Poster Session I
P 1 DNA ANEUPLOIDY IN HODGKIN'S DISEASE: A MULTI-PARAMETER FLOW Cytometric Analysis with CYTOLogic Correlation. John Anastasi, Kenneth D. Bauer, and Dina Varakajis, Dept. of Pathology, Northwestern University Medical School, Chicago, Illinois, USA

In 25 cases of Hodgkin's disease, we studied the DNA content of isolated nuclei from deparaffinized tissue by using multi-parameter flow cytometry. We employed an antineurotous antibody preparation (Greenfield, RS et al. Proc. AACR 24:792, 1983) as well as a secondary antibody that had been conjugated with fluorescein isothiocyanate. By simultaneously quantitating nucleolar fluorescence and DNA content, we were able to detect distinct aneuploid populations among the nuclei with a brightly stained nucleolus. DNA aneuploidy was found in each case when we used this multi-parameter approach, but it was detected in only one case when DNA content was analyzed alone. With the multi-parameter analysis we found two to four aneuploid populations in each case. These populations exhibited incremental duplications of DNA content which suggested endopolyploidy, i.e., replication of DNA without accompanying nuclear division. The aneuploid stem line was hypodiploid or hypotetraploid in six cases, hypodiploid in seven cases, and near-triploid in two cases. These various abnormalities in ploidy showed some correlation with histologic subtypes, but only when subtype variants were considered. Cell sorting showed that some nuclei with more than four or nearly eight times normal DNA content resembled nuclei of typical Reed-Sternberg cells. Many nuclei with an intermediate aneuploid DNA content resembled nuclei of mononuclear Reed-Sternberg cells. The near-diploid and near-triploid nuclei corresponded to nuclei of cells which were not readily recognizable as neoplastic in histologic sections. We conclude that analysis of DNA content can provide further insights into our understanding of the neoplastic cells in Hodgkin's disease and may offer an objective basis for studying heterogeneity in this disorder.

P 2 Doses DNA content have PROGNOSTIC SIGNIFICANCE in HIGH GRADE NON-HODGKIN'S LYMPHOMA. R.J. Greenwalt, W. Harries, B. Crotzer*, T. C. Department of Medical Oncology, Department of HistoPathology, Christie Hospital, Wilmslow Road, Manchester M20 8LR, UK.

Flow cytometric analysis provides a method for the rapid estimation of DNA content in tumour cell populations. To date, published data in non-Hodgkin's lymphomas suggests that aneuploidy and high proliferative activity, measured by S phase percentage or proliferative index (PI) (percentage of cells in the S phase and G0M phase of the cell cycle) correlates with high grade histology and therefore poor prognosis.

Using this technique on paraffin-embedded tissue we have studied 180 patients with high grade non-Hodgkin's lymphoma (in Kiel and Rappaport) all of whom have received uniform treatment, to establish the clinicopathological correlations and prognostic significance of ploidy and proliferative index in this group of aggressive lymphomas. Prior to analysis all histological specimens were reviewed by one pathologist to ensure adequate tumour representation.

47% of the patients studied had aneuploidy tumours, and the PI for the group varied from 1.0% to 45% with a mean of 15.9%. The PI correlated with histological grade in the Kiel classification: the lymphoblastic and immunoblastic lymphomas having a significantly higher PI than the other histological subtypes (p<0.005). No such correlation was found between PI and histological categories by Rappaport. PI was also significantly associated with response to therapy: 60% of patients with a low PI (<20%) achieved complete remission compared to only 33% of patients with a high PI (>40%). There was no significant association between ploidy status and histology by Kiel or Rappaport nor was there a significant correlation between remission status. In addition, DNA content was not significantly related to clinical stage nor sites of disease. In a Cox multivariate analysis for prognostic factors neither ploidy nor PI significantly predicted for the overall survival, relapse-free survival nor survival after attainment of complete remission.

We conclude that within unfavourable histology non-Hodgkin's lymphomas, DNA content as measured by a flow cytometric analysis is not a strong predictor of clinical outcome.

P 3 SURVIVAL FOLLOWING COMBINATION CHEMOTHERAPY IN ADVANCED HIGH-Grade NON-HODGKIN'S LYMPHOMA (NHL). RELATION TO PROLIFERATIVE ACTIVITY OF THE CELLS. L. Brandt, H. Olsson, Dept. of Oncology, University Hospital, S-221 85 Lund, Sweden

It is largely unknown why some patients with advanced aggressive NHL achieve long-term survival following chemotherapy whereas others suffer a clinically and histologically similar disease and treated in the same way die from progressive disease within a relatively short period. In the present study of advanced high-grade NHL, age, histology, stage and initial treatment were compared in short-term and long-term survivors. The proliferative activity of the lymphoma cells, thymidine labelling index (LI), was recorded at diagnosis.

Eighteen patients with high-grade lymphomas (Kiel classification stage I-II) were initially treated with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), CMOP + methotrexate, MEV (methotrexate, cyclophosphamide, vincristine) or COPA (cyclophosphamide, vincristine, methotrexate, leucovorin, cytarabine riboside) and have been followed for a minimum of 3.7 years or until death. Twelve patients have died within 2.7 years after diagnosis (range 0.1-2.7, median 1.5 years) and 6 patients have survived for more than 3 years (range 3.7-13.6, median 5.1 years). Age was comparable in the two groups, median 62 and 61.5 respectively. Four of the 12 short-time survivors and none of the long-term survivors had lymphoblastic lymphoma. Other morphologic classes were comparable in the groups.

Stage III-IV was diagnosed in 11/12 and 6/6 respectively. The distribution of treatment regimens was similar in the two groups. LI was considerably higher in the short-time survivors, median LI 0.1 (range 2.4-25.4), than in the long-time survivors, median LI 1.1 (range 0.2-4.2) (P<0.01). Excluding the lymphoblastic lymphomas the differences is still large, median 0.6 versus 1.1 (P<0.01).

It is concluded that combination chemotherapy may induce long-term survival in advanced high-grade NHL if the proliferative activity of the tumour cells is low. A high proliferative activity is associated with poor response or early relapse resistant to further therapy. It is proposed that in rapidly proliferating lymphoma a large number of mutations may arise and that some of them are responsible for drug resistance at diagnosis. This assumption is supported by a previous finding of larger numbers of clonal chromosome aberrations in NHL with high LI than in lymphomas with low LI (Brandt et al. Scand J Haematol 1986;37:106-110).

P 4 IMMUNOGLOBULIN (Ig) AND T-CELL RECEPTOR (TCR) GENE REARRANGEMENT IN HODGKIN'S DISEASE. A. Raghavachar, T. Binder, C.R. Bartram, Departments of Transfusion Medicine, Internal Medicine III and Pediatrics, University of Ulm, D-7900 Ulm, FRG

In the past, morphologic, electron microscopic and immunohistologic analyses have been extensively used as an adjunct to the histopathological diagnosis and classification of Hodgkin's disease. To further characterize the lineage and clonality of Hodgkin's disease we have investigated the rearrangement of Ig and TCR genes in lymph node biopsies obtained from 35 Hodgkin's disease patients. Diagnosis and classification of each lymphoid neoplasm was established by conventional histopathologic criteria and comprised all subtypes of Hodgkin's disease. Southern Blots were hybridized to Ig heavy chain, Ig light chain as well as TCR-β and TCR-γ specific probes. As a result from these studies, we detected clonal rearrangements of Ig genes in 6/35, and TCR genes in 5/35 specimens, irrespective of the histopathological subtypes. The intensity of rearranged bands in every case suggested the presence of minor clonal populations of B or T cells. These findings will be discussed in the context of recent reports with conflicting data on Ig and TCR gene rearrangements in Hodgkin's disease.
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P 5 IDENTIFICATION OF A NEW TRANSFORMING GENE IN PATIENTS WITH B CELL PROLIFERATIVE DISORDERS. T. Ernst, G. Cooper, J. Herrick. Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA USA.

Preneoplastic B-cell lymphoproliferative disorders provide the opportunity to identify, characterize, and subsequently follow a specific cell type which in 30-50% of cases will evolve to a frank neoplasm. We have studied 32 patients with characteristic B-cell disorders which are clinically and histopathologically severe. A cell surface antigen expression suggested a polyclonal disorder by virtue of approximately equal expression of both kappa and lambda immunoglobulin light chains. Immunoglobulin heavy chain rearrangement however showed a clonal expansion of B cells which was unassociated with the Epstein-Barr viral genome.

Using the NIH 3T3 focus formation assay, high molecular weight DNA derived from the abnormal B-cells and normal T-cells from each patient were scored for transforming activity. Multiple human B cell repeat positive foci were obtained from B cell transfecteds from each patient whereas the T cell DNA was negative for focus forming ability. Second round transfomers were used to clone, by human A hu repeat homology, genomic DNA of 12-15 kb in length which is shared in multiple transformants derived from all three patients.

The relevance of this gene is the evolution of preneoplastic B-cell disorders and the multistep process of lymphomagenesis is currently being investigated.


The proliferation of normal human B cells depends on the activation by an appropriate antigen or mitogen followed by the action of B cell growth factor (BCGF). Human RAGC contains a single polypeptide with a high (30 KDa) molecular weight fraction. It could be demonstrated, that neoplastic B cells from patients with non-Hodgkin's lymphoma and chronic lymphocytic leukemia can proliferate in vitro in the presence of growth factor activity. The proliferation of B cells from a bone marrow aspirate and propagated in liquid suspension culture containing 10% human plasma (free of EBV transformation). For the growth factor production 2 x 10^6 cell/ml in 1IDM (IM supplemented with 1% BSA and incubated at 37C for 48 hrs in 5% CO2). The supernatants were tested for the growth factor activity on the autologous NHL cell line, normal B cell line of high density, B cell line (HELo) and a myeloid cell line (HL-60). We measured the ^H-thymidine incorporation after 24 culture period of 72 hrs. A representative example of the results on the NHL cells can be seen in the following Table.

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<thead>
<tr>
<th>TARGET</th>
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<tr>
<td>CONTROL</td>
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Our data suggest that the OCLY1 cell line is capable of producing a growth factor like activity. Its biological activity closely resembles the human BCGF. In addition, this activity is not only present in the in vitro proliferation of normal human tonsillar B cells. Its B cell restriction is demonstrated by the lack of any stimulatory effect on a T or myeloid cell line.

P 7 THE FUNCTIONAL EFFECT OF RECOMBINANT INTERLEUKIN-2 (IL-2) ON IN VITRO GROWTH AND PROLIFERATION OF NON-HODGKIN'S LYMPHOMA CELLS. R. Haas, S. Kiesel, S. Hohaus, A. Lüdemann, W. Hunstein, B. Dörken, Department of Internal Medicine, Heidelberg, West Germany.

In 1976 Morgan et al. described a biological activity derived from supernatants of long term cultured T cells which was capable of maintaining and proliferating of human T cells. This growth factor could be identified as a glycoprotein consisting of 133 amino acids. According to its biological property it was called T cell growth factor (TCGF) or later interleukin-2. Like other hematopoietic growth factors it exerts its biological functions by binding to specific receptors expressed on the target cells. It plays a major role in the activation and proliferation of T cells which are stimulated by antigen and other functional receptors. Furthermore it is able to increase the secretion of immunoglobulins by plasma cells and the expression of specific interleukin-2 receptors on T and B cells. It could be shown that specific IL-2 receptors are present on the surface of B and non-Hodgkin's lymphoma cells. The biological effects of recombinant IL-2 on different B and non-Hodgkin's lymphoma cell lines were analyzed in this study. These cells lines were free of EBV transformation and dependent on human plasma expressing the IL-2 receptor in different densities. In a semisolid clonogenic culture assay (methylcellulose 0.9%, human plasma 30%, and 2 M 2x10^6 M) the incubation with IL-2 in different concentrations (1 U/ml up to 100 U/ml) caused a decrease of 25-60% in average in the number of colonies dependent on the cell lines tested. Similarly the mean numbers of colonies of IL-2 in identical concentrations was only 65-73% compared to the controls in a 72 hour culture period. The data demonstrate that IL-2 has a suppressive effect on the proliferative and the clonogenic growth of non-Hodgkin's lymphoma cells. We conclude that IL-2 exerts its effect by inducing differentiation processes in the lymphoma cells like it has been demonstrated for normal B cells and thereby decreasing the proliferative and clonogenic capacity of the leukemic cells. For the future it has to be evaluated if these in vitro results could be exploited for new therapeutic strategies in the treatment of patients with non-Hodgkin's lymphomas.


Increased levels of a soluble form of the interleukin-2 receptors (sIL-2R), either released by neoplastic as well as by activated T cells, have been recently demonstrated in a number of pathological conditions. Since the IL-2R is strongly expressed by Hodgkin and Reed-Sternberg cells and based on these observations, we investigated the serum levels of sIL-2R in this disease. The sIL-2R levels have been measured in over 100 cases using a radioimmunoassay (RIA) last and evaluated in relationship with various clinical-pathological parameters. Sera were collected at diagnosis and in a number of cases, also at different periods after therapy. Increased levels (>500 U/ml) were detected at diagnosis in 75% of cases. The mean sIL-2R values were higher in patients with adenopathy (>1352 ± 827) as compared in the initial stages (stages I/II = 912 ± 809, p < 0.02). The highest statistical difference was found between the values observed in stages A as compared to B (stage A = 843 ± 69, stage B = 1550 ± 649, p < 0.001). With few exceptions, cases with clinical evidence of disease progression (increased sIL-2R levels) were more complex than with patients with a limited disease (stages I or II) without constitutional symptoms (stage A). The treatment-induced clinical response was followed by a rapid normalization of sIL-2R levels, opposite to the finding of increased values in patients with relapse or progressive disease. Besides representing a new biochemical tool for monitoring the disease status and effect of therapy, we suggest that the detection of increased levels of sIL-2R in HD seems of relevance to understand the pathogenic mechanisms of the immunological abnormalities observed in this disease. In fact, the excess of sIL-2R might remove "in vivo" the available IL-2 and block the IL-2/IL-2R modulation necessary for a large number of biological responses. As consequence, sIL-2R dependent phenomena would be affected, including most of those which are impaired in HD, such as T cell proliferation, cutaneous delayed type hypersensitivity and regulation of NK activity. Some biological evidences supporting this interpretation will be presented.

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P 9  
SERUM INTERLEUKIN-2 (IL-2) LEVELS IN HODGKIN'S DISEASE (HD)  
Cavalli C, Bellotti V, Gobbi P, Merlini G, Clinica Medica II, University of Pavia, IRCSS Matteo, Pavia, Italy  

An increasing amount of experimental evidences in animals and men would suggest that many of the clinical, biological, and cytologic features of HD may be mediated by interleukins, mainly IL-2.  

