radiotherapy. The CR rate per whole group was 54% (67% for ALL-treated versus 40% for lymphoma-treated patients; p=0.05), with a median survival for remitters of 28.5 mos. ALL-treated patients had a median survival of 16.5 versus 10 months of lymphoma-treated ones (p=0.05). The 3-yr survival was 24 and 10% for the two groups, respectively. Relapse-free survival for whole group was 65% at 12 and 25% at 24 mos. Nine out of 15 patients who achieved CR relapsed in a 24-months interval from remission; three cases relapsed in new sites of disease (mediastinum, CNS, bone marrow with leukemia), five in both previous and new sites and a single in previous sites only (bone marrow and CNS). Bone marrow involvement at diagnosis and therapy program did not significantly influence the duration of relapse-free survival. Central nervous system involvement was diagnosed in 8 out of 30 patients (27%). No patients who underwent CNS prophylaxis had neurological complication or developed later CNS relapse. The better prognosis of ALL-treated patients, in spite of bone marrow positivity, argues in favor of an ALL-like therapy in all adult lymphoblastic lymphomas, in term of CR rate, overall survival, and absence of CNS relapse: this therapy should be adopted irrespective to bone marrow findings, and no matter how localized the lymphoma appears to be.

85 RESULTS OF IFOSFAMIDE - VP-16 SALVAGE COMBINATIONS FOR PATIENTS WITH RECURRENT OR REFRACTORY AGGRESSIVE LYMPHOMA. F. Cabanillas, F.B. Hagemeister, S. Riggs, P. Salvador, W. Velasquez, P. McLaughlin. M.D. Anderson Hospital & Tumor Institute, Houston, Texas 77030.

Primary refractoriness to induction chemotherapy or relapse from remission usually carries a dismal prognosis for patients with intermediate or high grade ("aggressive") lymphomas. During the past six years we have used Ifosfamide - VP-16 based salvage regimens to treat 154 pts with recurrent or refractory aggressive lymphoma & an additional 7 pts who were partially refractory to front line therapy. Partial refractoriness was defined as achievement of a PR as the maximum response after a minimum of six courses of front line adriamycin containing combinations. These partially refractory pts were crossed over to the Ifosfamide - VP-16 based regimen before relapse occured on front line therapy. The salvage regimens used consisted of the following combinations: IMVP-16 (Ifosfamide, MTX, VP-16), AIVP-16 (AMSA, Ifosfamide, VP-16) & MIME [Methyl Gag, Ifosfamide, MTX & Etoposide (VP-16)]. Response rates in patients with recurrent or refractory disease were:

Regimen	N	CR(%)	PR(%)	Median RFS of CR's	P Value
IMVP-16	33	11 (33)	11 (33)	9 Mos.	
AIVP-16	25	12 (48)	2 (8)	9 Mos.	> .05
MIME	96	33 (34)	29 (30)	16 Mos.	
TOTAL	154	55 (36)	42 (27)		

Of 48 CR's who have been at risk >1 yr, 15 (31%) are still in CR. Response according to histological type was as follows:

	N	CR(%)	PR(%)
Large Cell	119	39 (33)	33 (28)
Lymphoblastic	13	6 (46)	2 (15)
Diffuse Small Cleaved (DPDL)	15	7 (47)	5 (33)
Diffuse Small Non-Cleaved (DUL)	7	3 (43)	2 (29)

In addition there were 7 partially refractory patients treated with these regimens & 6 (86%) achieved CR. Three of these 6 are still in CR >2 yrs. Ifosfamide - VP-16 based salvage combinations are effective in producing responses in pts with recurrent lymphoma. The quality of the CR's in the MIME regimen appears to be slightly superior although this hasn't reached statistical significance. The early use of these regimens in partially refractory pts (before relapse occurs) results in a high % of CR's of long duration. Toxicity consists mostly of infection (28%), and hemorrhagic cystitis in 20% of pts. A modest fraction of pts with recurrent or refractory lymphoma and a high fraction of partially refractory lymphomas appear to be potentially curable with these salvage regimens.

86 METHOTREXATE PLUS HIGH DOSE CYTARABINE IN ADVANCED REFRACTORY LYMPHOMA. R. Opfell*, J. Schottinger+, N. Schlutz+, H. Ballard°, and S. Armentrout+. *New York University, New York, NY, +Univ. of California, Irvine, CA, °Manhattan Veterans Administration Hospital, New York, NY.

Methotrexate and Cytarabine are reportedly synergistic. Eight patients with advanced refractory lymphoma were treated with Methotrexate 40 mg/M2 x 1 dose followed in one hour by Cytarabine 3gm/M2 x 4 doses q 12 h. The regimen was repeated q 21 days. Patients included 2 Hodgkins, 1 DUL, 2 DHL, 1 NPDL, 1 plasmacytoid lymphocytic, and 1 T cell prolymphocytic leukemia; ages 24-71 (median 46). All were heavily pretreated, had progressed on adriamycin containing regimens, and 3/8 had received prior radiotherapy. Prior chemotherapy consisted of 4-10 drugs (median 7) and 5-18 cycles of therapy (median 9). There were 6/8 major responses with 4 CR and 2 PR. One patient had MR with relief of abdominal pain and pedal edema. The patient with DUL had CNS involvement, no measurable disease, expired of cardiac arrest apparently unrelated to toxicity after two cycles. One patient with Hodgkins was in CR after 2 cycles, relapsed after no therapy and responded with a PR after 2 cycles. 6 of 8 patients survive for 4-12 months. Therapy was well tolerated: the major toxicity was myeloid, without CNS toxicity or mucositis. Granulocyte nadirs below 1,000 and platelet nadirs below 35,000 were seen in every patient. There was rapid recovery with return of leukocyte count to at least 3,500 and platelet count to at least 100,000 within 21 days in 90% of the cycles. This combination produced rapid responses in the majority of this group of heavily pretreated patients. De-escalation of the dose of cytarabine will be done to determine whether similar antitumor responses can be obtained with less myeloid toxicity.

87 A NEW COMBINATION REGIMEN OF EXPERIMENTAL DRUGS FOR THE TREATMENT OF RELAPSED LYMPHOMA: GALLIUM NITRATE, METHYLGLYOXAL BIS(GUANYLHYDRAZONE) AND ETOPOSIDE.
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Current combined modality treatment with chemotherapy and radiation can produce complete remission (CR) and prolonged survival in ≥ 50% of patients (pts) with advanced-stage Hodgkin's disease (HD) and diffuse large-cell ("histiocytic") lymphoma. However, the prognosis for most pts who fail to respond or who relapse from such aggressive therapy remains extremely poor. Previously, we found that both methylglyoxal bis(guanylhydrazone) (MGBG) and gallium nitrate (GN) had major anticancer activity as single agents in pts with malignant lymphoma. We have combined these non-myelosuppressive drugs with etoposide (VP-16-213) in a new regimen for the treatment of patients with advanced, relapsed lymphoma. In this protocol, GN was administered by continuous infusion for 7 days (d) at a dose of 300 mg/sq m/d. MGBG was given on days 1 and 10 (600 mg/mq m) and etoposide was given daily x 3 days (100-125 mg/sq m/d) on days 2, 3 and 4. Subsequent cycles were given every 3-4 weeks.

