CHROMOSOMAL ABERRATIONS IN LOW-GRADE MALIGNANT B-CELL LYMPHOMA PROLIFERATIVE NEOPLASMS. G. Czarnocki, C. Juhlinson, K.-H. Räbér, l. I. Zech, Division of Clinical Hematology and Oncology, Department of Medicine, Huddinge Hospital and Karolinska Institute, Huddinge, and Institute of Medical Cell Genetics, Karolinska Institute, Stockholm, Sweden.

Forty-seven patients with low-grade malignant B-cell lymphoproliferative neoplasms were studied. According to the kiel classification 20 patients had classical (CL) 23 immunocytoma, 2 prolymphocytic leukemia (PLL) and 1 centroblastic-centrocytic lymphoma (CCL). One patient could not be subclassified. Chromosome analysis was made after stimulation of peripheral blood lymphocytes and/or cells from lymph nodes with lipopolyosaccaride from E. coli (IPS) or Epstein-Barr virus (EBV). The G-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 t(4;14) abnormality, and 3 patients had deletion of chromosome 11. Three patients had abnormalities of chromosome 16. 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 risen through chromosome exchange.

Patients with 2 or more clonal aberrations had the shortest survival. Patients with t(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 t12.

In conclusion, chromosomal aberrations occur in more than 50% of patients with low-grade malignant B-cell lymphoproliferative neoplasms. 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 characterized 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.

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 systems 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 rare. 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. Lene, 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 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-lym 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 differs by restriction endonuclease sensitivity from the gene activated in T-lymphoid neoplasms representative of a more mature stage of differentiation. Tlym-1 was isolated by molecular cloning and is 4.4kb in size. The gene shares homology with genes encoded within the MHC class I region, and is somewhat novel in that it behaves as a secreted protein. Our current speculation is that Tlym-1 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.


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 1960-1977 at P.M.H. The actuarial overall survival, cause-specific survival (death from disease and prior) and relapse-free rates at 10 years were 79%, 88% 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>
<thead>
<tr>
<th>Age</th>
<th>Histology</th>
<th>Upper Abdominal</th>
<th>Other Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>1/10</td>
<td>Group I</td>
<td>Group II</td>
</tr>
<tr>
<td>50</td>
<td>1/10</td>
<td>Relapse Rate 1/10 (88%)</td>
<td>Relapse Rate 63/187 (36%)</td>
</tr>
</tbody>
</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 alone.

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.
ABSTRACTS - Second International Conference on Malignant Lymphoma, Lugano


Between May 1977 and May 1980, 72 consecutive previously untreated patients, clinical supradiaphragmatic stages IA and IIA biopsy-proved 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 initially involved (P). No spleno-lumbar irradiation was performed in any of the two series.

<table>
<thead>
<tr>
<th>(P)</th>
<th>(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>male</td>
<td>25</td>
</tr>
<tr>
<td>female</td>
<td>11</td>
</tr>
<tr>
<td>IA</td>
<td>21</td>
</tr>
<tr>
<td>IIA</td>
<td>15</td>
</tr>
</tbody>
</table>

The complete remission rate was 98.5% (1/7) at 5 years. Actuarial survival rate was 99% in both series: disease-free survival rate was 85% in (P) and 80% in (S) series. In the (P) series, no patient relapsed in non-irradiated adjacent areas; 2 patients in (P) 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 prophylaxis by comparison between localised versus extended field irradiation. Furthermore we evaluated the efficiency of such a chemotherapy on subdiaphragmatic occult disease from a clinical point of view that is the incidence of relapses in infra diaphragmatic areas. From our data, it seems possible to assume that 1) when such a prior chemotherapy is given, 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.

55 MOPP VS RADIOTHERAPY/MOPP FOR EARLY-STAGE HODGKIN'S DISEASE (HD)- A SIX YEAR FOLLOW-UP. Peter J. O'Dwyer, Michael B. Stewart, Peter H. Wierink. 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 IIB to IIIA were randomized to treatment with extended field radiotherapy followed by MOPP (RTIC) or MOPP (C) alone. Distribution of histological subtype, age and sex were similar in both groups. Two pts in each group were invaluable: I died before treatment began, I had a non-Hodgkin's lymphoma, and 2 did not complete chemotherapy. The 17 evaluable pts in the RTIC group included 1 stage IIA, 7 IIB, 2 IIIB, and 3 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, 1 PK, and 1 non-responders (NR). The PR and 1 NR subsequently achieved CR with radiotherapy neither has relapsed, though the former has now developed a secondary leukaemia. Three pts relapsed 1-24 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 morbidity was more prevalent in the RTIC 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 an effective and less toxic than combined modality therapy, and that restriction of radiation therapy for incomplete responders to chemotherapy may result in equal survival.
### ABSTRACTS - Second International Conference on Malignant Lymphoma, Lugano

#### 56 RANDOMIZED STUDY OF CHEMOTHERAPY ALONE VS CHEMOTHERAPY PLUS RADIOTHERAPY IN CLINICAL STAGE IA-III A.

S. Pavlovsky, J. Dupont, E. Jinfnes, F. Saemann Muriel, C. Montero, G. Garay. From Grupo Argentino de Tratamiento de la Leucemia Aguda (GATLA) and Grupo Latinoamericano de Tratamiento de Hemopatias 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-III A (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/m²/day 1; vinblastine 6mg/m²/day 1; procarbazine 100mg/m²/day 1 to 14 and prednisone 40mg/m²/day 1 to 16 (CVP). A total of 31 patients were < 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:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. Pts.</th>
<th>CR</th>
<th>DCR</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>47</td>
<td>42</td>
<td>89</td>
<td>862</td>
</tr>
<tr>
<td>CT-RT</td>
<td>43</td>
<td>39</td>
<td>91</td>
<td>855</td>
</tr>
</tbody>
</table>

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 obtain CR one died of sepsis at 5 months and 3 died of progression of disease 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 conclude that combination chemotherapy CVP produces a similar rate of CR, duration of CR and survival as CVP plus radiation therapy in clinical stages IA-III A of Hodgkin’s Disease.

This study was supported in part by the Cooperative Cancer Treatment Research Program which is a project of the NCI and PCRI, Contract No. HDI-CH-27991.

#### 57 COMBINED MODALITY THERAPY (CHEMOTHERAPY PLUS RADIOTHERAPY) IN HODGKIN’S DISEASE, CS IA TO III B.


Hematology, Hopital Larreque - 75540 Paris, France.

From January 1977 to April 1980, 179 patients (pts) with Hodgkin’s disease (HD), clinical stages (CS) IA to III B were prospectively treated at Hopital Saint-Louis (Paris). Their initial characteristics were: age - sex - males 102/ females 77 - age: 5 to 65 years, median 28; CS: IA 42, IIA 63, IIB 46, IIIA 9, IIIB 11 - histological type: L 126, LL 11, III 54, IV 6, unclassified 15. The 79 pts with CS IA and II A (only one was 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 mediastinum or an inverted Y plus spleen radiotherapy according to initial presentation. The 74 pts with CS IIA A (3 or more areas involved), 16, IIB followed the randomized H 7702 trial: the patients received at random 3 cycles of MOPP or CVP (CCNU, Vinblastine, Procarbazine, Prednisone) partial and complete responders underwent a laparotomy with splenectomy followed by megadose and adjuvant irradiation (a lombo-sacral field was added in case of positive laparotomy). The 20 pts with CS III followed the H 7703 trial: 3 cycles of MOPP or CVP (at random) were first given; a splenectomy was then performed followed by total or subtotal nodal irradiation. At completion of therapy, 167 pts (94.5%) were in complete remission (CR). Twenty pts relapsed (in situ or marginal 3, non irradiated lymph nodes 9, visceral areas 5) after 3 to 60 months of CR (median 12); after individual retreatment 12 of these are alive (8 in second CR). Eighteen pts died (initial failures 4; complications of chemotherapy 2; relapsing pts 8; deaths in first CR: A including 2 acute leukemias, 1 esophageal cancer and 1 overwhelming infection). In January 1984 the median follow-up was 45 months (min 22, max 84). Actuarial probabilities (7 years) of survival (calculated from diagnosis) and disease free duration (calculated from completion of therapy) of the whole group of patients are 87.8% and 70.2% respectively (IA 91.1% and 88%; II 92.1% and 89%; IIB 81.2% and 78.7%; IIIA 80.9% 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 3CVP (trials H7702 and H7703). Survival (but not disease free duration) is significantly lower in pts over 40 years of age (P0.05).
38. COMBINED MODALITY TREATMENT OF Hodgkin's disease confined to lymph nodes: Janice P. Dutcher, MD and Peter H. Wierlik, MD
Albert Einstein Col of Med and Montefiore Med Cent, Bronx, NY USA