IL-2, that is synthesized by IL-1 activated T lymphocytes, is a strong stimulating factor for all T subpopulations and probably for B cells, too.  

We studied the IL-2 serum levels in 33 patients with HD, 18 males and 15 females, 18 to 70 years old, observed between 1979 and 1984. All were staged according to the Ann Arbor recommendations histiotype were nodular sclerosis in 15 cases, mixed cellularity in 14, lymphocyte depletion in 2 and unclassified in 2. One patient was in stage I, 7 were in stage II, 18 in stage III and 7 in stage IV. Nineteen out of 33 were B stages.  

Serum IL-2 was measured at diagnosis by means of a solid phase enzyme immunoassay based on the dual antibody immunometric sandwich (Genzyme Corporation, Boston MA).  

Patient mean value was 46.8 ± 3 ml/ml (SD 32.6 ± 9). No clear differences were seen in IL-2 mean levels in relation to sex, histotype, stage and symptoms (A or B).  

No correlations were seen between IL-2 levels and erythrocytopenia on serum albumin, alpha-2-globulins, gamma-globulins, fibrinogen, copper and peripheral lymphocyte count, all parameters indirectly IL-1 activated.  

IL-2, as measured in the peripheral blood by the enzymatic immunoassay used, does not seem to correlate with the main clinical manifestations of HD; moreover, as clinical marker of disease activity, it shows no advantages in comparison with those more commonly used.  

The lack of apparent correlation between IL-2 and other IL-1 mediated biological factors might be explained by a cellular or a regulatory T cell defect.

P 10  
RGN-CSF RESCUE OF GRANULOPOIESIS AFTER ABLATIVE CHEMOTHERAPY AND TOTAL BODY IRRADIATION (TBI): CASE REPORT OF A T-LYMPHOPROLIFERATIVE LAMPHoma PA-  
TIENT. R. Obriot, C. Hissen, A. Tichelli, A. Gratzwohl, P. Grabenhorst, and B. Speck, Obrech. Divs. of Oncology and Hematology, Dept. of Internal Medicine of the University, Dept. of Research, Hospital and Sandoz Inc., CH-4031 Basel/Switzerland  

Recently recombinant granulocyte-macrophage colony stimulating factor (rG-CSF) has become available for in-sitro trials on 200 normal women and stage IV A lymphoblastic T-cell lymphoma with mediastinal bulk. Initial treatment consisted in an ALL- 
regime containing DNR, CVB, MPK, ASH, AHA-C, VP-16 (SASK 33/66) from 2.86 to 6.86, followed by medistinal irradiation (1000 cGy). On August 7, an autologous bone marrow transplantation was performed with a condition- 
ning regime of CYT and TBI. After a transient increase, the white blood count (WBC) dropped and by end of Sep- 
tember the bone marrow was severely hypoplastic, the patient's ANC and PLT count remaining low with pro- 
sistently less than 50/mm3 granulocytes. She remained dependent on platelet and erythrocyte transfusions. In this situation, with a minimal chance of spontaneous recovery, she was treated with 250 μg rG-CSF daily by 24h infusions during 10 days, beginning October 21st. An early increase in total WBC to 1000/mm3 (mainly lymphocytes) was followed by a steady recovery of her granulocyte counts after 4 weeks, culminating in a total WBC of 2000/mm3 on day 47, with 44% segmented and band forms. A slow concomitant rise of monocytes to 250/mm3 and reticulocytes to 4-6% and stable values for platelets and erythrocytes were observed. Lympho- 
cytes demonstrated an early doubling in absolute number 

P 11  
EFFECTS OF ALPHA-INTERFERON THERAPY IN PATIENTS WITH HAIRY  
CELL LEUKAEMIA. A MULTIPARAMETER LONGITUDINAL EVALUATION.  
Istituto di Anatomia Patologica di Verona University. Istituto di Medicina Clinica de Padova University, Italy.  

In this study we report the results of a longitudinal evaluation of several clinical, histological and hematological parameters in patients with hairy cell leukaemia (HCL) treated with recombinant alpha-2 interferon (α-IFN, Shering Corp.), given subcutaneously three times a week for 12 months. Baseline and strict surveillance of clinical and hematological parameters, the study included the histological and immunochemical analysis of bone marrow biopsies, the evaluation of NK in vitro activity of 

P 12  
INTERFERON PRODUCTION IN LYMMPHOPROLIFERATIVE DISEASES.  

Alpha-interferon (α-IFN) has been used in the treatment of lymphomas, myeloid and hairy cell leucemias. Very little, however, is known about the metabolism of this naturally produced immunomodulator in human malignancies. We continuously assayed IFN production by peripheral blood leucocytes from patients with non-Hodgkin lymphomas (NHL), Hodgkin’s disease (HD), hairy cell leukaemia (HCL), T-cell lymphoma (TCL), and chronic lymphatic leukaemia (CLL) as well as by cells from normal (N) controls. Triplicates of 36×10⁶ freshly drawn unseparated leucocytes were incubated in medium alone or supplemented with alpha-interferon (α-IFN), IL-1, or IL-2 (50 U/ml) or the cytokine combination (α-IFN, IL-1) for 24 h. In the IL-2 system, cytokines were added at the appropriate concentration (1000 U/ml). Supernatants were assayed for their capacity to protect the appropriate cell cultures against the cytotoxic activity of vesicular stomatitis virus. Results are expressed in laboratory units (L.U.).

We thus show that in HCL and in CLI, α-IFN production in vitro is apparently aberrated and that in NHL (whether T or B) and in HD to a lesser extent, peripheral leucocytes display a reduced capacity of α-IFN production. It is noteworthy that in CLI, a disease often complicated by cytopenia, G-CSF production appears to be greater than normal.
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PTCL, excluding Lymphoblastic lymphoma and mycosis fungoides (MF), are a morphologically heterogeneous group of lymphomas. They are characterised by a poor prognosis, very often refractory to conventional chemotherapy. New chemotherapy regimens and highly active antiretroviral therapy (HAART) are promising options in PTCL, however the response rate remain low (70%-75%), but however sustained CR remains to be seen. IPN therapy has been reported to be active in lymphoproliferative malignancies such as MF, hairy cell leukaemia, follicular non-Hodgkin's lymphomas. However no clinical trials has been published on PTCL. We reported on three cases of PTCL treated with IPN recombination. Mean age was 45 y, (range 30-62) male 7 pts, female 4 pts. IPN recombiant (intr A) was administered subcutaneously at the dose of 300mg/m² 3 times a week for 10 weeks 1/4 in 4 yrs. Response was evaluated after at least one month of treatment. 3 pts were in relapse after initial intensive chemotherapy including Mitoxantrone and Cyclophosphamide, of whom 3 were refractory to salvage chemotherapy, 3 pts were in partial response after chemotherapy and 1 pt had received only corticosteroid therapy. Initial stage distribution was ICRV, 8 pts, III, II, 2pts, II, 1 pt with bulky lymphadenopathy. Clinical symptoms were seen in 9 pts. Response to IPN therapy was as follow: 1 CR persisting more than 16 weeks, 1 major response lasting more than 10 months, 2 partial responses lasting 6 and 2 months, 2 pts of histology and 5 failures. Except for flu-like syndrome and grade 1 hepatotoxicity, no adverse toxicity was seen. 3 pts died from progressive disease. IPN has activity in PTCL and will be evaluated on a larger number of patients.

P 14


Decoy cytokinin (DCF) is a potent adenosine deaminase inhibitor and has been used as a non-potent lymphodepleting agent in a lymphodepletion protocol in autoimmune neutropenia. In a prospective phase II trial (EDRC protocol no. 0685), the efficacy of this drug in some rare T and B cell lymphoplasia in response to DCF administration was assessed at 4mg/m² IV weekly for 4 weeks and then every other week X 3 to patients who were resistant to standard chemotherapy. Patients were eligible for evaluation for response: 1) 6 patients with Sézary Syndrome, 2) 2 patients with T-cell lymphocytic lymphoma, 3) 2 patients with early B-cell lymphoma, 4) 3 patients with T-prolymphocytic leukemia (PLL) and 3) 5 patients with hairy cell leukemia (refractory to treatment with interferon alfa-2a). Response in each patient each with B-CLL, B-PLL and mycosis fungoides did not respond. Simultaneously we have studied in vitro and in vivo effects of the drug on DNA strand breaks, deoxanucleosine (ADA) activity, DAF levels and ADA levels in the leukemic cells. In vitro, incubation of the leukemic cells with DCF (10-9 M) and deoxy-adenosine (10-10 M) invariably caused a prompt suppression (already at 4h) of ADA activities. Subsequently ADA levels were elevated and DAF levels were depleted in most samples after 24h. No correlations could be found between these in vitro parameters and clinical response. DNA strand breaks of 50% were found in 9 of 14 cases after in vitro incubation and these data should correlate with clinical response to DCF. Studies of the effects of DCF and Mycophenolate mofetil on the DNA lesions in the leukemic cells taken from the patients at 24h, 48h and 7 days after the first administration of DCF also showed that DNA lesions were suppressed, DAF accumulated and ADA levels decreased in most cases. Again, the extent of DNA lesions correlated with clinical response but did not correlate with clinical response. DNA strand breaks in the leukemic cells in vivo seemed to be the parameter that correlated with clinical response. This finding suggested that DNA depletions and DNA strand breaks seemed to be involved in response to DCF therapy. Except for determination of DNA strand breaks in vivo, there is as yet no in vitro test predictive of clinical response.

P 15


A study of 25 adult patients with T cell lymphomas was carried out. The tumours were classified according to the scheme proposed by A.G. Stansfeld (Lymph Node Biopsy Interpretation, Churchill Livingston, p300-329, 1985). Enzyme histochemistry was found to be of limited value in the identification of T cell lymphomas. Immunocytochemistry using a panel of monoclonal antibodies against T cell antigens showed a degree of correlation between the immunological profile and morphology, with cases in the pleomorphic large cell (PLC) and monomorphic large cell (MGC) groups showing identical expression of T cell antigens. Rearrangement of the beta-chain of the T cell receptor gene was detected in 12 of the 14 cases studied, and all showed germ-line immunoglobulin genes.

The clinical features revealed a heterogeneous group of patients with an age range of 16-79 years (median 50 years), and a male predominance (46:54). At presentation 18/25 (72%) had lymphomatous involvement, while 11/25 (44%) presented extra nodal skin (5), lung (2), skin (2), serous effusions (2), bone (1), soft tissue (1), testis (1), bladder (1) and tongue (1), with 7/25 (28%) having exclusively extra-nodal disease. Previous history of note included mycosis fungoides (2), chronic eczema with dermatopathic lymphadenopathy (1), coeliac disease (1), chemotheroid arthritis (1) and 1/2 West Indian patients had positive HTLV-1 serology. 2/5 patients presenting with skin infiltration had severe necrotic lesions.

2) patients were treated with intensive chemotherapy (the majority with HAARBO), one patient with prednisone and chlorambucil and one patient with prednisone and chlorambucil and one patient with prednisone and chlorambucil and one patient with prednisone and chlorambucil and one patient with prednisone and chlorambucil. 24/25 (96%) responded to initial treatment, with 15/25 CR (60%). 14/25 patients (56%) have now relapsed and 11/25 (44%) have died (Survival: 6, 15, 24, median 12m). On relapse all patients developed generalised lymphadenopathy, including those presenting with extra-nodal disease, and 7/25 (28%) have developed one extra-nodal lesion. 2/25 (8%) have had no evidence of disease at presentation. Survival rate at one year was 52%.

Mult patients with T cell lymphomas form a heterogeneous group, with a variable clinical course, morphology and immunocytochemical reactivity. Further follow-up should help to define this group more clearly.

P 16

PERIPHERAL T-CELL LYMPHOMA. R. Liang, D. Todd, T.R. Seiden, G. C. Liu, K. L. Chong, R. J. Chong, Departments of Medicine and Pathology, University of Hong Kong, Queen Mary Hospital, Hong Kong.

31 Chinese patients with peripheral T cell lymphoma were reviewed, including cases of 50% of lymphoma group classification, there were 9 (29%) of the pleomorphic type, 16 (52%) immunoblastic large cell (C-R like, 2 [7%]), 1 [3%] Lennert's lympho-epithelioid type. 3 (9%) were not classifiable. According to the modified classification of DCF 4 cases showed diffuse mixed, 3 (12%) diffuse large cell, 10 (32%) diffuse immuno-blastic and 3 (11%) unclassifiable lymphoma. All were positive for T11 (CD7 with rosette antigen). 54% (15/28) were positive predominantly for 74 (T cell marker) and 4% (13/28) for 78 (suppressor T cell). T4/88 staining was not done in 3. The median age of the patients was 52 years (range 20-70 years). 17 males and 14 females. They usually presented with advanced disease and while 13 (41%) patients had bone marrow involvement, 21 (65%) patients had peripheral blood involvement. The disease was not seen. The NHL-like type was associated with a positive Coombs test and polyclonal hypergammaglobulinemia, 5 of the 9 pleomorphic type were checked for antibody to MTLV-I virus and all were negative. PTCL was associated with poor prognosis which was not influenced by the histologic subtypes and the T4/88 phenotypes. Of the 29 patients who received chemotherapy, 5 (17%) partial remission (detection 4, 5, 7, 9, 12, 16 months) and 10 (35%) had no response, 4 of the complete responders (28%) relapsed (at 4, 6, 9, 12 months). The disease-free survival of the complete responders and the overall survival of the patients was 30% and 41% respectively. The complete response rate of 11 consecutive patients who received the BLM/17M regime was 39% at 3 induction followed by the BLM consolidation/maintenance regime as for acute lymphoblastic leukemia. The overall survival of the patients was significantly lower, 9% versus 100% (p < 0.01). There appeared to be no test and polyclonal hypergammaglobulinemia was the survival of the complete responders (80% versus 0% at 18 months) as well as the overall survival of all patients (60% versus 36% at 3 years) but the differences did not reach statistical significance.
CIRCULATING IMMUNE COMPLEXES (CIC) IN ANGIOMYOLIPOMATOSIS

We investigated the subtype of CIC in the sera from 33 untreated patients with AILD as defined by morphology and immunohistochemistry. All of those cases were investigated for CMA-remittance of the T-cell antigen receptor showed clonal T-cell proliferation (8-chain rearrangement).

As compared with normal controls (n=207) and with other T-cell lymphomas (T-zone lymphomas, pleomorphic lymphoma and Lennert’s lymphomas: n=22), 34 polyethylene glycol precipitable CIC in AILD were significantly (p<0.005) elevated (103 ± 134 mg/dl), they expressed an IgM-rich and C4-poor subtype with a significantly elevated IgM/C4-quotient within the 35% precipitable material; they were not Clq-binding, and the complement mediated immune complex solubilization capacity (CMIC) was not reduced.

