ABSTRACTS

POSTER PRESENTATIONS
Poster Session I

BIOLOGICAL STUDIES
ABSTRACTS - Fourth International Conference on Malignant Lymphoma, Lugano

P 1 GROWTH MODULATION OF TWO LYMPHOMA CELL LINES BY A NOVEL CALCIUM CALCULOR ANTAGONIST MC90. Hickish T, Scoop M, Miller BC, Purvis H, McDowat T, Cunningham D. Royal Marsden Hospital, Sutton, Surrey, UK. Glasgow Royal Infirmary, Scotland.

After apparently successful induction chemotherapy almost all patients with low grade non-Hodgkin's lymphoma relapse, therefore there is a requirement to develop novel treatments for application to the maintenance phase. In this phase we have previously shown that ascobol (which is mineralised to calcium) can induce apoptosis in 42% of patients with low grade non-Hodgkin's lymphoma. The dose limiting toxicity of ascorbic acid is hypercalcaemia but the analogue MC90 has similar anti-proliferative effects to ascorbic acid but 100 times less of an effect on mineral metabolism. We have studied the growth modulating effect of calcium and MC90 (Leo laboratories) on two diffuse histiocytic cell lines SU-DHL-4 and SU-DHL-4M. The latter has a (1+1+18) characteristic of 80% of follicular small cleaved lymphoma. Toxicity was measured using the incorporation of [3H]thymidine and by the growth of colonies in soft agar. Results are shown below.

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<th>Controls</th>
<th>Calcitrol</th>
<th>MC903</th>
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These data show MC903 and calcitrol produce a similar reduction in the thymidine uptake suggesting an anti-proliferative effect on both cell lines. The clonogenic assay shows an anti-proliferative effect that is similar for the two drugs on the clonogenicity of SU-DHL-4 cells.

These data suggest MC903 may be an effective anti-proliferative agent in lymphoma and indicate a role for calcitrol analogue in the maintenance phase of low grade lymphoma.

*Supported by A Episien

P 2 MALIGNANT HISTIOCYTOSIS MAY DERIVE FROM AN ME-COMMITTED PROGENITOR. V. Genteli, A. Carboni, M. Aloisi, V. Zappoli, A. Pintor. Leukemia Unit, C.R.O., 33081, Aviano, Italy.

Malignant histiocytosis (MH) is a rapidly progressive hematological disease sharing several clinical and pathological features with monocytemonocytic (Mc-Mo) neoplasms. The cellular origin of MH remains however controversial in that the presence of both T lymphoid (CD2, CD4, CD8) and B lymphoid (CD20, CD19, CD22, EBV positive) markers has beenreported by EBV infected cells. We observed four MH cases which were consistently immunologically monocytic and showed a clone of EBV gene rearrangement studies. Our results show that MH cells from all patients displayed NK-related surface markers along with a restricted number of T cell accessory antigens. MH cells were heterogeneously expressed. In particular several mononuclear antigens (MoAbs) recognizing H-2 (MoAbs) recognizing H-2.

In our four cases, CD3 MoAbs were also detected on malignant histiocytosis cells. MH cells were more strongly reactive with anti CD4 MoAbs and, in these four out of six cases, CD2 antigens were also detected. Malignant cells did not react with other T cell antigens and lacked CD30 expression.


Among the first 1000 patients included in the CELA treatment protocol for aggressive lymphomas, 78 cases were classified initially as anaplastic large cell lymphomas, 72 of which were confirmed on review by a panel of 5 hematopathologists. These cases were further subclassified into the following categories: "common" (60 cases), giant cell-rich (9 cases), Hodgkin's related (9 cases), atypical (18 cases), and large cell lymphoma with a significant anaplastic component (12 cases). Immunohistochemical studies were performed on paraffin sections using antibodies against CD antigens (CD3, 15, 20, 30, 43 and 58) and other markers (UCHL1, MB2, L26, L2, EMA, BNA19). In addition 34 cases were studied in frozen section. Most cases were positive for CD30 (83-1) and CD45 (68-63 cases respectively), whereas CD5 was found in only 30% of cases (45-67, 28 cases (29%) considered to be T cell origin, and 25 (32%) as B cell neoplasms. 21 cases (29%) could not be identified as being of T or B cell origin, including 2 cases in which antigens associated with both T and B cells were co-expressed. T cell neoplasms were commonest among the "common" type, and those of B cell origin among the large cell group with an anaplastic component.

Hodgkin's-related cases were mostly of "null" phenotype. No cases was considered to be of true histiocytic origin, although staining for CD20 (antibody KIP1) disclosed numerous reactive histiocytes, often showing erythrophagocytosis. Antibody BNA19 (against the H and Y blood group antigen) was found in 14/62 cases (23%), 12 of which were of common or giant cell type.

These results emphasise the heterogeneity of anaplastic large cell lymphoma. Since all patients had been treated according to standardised regimens of the CELA treatment trial, and then followed up regularly, the prognostic significance of the different histological and phenotypic features could be evaluated. The results of this correlating review will be presented.

P 4 Angio-destructive Lymphoma (ADL): A novel subtype mononucler with unfavorable prognosis. J ITAMI, W ITAMI, J TAMARU, T ARUGA, A MIKATA, R ARIMIZU. Department of Radiology and Pathology, Chiba University Hospital, Chiba, Japan.

ADL is clinically discovered mainly as midline lethal granulomas of the upper respiratory tract. To study the clinicopathologic feature of ADL, retrospective study was undertaken.

MATERIAL AND METHOD By reviewing the pathology slides of head and neck lymphomas treated in our Department from 1975 through 1985, seven cases with prominent angiodestruction were found. The formalin-fixed paraffin-embedded material was studied with monoclonal antibodies (MT-1, MB-1, L-26, UCHL-1).