To date, 29 pts are evaluable. Each pt had received extensive prior chemotherapy (median of 2 combination regimens (range 1-4) and 6 drugs (range, 4-12). Eighteen pts had also received radiotherapy, of the 29 evaluable pts 15 (52%) had major responses (4 CR, fully restaged; 11 PR). Response according to Rappaport classification was: 9/13 DHL, 3/3 Hodgkin's; 2/5 DPDL; 0/3 NPDL; 1/5 other NHL. Median response duration exceeds 4 months. The major toxic reaction to this regimen has been myelosuppression (leukocytes 1000/cu mm in 39% of pts, platelets 40,000/cu mm in 30%). Twenty percent of pts developed an increase in serum creatinine ≥ 1.0 mg/dl. Four pts developed optic neuritis which was associated with substantial reduction of visual acuity in 2 pts.

This new drug regimen has major activity in patients with relapsed lymphoma. The individual drugs do not share mechanisms of action or toxic effects which are similar to other agents conventionally used for the treatment of lymphoma. Therefore, this regimen may not be cross-resistant with standard chemotherapy and may prove useful as an alternating regimen for the therapy previously untreated patients.

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88 CLINICAL INTERFERON (IFN) STUDIES IN LEUKAEMIA AND LYMPHOMA

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The potential clinical relevance of the antiproliferative effect of the α interferons initially demonstrated in murine leukaemia models, has been investigated in patients with lymphoma and leukaemia.

Phase I studies with leucocyte lymphoblastoid and recombinant DNA have shown that the maximum dose given over a prolonged period compatible with a normal ambulatory existence is less than $10x10^6$ IU daily and that the maximum dose given over a short period is $100x10^6$ IU daily. The dose limiting side effects are central nervous system toxicity and metabolic disturbance.

The Phase II results available at present may be summarised as follows: Responses, although rarely complete, have been observed in lymphoma treated at doses between $2x10^6$ IU/m^2 to $50x10^6$ IU twice weekly. The highest response rate 16/25 (64%) has been reported in low grade Non Hodgkin's lymphoma (NHL), treated with $50x10^6$ IU/m^2 thrice weekly and IFN-αA, confirming early experience with IFN-α at lower doses. Less impressive responses of short duration have also been achieved in chronic lymphatic leukaemia (9/28), high grade NHL (4/19) and Hodgkin's disease (4/12).

A clear demonstration of the antiproliferative activity of IFN-α (leucocyte) has been made in chronic myeloid leukaemia with indefinite administration of 3 to 9 $x10^6$ IU daily. The peripheral blood count returned towards normal in 22/25 (88%) patients, although splenomegaly frequently persisted, and the Philadelphia chromosone remained. Very high doses of IFN-α_2 given by continous intravenous infusion reduced the white blood count more rapidly, but the effect was only transient in 4/4 patients. Preliminary results suggest that complete remission can be achieved with this dose of IFN-α in patients with hairy cell leukaemia (3/7). No benefit has been shown for any patient (0/23) with acute myelogenous leukaemia, receiving either high dose continuous infusion of lymphoblastoid IFN-α or recombinant DNA IFN in spite of an in vitro evidence of activity at the serum levels achieved.

Studies are currently in progress to evaluate the differentiation effect of IFN- in leukaemia, and the possible synergistic action of α IFN with cytotoxic chemicals in lymphoma.

89 NEW DRUGS IN MALIGNANT LYMPHOMAS.

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Malignant lymphomas are sensitive to a broad range of chemotherapeutic agents and a number of highly active regimens have been tested and found to be clinically useful. The search for new chemotherapeutic agents with useful activity against malignant lymphomas is becoming increasingly more difficult because patients suitable for phase II studies have received extensive prior therapy with radiation therapy and/or a variety of different drugs, resulting in increased likelihood of their tumors possessing multiple cross-resistance phenotypes and a high probability of reduced bone marrow reserve in the majority of subjects. The consequence of this is that successful new agents must possess reasonable inherent anti-lymphoma activity and safety AND be relatively non-cross resistant with drugs the patient has already received AND in many cases have either a different spectrum of toxicities from other drugs or at least have minimal toxic impact on the bone marrow. These considerations make impractical suggestions that lymphomas might be used as a clinical model for screening anticancer agents prior to their use in solid tumors.

In spite of these difficulties new agents continue to be tested in lymphomas. Using the 1983 edition of the Compilation of Experimental Cancer Therapy Protocol Summaries prepared by the International Cancer Research Data Bank as a representative collection of cancer studies throughout the world, 105 study protocols were reviewed. Fifty three of the 105 trials (50%) utilize one or more new agents for some phase of treatment and 40 trials (38%) are specific for previously treated patients. The most common used new agents include: etoposide (VP-16), teniposide (VM-26), MeGAG, spirogermanium, ifosfamide, amsacrine, and deoxycoformycin. Of the 53 trials using new agents, 41 (77%) use one or more of these seven agents. In addition, a smaller number of trials (7 studies) introduce the use of biologic response modifying agents and immunological manipulations. These agents include BCG and Interferon. Six of the 7 trials using these agents allow entry of patients with no prior systemic therapy, and it is notable that 4 of the 7 trials are randomized and that 3 of these 4 trials have untreated control groups.

Additional agents about to enter early trials in lymphomas include: a pair of platinum analogs, carboplatin, and iproplatin; a bleomycin analog, tallysomysin S10b; a pair of antimetabolites, FAMP and fludarabine; and a number of other agents. Interest in developing new agents remains high and this is reflected in the surprisingly high percentage of studies utilizing new agents for the treatment of lymphomas.

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SELF-RECOGNITION MECHANISM AND IMMUNE REACTIVITY IN H-2 INCOMPATIBLE BONE MARROW RADIATION CHIMERAS. G.JM Maestroni[1], W. Pierpaoli[2], G. Losa[1]. 1: Laboratory of Cellular Pathology, Istituto Cantonale di Patologia, 6604 LOCARNO, Switzerland. 2: Institute for Integrative Biomedical Research, 8123 EBMATINGEN, Switzerland.