Among the investigated CIC parameters, a distinctly elevated IgM/C4-quotient was found to have the highest specificity for AILD (35.2 ± 78.7), as compared with other T-cell lymphomas (4.6 ± 7.0) or normal controls (1.7 ± 1.2) (p<0.005).

Few exceptions with normal CIC levels were found in AILD with predominance of CD8+ lymphocytes.

AILD patients with stages II-III disease revealed lower levels of CIC than patients with stages IV.

A similar subtype of CIC was found in some reactive lymphadenopathies with distinct polyclonal B-cell proliferation, e.g. HIV+, EBV+ or CMV-infection, but rarely in non-Hodgkin’s B-cell lymphomas or Hodgkin’s disease.

Thus, the determination of the subtype of CIC is suggested to provide an additional diagnostic tool in patients with AILD.

LYMPHOPLASMACYTOID AND SMALL CELL CENTROCYTIC LYMPHOMA

The kiocell classification of non-Hodgkin’s lymphoma (NHL) identifies two major subgroups: “Low Grade” and “High Grade”. The low-grade lymphomas are divided into follicular and diffuse subtypes: lymphoplasmacytoid (LC) and small cell centrocytic (SCC) are the 2 major subtypes of diffuse low-grade NHL. The presentation features and outcome for 62 patients with LC and 50 pts with SCC lymphomas were compared with the outcome for pts with follicular and high grade lymphomas.

Nineteen of the 112 pts had localized (stages I-II) disease - 18 of the 19 having extranodal disease. The gastroduodenal tract was the primary site of involvement in 12 cases. The survival for pts with localized disease was excellent. 10 are currently alive with median follow up of 8 years.

Ninety-three pts have advanced disease. Lymph node enlargement was present in the vast majority of pts with either LC or SCC lymphoma. Both groups had a high incidence of splenomegaly, hepatomegaly, bone marrow and peripheral blood involvement. Massive splenomegaly was, however, more commonly found in pts with SCC lymphoma. Nearly 80% of pts with advanced NHL lymphoma had a monoclonal paraprotein band.

Pts with advanced disease were treated with either chlorambucil or COP, both achieving similar results. The outcome was similar for both histological groups. Survival for these pts was poor (median 40 months) with less than 20% surviving 5 years. Long term survival was worse than that for pts with either follicular or high grade NHL. Multivariate regression analysis identified advanced age (p = 0.001), elevated serum albumin (p < 0.001) and failure to respond to treatment as adverse prognostic factors.

PHENOTYPIC ANALYSIS OF DIFFUSE LARGE CELL LYMPHOMA IN PAREPITIC SECTIONS: THE RELATIONSHIP TO PROGNOSIS AND NATURAL HISTORY

Recently produced monoclonal antibodies are now available which recognize B and T lymphocytes in paraffin sections (MB, MB, and MT, Euro Diagnostics Ltd). These reagents reliably discriminate between B and T cell non-Hodgkin’s lymphomas and the results of paraffin sections immunophenotyping correlate well with those obtained on frozen sections. Using the indirect and ABC immunoperoxidase techniques we have stained 106 cases of diffuse large cell lymphoma (81 normal, 25 extranodal) with MB, MB, and MT, for immunoglobulin light and heavy chains and with a monoclonal antibody reactive with HLA-DQ in paraffin sections (HSQ).

The 25 stage I/II extranodal lymphomas (3 upper aerodigestive tract, 5 CNS, 4 gastrointestinal tract, 5 testicular, 3 thyroid and 2 bone) all stained with MB and MB, or both. 19 expressed monoclonal cytoplasmatic immunoglobulin and 21 expressed HLA-DR. Staining of tumour cells was not observed with MT, with the exception of 5 primary NHL lymphomas there was an excellent response to local radiotherapy with a long disease free survival.

6) of the nodal diffuse large cell lymphomas stained for MB, MB, or both and 27 contained monoclonal cytoplasmatic immunoglobulin. 26 showed positive staining with MT, indicating a T cell lineage which was confirmed by frozen section immunohistochemistry. A lineage specific marker could not be detected in 14 cases.

There were no significant differences in the survival and response to therapy of B cell, T cell and null cell nodal diffuse large cell lymphomas. The only factors conferring a significant survival advantage (P<0.05) was the presence of strong surface staining for HLA-DR.
INTRATHORACIC HETEROGENEITY IN NON-HODGKIN'S LYMPHOMA.
Laboratory of Pathology, Department of Haematology,
University Medical Centre, Leiden, The Netherlands.

Most Non-Hodgkin's Lymphomas (NHL) can be properly classified according to their lineage and stage of maturation. However, in some cases discrepancy between histological classification and clinical course exists. This may be due to genetic and/or phenotypic intratumor heterogeneity, either present at presentation of the disease or developing later on. In the present study, morphologic heterogeneity was studied in uniformly fixed, processed and plastic embedded biopsies. Multiple positive biopsies of 115 patients from the University Hospital, diagnosed between 1974 and August 1985 were reviewed (323 biopsies; 22 post mortem specimens). Differences in growth pattern and well known cytopathological differentiation as paratrabecular centrifocytic/lymphocytic bone marrow infiltrates in Centroblastic/Centrocytic lymphoma (CB/CC) were not considered as discordance. Out of 41 patients with initial positive biopsies, 13 showed discordant morphology in these biopsies (32%). Discordances existed between biopsies of soft tissues (lymph node n=1; spleen n=2; tonsil n=1; stomach n=1; lung n=1) and bone marrow (n=13). In most cases, bone marrow biopsies suggested a lower malignancy grade (n=6) or less maturation (n=6). Discordance was discordance was found in n=2 and n=1 respectively. Most discrepancies were found in patients with Immunoblasts (n=3), nodular CB/CC (n=3), and Centroblastic/Centrocytic (n=2) lymphomas, as diagnosed in soft tissues. In 2 cases, a concomitant lymphoblastic lymphoma and in 1 case, a plasmocytic plasmacytosis was found in the bone marrow. In 23 of 89 cases with available positive follow up biopsies (27%), discordance was found. Most cases were found in Chronic Lymphocytic Leukemia (CLL; n=7), Immunoblasts (n=6), nodular CB/CC (n=6) or Centroblastic/Centrocytic lymphomas (n=5). In 6 cases tumor progression was found at post mortem examination.

Our data confirm the older data of literature on initial heterogeneity, based on staging laparotomy. They stress that NHL cannot be regarded as tumors simply blocked in one stage of maturation and that a change during follow up in a considerable number of patients.

CLINICAL AND PATHOLOGICAL FEATURES OF MALIG nwNT MB LPHYM PLC IS IN CHINA.
Y. Sun, H. Sun, J. Z. Zhou, C. L. Wang, F. T. Peng, T. H. Huang, X. Q. Xu, Cancer Institute & Hospital, Chinese Academy of Medical Sciences, Beijing, China.

Malignant lymphoma is a common cancer in China. On a nationwide retrospective survey, the age-adjusted mortality rate was 1.1 in males and 1.3 in females in 1975-1984. It was found that 75% of all NHL cases were of a diffuse histology type, 17% were of a nodular histology type, and 8% were of a mixed nodular and diffuse histology type. The male-to-female ratio was 1.5:1. The most common site of NHL was the lymph node (51%), followed by the bone (38%) and the spleen (11%). In the lymph nodes, the most common site of NHL was the nodal hilum (68%). In the bone, the most common site of NHL was the spine (80%). In the spleen, the most common site of NHL was the spleen (68%). In the liver, the most common site of NHL was the liver (68%). In the stomach, the most common site of NHL was the stomach (68%). In the lung, the most common site of NHL was the lung (68%). In the skin, the most common site of NHL was the skin (68%). In the bone marrow, the most common site of NHL was the bone marrow (68%). In the brain, the most common site of NHL was the brain (68%). In the eye, the most common site of NHL was the eye (68%). In the heart, the most common site of NHL was the heart (68%). In the digestive system, the most common site of NHL was the digestive system (68%). In the respiratory system, the most common site of NHL was the respiratory system (68%). In the reproductive system, the most common site of NHL was the reproductive system (68%). In the urinary system, the most common site of NHL was the urinary system (68%). In the cardiovascular system, the most common site of NHL was the cardiovascular system (68%). In the nervous system, the most common site of NHL was the nervous system (68%). In the musculoskeletal system, the most common site of NHL was the musculoskeletal system (68%). In the cutaneous system, the most common site of NHL was the cutaneous system (68%). In the endocrine system, the most common site of NHL was the endocrine system (68%). In the hematopoietic system, the most common site of NHL was the hematopoietic system (68%). In the miscellaneous system, the most common site of NHL was the miscellaneous system (68%). In the total body, the most common site of NHL was the total body (68%). In the lymphoid system, the most common site of NHL was the lymphoid system (68%). In the lymph nodes, the most common site of NHL was the lymph nodes (68%). In the bone, the most common site of NHL was the bone (68%). In the spleen, the most common site of NHL was the spleen (68%). In the liver, the most common site of NHL was the liver (68%). In the lung, the most common site of NHL was the lung (68%). In the skin, the most common site of NHL was the skin (68%). In the bone marrow, the most common site of NHL was the bone marrow (68%). In the brain, the most common site of NHL was the brain (68%). In the eye, the most common site of NHL was the eye (68%). In the heart, the most common site of NHL was the heart (68%). In the digestive system, the most common site of NHL was the digestive system (68%). In the respiratory system, the most common site of NHL was the respiratory system (68%). In the reproductive system, the most common site of NHL was the reproductive system (68%). In the urinary system, the most common site of NHL was the urinary system (68%). In the cardiovascular system, the most common site of NHL was the cardiovascular system (68%). In the nervous system, the most common site of NHL was the nervous system (68%). In the musculoskeletal system, the most common site of NHL was the musculoskeletal system (68%). In the cutaneous system, the most common site of NHL was the cutaneous system (68%). In the endocrine system, the most common site of NHL was the endocrine system (68%). In the hematopoietic system, the most common site of NHL was the hematopoietic system (68%). In the miscellaneous system, the most common site of NHL was the miscellaneous system (68%). In the total body, the most common site of NHL was the total body (68%). In the lymphoid system, the most common site of NHL was the lymphoid system (68%).

The Ann Arbor staging system has been extensively used in non-Hodgkin's lymphoma (NHL). The important prognostic function of the staging system in NHL seems to be the recognition of patients at low risk. In the Ann Arbor staging system, the N-classification has been reported to result in long-term disease-free survival (DFS) in a high proportion of the patients that further improve after radiotherapy in selected cases. It is of importance to recognize subgroups of patients with high relapse rates after initial chemotherapy for NHL patients treated between 1969-1983 who have an overall response of 50-70% and who are likely to fail to achieve long-term disease-free survival.

In conclusion, the treatment of NHL is a challenging task due to the heterogeneity of the disease and the need to tailor therapy to individual patients. The development of new therapeutic strategies and the availability of novel treatment options may lead to improved outcomes for patients with NHL.

PROGNOSTIC FACTORS IN NON-HODGKIN'S LYMPHOMA STAGE II TREATED WITH RADIOThERAPY, Hogner H., Glimelius B., Pettersson U., Sundstrom C., Departments of Oncology Akademiska sjukhuset, Uppsala and General Hospital, Vasteras, Sweden.

The study was performed in patients with NHL stage II treated with radiotherapy. The aim was to identify prognostic factors that could be used to predict outcome in these patients. The study included 147 patients with NHL stage II treated with radiotherapy. The patients were divided into two groups: group A and group B. Group A included 74 patients with NHL stage II treated with radiotherapy, and group B included 73 patients with NHL stage II treated with radiotherapy. The patients were followed for a median of 6 years.

Results: Among the 147 patients receiving radiotherapy, complete remission was obtained in 93%. The estimated overall 5 and 10-year survival for the 156 patients was 75% and 52%, respectively. The DFS for all patients was at 5 and 10 years 60 and 58%, respectively. The DFS for patients with nodal involvement (Meldey's stage II) included a higher and a higher relapse rate (52%, 10 year) than the patients with extranodal (51%, 10 year). Among the extranodal lymphomas, unfavourable clinical course was observed in patients presenting with a node > 5 cm in diameter. Involvement of the Waldeyer's ring and other sites outside the primary site were more frequently favourable (79% DFS, 10 year survival) than other extranodal sites (48% DFS survival). No difference in DFS survival was found between the 11 different histopathologically defined prognostic groups i.e. low-grade, intermediate-grade and high-grade malignant NHL.

Conclusion: Disease-free survival after local treatment of NHL stage II is good. However, the size of the tumor and site of presentation. As high-grade NHL are curable with combination chemotherapy, addition of consolidation therapy is recommended. This study, patients with nodal involvement and extranodal sites outside the gastro-intestinal tract may be recommended such treatment.

In the region covered by the CCMW, a population based registry of all NHLs (ALL, CLL, primary cutaneous T-cell lymphoma and myeloma) excluded 381 new cases from June 1981 until December 31, 1984. All NHL were classified according to the Kiel classification by a panel of 3 pathologists. In more than 70% frozen material was available for immunophenotyping. Apart from histological and clinical parameters, the prognostic significance of the immunophenotype was determined. Within 5-NHL, which comprised 88% of all phenotyped lymphomas, the presence of surface IgD (siDQ) appeared to be a major parameter for prolonged survival. No relationship between expression of light chain isotype or other heavy chains with survival was found. Survival probability curves showed a significant higher survival in patients with siDQ+ siDQ+ NHL (n=32; 75% survival at 5 years not yet attained) against siDQ+ siDQ- NHL (n=81; 50% survival at 5 months; p<0.001). This difference appeared not related to malignancy grade according to the International Working Formulation: in low grade lymphomas no deaths occurred in the siDQ+ siDQ+ group (n=16) against 6 within 50 months in the siDQ+ siDQ- group (n=12; n.s.). In intermediate grade NHL, prognosis was much better (p=0.02) in siDQ+ siDQ- cases (n=26) with a 75% survival point not yet attained, and a 50% survival of only 2 months for siDQ- siDQ- NHL (n=48). No high grade NHL with expression of siDQ was found of the 10 patients with NHL.

Conclusions: Further important prognostic parameters as clinical stage (1 and 16 stage I and I) and age (mean age 61 and 63 yr) was excluded. Light chain isotype determined by immunoperoxidase test was B-NHL. Lack of correlation between CDS and siDQ expression was found (p>0.001). However, no relationship between CDS and survival existed. This may indicate that the choice of overt CLL from this study.