The male: female ratio was 6:2 with a mean age of 60. Clinically 6 cases had only localized involvement (Ann Arbor St I) and remaining two more advanced disease (One St II and one St IV). Seven out of the 8 had involvement of nasal cavity and remaining one had cheek involvement. Six patients with St I and II were treated by involved field RT with/without simultaneous mild chemotherapy. CS IV patient was treated with CHOP. Remaining one with St I is now under treatment. [RESULT] Immunohistochemical study showed that all but one had T-cell phenotype. Remaining one had B-cell marker. According to WF, DL was the most predominant subtype. All cases belonged to grade 2 or 3 by Jaffe's criteria. It is notable that 5 cases repeated biopsy more than twice was necessary to reach the diagnosis. Two cases had long standing history allergic rhinitis. Out of 7 patients who complained of tumor-related disease free after 3 year-follow-up, while remaining 6 all succumbed to fatal recurrence. Local recurrence occurred in nasal cavity was always accompanied by widespread disease primarily in the lungs, spleen and skin. A patient treated by CHOP was totally reversible to it. [DISCUSSION] Although some literature has suggested the RT is curative in MLR, our results revealed that ADL of grade 2 or 3, which seems to comprise most of the MLR, is not amenable to RT even when limited to the primary site. Site of improvement of prognosis of these patients, aggressive approach employing intensive chemotherapy will be warranted.
P 5 CLINICAL COURSE OF ANGIOIMMUNOBlastic LYMPHADENOPathy UNDER A STANDARDIZED TREATMENT - RESULTS OF A PROSPECTIVE MULTICENTER TRIAL.


Angioimmunoblastic lymphadenopathy (AILD) is a rare lymphoproliferative disorder mostly characterized by lymphadenopathy or extranodal lymphomas of low-grade malignancy. The finding of clonal chromosome abnormalities (9;22, +5) and of rearrangements of T-cell receptor genes in most of the cases proves the concept of its clonal origin. Retrospective data demonstrate the usually aggressive course of AILD, although spontaneous remissions were reported occasionally. There is little information about the value of cytoreductive treatments. Therefore, a prospective study was designed to define the responsiveness of AILD to a standardized therapy. The protocol consisted of an initial treatment with prednisone (Pred) 2 mg/kg for 2–4 weeks. Patients achieving a complete remission (CR) did not receive further therapy. Patients failing to respond or relapsing after achievement of CR or presenting already initially with life threatening tumor progression then received CVP-BALAM/BVP-V (CHOP). 52 pts were evaluable. Their median age was 64 (range 25–88) years. Seventy-four of 51 (63%) pts received predna steroid treatment (P). 21/51 (40%) received therapy with aclacinomycin (AC) and 27/51 (54%) received therapy with cyclophosphamide (CYC). Response rates were 29% CR in A, 57% CR in B and 37% CR in C with a median first CR duration of 4.5 months (KOH, A, B, C: 11, 7, 7, and 7 months, respectively). The relapse rate was high in A (B:10) and lower in B (2/12) and C (3/7). In a subgroup analysis, the survival curve for pts with primary CHOP and 10 mo for pts with Pred +/- CT (n.s.). The probability of survival at 2 years was 46% for both treatment groups. The probability of event-free survival at 2 years was only 24%. These results emphasize the aggressive clinical course in most of the patients. However, further data are required for a precise evaluation of this T-cell lymphoma including the definition of prognostic subgroups and their appropriate treatment.

P 6 IMMUNOREACTIVITY OF CYTOMETRIC MEASUREMENT OF DNA CONTENT AND CELL-SURFACE IMMUNOMARKERS: A NEW APPROACH TO STUDYING CELL PROLIFERATION IN NON-HODGKIN'S LYMPHOMA.

Hans P.P.M. Reinders, Hanno J.M.M. Koppelman, Roeland P.G.J. van Nunspeet, Kees K.L. van der Wall, Department of Pathology, University Hospital Nijmegen, The Netherlands.

Several studies have shown that S-phase DNA content (S-DNA), an indicator of cell cycle phase, is predictive of prognostic relevance in Hodgkin's lymphoma (HL). However, controversies still exist. Due to admixture of non-tumor cells (up to 60%) as well as ploidy heterogeneity, a reliable analysis of S-DNA in tumor cells can be jeopardized. Therefore, we measured S-DNA of distinct subpopulations defined by cell-surface immunomarkings.

The tumors were labeled with unconjugated monoclonal antibodies against T-cells (CD3; CD4; CD8), B-cells (CD19; CD20; CD22), monocytes/macrophages (CD14), and Thy-1 (TAC) conjugated antibodies. Cellular DNA was proportionally stained for 24 h on ice with propidium iodide in hypotonic citrate. Cells were analyzed on a single-laser flow cytometer. The percentages immunospecific cells were essentially unaltered after DNA staining. Of the 16 NHL investigated so far, 8 were low-grade (6), 4 intermediate grade (2) and 5 high grade (6) NHL. Eleven were of B-cell and 3 (all NHL) were of T-cell (CD4+) phenotype. Considerable admixture of T-cells (CD3+) were seen in the B-cell NHL (mean 19.1%) and of B-cells (CD4+ or CD20+) and mature T-cells (CD3+) in the T-cell NHL (mean 11.3% and 10.3%). DNA aneuploidy was observed in 1/5 NHL, 4/10 NHL, and 2/5 NHL NHL, all B-cell NHL. In all but one of these cases, analysis of S-DNA in the total cell population was not feasible because of unambiguous and diploid DNA histograms. However, the most predominant B-cell populations (CD19+, CD20+ or CD22+) were almost always aneuploid whereas 2–5% aneuploid cells were seen in the CD3+- cells. This enabled calculations of S-DNA in the subpopulations. In NHL, the admixture of T-cells (CD3+) and the most predominant B-cell populations (CD19+, CD20+ or CD22+) were relatively high S-DNA of the CD3+ cells (mean 11%)), whereas in the B-cells (CD19+ or CD20+) and mature T-cells (CD3+) a low S-DNA was measured. These findings were reproduced in a second NHL.