Timed administration of urmanipulated donor (P1) bone marrow cells suspended in a solution of recently identified microenvironmental components of the bone marrow into lethally irradiated recipients (P2) makes for the induction of complete, GVHD-free and stable allochimerism. Depending on the donor-recipient combination, P1→P2 allochimeras may or may not show depressed primary immune responses against T-dependent antigens. Conversely, alloreactivity was perfectly normal in all combination used. Chimerism of established (>3-4 months after bone marrow transplantation, BMT) P1→P2 allochimeras cannot be adoptively transferred to new irradiated recipients. This fact denies existence of suppressive mechanisms in chimeric bone marrow or spleen cells in contrast with the unresponsiveness shown in vitro in mixed lymphocyte cultures of chimeric lymphocytes against normal P1 or P2 lymphocytes. However, established P1→P2 chimeras are able to "suppress" passively transfused immunocompetent P1 and/or P2 lymphocytes. Large amounts ($80\text{-}90 \times 10^6$) of P1 and/or P2 immunocompetent leukocytes (spleen cells) passively transfused into established and GVHD-free P1→P2 allochimeras failed to show effector functions. Normal, immunocompetent P1 spleen cells inoculated into P1→P2 chimeras did not reconstitute primary responses against T-dependent antigens nor elicited GVHD, while normal immunocompetent P2 spleen cells failed to reverse chimerism. In both cases the transfused chimeras remained healthy and retained their chimerism. Moreover, GVHD-free P1→P2 allochimeras showed the surprising ability to reject P2 skin grafts. Both these phenomena are dependent upon the age (time after BMT) of the established chimeras. Preliminary ultrastructural studies of chimeric spleens have revealed an abnormal number of cells with plasmocytoid features. These findings pointed to the existence of an "unknown suppression-rejection principle" operating in the chimeras. In other words, a principle that mediates P1 lymphocyte suppression and possibly P2 lymphocytes rejection. Furthermore, the impairment of primary responses against T-dependent antigens seems not to depend on thymus directed H-2 restricted T-B cells recognition mechanisms. In fact, normal immunocompetent P1 lymphocytes did not reconstitute those P1→P2 allochimeras showing reduced primary responses against T-dependent antigens. All together, these data open fundamental questions about the mechanisms of self-recognition and their effect on the immune reactivity of allogeneic bone marrow chimeras.

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APPLICATION OF IMMUNOTOXINS TO AUTOLOGOUS BONE MARROW TRANSPLANTATION. F.Uckun, S.Ramakrishnan, L.L.Houston and M.Aksoy. Dep. of Hematology, University of Istanbul and Dept. of Biochemistry, University of Kansas, USA.

Current strategies for effective autologous bone marrow transplantation(ABMT) in leukemia and high grade malignant lymphoma include the in vitro use of immunotoxins-monoclonal antibodies covalently bound to a toxin such as ricin or a hemitoxin such as pokeweed antiviral protein (PAP),a potent inactivator of ribosomes.The present study was performed to assess the selective clonogenic lymphoma cell elimination from human marrow by in vitro use of an immunotoxin of pan-B-IgG1(κ) monoclonal antibody B43 linked to PAP and to define optimal conditions for application of B43-PAP to ABMT.PAP was purified from spring leaves of Phytolacca americana and linked to B43 by a disulfide bond using N-succinimidyl-3-(2-pyridyldithio) propionate(SPDP).The molar ratio of PAP to antibody was estimated to be 2:1 by a specific homologous radioimmunoassay.To quantify the target cell selective cytotoxicity of B43-PAP,we applied a highly sensitive clonogenic assay which can measure elimination of almost 6 logs of clonogenic lymphoma cells from human marrow.The stem cell toxicity of B43-PAP was evaluated by conventional in vitro clonal assays using highly purified stem cell suspensions. Treatment with B43-PAP under standard assay conditions (8h at 37°C) selectively inhibited protein synthesis in target lymphoma cells by more than 95% eliminating some 4 logs of clonogenic lymphoma cell contamination from a 100-fold excess of normal bone marrow.In contrast to this very high anti-tumor activity,less than 50% of pluripotent stem cells(CFU-GEMM) were lost.Chloroquine,an agent that raises lysosomal pH,specifically enhanced the rate of protein synthesis inhibition by B43-PAP at concentrations not affecting the growth of clonogenic lymphoma cells or pluripotent human hemopoeitic progenitors in culture and extended the final level of kill more than 1,5 logs compared to its absence.The almost 6 logs of selective lymphoma cell elimination achieved with B43-PAP in the presence of chloroquine suggests that in future clinical trials,B43-PAP or other PAP conjugates of monoclonal antibodies can be effectively used to eliminate residual clonogenic tumor cells from autologous stem cell grafts.

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92 IN VITRO PURGING WITH HYDROPEROXYCYCLOPHOSPHAMIDE (4-HC) AND ITS EFFECTS ON HEMATOPOIETIC AND STROMAL ELEMENTS OF HUMAN BONE MARROW. Salvatore Siena, Hugo Castro-Malaspina, Subhash Gulati, Li Lu, Teresa Cartagena, Richard J. O'Reilly, Bayard D. Clarkson, and Malcolm A.S. Moore. Memorial Sloan-Kettering Cancer Center, New York, NY 10021, USA.

Transplantation of 4-HC purged autologous bone marrow(ABMT) after high-dose chemoradiotherapy is a promising approach to the treatment of lymphoma and leukemia. This is based on the assumption that the dose of 4-HC employed selectively kills malignant cells without eliminating the cellular progenitors responsible for the hemopoietic reconstitution of the host. Recent clinical observations indicate that 4-HC purging techniques while depleting the graft of granulomonocytic (CFU-GM) and erythroid (BFU-E) committed stem cells, do not affect its capacity to repopulate the host hemopoietic system. In this respect the role of marrow stromal cells (MSC) and pluripotential stem cells (CFU-GEMM) has not been defined. The purpose of this investigation was to analyze the effects of 4-HC on MSC and CFU-GEMM. MSC were quantitatively studied by the marrow fibroblast colony-forming cell (CFU-F) assay and functionally by the long-term marrow culture assay (LTMC). The 4-HC toxicity on MSC and hemopoietic progenitors was dose and cell concentration dependent. The following ID_{50} (μM 4-HC) were found:

Clonal Assay	Cell Concentration	
	20×10^5/ml	10×10^5/ml
CFU-F	235	115
CFU-GEMM	31	n.d.
BFU-E	41	n.d.
CFU-GM	89	22

Treatment of marrow cells with 100 μM 4-HC, which is the dose we currently use for ABMT, resulted in depletion of hemopoietic progenitors (CFU-GEMM 0%, BFU-E 3.2 %, CFU-GM 26.6%). All 6 patients with NHL transplanted after supralethal chemoradiotherapy with autologous 100μM 4-HC purged marrow showed full hemopoietic recovery. This suggests that the CFU-GEMM may not represent the stem cell responsible for hemopoietic reconstitution in the transplanted host. In contrast, the MSC progenitor CFU-F was relatively resistant to the in vitro action of 4-HC. Moreover, 4-HC treated bone marrow in LTMC gave raise to stromal layers composed of fibroblasts, endothelial cells, adipocytes, and macrophages similarly to controls, although a higher number of cells per inoculum was required. Coculture of these heterogeneous stromal layers with freshly isolated autologous hemopoietic cells demonstrated that the stroma grown from 4-HC treated marrow sustained the long-term production of CFU-GM similarly to controls. Thus, MSC are relatively resistant and not functionally affected by 4-HC. This is sharp contrast with the high sensitivity of hemopoietic progenitors. Taking into account the notion of transplantability and radiosensitivity of MSC, the relevance of MSC in the area of bone marrow transplantation will be discussed. Furthermore, an in vitro ABMT model employing a coculture system in LTMC will be presented.