Lightly seven patients (pts) with newly diagnosed hodgkin's disease (HD) of low intermediate stage IIA, IIAp, IIB, IIBp, IIIA, IIb were treated with standard therapy with RT followed by 6 courses of MOPP chemotherapy (PMHC). All 5 stage I 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 IIB disease. Of 16 evaluable pts with less than stage IIIA, 29 received RT only and 17 received RT+CM. Of 28 evaluable pts with stage IIIA, 12 received RT only and 16 resolved RT. After a minimum of 5 years follow-up, 35% of early stage pts treated with RT only are in continuous remission, compared to 89% of pts who received RT+CM (p<0.05). 8 pts treated with RT only have relapsed: 2/2 pts with ILD (both died of HD) and 2/2 pts with ILDP (both died of HD). 6/18 pts with stage IIB disease have relapsed (2 died), including one at 94 months in remission. One of 17 pts who received RT+CM has relapsed and is alive at 134 months. 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+CM (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 IIB disease (both died of HD). One pt treated with RT+CM has relapsed and is alive at 118 months. If deaths due to all causes are included, there is a significant difference in survival between groups (p=0.03). No deaths from HD occurred in pts treated with RT+CM. Deaths from other causes in pts with stage IIIA treated with RT+CM include 3 cardiac, 2 lung Ca, and 1 early leukemia. No pts with IIA, IIB treated with RT+CM have died. 5 pts with IIB treated with RT only have relapsed and died of HD. 3 pts with early stage disease treated with RT+CM and 1 only have died of lymphoma. 1 pt died of lymphoma. 1 pt died of CR (Maier's disease) in the RT port. 1 pt died of suicide and 1 pt died of other (alcholism). 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. CHMOTHERAPY ALONE VS. COMBINED MODALITY THERAPY FOR STAGE III HODGKIN'S DISEASE: A FIVE-YEAR FOLLOW-UP OF SOUTHWEST ONCOLOGY GROUP (SWOG) STUDY 7518. P.M. Grosjean, E.J. Domenico, C.A. Goldman, C.J. Flicker, P.S. Mason, P. Dixon and S.G. Jones, University of Oklahoma Health Sciences Center, Oklahoma Medical Research Foundation, P.O. Box 26901, Oklahoma City, OK, 73110, and the Southwest Oncology Group, San Antonio, TX, 78219.

The SWOG initiated in October 1975 a clinical trial in pathologic (laparotomy) stage III Hodgkin's disease with randomization to chemotherapy alone consisting of 10 courses of MOPP plus low dose bleomycin (LB) or combined modality program of 3 courses of the same chemotherapy followed by total nodal irradiation (TNI). Systematic restaging has been performed with additional cycles of MOPP plus LB 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 study the survival of the surviving patients the results are as follows:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>5-yr. relapse</th>
<th>5-yr. survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOPP + LB</td>
<td>7%</td>
<td>86%</td>
</tr>
<tr>
<td>MOPP + LB + TNI</td>
<td>9%</td>
<td>91%</td>
</tr>
<tr>
<td>P</td>
<td>0.27 (2 sided Chi square)</td>
<td>0.48 significance</td>
</tr>
</tbody>
</table>

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 arm 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. Hematologic toxicities, generally, allowed 59% of the patients on the chemotherapy alone limb to complete the ten cycles of MOPP plus LB and 66% of the patients on the combined modality limb to complete the full TNI (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 gastrointestinal 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 histologic type of nodular sclerosis for which combined modality treatment should be considered - presumably with reduced dose of TNI or involved field TNI 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 (MOPP) FOR PATIENTS WITH STAGES III B
AND IV M. Hodgkin's disease (HD) WITH AN ASSESSMENT OF PROGNOSTIC
FACTORS.
G.W. Steward*, J. Wagstaff*, J. Todd & D. Crossman, Depart-
ment of Medical Oncology, Christie Hospital, Manchester M6 9BR,
Department of Radiotherapy, Christie Hospital.

118 patients with previously untreated stages III B and IV HD
were entered into a prospective study of treatment with chemotherapy,
using MOPP, 15gpm i.v. days 1, 8, 15 & 21. Vinblastine, 4mg/m2 i.v.
days 1 & 8, Procarbazine, 100mg/m2 orally daily, days 1-14 and
Prednisolone, 40mg, orally daily, days 1-14 (MOPP), repeated every
six weeks to six courses beyond complete resolution (CR) followed by
radiotherapy to sites of previous bulk disease.

32 patients had stage III B, 20 patients, stage IV A and 66
patients, stage IV B disease. The bone marrow was involved in 16
patients (13%), the liver in 44 patients (37%) and lung parenchyma
in patients (19%). Median follow up was 60 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 = 0.035) and raised serum
alkaline phosphatase levels (p = 0.039).

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

61 STAGING AND TREATMENT WITH CYCLOPHOSPHAMIDE, VINCristine AND
Prednisone (CVP) IN ADVANCED CUTANEOUS T-CELL LYMPHOMAS (CTCL): A.
Trevisi, A.Carboni, A.Veroni, E. Galligioni, M. Ronca, R., G.
Oncology, General Hospital, Pordenone; Centro di Riferimento Oncologico, Aviano,
Pordenone, Italy.

The purpose of the study is 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 undergoing
staging evaluation between Jan '75 and Nov '83. The routine staging pro-
cedures included chest x-ray, peripheral blood count and cytormorpho-
ogy, bone marrow aspirate and biopsy, lymphangiogram, peritoneoscopy
with multiple spleen and liver biopsies. Lyphodermal 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 II B for skin tumors; 1 pt stage III for generali-
zed erythroderma and 13 pts stage IV for lymphodermal histological in-
volution(9 pts) and/or visceral histological involvement(5 pts). Am-
ong pts with stage IV, 6 pts had skin tumors and 7 pts generalized ery-
throderma. 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 were
then 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
CR, only 14 pts are evaluable for response, since 2 pts are still
receiving their first cycles of CVP. CVP induced a 57% overall objec-
tive 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 = 0.02). Five pts died of disease. Toxicity
was quite acceptable. We conclude that: 1) pts with CTCL, if properly
staged, often present with advanced stage II B-III A-IV for cutaneous
(stage IV) disease(59% and 52% respectively in our series), in agree-
ment with HCl 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 com-
pared to 25% of Bunn Jr et al series; 2) The experience with combination
chemotherapy alone in CTCL is limited (approximately 60 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.

CTCL (mycosis fungoides and Sezary syndrome) patients refractory to prior chemotherapy were treated with 50000U units/m² of IFN-α in three times weekly (200Ps) or 100 mg of TIOI monoclonal antibody in 8 patients via an intravenous infusion over 2-24 hr to determine the effectiveness and toxicities of these therapies. The patients had advanced stages (3 with cutaneous tumors, 9 with erythroderma, 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 Mop in 26, PUVA in 17, whole skin electron beam irradiation in 12, and systemic chemotherapy in 21). After IFN-α there were partial responses in 9/17 evaluable patients (3 too early for response evaluation), minor or mixed responses in 5/17 patients, and no responses in 3/17 patients. Partial responses lasted a median of 5 mo with 5 continuing responses of 6 to 15 mo duration. Toxicity consisted of a flu-like syndrome consisting of fatigue, anorexia, weight loss, malaise, and decreased performance status sometimes accompanied by mental confusions. No dose reductions occurred 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. TIOI produced improvement in skin lesions in 2 patients, each 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, inhomogenous tissue uptake, development of anti-murine antibodies or lack of direct cytotoxicity. We conclude: IFN-α has definite activity in CTCL, but new doses and schedules should be explored to reduce toxicity and achieve complete responses; TIOI is relatively non-toxic but new approaches such as radio-drug-labeling are necessary to enhance cytotoxicity.