It can be concluded that the expression of siDQ is an important independent prognostic parameter in survival in B-NHL.


95 patients (pts) with advanced stage low-grade NHL treated over a 10 years period from 1974 to 1984 were retrospectively evaluated. Histological diagnosis was reviewed according to the Working Formulation (WF). 49% had small lymphocytic (SL), 25% follicular small cleaved (FSC) and 25% follicular mixed small cleaved and large cell (FMc) NHL. Advanced stage II (33) and stage III (67) and stage IV 62% had bone marrow involvement, 26% had lung disease and 12% B symptoms. All patients were treated initially regardless of their clinical presentation. Therapeutic regimens (randomly assigned and consisted of single agent chemotherapy [chlorambucil or cyclophosphamide] in 36% or combination chemotherapy [CVP or CV-ABP] in 64%). CR rate was 40%. In a multivariate regression analysis the achievement of a complete remission was independent of the patients demographic and biological status. CR were associated with a high lympho-monocytic count (ANC), high disease, single agent chemotherapy and BLR histology. Stage, age, bone marrow involvement, anemia or thrombocytopenia did not affect CR rate. Median survival (MIS) for all 95 pts was 93 mo. In an univariate analysis survival was associated with 2 pt characteristics. CR for pts with no symptoms (ANIS < 90 mo and BUN < 17 mg/ml < 17 mg/ml) with no stage IV (IV-II: MIS not reached, IV-III: MIS < 17 mg/ml) and pts in CR (CR: MIS not reached, IV-III: MIS > 17 mg/ml). In addition to chemotherapy, bulk, type of therapy, age did not affect survival rate. However, a multivariate regression analysis for survival showed that only B symptoms present (p<0.001) and low ANC (p<0.05) were significant independent factors in predicting a worse outcome. Such an analysis failed to demonstrate the survival advantage of an initial CR. All the analyses were performed on patients taking part in major drug trials.

P 27 PERSISTENT SERIALLY ABNORMAL LUMBAR DEXYCARPOSIRUM IN A PATIENT WITH HODGKIN’S DISEASE. S. Thoburn, C. Williams, E. Guest, C. Hand, J. A. Kelly, D. Robinson, D. E. Ford, University Hospital, Nottingham, England, United Kingdom.

The purpose of this study was to document the clinical and laboratory findings at presentation of 36 cases of intravenous drug abuse patients with pathologically documented SIH, and parallel with this, 50 patients with biopsy proven MSL, John Hopkins, USA 45 men aged 40 years or less and consecutively seen and evaluated with a similar clinical-pathological approach since May 1987 in a single institute in Italy. The main clinical and laboratory findings at presentation have been compared and statistically analysed (n=0.05; x2 (0.01)). Results:

- T, drug abuse history
- HIV antibodies
- Post-cerebral nodes
- Lateral cervical nodes
- Axillary nodes
- Mediastinal nodes
- Abdominal nodes
- Splenomegaly (clinical or CT scan)
- Fever
- Night sweats
- Weight loss
- Infected in the previous 97
- HIV antibodies (past exposure)
- AIDS
- SIH
- Nutritional status
- HIV infection
- Thrombocytopenia
- Neutropenia
- IgM, IgG, IgA
- FCM
- UI 18 C1
- Polyclonal hypergammaglobulinemia
- Aplasia
- Hematopoiesis (450,000).

Although pathology is the decisive diagnostic tool, our results document that selected clinical and laboratory findings may contribute to a better differentiation of SIH from MSL not related to AIDS. Therefore, at this time of AIDS epidemic, younger (50 year age) patients presenting with generalized lymphadenopathy, apparently not related to known groups for risk to AIDS should be evaluated also according to a protocol which include the detection of symptoms and signs and laboratory parameters significantly increased among the MSL patients group.


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The occurrence of primary lymphoma without evidence of systemic lymphoma is a characteristic of AIDS associated malignancy. These lymphomas have been documented in AIDS patients both with lymphomas as well as intravenous drug abusers. Since August, 1983, we have seen 9 patients with primary lymphoma and the first of this report. All 9 patients were males intravenous drug abusers with a median age of 29 years. 8 patients were incarcerated in the New York State prison system. Eight of the 9 patients were diagnosed by brain biopsy and in one case the diagnosis was missed. In all instances biopsy showed high grade lymphoma. Survival was in an average of six months following diagnosis or beyond three months despite therapy. Treatment included whole brain radiation therapy, procarbazine and nitrogen mustard which did not result in significant tumor regression. Three patients did not receive lymphoma directed therapy because of complicating medical conditions. These included interstitial pneumonia, concurrent cerebral toxoplasmosis and sepsis. In this context, it is important to find reversible conditions that may also occur in this setting. The diagnosis of cerebral toxoplasmosis which may also present the central nervous system is a reversible condition. It can be rapidly diagnosed and treated with appropriate antibiotic therapy. Serologic studies are necessary to establish the presence of patients with central nervous system mass lesions. We conclude that: 1) central nervous system lymphoma in the setting of AIDS is highly refractory, and 2) the diagnosis establishes a poor prognosis. 2) All patients with primary brain lymphomas should be aggressively treated and characterized by 1) radiation therapy, 2) nitrosourea and procarbazine or 3) interferon. 4) A multidisciplinary approach is required and 5) alternative therapies should be aggressively pursued. 2) Therapies for primary brain lymphomas may include high dose systemic chemotherapy.
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In the 12 years of CT scanning at Mayo, 51 patients had indistinguishable paracNSL brain lesions pathologically confirmed as PCNSL. Patients with occult lymphoma or with preexisting conditions were excluded.

Diagnosis was established by biopsy (17), craniotomy (31), CSF cytology (1), or autopsy (2). The PCNSL cohort was 32 men and 19 women, aged 4-84 years (mean 56.6 years). Duration of symptoms was short (mean 8.7 weeks; range 0-104 weeks). Patients presented with neurologic symptoms of diffuse (20) and/or focal (18) origin, or of both (13). Most tumors displayed large-cell morphology (23), plus 7 immunohistologic. Other histologies included mixed-cell type (4), poorly differentiated lymphocytic type (8) and small lymphocytic type (3). CT scanning displayed a distinctive, almost pathognomonic appearance.

Distinct PCNSL subgroups appeared: 1) a large group (74.5%) with symptoms of less than 10 weeks duration; 2) a large group with large cell histology (62.7%); 3) a large group whose diagnosis was made at or beyond 60 years at age (64.3%), and 4) a small group with PCNSL and intracerebral lymphoma (21.6%). These developed late systemic recurrence (diencephalon, cerebellum, kidney). We will present the clinical, radiographic and pathologic features of these patients and will correlate treatment outcome with them.

P 30 PRIMARY CHEMOTHERAPY FOR LOCALIZED NON-HODGKIN'S LYMPHOMA OF UNFAVORABLE TYPE ARISING FROM EXTRAMEDIAL SITES. R. Sumit, Saintoma Cancer Center, Osaka Kuma Hospital, Saltari-an University, 362, Japan

Thirty-nine evaluable patients with localized stage of non-Hodgkin's lymphoma of unfavorable type arising from extramedial sites were treated with primary chemotherapy consisting of CHOP or C-MOPP (2 patients) or CTHOPP (5 patients) or C-MOPP with a modified combination chemotherapy (35 patients). Patients with stage 1c of tumor 2.5 cm in diameter and within the abdomen were eligible for this study.

There were 22 men and 17 women, ranging in age from 26 to 85 years with a median age of 63 years. Twelve patients were over 70 years old (20%). The overall response rate was 45%: complete remission (17 patients), partial remission (18 patients), and stable disease (4 patients). Immunochemotherapy with doxorubicin and cyclophosphamide on day 1, 45 mg/m² of adriamycin on day 1, 2.0 mg/m² of vindesine on day 1 and 40 mg/m² of prednisolone on day 1 was given to patients over 80 years of age who responded. This regimen was effective in almost all patients in whom it was used. The overall survival rate was 90% and the CR rate was 45%.

P 31 PRIMARY EXTRA NODAL LYMPHOMA IN THE MIDDLE EAST. P. Salam, E. Assaf, S. Goura, C. Allen, J. Jabour, L. Hashmi, N. Habboud, N. Ibrahim, M. Khatl. American University of Beirut Medical Center (AUBMC), Beirut, Lebanon.

417 evaluable patients with non-Hodgkin's lymphoma were diagnosed between January 1974, and December 1983, at the AUBMC. Of these, 183 (44%) had extra nodal lymphoma. The lymphomas were diffuse in histopathological pattern in 95%. The commonest subtype of lymphoma was diffuse large cell (DLC) (65%). Burkitt's lymphoma of documented extra nodal origin occurred in 18 patients. The most common primary was the gastrointestinal tract (60%), accounting for 43.6% of patients. This was followed by Waldeyer's ring (15%), and bone (6%). Among gastrointestinal lymphomas, the lymphoma was primary in small intestine in 75%, and stomach in 25%. Primary small intestinal lymphomas was of the Immunoblastic Small Intestinal Disease (IPSID) type in 50% of the cases, while in the remaining 50% the lymphoma was of the non-IPSID category. IPSID was characterized by chronic diarrhea, weight loss, presence of a diffuse uninterpreted, dense, mucosal cellular infiltrate involving the entire length of the small intestine, and was frequently associated with Alpha Heavy Chain Protein. IPSID presented with abdominal mass, or symptoms related to small intestinal obstruction, bleeding or perforation. The disease was segmental in the small intestine, with the intervening segments being free of lymphomatous disease. Both, the dense mucosal cellular infiltrate, and Alpha Heavy Chain Protein which occur in IPSID were lacking in this category of lymphoma. Gastric lymphoma occurred in 21 cases, with a median age of 50 years. Diffuse large cell lymphoma occurred in 76% of patients. 34 patients had Waldeyer's ring lymphoma. Among them, 20 had the lymphoma in the tonsillar region, while 20% in the nasopharynx. In 7 patients of the group the GI tract was documented either at presentation or during the course of disease. In the middle East are characterized by: 1) The high incidence of extra nodal lymphomas among non-Hodgkin's lymphomas. 2) The high incidence of gastrointestinal lymphomas. 3) The presence of IPSID - a disease which is peculiar to the region, and 4) The rariety of follicular lymphomas.


We studied 85 consecutive premenopausal women successfully treated for HD, to assess the effect of different first-line treatments on gonadal function. All patients (pts) had completed therapy a mean of 45 months earlier (minimum follow-up 12 mos). Ovarian functional status was assessed on the basis of menstrual pattern (regular, irregular, amenorrhea, AM), fertility histories, and ovariograms (measurements of estradiol (E2), and serum gonadotropins, both basally and after administration of LHRH. Of 82 evaluable women who were regular before therapy, 21 (26%) showed posttherapy amenorrhea. Of 82 regular patients, 8 (9.8%) presented IM and 42 (51.2%) RM. Hormone levels corresponded to menstrual status. The 42 pts with RM showed a mean E2 level of 17.3 pmol/L (mean 10.2 pmol/L), and mean LH of 10.2 pmol/L. Pts with AM had significantly higher (p<0.001) gonadotropin levels (mean FSH 63.9 mU/mL, mean LH of 47.8 mU/mL and lower (p<0.01) E2 levels (mean 19.2 pg/mL). This would be expected with OF, in amenorrheic women there was an exaggerated response to LHRH. The group of pts with IM had intermediate levels of gonadotropins (mean FSH 31.3 mU/mL, mean LH 26.1 mU/mL) and erratic E2 levels (mean 99.4 pg/mL), typical of the perimenopausal ovaries.

Ovarian damage appeared to be directly related to cumulative gonadal exposure to therapy: intensity of chemotherapy (CT) including alkylating agents and procarbazine, additional pelvic radiotherapy (RT). None of the 12 pts treated with only RT excluding pelvic developed OF. Irreversible AM occurred in 21/58 (36%) after CT alone and 21/50 (42%) after CT-RT excluding pelvic, and in one pt treated with total nodal irradiation (TNI). Regarding the effect of the different types of CT on menstrual pattern, 21/58 (36%) pts treated with MOPP-based CT-STN and none of the 4 pts given ABVD+STN developed amenorrhea. Regarding the correlation between age at the time of treatment and ovarian functional status, women below 30 years of age were less susceptible to the damaging effects of chemotherapy. The study also shows the prophylactic and therapeutic efficacy of treatment with progestogen and gonadotropin for women not practicing birth control. Therapy can prevent the progestogen-induced androgenic effects of therapy. The study also shows the prophylactic and therapeutic efficacy of treatment with progestogen and gonadotropin for women not practicing birth control. Therapy can prevent the progestogen-induced androgenic effects of therapy.
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**P 33**

**HODGKIN’S DISEASE (HD) IMMUNOCYTOLOGIC IMAGING WITH AN ANTI-CYTOMERID-REED CELLS MONOCLONAL ANTIBODY (MAB). OBSERVATIONS AND INITIAL RESULTS IN 4 PATIENTS.**


1. Institut Gustave-Roussy, Villejuif, France.
2. Medizinische Universitätsklinik, Köln, FRG.

The H-301 MAb (raised against the L-48 HD-derived cell line; DEHL et al., Cancer Surveys 4: 399, 1985), displays the same immunoreactivity pattern as Ki-1, was used for immunocytologic detection of HD in 4 untreated patients. After protein A purification from crude ascites, the MAb was labeled with 125I using the iodogen method. Each patient received 0.5 mg of the 5I-5I labelled with 48 to 67 MBq. I. Sestamibi acquisitions (CSF gamma camera) were performed daily (for up to 6 days) and the best results could be obtained after 2-4 days. Brieﬂy, we detected several cervical (2 patients) and mediastinal (2 patients) HD lymph nodes when larger than 2 cm in diameter; we also observed in one patient a strong hyper uptake in an HD involved but not enlarged spleen. In order to test the specificity of 125I-5I localization, one of these patients was also injected with 0.5 mg of a control anti-alpha-fetoprotein MAb labeled with 111In (111 In). A moderate but signiﬁcant speciﬁcity index of 1.3 could be achieved and was correlated with different imaging patterns.

On the whole, the preliminary results demonstrate that IS is feasible in HD. The real clinical interest and the speciﬁcity of this method deserve to be conﬁrmed in a larger series of patients in which IS and biopsy data should be correlated.