This method is promising for studying proliferation activity in NHL, especially in view of heterogeneity of tumour composition due to aneuploidy and admixture of non-tumor cells.

P 7 HISTOMPORPHOLOGIC AND IMMUNOPHENOTYPIC SPECTRUM OF PRIMARY GASTROINTESTINAL T CELL LYMPHOMAS.

Peter Möller and Birgit Miekle. Institute of Pathology, University of Heidelberg, 6900 Heidelberg, Federal Republic of Germany.

In order to compare primary gastrointestinal B cell lymphomas histopathologically and immunophenotypically with orthostatic steps of B cell differentiation within the mucosa-associated lymphoid tissue (MALT) of the gastrointestinal tract, a comprehensive panel of well characterized leucocyte differentiation antigens was composed. It comprised immunoglobulins and, CD5, CD10, CD11c, CD23, CD24, CD30, CD32, CD38, CD9, CD75, CD76, and L26 antibodies. Taken together, these antigen yield characteristic immunoprofiles for the following B cell compartments of the MALT, per se closely linked to cytologically distinct B cell phenotypes: mantle zone (MZ), extracellular compartment (ECF), follicle center (FC), and plasma cell compartment (PC). An unselected set of 27 MALT B lymphomas (14 of low and 13 of high grade malignancy) was first classified histologically in routine preparations and subsequently characterized immunohistochemically using fresh frozen tissue, monoclonal antibodies against the antigen panel listed above and an indirect immunoperoxidase method. The final classification considered both, morphologic and immunophenotypic of tumor cells. Seven tumors were "typical" in both respects: one closely corresponded to MZ, three to EF, two to FC and one to PC; they all belonged to the subclass category of low grade malignancy. Two further tumors showed two morphological distinctly subpopulations and also bi-phenotypically on the antigen level. The remaining 18 cases were characterized as "atypical" because of anaplastic cytoplasmic and/or abnormal expression and/or loss of antigens. A hybrid ECF/FC phenotype was most frequently observed together with centrocyte-like or centrocytic anaplastic cytoplasm of tumor cells. We conclude that MALT B cell neoplasia comprises a broad spectrum of histo- and immunophenotypes ranging from well differentiated forms closely mimicking normal B cell development to highly abnormal tumors which cannot be subclassified.

P 8 IMMUNOHISTOCHEMICAL CHARACTERIZATION OF SPINAL BURKITT'S LYMPHOMA CELLS AND THEIR NORMAL COUNTERPARTS.


We have investigated the immunologic features of 90 pediatric and 4 adult Burkitt's lymphoma (BL) specimens, to assess the degree of genetic heterogeneity and to determine which markers are of diagnostic relevance for differentiating with other lymphoid tumors derived from T cell (TCL) derived B cell malignancies. The majority of cases were positive for CD10, CD19, CD20, CD22, CD79a, CD34, and CD43. In the T cell cases, the majority of cases were positive for CD3, CD7 positivity was associated with T-helper lineage. In the B cell cases, CD20 and CD22 positivity was associated with B cell lineage. Furthermore, we found that CD10 (in 91% of CD10 and 18% of CD20 MBs) and ICAM-1 (CD54) adhesion molecules, shown to be associated with an 'inactive' antigenic status, were identified in 45% of CD10+/CD77+ (45%) in CD10+/CD77- (55%). Furthermore, we observed coexpression of CD10 (in 91% of CD10 and 18% of CD20 MBs) and ICAM-1 (CD54) adhesion molecules, shown to be associated with an 'inactive' antigenic status, were identified in 45% of CD10+/CD77+ (45%) in CD10+/CD77- (55%). Furthermore, we observed coexpression of CD10 (in 91% of CD10 and 18% of CD20 MBs) and ICAM-1 (CD54) adhesion molecules, shown to be associated with an 'inactive' antigenic status, were identified in 45% of CD10+/CD77+ (45%) in CD10+/CD77- (55%). Furthermore, we observed coexpression of CD10 (in 91% of CD10 and 18% of CD20 MBs) and ICAM-1 (CD54) adhesion molecules, shown to be associated with an 'inactive' antigenic status, were identified in 45% of CD10+/CD77+ (45%) in CD10+/CD77- (55%).
ABSTRACTS - Fourth International Conference on Malignant Lymphoma, Lugano


GELA-LAB, D'ANATOMIE PATHOLOGIQUE HOTEL-DIEU PARIS

The first 1200 cases included in the GELA multicentre aggressive lymphoma treatment trial were reviewed by at least 3 hematopathologists and 1106 cases were intermediate or high grade lymphomas according to the Working Formulation (WF). The 94 remaining cases were classified as low-grade lymphomas (75 cases), Hodgkin's disease (10 cases), carcinoma (6 cases) and other tumour types (3 cases). The 1106 cases comprised follicular large cell (5,2%), diffuse small cleaved (2,35%), diffuse mixed (10,5%), diffuse large cell non-cleaved (55%), immunoblastic (7%), lymphoblastic (3%). Burkitt's (2,6%), anaplastic (8,4%); 2,8% could not be classified according to the WF and 2% were technically unsatisfactory. An immunohistological study was performed in all cases on paraffin sections, using B-cell markers (L26, MB2, LN1) and T-cell markers (UCHL1, CD2) markers. In addition, 108 cases (35,5%) were studied on frozen sections. 770 cases (70%) were classified as B-cell lymphomas and 155 (14%) as T-cell lymphomas; 181 cases (16%) could not be assigned to a B or T lineage. This phenotypic study allowed a more precise subclassification, especially of mixed and large cell groups, according to the Kiel classification. In the diffuse mixed type, 40% were of B-cell origin (centroblastoid-centrocytic, 11%; polymorphous lympho-plasmacytoid 29%); 51% were of T cell origin (Lennert's lymphoma, 12%; T-zone, 11%; LAL-1 like, 18%; others, 10%), and 9% were phenotype unclassifiable. In the diffuse large cell group, 78% were of B-cell type (centroblastoid 65%; immunoblastic, 9%; anaplastic, 4%); 8% T-cell type (plasmocyte, 4.5% anaplastic, 3.5%), and 14% were uncertain phenotype. The majority of cases which could not be classified according to the WF were of T-cell lineage. It will be possible in the future to assess the prognostic value of this immunohistological study since all patients had been entered in the same prospective treatment trial of the GELA protocol.