The AIDS syndrome is an almost uniformly fatal, transmissible 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 (HIV-I) 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 100% in the male homosexual risk group and is less than 1% 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 (in Memorials 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 T4/8 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 10%. During therapy most patients had a 30-40% 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 (80%) 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). C. Oda, J. M. Naggia. NYU Medical Center, NY, NY 10016.

Since the recognition of AIDS, the medical community has become increasingly aware of other medical conditions emerging among homosexual men. Among 15 homosexual males, ages 20-74, who have been seen at NYU with lymphoma, 1 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. Dated data are summarized in the table.

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Stage/Site</th>
<th>Therapy</th>
<th>Outcome Associated</th>
<th>Disease Ears (mo)</th>
<th>Disease OI (mo)</th>
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<tr>
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<tr>
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<td>Died(2mos)</td>
<td>Relapse(3mos)</td>
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<tr>
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<td>None</td>
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<tr>
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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 10/100,000 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 T.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 T.V. drug users/prisoners than Kaposi's sarcoma.

Over the last two years, an increased incidence of lymphomas in homosexual males has been noted in several cities in the United States. Between the period 1981-1983 we have evaluated and 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 (NPDLL), 1 had well differentiated lymphocytic (WELL), & 1 had unclassifiable lymphoma. All 5 pts with DLCL had focal brain lesions, with 2 of these presenting as primary CNS lymphomas. In contrast, only 1 of the DUL pts had CNS involvement, which was meningeval. Three of the DUL 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 testicular 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 tumors cells confirmed IgD (3), IgA (1), & IgM (1). All 3 DUL pts tested had the 8 to 14 chromosome translocation in lymphoma tissue, & 2 of the 3 also had an Xc abnormality in the malignant cells. A bizarre finding in the WDL pt was extensive bilateral lymphoma of the ear lobes. All pts tested had T lymphocyte helper/suppressor ratios less than 1 & a decreased skin test delayed hyperresponsivity, with the most marked abnormalities occurring in the DLCL pts. Antibody titers for toxoplasmosis & Epstein-Barr virus were positive in 10/11 & 11/11 pts tested, respectively. Antibodies to the human T lymphoma-lymphoma virus were present in the sera of 2 DLCL & 1 DUL pt. Four of the 3 DUL pts had severe prohemotherapy opportunistic infections, including pneumocystis, candida, & toxoplasmosis. No pts had autoimmune hemolytic anemia or chronic myeloproliferative disease. Responses to treatment & survival have been poor in all 5 DUL pts, with 4 deaths & median survival of 3 mos. Five of the 7 DUL pts achieved a complete remission (CR) & 3 of these remain in CR at 1, 7, & 22 mos; none have died. The DUL & WDL pts all responded to treatment & are alive >18 mos. 10/11 pts had ≥ 3 of these abnormalities, though none had ALL. 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 chemotherapeutic-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.

OVERVIEW ON CURRENT STRATEGY OF THE TREATMENT OF NON-HODGKIN'S LYMPHOMAS. J.E. Ullman, E.H. Guyor, University of Chicago Cancer Research Center, 1841 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 lymphoma 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.
ABSTRACTS - Second International Conference on Malignant Lymphoma, Lugano

68 UPDATE OF FAVORABLE (LOW GRADE) NON-HODGKIN'S LYMPHOMA.
S.A. Rosenberg, Stanford University, Dep. of Medicine, Stanford, CA 94305

The favorable or low grade non-Hodgkin's lymphomas (NHL) include three major subtypes, small lymphocytic (SL), follicular, and mixed small cleaved and large cell type (FMI). 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 individu-
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 combina-
tion 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 the 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 Glattstein, Louis A.
Matis, Richard L. 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 lym-
phocytic (NPDL), nodular mixed (NML), diffuse well-differentiated
lymphocytic (DWDL), diffuse intermediately differentiated lymphocytic
(DIDL), and diffuse small cleaved cell lymphoma (DSCCL), is contro-
versial. 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 signifi-
cant differences in overall survival. In addition, with the possible
exception of NHL, the survival of favorable prognosis lymphoma pa-
tients 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 aggres-
sive 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 aggres-
sive attempt at remission induction with ProMACE-MOPP flexotherapy
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 treat-
ment of favorable lymphomas. Are conservative and aggressive treat-
ment 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
treatment to palliative therapy outside a clinical trial setting delays the development of better treatment approaches.
ABSTRACTS - Second International Conference on Malignant Lymphoma, Lugano

70 TREATMENT OF DIFFUSE LARGE CELL NON-HODGKIN'S LYMPHOMA.
Richard L. Fisher, Vincent T. DeVita, Dan L. Longo, Daniel C. Nune, and Robert C. Young, National Cancer Institute, Bethesda, MD 20010.

Until the mid-1980'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 43% of all patients with advanced stage, large cell, and undifferentiated non-Hodgkin's lymphomas 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 (median not reached). Although histologic diagnosis did not determine the prognosis of these patients, clinical factors such as male age, 8 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-1980'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., 9/83). The ProMACE regimen includes cytoxan, adriamycin, VP-16, prednisone, and high dose methotrexate at 1.5 g/m² followed by leucovorin rescue. This dose of methotrexate requires hospitalization for intravenous hydration, allopurinol, 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 75% of all patients and 75% of these complete remitters remain disease-free in excess of 3 years. Hypoalbuminemia was a dose limiting with a 10% septic death rate. Improved results were seen in all patient groups. The fourth generation of 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, vincristine, and methotrexate) (AACR, 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, the 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.
Jones, S. Miller, T., University of Arizona Cancer Center, Tucson, Arizona 85724 U.S.A.

Historically, radiotherapy alone has been used to treat lymphomas of unfavorable histology with limited spread (stages I, II, III, IIE) but this has proven curative in only carefully selected patients with the most limited disease (stages I or II). The majority of patients with stage II or III 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 stages (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 I: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 III disease in 63%, age > 65 years in 33%, gastrointestinal tract involvement in 15%, and bulky disease in 55% of patients. The CR rate is 95% (46 of 49). At a median follow-up time of 41 months, 84% of 41 patients remain continuously free of disease. Eight relapses have occurred, 6 of which were curative. Twenty-four patients remain alive. None of the potential adverse prognostic factors listed above affected outcome of therapy including age > 65 years (2 relapses in 14 patients). Our experience with rapid clinical improvement 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.
ABSTRACTS - Second International Conference on Malignant Lymphoma, Lugano

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; Castlemans 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 Hodgkins 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.
LYMPHOCYTE DEPLETED HODGKIN’S DISEASE—DOES IT EXIST?

Elaie S. Jeffs, 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 (LDH) has been regarded by many as the poorest prognostic group of patients with Hodgkin’s disease. Others have suggested that LDH 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 LDH. The initial diagnostic biopsies from 39 of these patients were reviewed and revealed 10 with non-Hodgkin’s lymphomas, 9 with LDH, 13 with nodular sclerosing Hodgkin’s disease, lymphocyte depleted subtype (NSD), 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, polyclonal lymphadenopathy and hypercalcemia. In contrast to the non-Hodgkin’s lymphomas, complete remissions were attained by 67% and 85% of patients in the LDH and NSD 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 LDH and NSD groups with 23 and 29 years in the LDH and NSD groups. Lymphocyte depleted Hodgkin’s disease, adequately treated, is in our experience no worse than other histologic 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 the reason for literature reports of its more aggressive nature. The diagnosis of LDH should be made cautiously, particularly in patients with clinical features unusual for Hodgkin’s disease at presentation.

INUBRO-ELECTRON MICROSCOPIC STUDY OF IMMUNOLOBULIN PRODUCTION BY NON-HODGKIN’S MALIGNANT LYMPHOMAS.