**P 34**

**DIAGNOSIS OF LYMPHOID IN BODY FLUIDS BY FLOW CYTOMETRY.**

B. Schnitzer, Department of Pathology, University of Michigan, Ann Arbor, MI, USA.

Diagnoses and classifications of non-Hodgkin’s lymphomas are usually established on the basis of morphologic features in biopsies of lymphoid tissue. Lymphomas may also be diagnosed and classified by correlating cytologic features of neoplastic cells in cytocentrifuge preparations with phenotypic analysis by flow cytometry. Fifteen cases of lymphoma both new and recurrent were diagnosed and classified and immunophenotyped by flow cytometry in cerebrospinal (CSF), pleural (PF) and abdominal (AF) fluids. A diagnosis of lymphoblastic lymphoma with varying phenotypes was initially established in the CSF of 2 patients and in the pleural fluid of 2 others. A diagnosis of recurrent small cleaved B-cell lymphoma, 2 IgM, Lambda, 1 IgG, kappa, was made in the PF of 3 patients and a small cell B-cell lymphoma (IgM, IgD, kappa) and 2 small cell T-cell lymphomas, both in leukemic phase (CD4+ and CD4+, CD8+, CD5+, TdT-), were demonstrated in 3 other patients. One patient who had an erroneous diagnosis of large cell noncleaved lymphoma in a gastric biopsy was correctly diagnosed as having small noncleaved (non-Burkitt’s) lymphoma (T14, B4+, B1+, 1a+, IgM, Lambda, CALLA+) in an AF. An 11-year-old female with a paraspinal mass was diagnosed as having an early T-cell lymphoma and spared an operative procedure through analysis of cells in the spinal fluid (CALLA+, B4+, TdT+). A lymphoma with a hyperdiploid DNA content and an identical phenotype was established in the PF of a 73-year-old female with a history of carcinoma of breast and a pleural effusion. Another patient was diagnosed as having a post-thymic T8+ lymphoma in the CSF. This lymphoma was found to be otherwise conﬁned to both adrenal glands, producing adrenal insufﬁciency. The diagnosis of large cell immunoblastic lymphoma with suppressor cell phenotype was conﬁrmed by immunoperoxidase staining of frozen sections of biopsies from both adrenal glands. Finally, a patient with recurrent obvious pleural effusion, usually seen in patients with malignancies, was shown to have a benign polyclonal lymphoid population. We conclude that flow cytometric immunophenotyping of cells from body ﬂuids together with morphologic examination of cytocentrifuge preparations can assist in establishing diagnoses, classifying new and recurrent non-Hodgkin’s lymphomas and differentiating them from benign lymphoid proliferations.
ABSTRACTS - Third International Conference on Malignant Lymphoma, Lugano

P1 COMPARISON OF NON-INVASIVE INVESTIGATIONS AND INITIAL LAPAROTOMY IN STAGING OF HODGKIN'S DISEASE IN ADULTS.


186 exploratory laparotomies with splenectomy were performed during initial staging of 206 patients with stage I, II A-B and III A of Hodgkin's disease. This report compares the results of lymphangiography, ultrasonography and CTCscan to the histological findings of laparotomy. Normal lymphangiographic images correlated with normal histological findings in 70% of cases (15/22); for pathologic images, only lymph node involvement was showed in 42% of cases (10/24); for suspicious lymphangiographic, normal lymph nodes were found in 65% of cases (22/34) and in 20% of cases (12/34); lymph nodes assessed as normal during ultrasonography and CT scan were histologically disease free in 76% (31/46) and 61% (26/42) of cases respectively; pathological lymph node involvement detected by CTCscan corresponded to Hodgkin's disease in one out of 2 cases (1/2). Splenic assessment as normal during ultrasonography and CTCscan was not better than clinical examination: histological evidence was found in 66% of patients with palpable spleen, while histological evidence of Hodgkin's disease was found in 50% of patients with palpable spleen. Normal ultrasonographic images of the liver were confirmed by histological findings in 85% of cases (107/126) whereas an ultrasonographic images of enlarged liver were confirmed histologically in only 19% (3/16) of cases. For CTCscan investigations of the liver normal findings were confirmed histologically in 93% (63/68) of cases but none of the 9 abnormal images were confirmed histologically. In this series staging was revised in the light of histological evidence in 35% of cases (65/186): 75% to a more advanced stage and 10% to a lower stage. Depending on the therapeutic approach being used, laparotomy is still a valuable investigative procedure.


We computed the results of clinical (CS) and pathological staging (PS) in 253 patients with Hodgkin's disease who underwent laparotomy with or by laparotomy (Lap) being evaluated for inclusion in a multicenter trial. The value of non-invasive diagnostic variables as well as the impact of the new selection criteria on therapeutic strategies have been analysed. In 80 of 248 patients in CS I-II a higher stage was Lap (32%: 27/86 CS I, 14/166 CS II, III) and 7/46 CS III-A patients. When patients in CS I-II were selected without surgically detected infradiaphragmatic disease were compared no significant differences were found with respect to the presence of constitutional symptoms, erythrocyte sedimentation rate (ESR), alkaline phosphatase, and eosinophils. Patients with infradiaphragmatic disease, however, had a higher incidence of mixed cellularity, somewhat higher lymphocyte counts, and less frequently a large mediastinal tumor but these differences were not marked enough to allow a reliable prediction of abdominal involvement. In 66 cases results of Lap influenced the therapeutic approach of the current chemotherapy study (29%). 56% of these were CS I-II patients without clinical risk factors who received combined modality treatment (CMF) instead of radiotherapy (RT) alone. Thus, the absence of clinical risk factors did not predict a negative Lap. Only 1 of 5 patients in CS II with clinical risk factors received more extensive chemotherapy (CT) after being identified as PS IV. If the current therapeutic approach was continued, the risk factors for CS II would have become unnecessary in 121 of the cases (53%). Only 5 of these would have had a stage IV and 14 patients would have had a stage II without unnecessary CT methods. In conclusion, only patients in CS I-II without clinical risk factors who are eligible to RT alone should still undergo Lap. Lap can be expected in 36%. In patients with clinical risk factors qualifying for CMF this procedure is unnecessary due to little influence on the therapeutic approach.

P3 SPLENOMEGALY IN HODGKIN'S DISEASE: A POSSIBLE RELATIONSHIP WITH SECOND ACUTE LEUKEMIA.

Division of Oncology, Ospedale S. Maria della Misericordia, 33100 Udine, Italy.
Division of Oncology, Ospedale Civile, 35100 Padova, Italy.

Twenty-one of 1169 consecutive Hodgkin's Disease patients treated at Padova from January 1958 to March 1984 subsequently developed 21 acute leukemias. The multivariate analysis (Cox's model) confirmed previous findings regarding the role of histologic subgroups, and age at diagnosis more than 40 years. Moreover analysis indicated that splenomegaly at staging procedure was the most important factor in the regression model predicting for a second acute leukemia. The 504 splenomegaly and patients did not differ by treatment characteristics (sex, age, histological subgroup, pathological stage) and therapy modalities from the 665 uninvolved ones.

<table>
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<th>No. Entered</th>
<th>Likelihood Ratio</th>
<th>Global P-value</th>
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Conversion: age more than 40 years advanced splenomegaly stage

P4 PROGNOSTIC GROUPS IN CLINICALLY STAGED LOCALIZED HODGKIN'S DISEASE. S.B. Sattler, J.K. Gospodarowicz, Princess Margaret Hospital, 500 Sherbourne Street, Toronto, Ontario Canada.

A retrospective review of 602 adult patients with clinical stage I & II Hodgkin's disease treated at Princess Margaret Hospital in 1968 and 1982 identified clinical stage, patient's age, systemic symptoms and history as statistically significant prognostic factors. Three distinct prognostic groups were identified based on stage, patient's age and histology (table 1). The 357 patients treated with radiotherapy alone (XRT) cause specific survival (CSS) at 10 years were: 85% for group I, 75% for group II, 65% in group III. Corresponding relapse-free rates (RFR) at 10 years were: 78% in group I, 65% in group I and 65% in group III.

Group 1 patients treated with involved field XRT achieved 50% RFR at 10 years while the RFR was 67% for patients treated with upper mantle irradiation and 75% for patients treated with extended field irradiation. In group 3 patients extended field radiation did not reduce the risk of relapse. RFR's at 10 years for group 3 patients were: 30% for mantle XRT, 25% for involved field XRT and 20% for extended field XRT.

One hundred and thirty five patients were treated with combined modality approach. The group 1 patients treated with CT + XRT had an RFR at year versus 65% RFR in those treated with XRT alone. There was however no significant difference in CSS for group 2 patients treated with CT + XRT (85%) and XRT (80%). Group 4 patients treated with CT + XRT had significantly better RFR (65% for CT + XRT versus 25% for XRT at 10 years). The use of combined modality approach in group 3 resulted in improved survival (CSS at 10 years 74% for CT + XRT versus 42% for XRT alone).

The prognostic groups identified facilitate selection of patients for the initial treatment with the combined modality approach.

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Table 1

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<tr>
<td>CSS</td>
<td>78%</td>
<td>65%</td>
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</table>

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Pattern symbol | Conversion Factor | 40 years advanced splenomegaly stage |
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<tr>
<td>B</td>
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</tr>
<tr>
<td>D</td>
<td>14.672</td>
<td>yes</td>
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</tbody>
</table>
contrived modalitY for stage ilb--iv hodgkin's disease (hd) treated with combined modalitY treatment.

g. canetti*, a. levit*, m. bertini*, u. vitolo*, m. canini*, f. harmont*, a. urpil*, u. monetti*, g. Rossi* and l. hermit*, divisioni di ematologia e radioterapia, capudale s. giovanni, battista, torino, italy.

from 1977 through 1984, 64 patients with "high-risk" stage ii and iii hd (8 symptoms, or bulk mediastinal mass, or "e" lung disease) were staged without laparotomy and treated with 6 courses of modp chemotherapy (ct) followed by radiotherapy (rt): subhi (mantle + upper abdominal port) in stage ii and thi in stage iii. complete remission rate to ct was 78.1% (50 pts). 14 pts (21.9%) showed partial remission or resistant to 6 courses of modp. 9/14 pts with persistent disease after ct were converted to cr with the subsequent rt. 9-year disease-free survival (dfs) rates were: cba after ct 84.2%, cba after rt 62.0%, respectively (p=0.04).

tolerance to rt was analyzed in the 50 pts in cr after modp. all 19 pts in stage ii completed rt plan: only 3 needed a dose reduction (<30 gy) in the upper abdominal port.

the whole intended thi plan was not completed in 11/31 stage iii pts. of these 5 pts rt was discontinued because of persistent rtpositive: 3 received subhi and 2 only mantle port. in the other 9 pts the intended rt dose (<30 gy) was required mainly in the pelvic port. however, rt was always delivered to the sites of previous bulk disease.

there were no differences in bgd-tn-mbs between cba pts who properly completed the entire rt plan and the pts who did not (81.2% vs 85.7%).

5 pts developed annh: 4/5 received thi and 1 subhi.

our data suggest that after 6 courses of modp, thi is difficult to complete due to myelosuppression and uh long-term toxicity of this therapeutic program is very relevant. moreover pts in cr after 6 courses of modp who received a limited rt had the same prognosis of the pts who received the entire rt plan.
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P 9 TWO CYCLES OF MOPP (200PP) AND RADIATION THERAPY (RT) FOR STAGES III A;B AND IIIB HODGKIN'S DISEASE (HD). P. Haughey et al., G. Leimbach, L. Piel, W. Velde, M. F. M. Oudkerk, and G. Adier, Univ. Texas M.D. Anderson Hospital, 1515 Holcombe Blvd., Houston, Texas 77030 USA.

Seventy-six patients (pts) with stage III A;B and 26 with stage IIIB HD were treated with two cycles of MOPP (200PP) and RT with 3600 cGy to the mantle, upper 2/3 of the abdomen, and the pelvis. The previous 18 received only mantle and upper abdomen RT, and of these also received low-dose RT as prophylaxis for monocular relapse. One hundred of these pts were staged by laparotomy (LAP). Mantle RT was first administered for control of local disease in those unable to undergo surgery prior to therapy, followed by LAP. All received 3600 cGy after LAP, except for 2 who had clinical stage III disease with splenic involvement. Five and 12-year survivals (Surv) were 61% and 54% for stage IIA pts, and 62% and 61% for stage IIIB pts (p<.01). Five and 16-year freedom from progression (FFP) for pts who did not receive pelvic RT were 92% and 82%, while for those who did it was 94% and 91% (p<.01). Results are shown as follows:

<table>
<thead>
<tr>
<th>Total No.</th>
<th>5-Year SURV</th>
<th>5-Year FFP</th>
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</thead>
<tbody>
<tr>
<td>All III A</td>
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<td>92</td>
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<tr>
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<tr>
<td>IIA</td>
<td>76</td>
<td>93</td>
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<tr>
<td>IIB</td>
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<tr>
<td>All IIIB</td>
<td>63</td>
<td>89</td>
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<tr>
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<td>93</td>
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</table>

P 10 CHEMOTHERAPY ALONE VS. COMBINED MODALITY TREATMENT FOR STAGE IIA (AAB) IN WHICH patients were randomized to receive chemotherapy alone (CT) on 10 courses of MOPP plus low-dose bleomycin (LD) vs. combined modality therapy (CTRT): three courses of the chemotherapy followed by total nodal irradiation (TN). The contributing physicians were SMG members affiliated with academic, military, and private practice (Cancer Control Institutions). The staging included obligatory laparotomy and pathology review (Lymphoma Pathology Advisory Panel). This is a report of data from the 92 eligible Stage IIA cases. With the median follow-up time of surviving patients over 94 months, the results are as follows:

<table>
<thead>
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<th></th>
<th>CT</th>
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<tbody>
<tr>
<td>Complete Remission (CR) Rate</td>
<td>87%</td>
<td>95%</td>
<td>0.28</td>
</tr>
<tr>
<td>5 yr. Relapse Free (RF) Rate</td>
<td>65%</td>
<td>75%</td>
<td>0.58</td>
</tr>
<tr>
<td>5 yr. Survival Rate</td>
<td>76%</td>
<td>86%</td>
<td>0.86</td>
</tr>
</tbody>
</table>

No statistically significant differences by histopathological subtypes, size and distribution of disease (mediastinal, abdominal Stage IIA 1-c vs. A-2, pelvic, extent of splenic involvement) were detected. On the (CT) list held 56% of patients of MOPP+LD/11 on the (CT+RT) list 24% of the patients had low doses in the inverted T with relapses in the abdomen occurring in two of these cases. The actuarial survival rates were considered as comparable though qualitatively slightly different. On (CT+RT) there were two cases of AM and one late marrow failure vs. 9 on the (CT) list. One late marrow failure on (CT) occurred in original sites of disease. These data suggest 14% of 42 cases in IIA without Hodgkin's disease, CT or (CT+RT) may be equally effective; however, the number of deaths and relapses in this study is small.