93 INDICATION FOR BONE MARROW HARVESTING AND PURGING IN BURKITT LYMPHOMA : A 3 YEARS EXPERIENCE. I. Philip[1], T. Philip[1], M. Favrot[1], P. Biron[1], G.M. Lenoir[2]. 1. Centre Léon Bérard - Bone Marrow Transplant Team - 28 rue Laënnec 69008 LYON - FRANCE. 2. International Agency for Cancer Research - 175 Cours Albert Thomas - LYON - FRANCE.

Between 1980 and 1983 317 bone marrow aspirates from 63 Burkitt lymphoma were studied with an in vitro liquid culture monitoring system.

1. BL cell line was obtain in culture from 14 out of 15 patients studied with cytologically positive marrow. The in vitro monitoring system was shown to be usefull regardless of EBV status (7 EBV ⊕ - 8 EBV ⊖), patient status (9 at relapse, 6 at diagnosis) and cytogenetic anomalies (8 t(8;14) - 2 t(8;22) - 2 t(8;2) in 12 patients studied).

2. When bone marrow was cytologically normal or suspect (i.e. less than 5 % BL cells) the in vitro monitoring system was shown to be more sensible than cytologic examination in 25/56 i.e. 44 % of the cases. The sensitivity of the test is of 1/100.000 i.e. 3 logs inferior to cytology.

3. If bone marrow will be harvested for all patients in CR after 2 months of chemotherapy purging marrow will not be necessary (38/38 negative culture) but 7/10 patients will be harvested for nothing (30 % of indication for ABMT).

4. If bone marrow will be harvested at relapse or in PR purging procedure was shown to be necessary in 9/16 cases i.e. 56 % of the cases.

94 AUTOLOGOUS BONE MARROW TRANSPLANTATION FOR RELAPSED NON-HODGKIN'S LYMPHOMA (NHL): ANTI-B_1 MONOCLONAL ANTIBODY TREATED AUTOLOGOUS BONE MARROW. L. Nadler, T. Takvorian, R. Finberg, R. Bast, L. Botnick, S. Hellman, G.P. Canellos, S.F. Schlossman, Dana-Farber Cancer Institute and Joint Center for Radiation Therapy, Boston, MA

Five patients with relapsed B-cell NHL were treated with intensive chemo-radiotherapy and reconstituted with autologous bone marrow (BM) rendered free of tumor by in vitro treatment with the B cell specific monoclonal antibody anti-B_1 and rabbit complement. Median age was 46 years (range 43-57) and histology at relapse included diffuse mixed (1), diffuse large cell (3) and diffuse poorly differentiated (1). These patients had relapsed one to six times on conventional therapy with BM involvement in 4 of 5. They were re-induced into a minimal disease state, with $\leq$ 5% BM involvement, utilizing chemotherapy alone (3 patients) or with radiation therapy and chemotherapy (2 patients). The marrow in remission was harvested, treated in vitro with anti-B_1 and complement, and cryopreserved. Patients then received Cytoxan at 60mg/kg on days 1 and 2, followed by 3 days of fractionated whole body irradiation (200 rads twice daily), followed by re-infusion of the treated autologous bone marrow on day 6. All patients achieved a complete response with engraftment of the treated marrow by 4 weeks. Acute toxicity included self-limited nausea, vomiting and mucositis; culture negative low grade fever developed in 4 of 5 patients which responded to antibiotics. B_1 positive B cells were first detected at 1 month and achieved normal levels at 2-3 months whereas circulating levels of immunoglobulin did not return to normal until 6 months. Late toxicity included atypical pneumonia at 3 1/2 months and herpetic conjunctivitis at 7 months in one patient. One patient had localized Herpes zoster at 7 months. No other late toxicity has been seen. Three of 5 patients are presently disease free in an unmaintained remission at 13, 12 and 1 months. One patient with 6 relapses prior to autologous transplantation relapsed at 2 months with extensive disease and died of lymphoma. A second patient relapsed at 6 months at the site of former bulk disease but not in the bone marrow which was previously involved, and is being palliated. The present study suggests that anti-B_1 treated autologous BM can rescue the aplasia of intensive chemo-radiotherapy. Moreover, autologous BM transplantation with tumor cell depletion has relatively little toxicity compared to allogeneic transplantation, and preliminary evidence to date suggests that this approach may be useful in the future treatment of NHL, especially during the initial induction of high risk patients.

95 AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) FOR POOR PROGNOSIS LYMPHOMA. S.Gulati, L.Gandola, R.Vega, B.Shank, D.Straus B.Koziner, B.Lee, R.Mertelsmann, S.Kempin, M.Andreeff, R. Dinsmore, T.Gee, J.Yopp, R.O'Reilly and B.Clarkson. Memorial Sloan-Kettering Cancer Center, New York, NY 10021.

Patients with poor prognosis lymphoma,identified as having bulky mediastinal or abdominal disease and/or high serum lactic dehydrogenase level ($>$500 units/ml),even though initially responsive to conventional therapy have poor survival rates. Sixteen such patients with diffuse histiocytic lymphoma (DHL) had their bone marrow (BM) cryopreserved after induction chemotherapy consisting of cytoxan , adriamycin, vincristine and prednisone (L-17M protocol). At the time of transplant, radiation to the site of residual disease was followed by TBI (total 1320 rads) 11 doses over 4 days; then cytoxan 60mg/M^2/day x 2 days with ASCT rescue. Seven patients had ASCT soon after induction therapy (in CR or PR) ;all seven patients are doing well with follow-up of 22,16,12,11,7,7 and one months. Five patients progressed after L-17M induction and were then treated with ASCT protocol, Two of them have died of peritransplant complications;one has relapsed but is alive at 9 months and the other two are disease-free with follow-up of 4 and 2 months. Four patients were heavily pretreated before ASCT. One of these patients died few days after transplant; one patient relapsed but is alive at 4 months and the other two are doing well with 15 and 4 months of follow-up. Five of the above patients with initial BM involvement (2 progression on L-17M , 3 heavily pretreated) received 4-hydroperoxycyclophosphamide (4-HC) purged BM and all had good hematopoietic reconstitution. Two of these patients relapsed , but all are still alive. From these results, it appears that "superconsolidation" with TBI and cytoxan followed by ASCT has promise in improving the management of patients with poor prognosis lymphomas.Methods of purging bone marrow will also be discussed. (Support CA-08526;19117;20194) .

96 MASSIVE THERAPY AND AUTOLOGOUS BONE MARROW TRANSPLANTATION AS RESCUE PROTOCOL FOR BURKITT LYMPHOMA (EXPERIENCE OF 18 CASES). T. Philip, P. Biron, I. Philip, M. Favrot, G. Souillet, P. Hervé, E. Plouvier, J.L. Bernard, C. Raybaud, D. Frappaz, F. Freycon, B. Crozet, M. Brunat-Mentigny. Centre Léon Bérard - Bone Marrow Transplant Unit and France Autogreffe Study Group.