L. Lombardi, C. Dea Torre, R. Giardi, F. Rife, Istituto Nazionale Tumori, 20133 Milan, Italy.

Sixteen selected cases of non-Hodgkin’s lymphomas (NHL), representing different stages 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 0.1M sodium cacodylate buffer, incubated with biotinylated goat anti-human IgG heavy and light chains and with avidin-peroxidase conjugates in sodium-containing solutions, fixed again with 2.5% glutaraldehyde, treated with diaminobenzidine and H2O2, and processed for electron microscopy. Control cells were incubated with biotinylated 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.
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76 FLUO-CYTOFLUOROMETRIC DNA ANALYSIS IN NON-HODGKIN'S LYMPHOMAS. B. Christensson, P. Biberfeld, A. Ost, B. Tribukait, Dep. of Pathology, Immunopathology Laboratory, Dep. of radiobiology, Karolinska sjukhuset, Stockholm, Sweden 209 lymphomas were analyzed with respect to proliferative activity (5-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 center 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, 5-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-cytometry seems to be a marker of malignancy partly independent of the histopathological classification.

77 THE PROGNOSTIC SIGNIFICANCE OF CYTOLOGICAL SUBDIVISION OF NON-HODGKIN'S LYMPHOMAS: ANALYSIS OF 1156 PATIENTS. K. A. MacLennan, M. H. Bennett, A. Tu, M. J. Fastenberg, B. Vaughan Hudson, G. Vaughan Hudson and A. M. Jelleyon, British National Lymphoma Investigation, Department of Oncology, The Middlesex Hospital Medical School, London W.1. 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 categorized 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 analyzed together, there is a large difference between the survivals of the Grade 1 (64.3% 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 I 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 more advanced stage (79.4% five year survival) and this difference is statistically highly significant ($X^2 = 26.01; p<0.001$). The prognostic significance of stage is less marked in the Grade 2 histological group ($X^2 = 5.56; p<0.05$). It therefore appears that cytological subdivision is of great value in predicting prognosis.
ABSTRACTS - Second International Conference on Malignant Lymphoma, Lugano


Fifty five cell lines derived from endemic and non-endemic Burkitt's tumors (established by G. Lebher, IEC, LION) were characterized by morphometric means using a Leitz ADP semi-automatic quantitative analysis system on plastic embedded cell suspension pellets. Nuclear parametric discriminators computed on line were: size (with 1 log nuclear area classes previously defined), shape, area dispersion, general characteristics including geographical origin, EBER 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 2 and 4, with a low value for shape A area dispersion discriminant. The histomorphometrical classification emphasizes the cytological polymorphism of Burkitt's cell lines. In the size, shape, and house A area dispersion of the nucleus. 29 cell lines are mapped in the zone of large cell lymphomas (size class 3, shape A 5). Nuclear shape differs 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 nuclear 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: EBER + cell lines are significantly larger than EBER - ones, a pre-B phenotype (q<1) and an East African origin are significantly associated with largest cells; there is a strong relationship between African origin, pre-B phenotype, EBER + character, and large cells. Moreover, we were able to compare in some cases the cytological 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 EBER, especially in the cases of massive contamination, (2) the possibly different target cell in Burkitt's lymphoma, (3) the large spectrum of morphological pictures from small noncleaved to large cleaved, noncleaved and immunoblastic types.


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 nodes. 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 M Centroloblastic Centrocytic (MC CcC). Much more (21/48) cases of M Polymorphic Immunocytoma (ML PI) 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 CbC or MC Bb. One mediastinal NHL diffuse undifferentiated large cell (DLUL), which lacked immunologic 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 15 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 NHL and T-cell lymphoma: especially, 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), ADMIRACIN (A), CYCLOPHOSPHAMIDE (C), ORCHIN (O) AND ORABINONE (D), m-BACOD, IN ADVANCED DIFFUSE HISTOCYTIC LYMPHOMA (DHL). A.T. Skarin, D.P. Campo, D.S. Rosenchul, D.C. Case and J.M. Meiri. Dana-Farber Cancer Institute, Brigham and Women's Hospital and Harvard Medical School, Boston, MA 02115.

The use of high dose methotrexate (HDMTX) requires critically important urinary alkalization and hydration to avoid serious renal and other complications. In addition, assays of blood MTX levels must be measured and the drug schedule can be prohibitive. The M-BACOD program (Skarin et al., J. Clin. Oncol. 1:951-98, 1983) was therefore modified by employing moderate dose MTX (m) at 200mg/m² IV on days 8 and 15 of each 3-week cycle. Leucovorin factor rescue, 10mg/m² was given at 24 hrs q 24 hr x 5 to prevent toxicity; 8 (mg/m²/IV). A (0.5mg /m² IV), C (600mg/m² IV) and O (1.0mg/m² IV) were given on day 1, along with m (6mg/m² 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, III (10 pts), II (9 pts) or IV (34 pts) DHL. Only 4 patients had prior therapy, while 39 patients (75%) had no previous therapy. Sites of extramedullar disease included marrow - 7 patients (13%), effusion - 7 patients; bone, GI - 6 patients each; soft tissue - 3 patients; skin - 2 patients; other - 10 patients. A CR was achieved in 40 patients (75%): Stage I, II, III 5/10 (70%), Stage IV 5/12 (42%), and Stage IV 4/48 (8%).

The median follow-up time in CR patients is 13 mo. (range 5-21 mo.) from time of CR. 9 patients (13%) have relapsed (8/16 Stage IV) all within 1 year except for 2 (15 and 14 mo.). All PR patients relapsed within 3-9 mo. While m-BACOD was not designed for CMS prophylaxis, CMS relapse occurred in 1 CR and 1 PR patient. All 5 SR patients and 5/8 PR patients died from progressive disease, compared to only 3 CR patients (7.5%). The median follow-up time 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 minimal side effects, toxicity included mucositis mostly after day 8 MTX in 21 patients, representing 6% of courses, but no significant renal complications occurred. Leucopenia with fever occurred in 12 patients (25%) 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 the high dose MTX (H-MTX) 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 H-MTX (25%) can be achieved.
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82 A RANDOMIZED COMPARISON OF ADJUVANT VAP + M vs CMOOP 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 (DPL, DH, DM, DU) were treated with involved field radiotherapy (XRT). Post-XRT randomisation was to either six weeks VAP (Vinristine 2 mg i.v. weekly; Adriamycin 50 mg/m² i.v. every 2 weeks; Prednisolone 40 mg p.o. daily for 6 weeks) followed by two years oral maintenance (RMPI, 50 mg/m² p.o. daily; Methyltrexate, 10 mg/m² p.o. weekly and Cyclophosphamide, 200 mg/m² p.o. weekly; all for 2 years) or six cycles of CMOOP (Cyclophosphamide, 600 mg/m² i.v. days 1 & 8; Vinristine, 2 mg i.v. days 1 & 8; Procarbazine, 100 mg/m² p.o. days 1-14; Prednisolone, 40 mg p.o. days 1-14) at three weekly intervals.

Two patients failed to achieve CR (1%). Both developed disease outside the irradiated field, either before or shortly after starting adjuvant chemotherapy. The overall CR rate was 79% (VAP = 95%; CMOOP = 79%). The six week VAP programme was much better tolerated than CMOOP.

<table>
<thead>
<tr>
<th>RTN</th>
<th>Survival %</th>
</tr>
</thead>
<tbody>
<tr>
<td>XRT</td>
<td>2yr</td>
</tr>
<tr>
<td>VAP + M</td>
<td>90</td>
</tr>
</tbody>
</table>

Three deaths have occurred (VAP = 7, CMOOP = 3), five of these from intercurrent causes (Ca. ovary (VAP), melanoma (CMOOP), astrocytoma (VAP), coronary artery disease (VAP) and pneumocystis carinii (VAP)). A further patient died from respiratory failure with pulmonary oedema (CMOOP) but no postmortem was performed (Pneumomage, 1 year). 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 NPS or overall survival.

Seven patients with bulky disease (>5cm) have died versus three without it, but the RTN 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 CMOOP, 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 (RHD) LYMPHOMA.

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 NHL. 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 available (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 35/48 (521) with BACOP and 19/40 (471) in C-MOPP that achieved CR (P = 0.01). At 48 months, 60% of BACOP patients and 33% of C-MOPP patients who achieved CR are expected to continue in first CR (P = 0.01).