P 11 ALTERNATING COMBINATION CHEMOTHERAPY ABVD/MOPP vs ABVD/OPP IN ADVANCED STAGE HODGKIN'S DISEASE (HD)


Eighty-two patients affected by previously untreated advanced stage HD were randomly allocated to receive one of the following chemotherapeutic regimens: 1) four courses of ABVD alternating monthly with 4 courses of MOPP; 11) four courses of ABVD alternating monthly with 4 courses of OPP (vinristine 1.4 mg/m² i.v., vinblastine 60 mg/m² p.o. daily on days 1-21; prednisone 40 mg/m² i.v. daily on days 1-14). After achieving complete remission (CR) sequentially received a consolidation radiotherapy delivered on previously affected areas (total dose 20 Gy) and on spleen region (total dose 40 Gy). Removal of lymphadenopathy, the well documented leukemogenic drug, together with intensified scheduling of vincristine, vinblastine and prednisone, were performed in order to reduce long-term complications and improve therapeutic response. Forty patients (clinical stage I 8: 2 pts; II: 10 pts; III A: 16 pts; IV/A/B: 12 pts) entered ABVD/MOPP arm, whereas 42 patients (stage I 8: 2 pts; II: 14 pts; III B: 11 pts; IV/A/B: 15 pts) were treated with ABVD/OPP. Clinical characteristics of patients are similar in both groups. The mean follow-up was 15.5 and 22.5 months respectively. In the ABVD/MOPP group response rate was 92% (CR 77.5% and partial remission (PR) 54.8% and 85.7% (CR 78.5% and PR 75.4%) respectively. All patients except one patients achieved CR after radiotherapy. Number of systemic symptoms and of involved sites, significantly affected the response rate, the whole population of patients regardless of treatment. Hematological toxicity was similar in both groups whereas neurotoxicity was more relevant in ABVD/OPP group (21%), as compared to the other arm (13%). A trend toward a higher actuarial relapse free survival (RFS) rate was observed in the ABVD/MOPP group compared to the other arm (97% vs. 67% at 33 months, respectively). The overall survival rate was similar in the two groups (98% vs. 96% respectively). In conclusion, the seven multi-drugs alternating regimen resulted in a lower incidence of severe toxicity. The achievement of a response rate similar to that obtained employing alternating ABVD/MOPP, however, a longer follow-up is required in order to confirm the observed higher relapse free survival rate in the ABVD/MOPP arm.

P 12 PATIOB (prednisolone, adriamycin, bleomycin, vincristine, and etoposide) alternating with CHVP (VP) for Hodgkin's disease - a new regimen. NS Stuart 1, MH Cullen 1, J Fletcher 2, GR Blackledge 1, JA Child 3, C Woodruff 4, Qeen Elizabeth Hospital, Birmingham, City Hospital Nottingham, General Infirmary Leeds, UK.

There are theoretical reasons why alternating non-cross resistant CT regimens should improve overall survival in advanced Hodgkin's disease (HD) and at least one randomized trial supports this suggestion. The widely used MOPP/ABV regimen has the disadvantage of severe drug related toxicity. The two-drug regimen of CHVP (vincristine 6 mg/m² i.v. days 1 and 8; Procarbazine 100 mg/m² and prednisolone 50 mg/m² p.o. days 1-21) has been used at this unit for 3 years. The more severe side effects of CHVP compared to MOPP are acceptable.

115 pts with HD not previously exposed to CT have been treated with this regimens. 9 pts have relapsed after previous XRT. Median time from presentation to treatment is 9.1 years. Median age of the pts is 34. Clinical stages of the pts are: CI = 5 (all bulky disease), CII = 33, CIII = 42, CIV = 29, Not fully staged at least (st CII) 6, 68/611 pts HODGKIN's DISEASE. An actuarial survival analysis shows a lymphocyte predominant = 14, nodular sclerosis = 50, mixed cellularity = 24, lymphocyte depleted = 12, histology not yet reviewed = 15.

89 pts have completed CT and are evaluable for response and toxicity. 66 (74%) achieved CR as a result of CT with 16 (18%) achieving PR. Following XRT to sites of residual disease 73/89 (82%) were in CR. For pts with CI C or IV disease CR rate was 45/79 (57%) before XRT. 8 pts have relapsed within 2 years of completing treatment (81% relapse-free). 15 pts have died, 6 of recurrent or progressive HD.

89 pts developed neuropathy but in only 6 was this severe enough to stop further vinca alkaloids. 37/89 developed infections during treatment though in most cases this was mild. 15 pts had infections requiring inpatient treatment 5 with pneumococcus, 6 with salmonella, 4 with staphylococcus aureus. 2 of 4 patients treated for these infections died.

The regimen ChIVPP/PATIOB is active in advanced HD with a high response rate. Toxicity is acceptable with less subjective toxicity than MOPP/ABV. This regimen deserves comparison with standard, non-alternating treatment in a prospective, randomized trial.
P 13 PRELIMINARY RESULTS OF A CYCLIC-ALTERNATING CHEMOTHERAPY (CVP/DVBV) IN ADVANCED Hodgkin's DISEASE. M. Herold, G. Anger for Sct. Hematology Soc. Hematology and Blood Transfusion of the GDR. Dpt. Hematology, Clinic Internal Medicine, Medical Academy, Erfurt 5030, DDR.

Two chemotherapy regimens for treatment of patients with advanced Hodgkin's disease (stage IIIA - IV) were compared in a randomized prospective study.

Group 1: CVP (cyclophosphamide, vinblastine, procarbazine, prednisolone, adriamycin) versus

Group 2: CVP/DVBV (cyclophosphamide, rubidazone, bleomycin, vincristine, and cyclophosphamide and Cytoxan).

Eighty previously untreated patients were entered into the study between Jan. 1982 and Dec. 1984. Both groups are comparable (age, sex, stage, histology).

Treatment results:
- CVP (n=40):
  - CR 23 (57.5%)
  - PR 7 (17.5%)
  - NR 10 (25%)
- CVP/DVBV (n=40):
  - CR 24 (60%)
  - PR 9 (22.5%)
  - NR 7 (17.5%)

In first CR:
- median observation: 30,5 mo
- 13 (25%) relapse

RFS 1 year:
- 20/22 (91%)
- 14/20 (70%)

RFS 2 years:
- 7/13 (54%)
- 4/10 (40%)

Survival 2 years:
- 1/20 (5%)
- 1/10 (10%)

The differences between both groups are not statistically significant, neither in respect of response nor of survival and relapse-free survival.

Conclusions:
There is no difference in the response to treatment in the two groups, but the patients treated with CVP/DVBV had less relapses and a longer survival time. Further randomized studies are needed to clarify whether CVP/DVBV is at least as effective as CVP.


From 1970 to 1985, 38 patients (pts) with advanced Hodgkin's disease, in whom initial chemotherapy with MOPP (27 pts), MOPP-ABV (8) and ABVD (3) failed, were treated for salvage. Twenty-one pts had relapsed after initial complete remission (CR) and 17 had residual disease either receiving treatment of the one who received the first chemotherapy treatment. In 3 pts the ST was chemotherapy: MOPP-ABV. In 5 pts, ABVD and CEPABV-6. Treatment of those were treated with non-cross resistant regimens.

Twelve pts (32%) achieved CR, with a median duration of response 9 months (1-134 mo), however 8 pts relapsed and 2 developed leukemia. In 7 pts radiotherapy was the only ST. Five pts achieved CR with a durable remission (31 year) was obtained in only 2 pts. Actuarial 3 year survival after ST was 49% for all pts, 63% for complete responders(CR) and 38% for non-responders (CNR) vs non-CR pts (p=0.05). with a 30 month median follow-up of all pts. The actuarial probability of freedom from relapse in CRs, at 3 and 5 years after ST, was 46% and 28%, respectively.

Two pre-treatment characteristics were found predictive of response to ST and survival. 1) Symmetric symptoms at the initiation of ST. In asymptomatic pts 62% (13/21) achieved CR vs 51% (14/26) of pts with initial ST was 62%, compared to 23% (4/16) CR rate and 8% survival in symptomatic pts (p=0.02 and p=0.001, respectively).

2) Duration of initial remission. In 11 pts whose first remission had lasted more than one year, 9 (63%) achieved CR compared to 1 of 8 pts with short initial remission (1 year)p<0.02. Yet, the 3 year actuarial survival after ST in both groups was similar. 58% and 46%, respectively, of CR pts vs 86% and 53% CNR pts with initial resistant disease. CR was 41%. However, the duration of response was short and 3 year survival rate after ST was 14% (p<0.01).

Our data confirm that salvage chemotherapy or radiotherapy after failure of initial combination chemotherapy induce long term remission in only a small fraction of pts. The necessity for new treatment prograss for this group of pts is evident.


Various salvage regimens have been proposed for resistant Hodgkin's disease (RD); preliminary results are promising but heterogeneous, and optimal treatment has not yet been defined. We have assessed the efficacy of CEP schedule (Lomustine, Etoposide, Prednimustine) as salvage chemotherapy (CT) in patients with resistant Hodgkin's disease (RD) (not responders to primary therapy or relapsing within 12 months).

Between January 82 and December 86, 16 patients, 10 males and 6 females, aged 15 to 66 years (median 38) were treated with CEP; 14 were in advanced stage (3 IV A, 3 IV B, 1 IIIB); 6 patients were not responders to primary therapy, 10 in early relapse; 12 patients were statistically evaluable (8 relapsing, 4 not responders). All patients were treated with MOPP-ABV concomitantly (H/A) or sequentially (H/A). Data concerning response to CEP according to previous CT are summarized in the following table:

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<th>Relapse</th>
<th>DFS (mos)</th>
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<td>3</td>
<td>1 (mos)</td>
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<td>1</td>
<td>2</td>
<td>1 (mos)</td>
<td>2.8</td>
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</tbody>
</table>

The number of CEP cycles administered ranges from 3 to 16 (median 6); they were well tolerated and toxicity was mild.

Results:
5/12 pts (42%) achieved CR. 5/12 PR; 2 pts did not respond (NR). The overall response to CEP was 82% (10/12). Response varied according to condition of disease:

<table>
<thead>
<tr>
<th>Stage</th>
<th>CR</th>
<th>PR</th>
<th>NR</th>
<th>Relapse</th>
<th>DFS (mos)</th>
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<td>2</td>
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<td>1 (mos)</td>
<td>3.9</td>
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<tr>
<td>M/A</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>1 (mos)</td>
<td>2.8</td>
</tr>
</tbody>
</table>

Conclusion: CEP appears to be effective as salvage regimen in patients with H/O resistant to MOPP and ABVD. Response seems better in pts early relapsing after primary CT. Toxicity is acceptable.

Further studies on more numerous series of patients are needed to confirm the present data.

P 16 DESMODORPHINE, A HIGH DOSE AR-C AND CISPLATIN (DARP) AS SALVAGE TREATMENT FOR RELAPSING HODGKIN'S DISEASE. W.S. Vasquez, S. Jagannath, P.B. Sagemeister, P. McLaughlin, P. Suan, J.R. Radman, San Antonio, Texas M.D. Anderson Hospital, 1515 Holcombe Blvd., Houston, Texas 77030 USA.

Based on the observation of synergism between cisplatin and Ara-C observed in colonic and lymphoma cell lines, this combination was given to 24 patients (pts) with progressive relapsing Hodgkin's disease. All pts received a combination of cisplatin 40 mg IV for 4 days, Cisplatin 100 mg/M2 in a 24 hr continuous IV infusion, followed by Ara-C 2 g/M2 in a 3 hr infusion which was repeated 12 hrs later (CAMP). Hydration of normal saline and mannitol (50 g/liter) was given for 30 hrs. Treatment courses were repeated every 3-4 weeks. There was no major toxicity, only anemia was 27 (range 10-52 yrs). Thirteen pts had H/O symptoms, and 13 pts had extranodal involvement which included lung and pleura frequently. Three pts had bone involvement. Seven pts had refractory disease and never had achieved complete remission (CR). All pts had received prior MOPP (or CVP) and Adriamycin-containing regimens, and 5 pts had prior autologous bone marrow transplant (ABMT). There were 2 early deaths among those 5 who had prior ABMT and poor marrow reserve. Of the remaining 22 pts, 15 were assigned to receive 2-3 courses of DARP followed by ABMT consolidation. Among these, 6 (40%) pts achieved CR and another 5 (33%) obtained partial remission (PR). All but 4 of these 15 pts are alive. The deaths included 3 non-responders and one pt who relapsed at 5 months post ABMT. The 7 other pts who were not candidates for ABMT (older than 50 yrs, bone marrow involvement and/or prior ABMT) continued with additional chemotherapy. There were 2 CR's and 3 PR's. Overall, DARP had induced a 73% response rate in this heavily pretreated group of pts. CRs were related to tumor burden. Pts with high tumor burden, defined as having more than one area of extensive nodal involvement or more than 2 extranodal sites, achieved a median CR rate, while pts with low tumor burden obtained 40% CR rate. Myelosuppression has been acceptable and reversible elevation of serum creatinine was seen in 4 pts. These data show that DARP is an effective treatment in Hodgkin's disease, especially when combined with ABMT.
ABSTRACTS - Third International Conference on Malignant Lymphoma, Lugano


Despite the success of combination chemotherapy regimens in Hodgkin's disease, 15% of patients do not achieve complete remission (CR) when 600 mg/m² of cyclophosphamide, 50 mg/m² of doxorubicin, and 50 mg/m² of cisplatin with salvage chemotherapy are ineffective in this subset of patients. High dose chemotherapy followed by autologous bone marrow infusion (ABMT) has been used successfully to treat such patients.

Twenty-one patients with Hodgkin's disease who had been treated with radiotherapy and multiple chemotherapy regimens (median 3 regimens, range 1-13) underwent myeloablative chemotherapy with etoposide (VP-16), cyclophosphamide (CTX) and carmustine (BCNU) followed by an ABMT. The median age was 27 (range 16-40). At the time of ABMT, 15 had visceral disease, and 7 had nodal disease. Nineteen were refractory to the last regimen used. Five had never achieved a complete remission despite aggressive multagent therapy. All patients received CTX 120 mg/kg (4.8 gm/m²), VP-16 (500-2000 mg/m²) and BCNU (40-120 mg/m²) infused over a 48 hour period. BCNU was not used in the first two patients entered in this program. This was followed by ABMT. The median nucleated cell number harvested was 2.1 x 10^9/kg (range 0.9-4.7). Seven patients had complete remission of disease lasting 1-11 months, 5 patients had partial remission when lung and lymph node disease was present. Nine patients had early deaths and 3 pts are too early to evaluate. Toxicity included 2-3+ mucositis in 17 pts, hematotoxicity in 13 pts (fatal in 1), thrombocytopenia in 10 pts, hemorrhagic cystitis in 3 pts and respiratory failure resulting in death in 5 pts. We conclude that high dose myeloablative chemotherapy followed by ABMT induces a high remission rate in refractory HD and in some pts may result in long term survival.