Overall survival for children with Burkitt lymphoma raised from 42 % to 80 % in our group in a 3 years period. During the same period massive therapy (i.e. BACT) was investigated by us in two different groups of patients.

- In the first group 10 patients treated by the former protocol (i.e. CHOP) were selected for ABMT because of relapse (cases 1,3,4,5,6,7,9), PR after 3 months of CHOP (case 2), or long delay to reach CR (cases 8 and 10). 3 of the 7 relapses are still alive 930 ⊕ , 894 ⊕ and 410 ⊕ post ABMT. Patient 2 in PR is alive NED 990 ⊕ and one of the two long delay to CR is alive NED 184 ⊕ . 5/10 patients are alive NED (4 more than 2 years post ABMT).

- The second group is made of 8 patients aggressively treated during the period 1981-1983. 43 patients were treated by our group during this period and 8 selected for massive therapy and ABMT i.e. 1/7 localized disease because of early relapse → alive NED 163 ⊕ , 4/28 stage III because of PR (1), progression (2) or long delay to reach CR (1) → 1 alive NED 186 ⊕ , 3/8 stage IV because of PR or for consolidation of initial CNS involvement → 1 alive NED 260 ⊕ . A total of 3/8 patients are alive NED.

In this group of very bad prognosis BL 8/18 are alive NED 163 to 990 days post ABMT. 4 of the 10 relapsed patients are alive NED including 3 with more than one year survival (i.e. cure for BL). This report shows ① The BACT efficacy in BL. ② ABMT will concerned a maximum of 30 % of BL cases. ③ Necessity to purge at least some bone marrow. ④ Feasibility of purging marrow (5 cases).

97 TREATMENT OF REFRACTORY NON-HODGKIN'S LYMPHOMA WITH INTENSIVE CHEMORADIOTHERAPY AND AUTOLOGOUS BONE MARROW TRANSPLANTATION. G. Santos, A. Yeager, H. Braine, H. Kaizer*, M. Colvin, L. Munoz, and R. Levy**, The Johns Hopkins Oncology Center, Baltimore, MD, *Rush Medical College, Chicago, IL, and ** Stanford University, Palo Alto, CA.

The long-term survival is poor in patients with refractory or relapsing non-Hodgkin's lymphoma (NHL). We examined the efficacy of intensive chemotherapy and total body irradiation (TBI) followed by autologous bone marrow transplantation (auto BMT) with "purged" cryopreserved marrow in refractory or relapsing NHL. Sixteen patients, ages 3-39 years, received a preparative regimen consisting of cyclophosphamide, 50 mg/kg/day x 4, and TBI (300 rad/day x 4 or 180 rad B.I.D. x 8); 4 patients also received adriamycin, 30 mg/M^2/day x 3. Marrow was treated in vitro with 40-100 ug/ml of 4-hydroperoxycyclophosphamide (4HC) or, in patients with T-cell NHL, one or two monoclonal antibodies (Leu-1 + Leu-9) plus complement (C'). As of January 15, 1984, we have obtained these results:

In Vitro Rx	No. Pts.	No. Relapses (days post BMT)	No. in Remission (days post BMT)
4HC	7	3 (33,60,75)	4 (17+,122+,781+,797+)
Leu-1	4	2 (49,75)	2 (696+,1198+)
Leu-1 + Leu-9	5	3 (48,91,405)	2 (10+,52+)

We conclude that the combination of intensive chemoradiotherapy and auto BMT with pharmacologically or immunologically "purged" marrow may provide a significant opportunity for disease-free survival in relapsing or refractory NHL.

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98 Lymphoproliferative Diseases with Monoclonal Gammopathy

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In the past decade malignant lymphomas have been recognized and characterized as tumors of the immune system, with the neoplastic cells often manifesting morphologic and functional characteristics that mimic those of their normal benign counterparts. Lymphoproliferative diseases with monoclonal gammopathy result usually from the neoplastic transformation of clones of B-cells at or near the terminal stages of B-cell differentiation. To understand the morphology, pathogenesis, and clinical manifestations of these disorders, however, one must have an overview of the physiology and interrelationships of B-cells, T-cells, and cells of the mononuclear phagocytic system. In this presentation such an overview will consider initially both the normal immune system and selected congenital and acquired immunodeficiency states. In this context, it will become apparent that neoplastic lymphoproliferative disorders with monoclonal gammopathy arise from the milieu of the immune system and retain to variable degrees functional attributes demonstrable in terminally differentiated normal B-cells. Attention will focus mainly on multiple myeloma, macroglobulinemia of Waldenstrom, and the heavy chain diseases, with emphasis on their clinical, morphologic, and immunologic manifestations. A comprehensive review of the subject is available in the following reference:

Callihan, T.R., Holbert, J.M. and Berard, C.W.: Neoplasms of terminal B-cell differentiation: the morphologic basis of functional diversity. In Malignant Lymphomas: A Pathology Annual Monograph, pp. 169-268, Appleton-Century-Crofts, Norwalk, Connecticut, 1983.

99 ANGIOIMMUNOBLASTIC LYMPHADENOPATHY: CLINICAL COURSE, IMMUNOLOGICAL CHARACTERISTICS AND TREATMENT RESULTS IN 25 PATIENTS.

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We observed 25 patients with Angioblastic Lymphadenopathy (AILAP) between 1972 and 1983. Diagnosis was established by lymphnodebiopsy. Patients without histologically proven diagnosis from lymphnodes were excluded from this study. Median age was 50,4 years. 60% were male, 42% female. Initial clinical symptoms occurred 3 months before diagnosis: lymphnode enlargement (80%), fewer (60%), weight loss and nightsweat (44%), hepato-splenomegaly (48%), exanthema like erythroder mia and generalized pruritus (20%). Laboratory investigations at the time of diagnosis: rapid blood sedimentation rate (60%), thrombocytope nia < 100.000/mm^3 (52%), anaemia: Hb <12 g% (48%), leucopenia < 3000/mm^3 (24%) with > 10% eosinophilic granulocytes, liver enzyme - alterations (20%). Immunological characteristics during the active phase of AILAP: polyclonal gammopathy, increase of immune-complexes, cold haemagglutinins, antibodies against smooth muscles and EBV. Cellular analysis: T-lymphocyte depletion with low helper and high suppressor cell activity, normal NK-cell activity. B-lymphocyte - proliferation with high num ber of terminal mature B-cells. Reactivity with mitogens normal or low.