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: stage I: 71% and 66% (P = 0.2); stage II: 58% and 24% (P = 0.001). There have been 25 deaths in each group, with 32% in BACOP and 23% in C-MOPP alive at 48 months. Complete responders have 51% of possibility of continuing 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 71% of patients; 19% of relapses were in CNS but only 7% were isolated CNS first relapses. Toxicity of BACOP has not been more marked in terms of myelosuppression or clinically evident cardiac or lung toxicity. BACOP showed a higher duration of CR than C-MOPP only in stages II-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.

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ABSTRACTS - Second International Conference on Malignant Lymphoma, Lugano

84 Lymphoblastic Lymphoma in Adults: A Study on 30 Patients Treated with Two Different Programs According to Bone Marrow Findings. C. Bernasconi, G. Brusamolino, M. Lazzerini, L. Salvaneschi, P. Bernini. 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 using bone 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 (INCL, 1983). The median time for follow-up was 18 months (range 6-65 mos). Patients with bone marrow involvement were given an ALL-like program, consisting of vincristine 1.4 mg/m², daunorubicin 60 mg/m², cyclophosphamide 600 mg/m² iv, i.v. once a week for 6 weeks, and prednisone 40 mg/m² per os 4 days every week for the induction time. Patients in complete remission after 6 cycles had CNS prophylaxis with cranial irradiation with 30 Co (20 Gy) and five doses of intrathecal methotrexate (12 mg/m²). Maintenance therapy consisted of 4-mercaptopurine 50 mg/m² per os daily and of methotrexate 15 mg/m², iv, once a week for 3 months. The fourth week was covered by a reinduction course with vincristine 1.4 mg/m² and prednisone 40 mg/m². Every three courses, daunorubicin was added, up to the total dose of 165 mg/m². 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-like for 6 cycles of induction therapy every 5 weeks and 2 successive cycles of consolidation without further maintenance regimen or CNS prophylaxis. Bulky mediastinum was delivered to only high-energy radiotherapy. The CR rate per whole group was 56% (67% for ALL-like treated versus 40% for lymphoma-treated patients; p<0.05), with a median survival for remitters of 38.3 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 63% at 12 and 25% at 24 mos. Nine out of 15 patients who achieved CR relapsed in a 24-months interval from remissions; three cases relapsed in new sites of disease (mediastinum, CNS, bone marrow with leukemia), five in both previous and new sites of disease (bone marrow and CNS), bone new sites and a single in previous sites only (bone marrow and CNS). Bone marrow positivity, argues in favor of an ALL-like therapy in adult lymphoblastic lymphoma, in term of CR rate, overall survival, and absence of CNS relapse. The better prognosis of ALL-like treated patients, in spite of bone marrow positivity, argues in favor of an ALL-like therapy in adult lymphoblastic lymphoma, and no matter how localized the lymphoma appears to be.


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 156 pts with refractory or refractory aggressive lymphomas on 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 occurred on front line therapy. The salvage regimens used consisted of the following combinations: DMT-16 (Ifosfamide, MTX, VP-16), ATIV-16 (ADM, Ifosfamide, VP-16) & MINE (Nethyl Esg, Ifosfamide, MTX & Etoposide (VP-16)). Response rates in patients with recurrent or refractory disease were:

<table>
<thead>
<tr>
<th>Regimen</th>
<th>N</th>
<th>CR(%)</th>
<th>PR(%)</th>
<th>Median NPS of CR’s</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMT-16</td>
<td>17</td>
<td>12 (33)</td>
<td>5 (15)</td>
<td>9 mos.</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>ATIV-16</td>
<td>25</td>
<td>12 (48)</td>
<td>8 (32)</td>
<td>16 mos.</td>
<td>0.05</td>
</tr>
<tr>
<td>MINE</td>
<td>156</td>
<td>33 (40)</td>
<td>29 (30)</td>
<td>12 mos.</td>
<td>0.05</td>
</tr>
<tr>
<td>TOTAL</td>
<td>156</td>
<td>55 (36)</td>
<td>42 (27)</td>
<td>9 mos.</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Of 48 CR’s who have been at risk >1 yr, 33 (68%) are still in CR. Response according to histological type was as follows:

<table>
<thead>
<tr>
<th>Type</th>
<th>N</th>
<th>CR(%)</th>
<th>PR(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large</td>
<td>12</td>
<td>10 (83)</td>
<td>3 (25)</td>
</tr>
<tr>
<td>Lymphoblastic</td>
<td>13</td>
<td>6 (46)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Diffuse Small Cleaved</td>
<td>15</td>
<td>7 (47)</td>
<td>5 (33)</td>
</tr>
<tr>
<td>Diffuse Small Non-Cleaved</td>
<td>7</td>
<td>3 (43)</td>
<td>2 (29)</td>
</tr>
</tbody>
</table>

In addition there were 7 partially refractory patients treated with these regimens & 6 (86%) achieved CR. Three of these 6 are still in CR >7 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 MINE regimen appears to be slightly superior to early use of these regimens in partially refractory pts before relapse occurs results in a high % of CR’s of long duration. 4-mercaptopurine consists mostly of infection (28%), and hemorrhagic cystitis in 20% of pts. A modest fraction of pts with reoccurrent or refractory lymphomas and a high fraction of partially refractory lymphomas appear to be potentially curable with these salvage regimens.
ABSTRACTS - Second International Conference on Malignant Lymphoma, Lugano

86 METHOTREXATE PLUS HIGH DOSE CYTARABINE IN ADVANCED REFRACTORY LYMPHOMA. R. Opfell*, J. Schottinger*, N. Schlutz*, R. Balland*, 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 3g/m² x 4 doses 12 h. The regimen was repeated 21 days. Patients included 2 Hodgkin's, 1 DHL, 2 DDL, 1 NHL, 1 plasma-cell lymphoma, and 1 T cell prolymphocytic leukemia; age 24-71 (median 44). All were heavily pretreated; had progressed on adriamycin containing regimen, and 3/8 had received prior radiotherapy. Prior chemotherapy consisted of 4-10 drugs (median 7) and 3-18 cycles of therapy (median 9). There were 6/8 major responses with 6 CR and 2 PR. One patient had MR with relief of abdominal pain and nodal edema. The patient with DHL had CNS involvement, no measurable disease, expired of cardiac arrest apparently unrelated to toxicity after two cycles. One patient with Hodgkin's was in CR after 2 cycles, relapsed after no therapy and responded with a PR after 2 cycles. 6 of 8 patients survived for 6-12 months. Therapy was well tolerated; the major toxicity was myelosuppression, 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 3,200 and platelet count to at least 100,000 within 21 days in 93% 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 response can be obtained with less myeloid toxicity.

87 A NEW COMBINATION REGIMEN OF EXPERIMENTAL DRUGS FOR THE TREATMENT OF RELAPSED LYMPHOMAS: GALIUM NITRATE, METHYLGLYOXAL BIS(GUANYLHYDRAZONE) AND ETOPOSIDE.


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 antitumor 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/m² d/m². MGBG was given on days 1 and 10 (600 mg/m² d) and etoposide was given daily x 3 days (100-125 mg/m² 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 regimes (range 1-6) and 6 drugs (range, 4-12). Eighteen pts had also received radiotherapy, of the 29 evaluable pts 15 (52%) had major responses (CR, fully restaged; 11 PR). Response according to Rappaport classification was: 9/13 DHL, 3/3 Hodgkin's, 2/5 DPD, 0/3 NHL; 1/5 other NHL. Median response duration exceeds 4 months. The major toxic reaction to this regimen has been myelosuppression (leukocytes 1000/mm³ in 39% of pts, platelets 40,000/mm³ 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.
ABSTRACTS - Second International Conference on Malignant Lymphoma, Lugano

CLINICAL INTERACTION (IFN) STUDIES IN LEUKAEMIA AND LYMMPHOMA

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The potential clinical relevance of the antiproliferative effect of the a interferon initially demonstrated in murine leukemia models, has been investigated in patients with lymphoma and leukemia.