P 10 A DIRECT COMPARISON OF PERIPHERAL T-CELL LYMPHOMAS WITH THEIR B-CELL, COUNTERPARTS. B. Liao1, D. Todd1, D. Choy2, T. K. Chan1, E. Chu1, F. Ho3

1. University of Medicine and 2. Pathology, and 3. Institute of Radiotherapy and Oncology, Queen Mary Hospital, Hong Kong

The effect of immunophenotype on the clinical characteristics and prognosis of 114 patients with non-Hodgkin's lymphomas was determined. Well-described entities such as mycosis fungoides, lymphoblastic lymphomas and follicular lymphomas were excluded. There were 42 cases of T-cell and 102 B-cell lymphomas. B symptoms were more common in patients with T-cell lymphomas (52% versus 30%, p<0.05) and more patients with B-cell lymphomas had bulky disease (75% versus 71%, p<0.04). T-immunophenotype was associated with significantly higher incidences of liver (48% versus 24%), spleen (48% versus 20%), marrow (43% versus 18%), bone (29% versus 5%) and skin (29% versus 5%) involvement. Gastrointestinal involvement was however more common in B-cell lymphoma (26% versus 10%). Comparable chemotherapeutic regimens were used for patients with either B or T immunophenotype. Doxorubicin-containing regimens were used in 119 patients (CHOP 23, BACOP 47, m-BACOD 49). Other less intensive regimens (COHP or CVP) were used in 22 patients. Three patients received no chemotherapy. The immunophenotype did not appear to affect their complete remission rate, relapse rate, disease-free survival and overall survival.

P 11 IMMUNOPHENOTYPIC CHARACTERIZATION OF PRIMARY GASTRIC LYMPHOMAS USING PARAFFIN-EMBEDDED ENDOCYTOSIS BIOPSY SPECIMENS. M. Betti, N. Pavesi, M. Pastorero, G. Bottero, D. Robutti, D. Pizzamiglio, "Santo Spirito" Hospital, 15033 Casale Monferrato. 1City Hospital, 15100 Alessandria. Italy.

We reviewed the endoscopic biopsy samples of 15 of primary gastric lymphomas previously confirmed on gastrectomy specimens. All were of non-Hodgkin type and were classified using the Working Formulation. 11 were of high-grade lymphomas and 4 of low-grade. 2 of these latter featuring plasmacytoid differentiation. A full immunophenotypic work-up of formalin-fixed and paraffin-embedded biopsy tissue specimens was undertaken. A panel of both monoclonal and polyclonal antibodies effective on routinely processed paraffin sections was used: LC, L26, 4K85, UCHL1, Ber-H2, H1, MAC 387, IgM, kappa lambda, lysozyme and low-molecular-weight cytokeratin. All tumours were of B-cell lineage except in 2 cases of extranodal centroblastoid lymphomas. Being positive with either L26 and/or 4K85. No cases of T-cell or histiocytic lymphoma were present. A T lymphoid reaction was found inside the lymphomas in 8 cases. Light chain restriction of kappa type was demonstrated in only 4 cases, 2 of which were lymphomas with plasmacytoid differentiation. Antibody to cytokeratin highlighted the lymphoepithelial lesions found with variable frequency in several cases. This study emphasizes the usefulness of a panel of antibodies reactive in paraffin-embedded tissue which allowed immunophenotypic characterization even of small routinely processed biopsy specimens obtained from gastroscopic procedures.

P 12 SELECTIVE ELIMINATION OF TD-T-POSITIVE NEOPLASTIC CELLS. R. McCaffrey, K. Bulger, R. Duft, H. Safra. Boston University Medical Center, Boston, MA.

We have previously reported that the chain-terminating nucleoside analogue 2',3'-dideoxynucleosine (ddA) is specifically cytotoxic for TdT-positive (TdT+) cells, especially in the coexpression of the adenovirus transactivating VP16-containing HIV-1 (A/D) inhibitor cofactor (CF). The central role of TdT in mediating the ddA/CF cytotoxicity was established with a murine pre-B cell line made TdT+/CF+ by infection with TdT dDNA retroviral vector: significant cytotoxicity was seen in the TdT+ (daughter) line but not in the TdT-negative (TdT-) parental line. These data suggested the potential clinical utility of ddA/CF in TdT-positive neoplastic diseases. However, because of the concentration of ddA required for killing TdT+ cells (ex vivo 250 μM for 48-72hrs) probably exceeds what is clinically achievable, we sought a more potent ddA derivative. Since substitution of chlorine in the 2-position renders adenine and deoxycytidine resistant to deamination by A/D, we reasoned that 2-chloro-ddA would show similar A/D resistance, without loss of specific TdT substrate recognition properties, and thus be a more active TdT-specific cytotoxic agent. We now report that ddA does not recognize 2-chloro-ddA (Kd > 500 μM), whereas TdT continues to recognize 2-chloro-ddATP as efficiently as ddATP (Kd < 2 μM). After a continuous 72 hour exposure to 2-chloro-ddA, at 5-10 μM, 3 TdT-positive cell lines were killed (60-85% trypan staining), while 3 TdT-negative cell lines were unaffected under similar conditions. When given IP to Balb/C mice at 25μg/kg/d for 3 days, 2-Chloro-ddA caused a transient depletion of TdT-positive thymic lymphocytes (maximal at day 6, with recovery on day 10). As with the parent ddA compound, we speculate that cell death in TdT+ cells results from TdT-mediated 2-Chloro-ddAMP chain-terminating end-additions, which ultimately produce DNA fragmentation. The efficacy of 2-chloro-ddA in a TdT-positive murine disease model is now being studied.
P 13 INDUCTION OF IL2 RECEPTORS ON FRESH LEUKEMIA/LYMPHOMA CELLS. R. McCaffrey, K. Bulger, R. Duff, F. Heskeith, J. Murphy. Boston University Medical Center, Boston, MA.