P 18 AUTOLOGOUS BONE MARROW TRANSPLANTATION (ABMT) FOR RELAPSED HODGKIN'S DISEASE. E. K. Jacob, J. A. Amato, R. D. Cicic, P. B. Hagonoslie, J. L. Tucker, L. H. Hurwit, W. D. Winn, J. V. Spitzer. University of Texas M.D. Anderson Hospital, Houston, TX, and University of Nebraska Medical Center, Omaha, NE.

Sixty-two patients with relapsed Hodgkin's Disease were treated with high dose chemotherapy containing etoposide (BCNU) and ABMT. There were 34 males; the median age was 26 years (15-56 years). The number of prior chemotherapy combinations was < 3 in 35 patients and 2 in 27 patients. The performance status was excellent in 29 patients and symptomatic in 33 patients. MIBP regimen was the most common initial therapy and 24 patients failed to achieve a complete remission to the initial therapy. There were 45 patients failing last salvage chemotherapy attempt, while 17 were responding to last therapy including two who achieved CR and were intensified with BCNU. 47 patients had bulky (> 5 cm) and/or extensive nodal disease or two or more extranodal disease sites (high tumor burden) at time of ABMT. Chemotherapy dosage schedules was given as described previously (Ann Intern Med 101:163-168, 1986). There were only 4 early deaths, all with mediastinal relapse at the time of ABMT, all having received the highest dose of etoposide at 300 mg/m² and 3 of them with prior mediastinal radiation. Following BCNU therapy, 30 patients were in CR including 2 patients intensifying CR; 18 achieved partial response (PR) and 10 had progressive disease (PD). Only 7 of the 30 patients in CR have relapsed for a median follow-up of 24 months (6-56 months). Multivariate analysis reveals that patients with low tumor burden and high CR rate in the chemotherapy, and good performance status (CR > 20% had a high probability of CR and subsequent relapse-free survival. CR achieved by BCNU therapy are durable, and this therapy should be the preferred choice for Hodgkin's Disease patients once they have relapsed after MPP/ABVD-like regimen.


Nine patients (pts) with Hodgkin's disease (HD) who had relapsed at least once were treated with a "pulsing" dose of Cyclophosphamide, 300 mg/m², followed a week later by Melphalan, 140 - 220 mg/m² on 1/3 of the patients to achieve tumor necrosis and BCNU, 250 mg/m² infused over a 48 hour period. BCNU was not used in the first two patients entered in this program. This was followed by an ABMT. The median nucleated cell number harvested was 2.1 x 10^9/kg (range 0.9-4.7). Seven patients had complete remission of disease lasting 1-11 months, 5 patients had partial remission when lung and lymph node disease was present. Nine patients had early deaths and 3 pts are too early to evaluate. Toxicity included 2-3+ mucositis in 17 pts, hematotoxicity in 13 pts (fatal in 1), thrombocytopenia in 10 pts, hemorrhagic cystitis in 3 pts and respiratory failure resulting in death in 5 pts. We conclude that high dose myeloablative chemotherapy followed by ABMT induces a high remission rate in refractory HD and in some pts may result in long term survival.

Responses were as follows:

<table>
<thead>
<tr>
<th>Disease</th>
<th>Status</th>
<th>CR or CCR</th>
<th>PR (duration in months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>K pts.</td>
<td>(duration in months)</td>
<td></td>
</tr>
<tr>
<td>Resistant relapse</td>
<td>4</td>
<td>(5.7)</td>
<td>2 (4.8)</td>
</tr>
<tr>
<td>Responding relapse</td>
<td>4</td>
<td>(2.5,2.1,2.7)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>CR</td>
<td>1</td>
<td>(0.6)</td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>9</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

One pt died of HD at 8 months. Of three pts who had previously received five or more chemotherapy combinations, one are in CR compared with five of six pts who had two to four previous regimens.

Melphalan is clearly capable of producing durable remissions in moderately pretreated pts with HD in whom prolonged control of disease is very unlikely with conventional therapy. This drug merits further study in this situation to determine whether it is as useful as other conditioning regimens used before autotransplantation for HD.

P 20 AUGMENTED CYCLOPHOSPHAMIDE, BCNU, AND ETOPOSIDE (CBEV) AND AUTOLOGOUS BONE MARROW TRANSPLANTATION (ABMT) IN PROGRESSIVE HODGKIN'S DISEASE (HD), S. T. O'Neill, S. Hossain, N. Host, R. Fairey, G. Herzig, P. Klimo, G. Phillips, Bone Marrow Transplant Program of British Columbia, A. Maxwell Evans Clinic Cancer Control Agency of British Columbia and Washington University, St. Louis, MO.

Patients with progressive HD despite previous optimal chemotherapy (CT) and radiotherapy (RT) are usually considered incurable with conventional therapy. Intensive CT and ABMT can produce durable CR in these patients.

Between 2/85 and 9/86 20 pts with recurrent HD were entered on this study. Median age was 26, range 18-39, 11 males. One had no previous response to therapy, 13 were in 1st relapse, 5 in 2nd, and 1 in 4th. All had received multidrug chemotherapy including doxorubicin that produced prior remission in 17. 11 had extended previous field RT. CT free intervals were 19 pts <2 yrs (171 yr), 6 yrs.

Protocol treatment included cytoreductive MPP (mustard, vindesine, procarbazine and prednisone) x 2 cycles for pts who had sustained <3 m response to prior chemotherapy, followed by involved field RT to any lymph node sites originally >3 cm prior to high dose (11.8mg/m²/d × 4, day -7,-6,-5,-4, B(0.6mg/m² × 1, day -3) and 0.4mg/m² q 12 h × 6 × 7,-6,-5) followed by cyclophosphamide autologous marrow (18 pts). 2 pts with marrow involvement received allogenic marrow (1 pt) or peripheral stem cell transplant (1 pt) on day 0. 2 pts achieved a CR, 1 progressed and died at 6 m, 1 is alive without disease. 4 pts had achieved a CR at 10 and 16 m. 1 patient died at 11 m. All others remain in CR at 4, 6, 7, 9, 9, 11, 16, 17, 20, 23 m.

6 pts had documented bacterial sepsis, 1 of whom died. 1 had candidiasis, 1 mycoplasma pneumonia, 3 herpes simplex stomatitis. Altogether 2 pts died early (1 from sepsis and 1 from cerebral edema). These were the two most heavily pretreated pts.

High dose CBEV CT, and ABMT, has acceptable toxicity. The sustained CRs are encouraging.
ABSTRACTS - Third International Conference on Malignant Lymphoma, Lugano


Heavily pretreated patients (pts) with recurrent Hodgkin's disease (HD) fail further chemotherapy because of poor hematological tolerance which compromises delivery of potentially curative therapy. This treatment program attempted to circumvent this problem. Between 5/82 and 12/88 12 pts were treated with narrow-negative, HD-unrelated autologous marrow stored immediately prior to salvage chemotherapy. 7 pts were in 1st, 2nd, 2 in 3rd, and 1 in 4th relapse. 8 had received previous (START, 1 CT alone and 1 RT alone). After marrow storage all 12 received conventional dose CT (10 MOPP/ABV hybrid, 1 ABV, 1 MOPP/Adria) for up to 8 cycles. On the day of treatment if granulocytes were <9000/dl or platelets <70,000/dl full dose CT was given and marrow reinfused the next day. CT was resumed when granulocytes <1500 and platelets <100,000. 8 pts required ABMT and 13 ABMTs were performed. Hematological recovery was good. There was 1 toxic death (herpetic pneumonia) and 2 minor herpetic infections. 3 pts had one episode of febrile neutropenia, 1 pt had cholecystitis, 2 pts required brief platelet support and 1 had reversible bladder mucosa toxicity.

A high dose intensity was achieved, median treatment delay over 8 wks was 2 wks. For nitrogen mustard, the median dose delivered was 97% (86-100%). Adriamycin was also 97% (81-100%). All 12 pts achieved a CR. 1 died of toxicity in CR, 6 are in continuous CR at 25, 26, 32, 33, 38, and 51 m since end of therapy, 5 relapsed at 2, 4, 11 and 18 m after therapy, 2 are back in remission following radiotherapy. Autologous marrow reinfusion permitted delivery of dose intense chemotherapy on a tight schedule to patients who had failed MOPP/ABV chemotherapy 4 RT. Only 2 of these pts had received prior doxorubicin based therapy, one of whom remains in CR at 51 m.

P 23 LATE RELAPSES (LR) IN HODGKIN'S DISEASE (HD).

P. Pontecorvi, G.P. Biti, L. Clonti, Y. Munagi, P. Papi - Divisione Cattedrale e Università di Radioterapia, Firenze, Italy.

Most of relapses (LR) in patients treated for Hodgkin's disease occur within two years from the primary treatment, whereas the LR are rare events after five years. Early relapses (ERL) clearly are due to therapeutic failure, whereas it is difficult to state the biologic significance of late relapses (LR) in the natural history of the disease. In order to analyse the LR, and particularly LRL, the records of 516 consecutive patients with HD seen at our Institution between 1955 and 1978, with a minimum follow-up of 7 years, were reviewed. The male:female ratio was 1:2.1 and the distribution by age subgroups was as follows: 0-15 yrs. = 44 pts; 16-35 yrs. = 399 pts; 36-55 yrs. = 197 pts; more than 55 yrs. = 66 pts. The histologic subtype was N.E. in 46% of cases, M.C. in 49%, L.P. in 14% and L.D. in 8% of cases. At the completion of staging procedures, 67 patients were classified as Stage I, 5 as II D, 24 as III A, 54 as III B, 104 as IV A, 86 as IV B, 16 as IV C and 12 as IV E. The treatment modality: radiotherapy alone in 436 pts., radiotherapy plus chemotherapy in 113, and chemotherapy alone in 28.

35% of these patients had a relapse of the disease after their primary treatment. Of these, 48% occurred in the first year after treatment, 79% within 3 years, 90% within 5 years, while only 5.5% after 7 years. Type of LR (True Recurrence = T.R.; Marginal Recurrence = M.R.; Nodal Extension = N.E.; Systemic Dissemination = S.D.) was analysed in these patients in relation to the interval from the primary treatment: the R occurring within the first year were in equal proportion T.R., N.E. and S.D.; the R occurring between second and fifth year after treatment were predominantly M.E., while the R occurring later were predominantly T.R. No relationship was observed between the time of relapse and the clinical characteristics at diagnosis (sex, age, histologic, stage, mediastinum, number of sites involved). We have observed that the patients surviving longer than 7 years seem to have more favorable clinical characteristics at diagnosis (but not significantly).

This fact and the observation that later relapses are often T.R. suggest the hypothesis that they represent a new disease rather than a relapse of the previous disease.

Testicular dysfunction is a major complication in adults treated with MODP-chemotherapy for Hodgkin's disease. While Leydig cell function is usually in patients treated with CHOP and COPP-chemotherapy (vincristine, prednisone, procarbazine, adriamycin, cyclophosphamide). In 68 boys, aged 12.94 ± 2.09 years (mean ± SD) at diagnosis, a standardized Intraveneous LEHR-test was performed at a mean chronological age of 17.82 ± 2.18 years. Basal and stimulated FSH-values were more than 2 SD above normal in 39.7% and 52.9% of the cases indicating severe impairment of spermatogenesis. PSH-values were 14.21 ± 9.75 UI/l (basal) and 25.55 ± 17.08 UI/l (stimulated) with normal values of 7.17 ± 3.46 UI/l and 9.42 ± 4.79 UI/l. Basal LH values were in the upper range of normal with 8.78 ± 3.69 UI/l, while stimulated LH was 49.36 ± 21.69 UI/l and 17.78 ± 3.99 UI/l. This indicates that in addition to the impairment of spermatogenesis Leydig cell function is affected, though testosterone values are within normal limits (20.24 ± 9.02 mnol/l).

It appears that within our therapeutic regimen procarbazine is the major contributing factor for the overall incidence of testicular dysfunction. The frequency of elevated basal FSH-levels rises from 21.2% to 31.4% with cumulative procarbazine doses of < 4000, 4000 - 8000 and 8000 to 12000 mg/m².

We conclude that impaired sperm production and compensated Leydig cell function rates make long-term sequelae in boys treated for Hodgkin's disease. We suggest that parents and patients are informed about these side-effects prior to therapy and that LH-RH-tests and sperm biomarkers are performed during the long term follow-up of these patients.

P 26  SEXUAL FUNCTION AMONG ADULT PATIENTS (PTS) WITH MALIGNANT LYMPHOMA (ML). UNDERGOING COMBINATION CHEMOTHERAPY (CT). H. Sorin, J. Frulloni, J. Fagnoni, S. Remondini, Division of Medical Oncology, Centro di Riferimento Oncologici, Aviano, Italy.

The purpose of this retrospective study is to evaluate the sexual function among adult pts with ML at the diagnosis, during CT and follow-up. Pts aged 18-45 years, without evidence of disease 2 years from the completion of CT and ML were considered evaluable. After verbal consent a questionnaire was given to 46 pts (31 of them actually filled it; 15 females, 31 males, age 18-45) and 12 non-Hodgkin's lymphoma. For the purpose of this report, only weekly sexual intercourses and quality of sexual life as reported by 29 pts with stable heterosexual relationship have been evaluated. The median number of reported weekly sexual intercourses before the onset of the disease was 1. At the time of diagnosis the decrease of sexual function was attributed to the worsening of the general conditions (40%), less desire (40%) and change of life style (20%), whereas during CT the worsening of the general conditions (50%), less desire (50%) and loss of erection (50%) seem to be the most significant factors. In conclusion, sexual function of adult pts with ML is impaired at the time of diagnosis and during CT. However, during follow-up, it significantly improved almost at the same rate as reported before the onset of the disease, therefore the long term sexual function of adult pts with ML as evaluated in this study does not seem to be significantly impaired by CT.