Phase I studies with leucocyte lymphoblastoid and recombinant IFN have shown that the maximum dose given over a prolonged period compatible with a normal ambulatory existence is less than 1000 IU daily and that the maximum dose given over a shorter period is 10000 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 2x10⁶ IU/m² to 5x10⁶ IU twice weekly. The highest response rate 16/25 (64%) has been reported in low grade non Hodgkin's lymphoma (NHL), treated with 5x10⁶ IU/m² thrice weekly and IFN-α, confirming early experience with IFN-α at lower doses. Less impressive responses of short duration have also been achieved in chronic lymphatic leukemia (2/28), 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 leukemia with indefinite administration of 3 x 10⁶ IU daily. The peripheral blood count returned towards normal in 2/5 (40%) patients, although splenomegaly frequently persisted, and the Philadelphia chromosome remained. Very high doses of IFN-α given by continuous 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 leukemia (3/7). No benefit has been shown for any patient (2/23) with acute myelogenous leukemia, receiving either high dose continuous infusion of lymphoblastoid IFN-α or recombinant IFN-α.

As in vitro evidence of activity at the serum levels achieved, studies are currently in progress to evaluate the pharmacokinetic activity of IFN in leukemia, and the possible synergistic action of a IFN with cytotoxic chemicals in lymphoma.

NEW DRUGS IN MALIGNANT LYMPHOMAS: A. Lewis, M. Rosencrantz, Bristol-Myers Company, Pharmaceutical Research and Development Division, P.O. Box 6710, Syracuse, New York 13211-4755

Malignant lymphomas are sensitive to a broad range of chemotherapeutic agents and a number of highly active regimens have been devised and found to be clinically useful. The search for new chemotherapeutic agents with useful activity against malignant lymphomas has become increasingly more difficult because patients suitable for phase II studies have received extensive prior therapy with radiation therapy and 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 Protocols and in the International Cancer Research Data Bank as a representative collection of cancer studies throughout the world, 100 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 new agents include: etoposide (VP-16), cyclophosphamide (CMC), CHAAG, spirogeranium, ifosfamide, mitomycin, and daunorubicin. Of the 53 trials with 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 biological 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 trials in lymphomas include: a pair of platinum analog, carboplatin, and cisplatin; a biologic analog, tiallymycin; 5Fluorouracil; a pair of antimetabolites, FAMP and thioguanine; 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
IMMUNOLOGICAL BONE MARROW RADIATION CHIMERAS. G.M. Hastebrant 1. W. Pierpoli 2, G. Losa 2. 1. Laboratory of Cellular Pathology, Istituto Cantonale di Patologia, 6604 LOCMAND, Switzerland. 2. Institute for Integrative Biomedical Research, 8123 ENSWITEN, Switzerland.

Tumour administration of unmanipulated donor (91) bone marrow cells suspended in a solution of recently identified microenvironmental components of the bone marrow into lethally irradiated recipients (92) makes for the induction of complete, CD4+T-free and stable allogeneic chimerism depending on the donor-recipient combination. PI-92 allochimeras or may not show depressed primary immune responses against T-dependent antigens. Conversely, alloreactivity was perfectly normal in all combinations used. Chimerism of established (2-4 months after bone marrow transplantation, BM 91) PI-92 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 vivo in mixed lymphocyte cultures of chimeric lymphocytes against normal PI or PI lymphocytes. However, established PI-92 chimeras are able to "suppress" passively transferred immunocompetent PI and/or PI lymphocytes. Large Georges (90-900U) of PI and/or PI immunocompetent lymphocytes (Spleen cells) passively transduced into established and CD4+T-free PI-92 allochimeras failed to show effector functions. Normal, immunocompetent PI spleen cells inoculated into PI-92 allochimeras did not recieve primary responses against T-dependent antigens nor elicited CD4+T, while normal immunocompetent PI spleen cells failed to reverse chimerism. In both cases the transplanted chimeras remained healthy and retained their chimerism. Moreover, CD4+T-free PI-92 allochimeras showed the surprising ability to reject PI skin grafts.

Both these phenomena are dependent upon the age (time after BM) of the established chimeras. Preliminary ultrastructural studies of chimeric spleens have revealed an abnormal number of cells with pleomorphic features. These findings pointed to the existence of an "unknown suppression-rejection principle" operating in the chimeras. In other words, a principle that mediates PI lymphocyte suppression and possibly PI 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 PI lymphocytes did not reconstitute these PI-92 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.

APPLICATION OF IMMUNOTOXINS TO AUTOLOGOUS BONE MARROW TRANSPLANTATION. P. Uckun, S. Ramakrishnan, L.L. Houston and M. Asoy, 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 and monoclonal antibodies covalently bound to a toxin such as ricin or a hemotoxin such as pokeweed antiviral protein (PAP), a potent inactivator of ribosomes. The present study was performed to assess the selective chlrogenic lymphoma cell elimination from human marrow by in vitro use of an immunotoxin of pan-H-2 IgG1 which monoclonal antibodies B43 linked to PAP and to define optimal conditions for application of B43-PAP to ABMT. PAP was purified from spring leaves of Physostigma venenosus 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 lymphomas 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 (80 at 37°C) selectively inhibited protein synthesis in target lymphomas 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 hematopoietic 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 lymphoid 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 (H2-HP) AND ITS EFFECTS ON HEMATOPOIETIC AND STROMAL ELEMENTS OF HUMAN BONE MARROW, Salvatore Siena, Hugo Castro-Malaspina, Subhash Gullati, Li Lu, Teresa Carugno, Richard J. O’Reilly, Bayard D. Clarkson, and Malcolm A. S. Moore, Memorial Sloan-Kettering Cancer Center, New York, NY 10021, USA.

Transplantation of a HC-purged autologous bone marrow (ABMT) after high-dose chemotherapy is a promising approach to the treatment of lymphoma and leukemia. This is based on the assumption that the dose of a HC employed selectively kills malignant cells without eliminating the cellular progenitors responsible for the hematopoietic reconstitution of the host.

Recent clinical observations indicate that a HC-purging techniques while depleting the granulomonocytic (CFU-GM) and erythroid (BFU-E) committed stem cells, do not affect its capacity to repopulate the host hematopoietic system. In this respect the role of narrow stromal cells (MSC) and pluripotent stem cells (CFU-GEMM) has not been defined. The purpose of this study was to analyze the effects of a HC on MSC and CFU-GEMM.

MSC were quantitatively studied by the narrow fibroblast colony-forming cell (CFU-F) assay and functionally by the long-term marrow culture assay (LTMC). The a HC toxicity on MSC and hematopoietic progenitors was dose and cell concentration dependent. The following ID50 (μg a HC) were found: 

<table>
<thead>
<tr>
<th>Clonal Assay</th>
<th>Cell Concentration</th>
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<tbody>
<tr>
<td></td>
<td>10^6/mL</td>
</tr>
<tr>
<td>CFU-GEMM</td>
<td>37</td>
</tr>
<tr>
<td>CFU-GM</td>
<td>95</td>
</tr>
</tbody>
</table>

The a HC-purged autologous 100μg a HC-purged marrow showed full hematopoietic recovery. This suggests that the CFU-GEMM do not represent the stem cell responsible for hematopoietic reconstitution in the transplanted host. In contrast, the MSC progenitor CFU-F was relatively resistant to the in vitro action of a HC. Moreover, a HC treated bone marrow in LTMC gave rise to stromal layers composed of fibroblasts, endothelial cells, adipocytes, and macrophages similar to controls, although a higher number of cells per inoculum was required. Coupling of these heterogeneous stromal layers with freshly isolated autologous hematopoietic progenitors demonstrated that the stroma grown from a HC treated marrow sustained the long-term production of CFU-GM similarly to controls. Thus, MSC are relatively resistant and functional affected by a HC. This is sharp contrast with the high sensitivity of hematopoietic progenitors. Taking into account the notion of transplantability and radiosensitivity of MSC, the role of MSC in the 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, L. Philipp, T. Philipp, M. Favrot, P. Biron, G.M. Lemoïl, Centre Léon Bérard - Bone Marrow Transplant Team - 26, rue Laennec 69008 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 useful 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;12) in 12 patients studied).