High-affinity, p55/p70 IL2 receptors are constitutively expressed in several forms of leukemia/lymphoma. To take therapeutic advantage of a novel hybrid toxin, in which IL2 is linked to diphtheria toxin, we have asked whether leukemia/lymphoma cells which do not constitutively express IL2R can be induced to an IL2R-positive state, thus rendering them susceptible to killing by the IL2/diphtheria toxin. This hybrid toxin was assembled from an IL2 cDNA fused to a truncated diphtheria toxin gene, and expressed in E. coli. It specifically intoxicates leukemia and cell lines expressing high-affinity IL2R (ATL cells; Hut-102 cells; C91/P LL cells; IC50 < 1 x 10-7M) but not cells expressing p55 alone (MT-1 cells) or p70 alone (YT-2C2 cells)(IC50 > 1 x 10-7M). To date we have studied high-affinity IL2R-negative leukemia/lymphoma cells from 38 patients (32 CLL; 3 CML; 2 AML; 2 ALL), using as IL2 inducing agents Brostystin I, PHA, a-IFN, and IL3. IL2R status post-induction was defined by the appearance of CD25 reactivity. Scatchard analysis of IL2 binding, or sensitivity to IL2/diphtheria toxin. IL3- and a-IFN had no demonstrable IL2 inducing activity with any sample. PHA induced IL2R on 70% of the CLL samples; Brostystin I induced IL2R on 36% of the CLL samples. These data document that some leukemia/lymphoma cells can be converted eg from an IL2R-negative, hybrid toxin insensitive state, to an IL2R-positive, toxin sensitive state. In vivo modulation of IL2R status could render these forms of leukemia/lymphoma sensitive to the clinical administration of IL2/diphtheria toxin as novel therapy for leukemia/lymphoma.


Interleukin 2 (IL-2) exerts its biological activity through a specific membrane receptor. Using specific monoclonal antibodies directed against the IL-2 receptor, a soluble form of this receptor has been recognized in the serum of patients with malignancies. This soluble part of the human IL-2 receptor (s-IL2R) is released by 2 and 8 lymphocytes and plays a role in lymphoid cell growth regulation. We have measured s-IL2R in sera of 105 patients with hematological malignancies including multiple myeloma, Hodgkin's disease (HD), non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL) and hairy cell leukemia (HCL).

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*p = Mann-Whitney U test.

s-IL2R levels are particularly elevated in advanced stage NHL and CLL. When NHL were analyzed according to the Working Formulation, no significance difference were observed between low, intermediate and high grades. In HD, s-IL2R level increases primarily in patients with constitutional symptoms (P < 0.0003). Out of 9 patients with HD and 11 patients with NHL in complete remission, respectively 9 and 7 patients had a normal s-IL2R value suggesting that s-IL2R could be helpfull in the monitoring of these patients. In B-CLL soluble IL2-binding factor recently identified as CD25, is significantly (3 to 500 times) increased and correlated with the stage of the disease. A good correlation (R=0.61) between soluble CD25 and CD12 can exists in the serum of patients with B-CLL was demonstrated. The interest of both receptors in lymphoproliferative diseases will be discussed.

P 16 INTERACTIONS BETWEEN MEMBRANE-BOUND INTERLEUKIN-2 RECEPTOR (IL-2R), SOLUBLE IL-2R AND NATURAL KILLER CELL-ACTIVITY IN CUTANEOUS T-CELL LYMPHOMA PATIENTS. Gunnerus D, Nieminen P, Wode J, Schmate AJ, Brodin RP, Ziff S, Burg G. *Dermatological Department, 2Department of Virology and Immunology, University of Wurzburg, G. Germany.

Recently, a soluble form of the p55 protein of the interleukin-2 receptor in normal serum has been reported. High levels of this molecule have been demonstrated in normal mouse serum by immunoprecipitation and Western blotting. We have analyzed the soluble IL-2R (sIL-2R) and IL-2R in normal and cutaneous T-cell lymphoma (CTCL) patients. sIL-2R was determined by an enzyme-linked immunosorbent assay using monoclonal antibodies specific for the sIL-2R. The results show that sIL-2R levels were significantly elevated in CTCL patients compared to normal controls. The sIL-2R levels were correlated with the clinical stage of the disease. The sIL-2R levels were also correlated with the number of circulating lymphocytes. These findings suggest that the sIL-2R levels may be a useful marker for the clinical staging of CTCL. Further studies are needed to determine the biological significance of these findings.
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P 17 IL-2 and interferon-gamma production in follicular lymphomas.


Using in situ hybridization with specific RNA radiolabeled probes we analyzed the production of interleukin-2 (IL-2) and interferon-gamma (IFN-γ) in 21 follicular malignant lymphomas (FL). Lymphokine synthesizing-cells were demonstrated in all the 21 FL tested. These cells were present in the interfollicular and follicular areas. Enumeration of lymphokine synthesizing-cells allowed us to demonstrate an heterogeneous production of IL-2 producing-cells, 2 cases out of the 21 FL exhibiting a dramatically higher density of such cells ( 855 and 570 IL-2 producing-cells / cm2 ) when compared with the 19 remaining cases ( mean = 92.15 IL-2 producing-cells / cm2 ). Such an heterogeneity was not evidenced for IFN-γ producing-cells (mean = 77.8 IFN-γ producing-cells / cm2 ). The IL-2 / IFN-γ producing-cells ratio was as a mean 2.69±0.84, emphasizing a preferential induction of IL-2. When analyzed the fine distribution of lymphokine producing-cells we found that IL-2 and IFN-γ producing-cells were preferentially located into the follicular area. As a mean the follicular / interfollicular ratio was 1.82±0.16 and 1.92±0.19 for IL-2 and IFN-γ producing-cells, respectively.