Treatment decision was based on clinical symptoms and progression of AILAP. If tolerable to the patient we waited 4 weeks for spontaneous regression which was observed in 4/25 cases (16%). If AILAP was continuously progressing, therapy consisted either of Prednisone (slow progression: group A) or polychemotherapy (rapid progression: group B).
A: Prednisone 60 mg/m^2 p.o. daily for 4 weeks, subsequent stepwise reduction to maintenance level; if CR: therapy-stop after 4 months.
B: Cyclophosphamide 100 mg/m^2 p.o. daily, Vincristine 2 mg i.v. weekly, Prednisone 60 mg/m^2 p.o. daily ± Procarbacine 100 mg/m^2 p.o. daily (Cy and Pred: day 1-28, Vcr day 1,8,15,22, Pro day 1-14; q day 29)
After CR: Pred-maintenance. Patients not responding to A switched to B.
Results: Only A: 2 CR, 2 PR, 1 NC, 2 P (n = 7)
Only B: 0 CR, 0 PR, 0 NC, 6 P (n = 6)
B after A: 0 CR, 4 PR, 1 NC, 3 P (n = 8)
Median survival of all patients was 36,4 months. Median survival of non-responders was 9,4 months. Median observation time was 34,5 months. 7/25 patients showed a malignant transformation of AILAP: 4 Hodgkin's diseases, 3 Non-Hodgkin-Lymphomas (28%). 2/25 patients had synchronous secondary malignancies: AML and Cervical-Carcinoma. 13/25 patients died (52%), 12 are alive, 9 with no evidence of AILAP.
Conclusions: 1. There are three prognostically different clinical courses of AILAP: spontaneous regression, good response to Prednisone, poor response to either Prednison or polychemotherapy. There is no clear relationship to the stage of the disease or other characteristics like immunological malfunctions. 2. Further analysis of immunological impairments might help to develop new, more efficient kinds of therapy. 3. In many cases AILAP precedes malignant transformation or secondary malignancies.

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100 A CONTINUUM OF ALL AND NHL TYPES ACCORDING TO THE DIFFERENTIATION STEPS DETERMINED BY MONOCLONAL ANTIBODIES. CORRELATION WITH WHO, FAB AND NCI CLASSIFICATIONS.

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We have in a double blind fashion categorized according to WHO, FAB and NCI classifications all ALL and NHL after having characterized their immune types with monoclonal antibodies. Patients with ALL of which all OKT, cμ and sIg were negative had a WHO microblastic ALL , FAB L1. Patients OKT10+, OKT6, 3, 4 and 8-, B1, cμ, sIg- had a WHO prolymphoblastic T and FAB L2-3 ALL. Patients with all OK, cμ and sIg- but B1+ had the WHO prolymphoblastic of the B series ALL FAB L2-3. Patients with large cells OKT10 and OKT6+, OKT3, OKT4 and OKT8-, B1, cμ and sIg-correspond to the WHO T macrolymphoblastic ALL or NHL (cortico-thymocytic) and to the FAB-L2-3. Patients with large cells all OKT and B1-, cμ+ and sIg- correspond to the WHO pre-B-macroblastic ALL and to the FAB L2-3. Patients with OKT10 and OKT6, OKT3+, cμ-, sIg-, B1- correspond to the WHO T mixed lymphoblasto-prolymphocytic ALL or NHL and to the FAB L1-2. Patients with mixed-size cells all OKT-, cμ+ and sIg- and B1- correspond to the WHO pre-B mixed lymphoblasto-prolymphocytic ALL and to the FAB 1-2. Patients with all OKT-, $c\mu^{\pm}$ and sIg+ correspond to the WHO Burkitt'sleukemia and lymphoma or to FAB L3. All NHL of the B types are $c\mu^{\pm}$, this positivity being of various qualitative and quantitative types. The B lymphocytic NHL is sIgM+. The lymphoplasmocytic NHL is sIgM+. The small non cleaved nucleus cell type is sIgM+++, sIG+++. The small cleaved nucleus cell type is sIgM+, sIgG+. The large non cleaved nucleus cell type is sIgM++. The large cleaved nucleus cell type is sIgM+, sIgG+ and sIgG+. The B immunoblastic NHL (with convoluted or no nuclei) is sIgM+++ and sIgG+++. The T lymphocytic NHL is OKT4+ or OKT8+, OKT10 and OKT6-. Mycosis fungoide and Sezary disease (with cerebroid nuclei) are OKT4+, OKT10 and 6-. The Watanabe immunoblasto-pleiomorphic type is usually OKT4+, OKT8, OKT10, OKT6-. We have also observed cases of OKT8+, OKT4, OKT10, OKT6- NHL.

101 COMPARISON OF THE WORKING FORMULATION (WF) OF NON-HODGKIN'S LYMPHOMA (NHL) WITH THE RAPPAPORT (R), KIEL (K), AND LUKES & COLLINS (L&C) CLASSIFICATIONS. TERMINOLOGICAL CORRELATIONS AND PROGNOSTIC VALUE.

Jens Ersbøll, Henrik Schultz, Nis I Nissen, Philip Hougaard and Klaus Hou-Jensen. The Finsen Institute, Copenhagen, Denmark.

658 cases of NHL seen 1970-79 were reviewed and classified according to the R, K, L&C classifications and the WF. Each classification proved equally effective in separating patients into subgroups with prognoses ranging from a median survival of 1 year to 7 years. The R, K, L&C systems were compared one by one against the WF following the translation guidelines of the NCI-sponsored Study (Cancer 1982;49, 2112). The WF was more similar to the R and L&C systems than to the K system, since 82 %, 89 % and 75 % of the cases respectively were translatable according to the above-mentioned Criteria. The greatest similarities among the 4 systems were observed in FCC-lymphomas composed of predominantly small lymphocytes (93-98% accordance), in lymphomas of CLL type (80-100% accordance), and in FCC-lymphomas of small non-cleaved cytology (82-100% accordance). The greatest differences were seen in lymphomas composed of large lymphoid cells or of mixed cellular subpopulations. (58-90% accordance). The uncertain relation between the U-cell subtype of the L&C system and the lymphoblastic lymphomas of non-convoluted subtype accounted for the defective translation of this subtype (38-100 % accordance).
The Cox proportional hazards model was used to assess the prognostic effect of histologic subtype within each system after adjusting for the relative effect of age, sex, stage and symptoms. The following hazards are all compared to the F-SC subtype of the WF: SL (1.61,P=0.07 F-SC = 1, F-M (1.43,P=0.27), F-L (4.22,P <.0001), D-SC (1.68, P=0.06), D-M (2.61,P= .0002), D-L (3.28, P <.0001), IB (3.89, P<.0001), LB(5.0 P=<.0001), SNC (3.56,P <.0001). The intermediate malignancy grouping of the WF was prognostic heterogeneous, the SL and D-SC subtype had similar survivals (median 3.4 years), and the D-M,D-L and F-L subtypes had survivals similar to subtypes of the high grade grouping. By the use of the Cox model including two classifications simultaneous (WF compared one by one with the R,K, L&C systems) it was shown that the WF can substitute any of the established classifications in terms of prognostic value.