2. When bone marrow was cytologically normal or suspect (i.e. less than 5% BL cells) the in vitro monitoring was shown to be more sensitive 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 may 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.
AUTOLOGOUS BONE MARROW TRANSPLANTATION FOR RELAPSED NON-HODGKIN'S LYMPHOMA (NHL): ANTI-B, MONOCLONAL ANTIBODY TREATED AUTOLOGOUS BONE MARROW. E. Neidel, T. Tahvonen, R. Fazerg, R. Baxt, L. Botnick, S. Heiman, C.P. Canellos, S.F. Schlom, Dana-Farber Cancer Institute and Joint Center for Radiation Therapy, Boston, MA

Five patients with relapsed B-cell NHL were treated with intensive chemoradiotherapy and reconstituted with autologous bone marrow (BM) rendered free of tumor by in vitro treatment with the B cell specific monoclonal antibody anti-B 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 differenciated (1). These patients had one to six lines on conventional therapy with BM involvement in 4 of 5. They were re-induced into a minimal disease state, with <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, and complement, and cryopreserved. Patients then received Cyclophosphamide at 600mg/kg on days 1 and 2, followed by 7 days of fractionated whole body irradiation (200 cGy twice daily), followed by re-infusion of the treated autologous bone marrow on day 6. All patients achieved a complete response with eradication of the treated marrow by 4 weeks. Acute toxicity included malaise, nausea, vomiting and asthenia; culture negative low grade fever developed in 4 of 5 patients which responded to antibiotics. B-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 arthralgias in pulmonary 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 month. 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 treated autologous BM can rescue the aplastic effects of intensive chemoradiotherapy. 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.


Patients with poor prognosis lymphoma, identified as having bulky nodal or extranodal disease and/or high serum lactate 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-1M protocol). At the time of transplant, radiation to the site of residual disease was followed by TBI (total 3300 rad) 11 doses over 4 days, then cytoxan 60mg/m2/day x 2 days with ASTC rescue. Seven patients had ASTC 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 month. Five patients progressed after L-1M induction and were then treated with ASTC protocol. Two of them have died of transplant 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 ASTC. One of these patients died few days after transplant; one patient relapse at 5 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-1M, 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 ASTC has promise in improving the management of patients with poor prognosis lymphomas. Methods of purging bone marrow will also be discussed. (Support CA-88526, 19117, 20124).

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., CHOEP) were selected for ABMT because of relapse (cases 1,3,4,5,6,7,9). PR after 2 months of CHOEP (case 2), or long delay to reach CR (cases 8 and 11). 4 of the 7 relapsed are still alive 930 (1), 894 (2) and 410 (3) post ABMT. Patient 2 in PR is alive NED 930 (1), and one of the two long delay to CR is alive NED 184 (4). 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 (5), 4/8 stage III because of PR (1), progression (2) or long delay to reach CR (2) - alive NED 186 (6). 2/8 stage IV because of PR or for consolidation of initial CNS involvement - alive NED 260 (7). A total of 3/8 patients are alive NED.

In this group of very bad prognosis BL 8/18 are alive NED 163 to 930 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 concern a maximum of 30% of BL cases. (3) Necessity to purify at least some bone marrow. (4) Possibility of purging marrow (5 cases).

Treatment of Refractory Non-Hodgkin’s Lymphoma with Intensive Chemoradiotherapy and Autologous Bone Marrow Transplantation. C. Santos, A. Teager, H. Braine, H. Kelz*, 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 3-69 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 etoposide, 30 mg/m²/day x 3. Marrow was treated in vitro with 40-100 μg/ml of α-irradiated cyclophosphamide (VNC) 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:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. Relapses</th>
<th>Days post BMT</th>
<th>In Vitro K/No. Pls.</th>
<th>Retransplants</th>
</tr>
</thead>
<tbody>
<tr>
<td>VNC</td>
<td>7</td>
<td>3 (33.60,75)</td>
<td>4 (17,102,781,797)</td>
<td></td>
</tr>
<tr>
<td>Leu-1</td>
<td>4</td>
<td>2 (49.75)</td>
<td>2 (996,1198)</td>
<td></td>
</tr>
<tr>
<td>Leu-1 + Leu-9</td>
<td>5</td>
<td>3 (48,91,405)</td>
<td>2 (10,52)</td>
<td></td>
</tr>
</tbody>
</table>

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.

Supported in part by Program Project Grant No. 2P01-CA 15396, NCI, NIH, and by the William Smith Charitable Trust.
ABSTRACTS - Second International Conference on Malignant Lymphoma, Lugano

98 Lymphoproliferative Diseases with Monoclonal Gammopathy
C.F. Berard, Div. of Pathology, St. Jude Children's Hosp., Memphis, USA
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. Lymphoprolifera-
tive diseases with monoclonal gammopathy result usually from the
neoplastic transformation of clones of B-cells at or near the termi-
nal stages of B-cell differentiation. To understand the morphology,
pathogenesis, and clinical manifestations of these disorders, how-
ever, one must have an overview of the physiology and interrela-
tionships of B-cells, T-cells, and cells of the mononuclear phagocytic
system. In this presentation such an overview will consider ini-
tially both the normal immune system and selected congenital and ac-
quired immunodeficiency states. In this context, it will become
apparent that neoplastic lymphoproliferative disorders with mono-
clonal gammopathy arise from the milieu of the immune system and re-
tain to variable degrees functional attributes demonstrable in termi-
nal 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.F.: 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,

99 ANGIOIMMUNOBlastic LYMPHADENOPATHY: CLINICAL COURSE, IMMU-
NOLOGICAL CHARACTERISTICS AND TREATMENT RESULTS IN 25 PATIENTS.
R. van Rood, Dept. Med. Hochschule Hannover, Germany
We observed 25 patients with Angioimmunoblastic Lymphadenopathy
(AILAP) between 1972 and 1983. Diagnosis was established by lympho-
biospy. Patients without histologically proven diagnosis from lympho-
dases were excluded from this study. Median age was 50.4 years, 60% were
male, 42% female. Initial clinical symptoms occurred 3 months before
diagnosis: lymph node enlargement (80%), fever (60%), weight loss and
night sweats (44%), hepatomegaly (48%), generalized pruritus (28%). Laboratory investigations at the
time of diagnosis: rapid blood sedimentation rate (60%), thrombocytopenia
via 100,000/µl (52%), anemia: Hb 12 g/l (48%), leukopenia < 3000/mm³
(28%). With a 10% eosinophilic granulocytes, liver enzyme alterations
(20%). Immunological characteristics during the active phase of AILAP:
polyclonal gammopathy, increase of immune-complexes, cold haemagglut-
inins, antibodies against smooth muscles and EBV. Cellular analyses:
lymphocyte depletion with low helper and high suppressor cell activ-
ity, 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 spontane-
ous regression which was observed in 4/25 cases (16%). If AILAP was
continuously progressing, therapy consisted either of Prednisone (low
progression: group A), or polychemotherapy (rapid progression: group B).
A: Prednisone 60 mg/m² p.o. daily for 4 weeks, subsequent stepwise de-
duction to maintenance level, if CR: therapy-stop after 4 months.
B: Cyclophosphamide 100 mg/m² p.o. daily, Flucytosine 2 mg i.v. weekly,
Prednisone 60 mg/m² p.o. daily. Procarbazine 100 mg/m² 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 = 8)
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 35.5 months.
7/25 patients showed a malignant transformation of AILAP. 4 Hodgkin's
diseases, 3 Non-Hodgkin-Lymphomas, 2/25 patients had synchronous
secondary malignancies: 1. 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 Prednisone or polychemotherapy. There is no
clear relationship to the stage of the disease or other characteristics
like immunological malignations. 2. Further analysis of immunolog-
ic impairments might help to develop new, more efficient kinds of
therapy. 3. In many cases AILAP precedes malignant transformation or
secondary malignancies.
ABSTRACTS - Second International Conference on Malignant Lymphoma, Lugano