We herein show that T-cell activation defined by lymphokine production are present in FL lymph node, in direct contact with malignant cells. This lymphokine production may play an important role in tumor growth control which is the result of interaction between tumor cells and host derived immune reaction.

**GELF: Groupe d'Etude des Lymphomes Polyclonaux.

P 18 CYTOKINE PRODUCTION AND ENDOTHELIAL CELL ACTIVATION IN LYMPH NODES INVOLVED BY REACTIVE LYMPHADENITIS, HODGKIN'S DISEASE, AND NON-HODGKIN'S LYMPHOMA. L.P. Ruco, D. Ponzoni, A. Stoppani, and F. Monardo. Dipartimento di Biopatologia Umana, Universita' 'La Sapienza', Roma, Italy.

Cryostat sections of 58 lymph nodes were immunostained to investigate the distribution of cells containing IL-1 alpha (VMP18), IL-1 beta (Hvp20 and BRH33), or TNF alpha (B154.7). Furthermore, the presence of cytokines was correlated with the expression of activation antigens (HLA-DR), cells. Endothelial leucocyte adhesion molecule (ELAM-1) was recognized with two recently developed mAbs (SD11 and 29F2). Cells containing IL-1 and/or TNF alpha were mostly detected in those pathological conditions characterized by reactive or neoplastic expansion of the lymph node paracortex (21 cases of Hodgkin's disease, 4 non-Hodgkin's lymphoma T cell type, and 5 diffuse reactive lymphadenitis). IL-1 alpha was detected in scattered macrophages, interdigitating reticulum cells (IDRCs), endothelial cells and in neoplastic Hodgkin's cells. IL-1 beta was mainly observed in macrophages. TNF alpha was present in macrophages and in Hodgkin's cells. ELAM-1 was expressed by high endothelial venules (HEVs) in 17/21 cases of Hodgkin's disease, in 7/4 T cell NHLs and in 5/5 diffuse lymphadenitis. HEVs were stained for HLA-DR in 13/21 cases of Hodgkin's disease, in 4/4 T cell NHL and in 3/5 diffuse lymphadenitis. HEVs might be double negative, double positive for ELAM-1/HLA-DR, or single positive for either antigen. Moreover, cells containing IL-1/TNF alpha were often detected in close spatial relation with ELAM-1+ cells. In pathological conditions characterized by reactive or neoplastic B cell proliferations (12 cases of reactive lymphadenitis with follicular hyperplasia and 16 B cell NHLs) cells containing IL-1/TNF were extremely rare. A few ELAM-1+ cells were observed in 2/2 follicular lymphadenitis and in 1/6 B cell NHLs. HLA-DR+ HEVs were more numerous and were detected in 6/12 follicular lymphadenitis, and in 8/16 B cell NHLs. Our results suggest that tissue architecture involving B cell or T cell areas are regulated by different cytokine networks. Furthermore, they provide circumstantial evidence that IL-1/TNF production may be responsible for HEVs activation during immune responses involving the 1 cell area.

P 19 INTERLEUKIN 2 (IL-2) IN LYMPHOMAS. A PHASE II MULTICENTRIC STUDY.
Hôpital Saint-Louis - 75010 Paris - France.

Responses have been observed in lymphomas after IL-2 infusion with or without lymphokine activated killer cells (LAK). In order to better evaluate the activity of r-IL-2 a phase I/II study was started in non-Hodgkin's lymphomas (NHL) and Hodgkin's disease. Three type of lymphomas were included: 1) low grade NHL in progression after chemotherapy including an anthracyclines. 2) aggressive NHL refractory to initial treatment or refractory to salvage therapy. 3) Hodgkin's disease relapsing after autologous bone marrow transplantation (ABMT) or refractory to therapy. r-IL-2 (Hoechst UCLAF 49637) was administered by continuous infusion 20 MU/m2 for three cycles of 5 days, 4 days and 3 days at 9 days interval. 33 patients have been included, mean age 44 years, 11 low grade NHL, 15 high grade NHL and 7 Hodgkin's disease. In 12/89, 21 pts are evaluable for response. 26 pts received during their first cycle 100 % of the dose. 2 CR lasting 3-6 months were observed in aggressive lymphomas over 9 pts evaluable. 2 dissociated responses over 9 pts were observed in low grade lymphoma including one macroglobulin. No response has been observed among 3 Hodgkin's lymphoma. Severe toxicity in 6 pts led to interruption of treatment : cardiac 2 pts, neurological 2 pts, pulmonary 2 pts. 2 pts died of progressive disease. 1 pt refused to pursue treatment. r-IL-2 shows some signs of activity in heavily pretreated lymphomas. More patients will be included in the study to better determine response rate among the different subtypes of lymphoma and updated results presented.
An increased incidence of non-Hodgkin's lymphoma (NHL) is well recognized in primary as well as 2ndary ID states. The precise nature and mechanism for initiation and progression of these tumors is unknown. We undertook a retrospective study of 15 patients (pts) with 2ndary ID and NHL who were seen and treated at the University of Chicago between 1983 and 1989, to determine if there were distinguishing features among one group (gp) of pts with post-transplant lymphoproliferative disorders (PTLD) (29 pts) and a second gp of pts with 2ndary ID due to other causes (4 pts who received chemotherapy (CT) or radiation therapy (RT) for Hodgkins disease (HD) or for breast cancer (1 pt), and 1 pt with HIV-associated NHL). In the PTLD gp, there were 6 males (M) and 3 females (F), aged 1-62 yrs (median 41 yrs). All the pts had received cyclosporin; median time to development of NHL was 7 yrs but all but one had NHL in extranodal sites (3 pts in the allograft, 2 pts in the nasopharynx, 1 pt in the gastrointestinal tract, 1 pt in the brain and 1 pt in the abdominal wall). Pathologic diagnoses in this gp included 3 pts with immunoblastic lymphoma (IL), 3 pts with diffuse large cell lymphomas, 1 pt with small non-cleaved lymphomas, and 1 pt with polymorphic lymphoid proliferation. Immunoglobulin (Ig) gene rearrangements were observed in 3 of 4 pts in which the tests were performed. Cyto genetic analysis was performed on 3 pts. Trisomy 11 was observed in 2 pts; the third pt had a normal karyotype. Including these cases, trisomy 11 has now been observed in 4 of 5 pts with PTLD for which cytogenetic data are available. Three of the pts are alive and free of disease following reduction of cyclosporin; the remaining 2 pts died of other complications. In the second gp, there were 3 M and 3 F, aged 22-52 years (median 32 yrs), median time to development of NHL was 9 years. The 4 post-MD pts had received both CT and RT and were previously treated for recurrent HD. All the pts in this gp presented with stage IV disease. Pathologic diagnoses included 3 pts with small non-cleaved lymphoma, 2 pts with IL and 1 pt with lymphoblastic lymphoma. Cytogenetic analyses of 3 post-MD pts revealed abnormal karyotypes with multiple abnormalities; only 1 pt had a lymphoid specific abnormality involving 1q,22. The pt with HIV-associated NHL had a c(8;14)q(24;27). We are currently performing additional follow-up on these patients. Thus, based on our findings and the literature, PTLD tend to be heterogeneous, have a shorter latency period, progress from a polymporphic lymphoid proliferation aggressive NHL, may spontaneously regress and are associated with trisomy 11. NHL following other 2ndary ID states tend to have a longer latency period, present with high grade histology, and behave aggressively. This suggests that the mechanism for disease progression may differ in the two subgroups.