102 CLINICAL AND PROGNOSTIC RELEVANCE OF THE KIEL CLASSIFICATION OF NON-HODGKIN LYMPHOMAS (NHL): RESULTS OF A PROSPECTIVE MULTICENTER STUDY

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From 1975 to 1980, 1127 patients (pts.) with NHL entered a prospective multicenter observation study of the Kiel Lymphoma Study Group. During the first 3 to 4 years overall survival of the 782 pts. with low-grade malignant NHL (lymphocytic lymphomas, predominantly B-CLL: 23.1 %; LP immunocytoma = LP-IC: 18.9 %; centrocytic = CC lymphoma: 7,7 %; centroblastic-centrocytic = CB-CC lymphoma: 13,9 %) exceeded that observed in the 341 pts. with high-grade malignant NHL (centroblastic = CB lymphoma: 13,9 %; immunoblastic = IB lymphoma: 7,4 %; lymphoblastic = LB lymphoma: 5,3 %). Survival curves of pts. with low-grade malignant NHL declined with a flat slope without evidence of plateau. Prognostic superiority of CB-CC lymphoma and B-CLL over LP-IC and CC lymphoma could be recognized only after 2 years of followup. Survival curves of pts. with high-grade malignant NHL showed a rapid decline during the first 1 to 1 1/2 years and a subsequent plateauing. Intermediate course of survival curves of pts. with advanced stages of LP-IC, CC lymphoma and CB lymphomas between those of pts. with B-CLL and CB-CC lymphoma and those of pts. with IB and LB lymphomas suggest the existence of a group of NHL of "intermediate"-grade prognosis.
At presentation, 81 % of pts. with CC lymphoma showed stage IV disease. Only in pts. with stage I stable complete remissions (CR) could be achieved by radiotherapy. Survival curve of pts. with advanced stages showed a linear decline without evidence of plateauing. - Results of radiotherapy in pts. with stages I to III of CB-CC lymphoma support the concept that this NHL may remain restricted to the lymphatic system for a prolonged period of time. Strategy of "watchful waiting" for advanced CB-CC lymphoma is challenged by the unsatisfactory results obtained in this study and by improvement of prognosis observed in pts. achieving CR.
The high-grade malignant IB lymphoma was less favorable than CB lymphoma with respect to both clinical and prognostic features. Initial stages I and II were diagnosed in as many as 30 to 40 % of pts. with CB and IB lymphomas. Most of these pts. were treated by radiotherapy alone. However, only in stage I of CB lymphoma a sufficient proportion (80 %) of pts. achieved stable CR. Prognosis of patients with advanced CB, IB and LB lymphomas could only be improved by induction of CR but not of partial remission.
Poor risk factors for the individual NHL entities as evidenced by multiple regression analysis are discussed.

103 BONE MARROW AND BLOOD INVOLVEMENT BY NON-HODGKIN'S LYMPHOMA: CLINICOPATHOLOGIC FEATURES AND PROGNOSTIC SIGNIFICANCE IN RELATIONSHIP TO THE WORKING FORMULATION.

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One hundred and thirty-seven consecutive patients with malignant non-Hodgkin's lymphoma(ML) classified according to the Kiel system, who underwent routine bone marrow(BM) biopsy and peripheral blood examination as part of their initial evaluation, were reviewed according to the Working Formulation(WF). Patients with CLL, as well as cases with lymphoblastic lymphoma with blood and BM disease indistinguishable from acute lymphoblastic leukemia were excluded from this study. The median time of follow-up was 21 months (range 3-67+ mos). The overall incidence of BM involvement at diagnosis was 38%(52/137). The frequencies of BM disease in the three major prognostic groups of the WF were the following: 51%(28/55) for low grade (LGML); 32%(18/56) for intermediate grade (IGML) and 23%(6/26) for high grade malignant lymphomas (HGML). As regards the prognostic significance of BM involvement, the survival curves obtained grouping patients into low grade, intermediate grade and high grade malignancies were not significantly affected by the presence or absence of marrow disease at presentation. In fact, the lymph node histology proved to be the most important prognostic factor. Nevertheless, among patients with BM infiltration at diagnosis, a focal pattern of proliferation and a low extent of marrow disease (<30% replacement) discriminated groups with better prognosis.

Peripheral blood involvement by lymphoma was found at diagnosis in 42% (22/52) of cases with marrow disease; 17 cases showed leukemic spread during clinical course. As concerns prognostic significance of the leukemic spread, peripheral blood involvement at diagnosis in LGML appeared to have no important effect on the outcome of the disease, whereas late leukemic conversion heralded a rapid change to a more aggressive disease (median survival from the onset of leukemic phase 13mo). In fact, a shift to a less differentiated lymph node histology was documented in five patients with late leukemic spread. In patient with IGML, either initial or subsequent blood involvement was correlated with significantly worse prognosis (median survival 11,5 mo in leukemic patients; median not reached at 67 mo in non leukemic cases, $P<0.005$).As regards HGML, the median survival of leukemic and non leukemic cases did not differ statistically. Two major conclusions can be drawn. First, the presence of BM infiltration per se within each of the three major prognostic groups seems not to affect survival. Second, leukemic presentation in IGML and late leukemic conversion in LGML are associated with a worse prognosis.

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104 PATTERNS OF SURVIVAL IN NON-HODGKIN'S LYMPHOMA (NHL). T. Reichert, R. Christensen, A. Bartolucci, C. Walker, J. Moore. Duke University Medical Center, Durham, NC 27710, Entropy Limited, Lincoln, MA 011773, and SECSG Statistical Center, Birmingham, AL 35294.

NHL is a heterogeneous group of diseases which are often separated into two groups (favorable versus unfavorable) based on little more than the presence or absence of a nodular pattern of growth within the tumor. Refinements in description based on light microscopic criteria and even cell surface phenotype determinants have not yet provided information of additional prognostic utility. 334 previously untreated patients with advanced stage NHL were enrolled in a Southeastern Cancer Study Group (SECSG) clinical trial of cyclophosphamide, vincristine and prednisone (COP) versus the same regimen plus BCNU. No response or survival differences were noted between the regimens. Using a computer method which constructs constellations of patient characteristics and evaluates them for their ability to predict survival in a complete and exhaustive fashion*, we have divided the entire population of NHL patients into three groups. Those patients with performance status greater than 75%, "A" symptoms, and a normal value for the serum transaminase (SGOT) have a prolonged survival independent of disease histology and of their initial response to therapy. Those patients not so defined are also homogeneous in survival and in complete response rates except for a group having either low performance status (less than 70%) or night sweats at presentation. This latter sub-group is comprised almost entirely of patients with unfavorable histology disease. These patterns were discovered using 2/3 of the patients (224), were used to predict the survival of the remaining 110 patients in the study; and were then further validated on a dataset including all patients treated similarly at Duke University Medical Center. Nearly identical patterns were found analyzing favorable and unfavorable histology patients separately; and in other subsets of the data such as responders only. These patterns speak for the dominance of clinical heterogeneity over histologic diversity. They may well explain the wide variation in response and survival experiences reported by different institutions with similar treatment regimens (37-81% CR rate in favorable histology disease). They provide unambiguous guidelines for the deferral of treatment in a group of patients much larger than that suggested by earlier reports; and appear to explain the paradoxical survival gain reported in some series for patients with favorable histology disease who attain a complete response to therapy.