We have in a double blinded fashion categorized according to WHO, FAB and BCI classifications all ALL and NHL after having characterized their immune types with monoclonal antibodies. Patients with ALL of which all OKT, c and s Ig were negative had a WHO pre-B lymphoblastic ALL, Fab L1. Patients OKT+, OKT-3, 4 and 8+, 8+, s Ig- had a WHO prolymphoblastic T and Fab L2-3 ALL. Patients with all 8-, c and s Ig but 8+ had the WHO prolymphoblastic of the B series ALL Fab L2-3. Patients with large cells OKT+ and OKT+, OKT3, OKT4 and OKT8+, OKT8, 8+ and s Ig correspond to the WHO T macrolymphoblastic ALL or NHL (correlate to lymphoblastic ALL) and to the Fab L2-3. Patients with large cells all OKT and 8-, c and s Ig correspond to the WHO pre-B-macrolymphoblastic ALL and to the Fab L2-3. Patients with mixed-size cells all OKT+, c and s Ig correspond to the WHO Burkitt's lymphoma and/or to Fab L3. All NHL of the B types are cEp+, this positivity being of various qualitative and quantitative types. The 8 lymphoblastic NHL is sIg+. The lymphoepithelial NHL is sIg+. The small non cleaved nuclear cell type is sIg+++, sIg++. The small cleaved nuclear cell type is sIg+, sIg+. The large non cleaved nuclear cell type is sIg++, sIg+ and sIg+. The large cleaved nuclear cell type is sIg+, sIg+ and sIg+. The B immunoblastic NHL (with convoluted or no nuclei) is sIg+++ and sIg++. The T lymphocytic NHL in OKT8+ or OKT+, OKT8 and OKT6-. Nodular follicle and Seminarian disease (with cerebriform nuclei) are OKT8+, OKT8- and the Waldenström immunoblastic-plasmocytic type is usually OKT8+, OKT8, OKT8, OKT6-. We have also observed cases of OKT8+, OKT4, OKT8, OKT8- NHL.

101 COMPARISON OF THE WORKING POPULATION (WP) OF NON-BURKITT'S MALIGNANT LYMPHOMA (NHL) WITH THE HARVARD (H), KIEL (K), AND LIEGE (L) CLASSIFICATIONS. TERMOLOGICAL CORRELATIONS AND PROGNOSTIC VALUE.

Jose Ezzedini, Henrik Schultz, Ms J Nilsson, Philip Hugos and Klaus Hov-Jensen. The Finsen Institute, Copenhagen, Denmark.

659 cases of NHL seen 1970-79 were reviewed and classified according to the K, K, L.C. classifications and the WP. Each classification provided equally effective in separating patients into subgroups with prognoses ranging from a median survival of 1 year to 7 years. The K, L.C. systems were compared one by one against the WP following the translation guidelines of the WHO sponsored Study (Cançar 1982/49, 2112). The WP was more similar to the R and L.C. systems than to the K system, since 84%, 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 RC-lymphomas composed of predominantly small lymphocytes (92-94% accordance), in lymphomas of CLL type (90-100% accordance), and in FC-lymphomas of small non-cleaved cytology (92-100% accordance). The greatest differences were seen in lymphomas composed of large lymphoid cells or of mixed cellular subpopulations (58-80% accordance). The uncertain relation between the B-cell subtype of the H.C. system and the lymphoblastic lymphomas of non-convoluted subtype accounted for the defective translation of this subtype (36-100% 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-RC subtype of the WP: SL (1.61,F<0.01), F-SC = 1.43,F<0.01), F-W (4.22,F<0.001), D-SC (1.60,F<0.001), D+ (3.28,F<0.001), W (3.89,F<0.001), W+ (10.6,F<0.001), SNC (3.56,F<0.001). The intermediate malignancy grouping of the WP was prognostic heterogeneous, the SL and D-SC had similar survival (median 3.4 years), and the D-,W- and F-RC subtypes had survival similar to subtypes of the high grade grouping. By the use of the Cox model including two classifications simultaneously (or compared one by one with the H.C. systems) it was shown that the WP can substitute any of the established classifications in terms of prognostic value.
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102 CLINICAL AND PROGNOSTIC RELEVANCE OF THE KIEL CLASSIFICATION OF NON-HODGKIN LYMPHOMAS (NHL): RESULTS OF A PROSPECTIVE MULTICENTER STUDY


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 792 pts. with low-grade malignant NHL (lymphocytic lymphomas, predominantly B-CLL: 23.3%). LP lymphoma = LP-IC: 16.6%, 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: 13.8%, 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 lymphomas could be recognized only after 2 years of follow-up. Survival curves of pts. with high-grade malignant NHL showed a rapid decline during the first 1 to 1.5 years and a subsequent plateauing. Intermediate course of survival curve of pts. with advanced stages of LP-IC, CC lymphoma and LB lymphoma between those of pts. with B-CLL and CB-CC lymphoma and those of pts. with LB and LB lymphomas suggests 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 remission (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 refractory to the lymphocytic system for a prolonged period of time.

Strategy of "watchful waiting" for advanced CB-CC lymphomas is challenged by the unsatisfactory results obtained in this study and by improvement of prognosis observed in pts. achieving CR.

The high-grade malignant LB lymphoma was less favorable than CB-CC 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 LB lymphomas. Most of these pts. were treated by radiotherapy alone. However, only in stage I of CB lymphoma a sufficient proportion (40%) of pts. achieved stable CR. Prognosis of patients with advanced CB, LB 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.


One hundred and thirty-seven consecutive patients with malignant NHL were classified according to the Kiel system, who underwent routine bone marrow (BMM) 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 indistinguishable from acute lymphoblastic leukemia were excluded from this study. The median time of follow-up was 21 months (range 1-67 mos). The overall incidence of BM involvement at diagnosis was 38% (321/1127). The frequencies of BM disease in the three major prognostic groups of the WF were the following: 19% (62/315) for low grade (LCM); 39% (18/46) for intermediate grade (ICL) and 23% (56/262) for high grade malignant lymphomas (HCL). As regards the prognostic significance of BM involvement, the survival curves obtained grouped patients into low grade, intermediate grade and high grade malignancies which 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 local 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 lymphoid spread during clinical course. As concerns prognostic significance of the leukemic spread, peripheral blood involvement at diagnosis in LGM 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 13 mo). In fact, a shift to a less differentiated lymph node histology was documented in 5 patients with late leukemic spread. In patients with IGM, 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<0.003). As regards HGM, the median survival of leukemic patients was not different 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 IGM and late leukemic conversion in LGM are associated with a worse prognosis.
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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 have been provided in light microscopic criteria and even cell surface phenotype determinants have not yet provided information of additional prognostic utility. 33 previously untreated patients with advanced stage NHL were enrolled in a Southeastern Cancer Study Group (SECSCG) clinical trial of cyclophosphamide, vincristine and prednisone (COP) versus the same regimen plus IFN. No response or survival differences were noted between the regimens. Using a computer method which constructs correlations 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 transaminases (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 low white cell counts at presentation. This latter subgroup is comprised almost entirely of patients with unfavorable histology disease. These patterns were discovered using 2/3 of the patients (226), 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 (37-84% 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.
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Seventy five cases of primary intestinal lymphoma were diagnosed in adults at AUBMC during the period 1961-1988. Two additional cases with the pre-malignant phase of immunoproliferative Small Intestinal Disease (IPSID) were also studied. 41.5% of patients had IPSID and 58.5% 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 malnutrition were the prominent clinical features at presentation in IPSID, the presence of abdominal mass and/or complications like obstruction, bleeding and paraproteinemia 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 tumor 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 ileocecal region. c. The most frequent lesions in non-IPSID according to the Kiel classification was plasmacytic (43%), while in IPSID it was lymphoplasmacytic (43%). The cellular mucosal infiltrate in IPSID was usually lymphoplasmaclastic or plasmacytoid. 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 light chains (λ heavy chain protein). Like Burkitt's lymphoma, IPSID is a newly described disease which provides an opportunity to study the etiopathogenesis of lymphoproliferative disorders.
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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 much 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 identified. Moreover, the genes able to do this, contained in the viral genome, are packaged positive by the virus. This provides insights into the mechanism of transformation of the cell. By using techniques of molecular biology these onc 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 involved in a few studies investigators 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-onc in Burkitt lymphoma in collaboration with C. Creutz. Other approaches (DNA transfection) were also made by G. Cooper and his colleagues, have led to the discovery by these investigators of new gene (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.

2. 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 shown 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 mycophage lymphoma virus, feline leukemia virus, bovine leukemia virus, and feline papilloma virus are the etiological agents of naturally occurring lymphomas of chickens, mice, cats, cows, and chimpanzees respectively. Virus of these types 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.

3. In view of the known number of 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 greatly aided by the discovery of cDNA synthesis by 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 MLV 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 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 beginnings insights into the cause and pathogenesis of human lymphomas and has 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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