Without help of lymph node histology, distinction between chronic lymphocytic leukemia (CLL) and leukemoid reaction (LR) may be difficult. We investigated whether Southern blot analysis of peripheral lymphocytes for chromosomal translocations may be of help. The translocation t(11;14)(q13;q32) involving the immunoglobulin gene is infrequently involved in CLL, NHL and multiple myelomas. The BCL-2 gene is involved in the t(14;18)(q32;q11), and is characteristic of follicular lymphomas and a minor part of diffuse large cell lymphomas. The c-MYC oncogene is frequently rearranged in Burkitt's lymphoma. Immunoglobulin (Ig) gene, BCL-2, BCL-6 and c-MYC were studied in 64 blood, 2 bone marrow and 2 lymph node samples obtained from 49 patients with B-CLL. All but 2 leukemias were CD5 positive. All cases showed the Ig-heavy chain gene rearrangements. Eight cases had 3 or more rearranged JH bands, indicating oligoclonality or the occurrence of additional alterations within the IgH genes. No c-MYC rearrangements were found. One CD5 negative case had a BCL-1 rearrangement with an unusual translocation breakpoint, reciprocally involving 2 different JH-genes and 2 different parts of the BCL-1 locus. During follow-up this patient developed polymporphic hematoytosis. The other CD5 negative case showed clonification of strong rearranged BCL-3 and JH bands, indicating a t(14;18) in the tumor cells. Interestingly, 2 CD5 positive cases with multiple rearranged JH bands of different intensity, had a very weak rearranged BCL-2 band, suggesting either a partial deletion of the involved allele, or more probably, the occurrence of an independent B-cell clone with a t(14;18) additional to the CLL. In conclusion, the concurrence of rearrangements of BCL-1 and BCL-2 with the absence of CD5 expression further indicates that these particular leukemias represent leukemic NHL instead of B-CLL.

P 23 ACTIVATION OF CELLULAR ONCOGENES IN HUMAN LYMPHOMA. H. Thower, M. Jubier, A. Roepbroek, A. Van der Velden, Dr. L. ema, Klinischen Universitäten Köln, F.R.G. and Dept. of Biochemistry, University of Hiemgen, NL.
Cellular oncogenes are activated in tumor cells by various mechanisms. We investigated the role of cellular oncogenes in human lymphoma. Northern blot experiments indicate that several genes, i.e. c-met, c-fos, c-erb and c-fgr, are constitutively expressed in the lymphoma cells. Aberrant short transcripts of the c-fos gene were detected in about 50% of the Burkitt's lymphoma and Hodgkin's disease derived cell lines. cDNA cloning and S1-nuclease experiments revealed that the short transcripts use cryptic promoters, start within exon 16 of the c-fos gene and bear the protein kinase domain. There is no evidence for structural alteration of c-fos in the lines which express the aberrant transcripts which may indicate a novel mechanism for oncogene activation in human lymphoma cells.

P 24 Evaluation of transcription (t)14;18) by polymerase chain reaction and conventional Southern analysis of DNA from 29 cytogenetically positive patients. H. Land, P. B. Dield. M. Karlisen, M. Sohn, F. Kristiansen, S. Knuutila. Dept. of Med Genetics, Univ. of Bergen and Rad Therapy, University of Helsinki, Haartmaninkatu 3, 02290 Helsinki, Finland.
DNA from 29 Finnish patients with t(14;18) in their lymph node cells was studied by means of the polymerase chain reaction (PCR) and Southern blot analysis (SB) of DNA from 16 of these patients was studied both by PCR and Southern analysis. PCR amplification was carried out using the Taq polymerase (Geb) and two different primers to the 3' end of the Bcl-2 gene region on chromosome 18. 17 universal primer (3 ACCGTGAGGACGACC T5) was used for heavy chain-joining segments of the immunoglobulin coding region on chromosome 14. These regions are known to be the most recurrent junctional regions in the translocation (14;18). Four of the presumed rearrangement bands (positive cases) were confirmed with a radioactive labeled Bcl-2 specific probe. In Southern analysis of DNA, the restriction fragments were blotted on agarose gel on to nylon filters, and probed with a Bcl-2 major breakpoint probe, which is a 3.5 bp EcoRl fragment, complementary to the Bcl-2 gene. In our case Southern blot revealed only major breakpoint region (MBR) rearrangements. PCR analysis showed the presence of rearranged DNA from the 28 patients studied (97%). In Southern analysis only 6 of the 17 patients studied (35%) were positive with the MBR probe; however, 10 of the 11 Southern-negative patients were also PCR-negative. This means that PCR and Southern blot results were equal except in one case. In this case PCR was positive, whereas Southern blot negative.
Our results suggest that up to 57% of t(14;18) rearrangements in the MBR can be detected by PCR with previously described techniques. In the above study, PCR results to be at least as good as the Southern analysis of DNA in MBR rearrangement detection. According to other studies (Bo-Yee Ngan et al., Blood 73:1896:1759), up to 25% of breakpoints do not fall within the MBR region but occur at a second, distant genomic breakpoint. This might be the case in MCB rearrangements of the BCL-1 locus. This locus is common breakpoint region can be detected using only three oligonucleotide primers, because the MCR primers are complementary to the JH universal primer. Distinguishing rearrangement bands from occasional irrelevant bands is not always unambiguous. Probing PCR-amplified DNA fragments with both chromosome 14 labeled oligonucleotides may be a useful method to exclude such irrelevant bands. We are currently conducting studies using this technique.
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P 25