*Entropy Minimax: SWAPDP algorithm

105 PRIMARY INTESTINAL LYMPHOMA OF ADULTS IN THE MIDDLE EAST- COMPARATIVE STUDY OF IPSID VS NON-IPSID. L Hashimi, E Anaissie, C Allam, M Khalyl, P Salem. American University of Beirut Medical Center (AUBMC) Beirut, Lebanon.

Seventy five cases of primary intestinal lymphoma were diagnosed in adults at AUBMC during the period 1961-1980. Two additional cases with the pre-malignant phase of Immunoproliferative Small Intestinal Disease (IPSID) were also studied. 41.5% of patients had IPSID and 35% non-IPSID. In the remaining 23.5% it was difficult to distinguish IPSID from non-IPSID. IPSID differed from non-IPSID in the following: (1). Age: median age in IPSID was 25 yr while in non-IPSID 37 yr. (2). Clinical features: while chronic diarrhea and emaciation were the prominent clinical features at presentation in IPSID, the presence of abdominal mass and/or complications like obstruction, bleeding and perforation were the prominent features in non-IPSID. (3). Pathological features: a. IPSID was shown to involve the entirety of the small intestine as a diffuse cellular infiltrate predominantly confined to mucosa and submucosa, and in 36% of patients it was associated with tumoral masses. Non-IPSID on the other hand presented as one or more intestinal tumors in the absence of diffuse mucosal infiltrate. b. Gross pathological findings in IPSID were most conspicuous in the upper third of the small intestine while those of non-IPSID occurred primarily in the ileo-cecal region. c. The most frequent lymphoma in non-IPSID according to the Kiel classification was immunoblastic (45%), while in IPSID it was lymphoplasmacytic (41%). The cellular mucosal infiltrate in IPSID was usually lymphoplasmacytic or plasmacytic. In non-IPSID the mucosa distant to the site of tumor was free of infiltrate. (4). Immunological abnormalities: IPSID was associated with the synthesis and secretion of an abnormal IgA immunoglobulin free of light chains (α heavy chain protein). Like Burkitt's lymphoma, IPSID is a newly described disease which provides us with an opportunity to study the etiopathogenesis of lymphoproliferative disorders.

LO6 OVERVIEW: "THE IMPORTANCE OF VIRUSES IN LYMPHOMA"

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1. As "tools" in animal laboratory experiments to learn basic mechanisms of lymphomagenesis. Viruses of different forms cause different types of lymphoid neoplasias in many different animals. Sometimes this is limited to laboratory experiments, yet even in these instances more can be learned about mechanisms involved in the genesis of these lymphomas than from other causes because virus antigens and nucleic acids can be detected and the causative agent thereby can be followed. Moreover, the genes able to do this, contained in the viral genome, are packaged positive by the virus. This provides investigators with the opportunity of learning much about the genetic information which can cause lymphomas and mechanisms for their control. Some examples of such systems include the Herpes saimairi virus which apparently does not cause neoplasias in its natural host but can induce lymphomas upon inoculation of certain other monkeys and some retroviruses also by inoculation into heterologous species, e.g., lymphomas of sheep induced by bovine leukemia virus.

2. As "tools" to identify genes (onc-genes) in human DNA which may be critical to lymphomagenesis. Those animal retroviruses which cause cancers (often lymphomas) very rapidly contain a cellular derived gene, called an onc gene which codes for a protein leading to direct transformation of the cell. By using techniques of molecular biology these onc genes genes can be isolated and analyzed. Since the homologous genes in normal cells are conserved throughout evolution, they are also present in human DNA. Therefore, the isolated viral onc gene (v-onc) can be used to detect and isolate the corresponding cellular onc gene (c-onc) from DNA of normal human cells. This gene can be compared to the same gene from DNA obtained from human lymphomas to see if an important reproducible abnormality in the lymphoma gene can be found. The level of expression (transcription to mRNA) of the various c-onc genes from normal and lymphoma tissue can also be compared. We have been involved in a few studies like this which have led to interesting results, e.g., we have cloned several human onc genes, determined their chromosomal localization, and found the translocation of c-myc in Burkitt lymphoma in collaboration with C. Croce. Other approaches (DNA transfection) were chiefly made by G. Cooper and his colleagues, have led to the discovery by these investigators of new genes (e.g., B-Lym and T-Lym) which, like some other c-onc genes, may not only be involved in some lymphomas but quite likely in some aspects of normal lymphoid growth and differentiation. This technique and the above described work in animal retroviruses has opened up a new era of lymphoma research which offers us our first glimpse at the nature of genes important to lymphomagenesis and may lead to new ways to sub-classify and possibly to treat these diseases in the future.

3. As causes of naturally occurring animal and human lymphomas. In addition to producing lymphomas in the laboratory with various types of viruses (see #1), viruses are by far the most important known causes of naturally occurring lymphomas. This, of course, was first known from field animal studies and include, for example, the avian DNA virus (MDV) (a herpes virus) in Marek's disease of chickens and numerous animal lymphomas caused by RNA tumor viruses (retroviruses). Thus, avian leukosis virus, mouse amphotrophic leukemia virus, feline leukemia virus, bovine leukemia virus, and gibbon ape leukemia virus are the etiological agents of naturally occurring lymphomas of chickens, mice, cats, cows, and gibbon apes respectively. Viruses are now known to also be involved in the cause of human lymphomas. Thus, it has been suspected for some time that EBV plays a role in the early abnormalities which later due to several required additional factors leads to African Burkitt's lymphoma. The role of EBV, therefore, appears to be indirect.

In view of the known numerous animal retroviruses directly causing animal lymphomas, it was reasonable to believe that similar human retroviruses could be discovered. Thus, since Rous' discovery of the first retrovirus shortly after the turn of the century, numerous intense searches were made for this kind of virus in man. Work in this direction was greeted by pessimism and cynicism by the 1970s because of all the earlier failures. However, technological advances leading to very sensitive assays for retroviruses combined with our discovery of T-cell growth factor (IL-2), which enabled us to grow appropriate target cells for sufficient time, led us to isolate the first human leukemia/lymphoma retroviruses. Elsewhere, we have discussed the manner of isolation, nature of the HTLV positive lymphoid cell, characteristics of the disease, types of retrovirus isolated, and touched upon the epidemiology. Here I will expand on the epidemiology, and summarize some of the biological effects of these viruses and what is known or thought about the mechanism(s) involved in their induction of lymphomas. I will also describe the probable role of related retroviruses in the cause of AIDS.

4. Conclusion and Future. Work on tumor viruses has provided the beginning insights into the cause and pathogenesis of human lymphomas and already helped in lymphoma categorization. I anticipate that additional new isolates of such viruses will be found in the future and causatively linked to some other lymphomas and that work on c-onc genes will lead to new ideas of disease pathogenesis.

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