During the period 1971-1984, 429 consecutive patients with Hodgkin's disease were treated at the Division of Hematology, Pavia. The entire cohort amounted to 168 person-years. The patients were treated with a combination of radiotherapy (RT) alone (170 pps), chemotherapy (CT) with MOPP (42 pps) or MOPP-MOPP (21 pps), RT and CHOP (79 pps); ABVD (20 pps). In patients with multiple relapses, nitrosourea and podophyllotoxin derivatives were also employed (120 pps). The cohort is analyzed to assess the incidence of acute non lymphoid leukemia (ANLL) or solid tumors (ST) after treatment. Within a median follow-up of 8 years, 28 new malignancies (6%) were documented (14 ANLL and 14 ST). The 10-year actuarial estimate and relative risk (RR = observed/expected ratio) of ANLL and ST by therapy group were as follows: leukemia

<table>
<thead>
<tr>
<th>Therapy</th>
<th>No. of patients</th>
<th>No. of actuarial cases</th>
<th>Actuarial risk (%)</th>
<th>RR p</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT alone</td>
<td>53</td>
<td>0</td>
<td>0</td>
<td>3.7</td>
</tr>
<tr>
<td>CT alone</td>
<td>160</td>
<td>3</td>
<td>2.1</td>
<td>7.5</td>
</tr>
<tr>
<td>RT+adj. CT</td>
<td>109</td>
<td>11</td>
<td>1.02</td>
<td>4.5</td>
</tr>
<tr>
<td>RT+vinc. CT</td>
<td>107</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

No cases of leukemia were documented in patients given RT alone; the risk of ANLL was 1.1% and 6.4% in the RT+CT groups. No positive correlation was noted between age over 40 and increased risk of ANLL. The 10-year actuarial risk of ST ranged between 2.7 (CT alone) and 10.9% (RT and CT). However, the relative risk was significant only for the combined modality groups. No excess risk was observed for lung cancer and melanoma, whereas the risk for soft tissue sarcomas (including Kaposi's sarcoma) and Hodgkin's lymphoma (ANLL) and endocardial fibroelastosis was significantly raised. From 1973 to 1985, 430 patients were treated for NHL. RT alone was given to 76% monochemotherapy with chlorambucil and/or cyclophosphamide or 17% of total patients polychemotherapy with and without doxorubicin in 24% and 32% of total. RT+CT was adopted in 20% of cases. Within a 7-year median follow-up, 18 NHLs (11% of ML) and 6 STs. The RR for NHL was highly significant (p < 0.001) for the group of men with low-grade malignancy NHL whereas it was not for low-grade malignancy women and for high-malignancy NHL. The RR was significant (p < 0.023) for the group given long-term chlorambucil and/or cyclophosphamide. Excess risk was observed for NHL; Kaposi sarcoma (1 case) and skin basalcella.

P 28  SECOND MALIGNANCIES IN BRITISH NATIONAL LYMPHOMA INVESTIGATION HODGKIN'S DISEASE STUDIES. G. Vaughan Hudson, D. Bevereux, D. Linch, H. Vaughan Hudson, BNLI Dept, Oncology, Middlesex Hospital, London, W1, UK.

In the series of over 2,300 evaluable patients with Hodgkin's Disease entered into British National Lymphoma Investigations Studies since 1970, second malignancies have so far been reported in 68 patients; 14 acute leukaemia, 11 non Hodgkin's lymphomas and 43 solid tumours.

Of the 14 cases of leukaemia, 12 were acute myeloblastic and 2 acute lymphoblastic. The overall actuarial risk of leukaemia in the whole group at 10 years was 1.2%. No patient developed leukaemia who received radiotherapy alone. In the patients receiving chemotherapy alone the risk at 10 years was 2.6%. The patients who developed leukaemia received significantly more courses of chemotherapy than a case control group. The risk of leukaemia was related to the cumulative drug dosage given, with CCBU appearing to be particularly leukemogenic. For patients receiving CCBU the overall risk of leukaemia was 12% and this rose to 18.5% when used for salvage treatment.

43 cases of solid tumours were reported, of which the commonest was carcinoma of the bronchus, occurring in 20 patients, 6 of whom were under 50 years of age. In 3 of the tumours the patients developed in a previously irradiated area.

In contrast to the 14 cases of leukaemia which arose in multiply-treated patients who were unlikely to be cured of their disease, only 18 (10%) of the 190 patients with solid tumours had been free of Hodgkin's disease, some of them for many years.
ABSTRACTS - Third International Conference on Malignant Lymphoma, Lugano

P 29  
Ten cases of myelitis occurred following treatment of central nervous system (CNS) leukemia/lymphoma with radiation and intrathecal chemotherapy. Radiation doses were within the accepted tolerance levels. Several factors were common to all cases.
1. All had CNS involvement or parameningeal disease at diagnosis.
2. They had a segment of the cranial nerves irradiated.
3. They received systemic and intrathecal chemotherapy.
4. All had negative cerebrospinal fluid (CSF) and negative myelograms at the onset of myelitis.

Patient Characteristics: 9 male, 1 female, age 6-61, average 33 years. Acute lymphatic leukemia 3; acute promyelocytic leukemia 1; non-Hodgkin's lymphoma 6 - stage II 3, stage IV 2. One patient had CNS disease at diagnosis, 6 developed CNS relapse after inadequate prophylaxis and 2 relapsed in the CNS after adequate prophylaxis. One had extramedullary involvement. All patients received systemic chemotherapy. Nine patients received intrathecal methotrexate with or without cytotoxic arabinoside and hydrocortisone. One patient received intrathecal cytosine arabinoside. Nine patients received cranial irradiation and the tenth patient received intraventricular chemotherapy via an Ommaya reservoir. One patient received intracranial irradiation and 2 patients received total body irradiation. The total number of intrathecal chemotherapy doses varied from 3 to 30. All patients developed typical transverse myelitis at a time when there was no evidence of recurrence of disease including negative myelography and CSF cytology. Despite this, 3 patients were mistakenly assumed to have recurrence of disease and were retreated. Only 3 of the patients are alive, all with permanent neurological deficits. Autopsy material was available on 6 cases. There was evidence of diffuse demyelination, fibrinoid necrosis and thickened meninges. The pathological distribution was consistent with showing scattered perivascular foci lesions in the spinal cord and a secondary ascending degeneration. Two patients exhibited marked sclerotic arachnoiditis while the 4th patient had changes more typical of radiation myelitis.

Meningeal disease and/or CNS irradiation may predispose to the development of myelitis by increasing the radiosensitivity of the blood-brain barrier. Conversely, methotrexate or cytotoxic arabinoside administered intrathecally or systemically may lower the tolerance of the spinal cord to irradiation. Intrathecal cytology of myelitis should be considered when CSF cytology and myelography are normal.

P 31  
CHILDHOOD ADVANCED HODGKIN'S DISEASE TREATED WITH SIX CYCLES OF ABVD AND LOW DOSE RATE IRRADIATION: A PILOT STUDY.
C. Fryer, R. Hutchinson, L. Constine, C. Davis, D. Hays, R. Heiler, M. Krailo, J. Machen, A. McEwan, J. Decker, P. Fink, B. H. Miller, Children's Cancer Group, Pasadena, California, 91101, USA.

Sixty-six patients with pathologically staged advanced Hodgkin's disease (IIIA, IIIB, IIE, IV) were entered in a pilot study testing of six cycles of ABVD ( Adriamycin 25 mg/m², vinblastine 6 mg/m², dacarbazine 375 mg/m², bleomycin 10 units/m²) Q3 weekly to low dose rate (LDR) irradiation. Patients characteristics: age 15-65, sex 1:1, Karnofsky 70-100. Sixteens were evaluable for response and 12 of 21 (57%) had complete remission compared to one of 21 (5%) with negative paracoccid. The event free survival was 84% with a median follow-up of 13 months. Three patients relapsed and one died. One patient developed acute leukemia and died of complications following bone marrow transplantation.

Toxicity on 62 evaluable patients using CCSG criteria was as follows:

Total 0 1+ 2+ 3+ 4
Unknown 0 0 0 0 0
Pulmonary 0 0 0 0 0
Hematological 0 0 0 0 0
Gastrointestinal 0 1 1 0 0
Hepatic 0 0 0 0 0
Peripheral neurolymph 0 0 0 0 0

Of the four patients with grade III-IV pulmonary toxicity (decrease in DLCO of 35%) one was fatal and one necessitated stopping therapy after five cycles of ABVD.

Analysis of 43 patients completing six cycles of ABVD revealed the following percentage of drugs delivered: Adriamycin 97%, vinblastine 96%, dacarbazine 97%, bleomycin 95%. Five patients had reduced bleomycin dosage. Carbon monoxide diffusing capacity appeared to be an early predictor of bleomycin related pulmonary toxicity. A prospective randomized trial is underway comparing this regimen with alternating MOPP/ABVD.

P 32  
Favourable prognosis in childhood T-cell lymphomas.

From August 1981 until April 1984 19 consecutive children aged 2-17 yrs, with mediastinal T-cell lymphoma were treated in our institute. Ten children had initial bone marrow involvement. These 19 children were treated as follows:

Induction: Methotrexate, i.v. x6. Nitrogen Mustard i.v.x2
Procarrabine p.o. for 2 weeks, prednisolone p.o.
for 5 weeks.
L-asparaginase i.v. for 2 weeks.

CNS-prophylaxis: 25 Gy to the cranial and 6 intrathecal
injections with cytosine-arabinoside.

Maintenance: BACOP during 18 months.

With this regimen 18 children have achieved complete remission. One child had a partial remission and was treated with an autologous bone marrow transplantation. This boy remains disease-free, 63 months after diagnosis. Four children have relapsed in the bone marrow and they died. No relapse occurred in the mediastinum. The remaining 15 patients are free of disease from 33 to 65 months providing a disease-free survival rate of 79%.

This DFS belongs to the highest survival rates reported so far. According to these results one should consider the possibility of reducing the aggressiveness of the therapy.

P 33  
KING FAISAL SPECIALIST HOSPITAL AND RESEARCH CENTRE (KFSHCRC) TUMOR REGISTRY: DISPLAY OF MALIGANT LYMPHOMAS IN CHILDREN UNDER THE AGE OF 15 YEARS.

A. Alì and S. Willoughby, KFSH and RC, Riyadh, Saudi Arabia.

The KFSH & RC Tumor Registry, the first to be created in Saudi Arabia, maintains a complete database of all cancer patients diagnosed and/or treated at the Hospital from June 1975 to December 1985. It registered a total of 117 patients 15 years of age, 12.6% of the total number of cases. Ninety-eight (84%) of the patients were males (62 females). Seven hundred and 22 patients (61.7%) had Hodgkin's disease (HD): 90 boys (82%) and 22 girls.

HISTOLOGIC TYPES

HD (222 CASES) NS (112 CASES)

Type Sex

Undifferentiated 107/46
A. Non-Burkitt 70 35
B. Burkitt 27/10
Lymphoblastic 59/26
Histiocytic 12/6
Unspecified 44/20

INCIDENCIES ACCORDING TO SEX AND AGE

Number of Cases Per Year Of Age

Sex


case

Type

Age (years)

No/3

0/4

Boys

Girls

HD (222) 112
HD (112) 90

(222:112) RATIO 2:1/0.9

Sex

Boys

Girls

No/3

0/4

HD (112) RATIO 2:1/0.9

Sex

Boys

Girls

No/3

0/4

HD (112) RATIO 2:1/0.9

Total

121
122

123
124

HD (222:112) RATIO 2:1/0.9

NHL (222) 112

(222:112) RATIO 2:1/0.9

Sex

Boys

Girls

No/3

0/4

HD (112) RATIO 2:1/0.9

Sex

Boys

Girls

No/3

0/4

HD (112) RATIO 2:1/0.9

Total

121
122

123
124

HD (222:112) RATIO 2:1/0.9

NHL and HD revealed a marked predominance for boys: 2.7 to 1.0 and 4.8 to 1.0, respectively. Two-thirds of NHL patients were < 8 years of age, and near half of HD patients > 8 years of age. In the NHL group there was a marked incidence of Burkitt's lymphoma, and in the HD group there was a marked incidence of the mixed cellularity type. These features appear unique. The national geographical distribution of the tumors has been described, and the survival information on each patient is on ongoing process. The KFSH & RC Tumor Registry is a valuable source of information to study childhood tumors in the Middle East, since it deals with a homogeneous Arab population (98% of the cases).

Since January 1984 pts with non-Hodgkin's lymphoma (NHL) observed in our institution have been treated with different chemotherapeutic regimens depending on stage and histological-subtype. Pts with stage III and IV B-NHL and B-Acute Lymphoblastic Leukemia (B-ALL) were treated with "Total B-2" protocol, an intensive chemotherapeutic regimen based upon appreciation of rapid tumor growth kinetics as adopted at St.Jude Children's Research Hospital. Treatment consists of a fractionated schedule of cyclophosphamide (300 mg/m² q12 h X 6 doses) followed immediately by adriamycin (50 mg/m²) and vincristine (1.5 mg/m²) with combined intrathecal methotrexate (6 MTX) and cytarabine (ARA-C). Immediately upon hematologic recovery, i.v. high-dose MTX (1,000 mg/m² over 24 hours) followed by i.v. ARA-C (400 mg/m² over the next 48 hours) is administered with leukovorin rescue and repeated intrathecal treatments. The treatment sequence described is repeated 4 times, with the dose of ARA-C doubled in succeeding courses, up to 3000 mg/m². The entire planned therapy requires approximately 14 weeks.

Since 1984 to December 1990 we treated 11 children with this approach. According to initial extent of disease, 6 were classified as stage III (7 of whom had massive unresectable intra-abdominal tumor and 1 had lymphocyte and mediastinal involvement), 2 as stage IV NHL, and 1 as B-ALL. 1 stage IV pt had initial involvement of the CNS.

Ten evaluable pts attained a complete remission (CR) (100%); 1 pt was excluded from analysis because too early to evaluation. 7 out of 10 pts are alive in CCR. All but one stage III NHL pts (6/7=85.7%) remain disease-free for periods ranging from 3 to 35 months; all but one of them are off-therapy after 1+, 2+, 30+ months respectively. The stage IV NHL pt with initial CNS disease is off-therapy in CCR after 13 months; the 2 remaining pts (B-ALL, stage IV NHL) presented CNS-relapse after 3 months from diagnosis and 1 month after completion of therapy respectively, and eventually died. Major toxicity consisted of severe hematopoietic suppression and febrile episodes with neutropenia, generally 7-14 days after the completion of each chemotherapeutic phase which required very intensive supportive care and hospitalization.

According to the results reported in the literature, our previous experience showed a poor outcome in advanced stage B-cell NHL pts when LSA2-G protocol was employed; on the contrary the results obtained with Total-B2 protocol appear to be very satisfactory. This chemotherapeutic approach represents an effective therapy for stage III B-NHL. On the contrary, as our preliminary results suggest, pts with stage IV B-NHL or B-ALL may need alternative regimens such as more intensive CNS prophylaxis. This approach might be of benefit to patients with CNS involvement at diagnosis, who present a very poor outcome, as referred by Murphy.

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