Gunmar Jullum, Mari Miettinen, C Edvard Smith, Lennart Hammarström, and Gösta Cahtron. Department of Clinical Haematology and Oncology, Department of Medicine, and Department of Clinical Immunology, Karolinska Institute at Huddinge Hospital, S-141 86 Huddinge, Sweden

Clonal rearrangements of the T-cell receptor (TCR) genes are regular findings in T-lymphoproliferative malignancies, but are found also in some cases of non-T-cell acute leukemias and blastic lymphomas, and rarely in B-cell chronic lymphocytic leukemia (CLL). The TCRβ gene on chromosome 7 band q45. We have screened for evidence of clonal TCRβ gene rearrangements in B-CLL cases and compared the immune phenotype, cytogenetic findings, and clinical course of TCRβ- and TCRα-CLL cases.

Twenty-eight patients with B-CLL were studied. The clonal B-cell proliferation was always documented by cell surface markers (SmIg+, CD19+, CD20+) and by clonal immunoglobulin μ gene rearrangements. DNA was extracted from isolated leukemia cells, and digested with the restriction enzymes HindIII and BamHI. Cleaved DNA was separated by electrophoresis in an agarose gel, and then transferred to a nylon filter by Southern blotting. Filters were hybridized with 32P-labelled probes identifying μ and TCRβ gene segments. Clonal TCRβ rearrangements were found in five patients (10%). The SmIg phenotype of these cases were μκ, μκ, μδκ, μκλ, γλ, and γκ, respectively. One patient had a Rai stage 0 disease with disease progression for 4 years. One patient had stage 1 disease and no evidence of disease progression for 12 years. This patient was stage 0 disease with clinical transformation within 9 months from diagnosis. One patient with stage IV disease developed 6 months from diagnosis. Two patients with stage II disease developed clinical transformation within 5 years from diagnosis. One patient with stage IV disease developed 6 months from diagnosis.

Thus, about 10% of B-CLL cases was in TCRβ cases. No common immune phenotype or clinical features were identified, but there was a high incidence of 6q23 chromosomal deletions in TCRβ+ patients as compared to TCRα- patients.

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EXPRESSION OF c-myc P52 PROTEIN IN NON-HODGKIN'S LYMPHOMAS: ITS RELATION TO HISTologic SUBTYPE, CLINICAL STAGE AND RESPONSE TO THERAPY.

G.A. Pangalis, P. A. Ioannides, P. K. Nicolaoulopoulos, N.A. Boutsikas, A. Theofanous, and D.A. Spandidos. Department of Pathology, Athens School of Medicine, and the Laboratory of Pathology, University of Athens School of Medicine and Sibellion Research Center, Hellenic Research Foundation, Athens, Greece.

The expression of c-myc oncogene in the lymphoid tissue of 181 patients of non-Hodgkin's lymphomas (NHL) was studied using the specific monoclonal antibody c-myc 1-5E10 and the 3-step streptavidin-biotin immunoperoxidase method in paraffin sections. The staining pattern was mainly nuclear but cytoplasmic reaction was also occasionally observed. The percentage of positive cells per total cell population was estimated and all cases were classified into four groups: 0-15%, 16-30%, 31-45%, and >45% positive cells. In twelve reactive lymph nodes studied, mainly peripheral center cells were stained with a percentage of positive cells less than 15%. The distribution of positivity in relation to the histologic subtype using the Working Formulation was as follows:

<table>
<thead>
<tr>
<th>Grade of Malignancy</th>
<th>No of Cases</th>
<th>Percentage of positive cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>66</td>
<td>51%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>24</td>
<td>20%</td>
</tr>
<tr>
<td>High</td>
<td>31</td>
<td>5%</td>
</tr>
</tbody>
</table>

As it was clearly evident from this table fifty-six per cent of our cases had more than 15% positive cells and the percentage of positive cells was greater in the high grade than in the intermediate grade NHL. This correlation proved to be statistically very significant (p<0.001). When our results were compared with the clinical stage, response to therapy and freedom from the clinical stage, no relation was observed between c-myc protein expression and the clinical stage (p<0.01), response to therapy and relapse rate of our patients (p<0.05). We concluded from our study that the expression of c-myc p52 protein in NHL may predict their prognosis.

P 27

NON-IPSS IDENTIFICABLE LYMPHOMAS IN SERBIA

N. Milanović, S. Jelić, V. Kovčin, M. Babović, M. Marinčević, Institute za Onkologiju i Radiologiju, Belgrade, Yugoslavia

Non-IPSS identifiable lymphomas are characterized by the absence of more than 5% abnormal lymphoid cells and are supposed to be more or less confined to the tumor site. During the period 1985-1989 the authors have observed 20 patients with non-IPSS lymphomas. 11 males and 9 females, all patients originating from Serbia. In 6 patients the first symptoms were abdominal colics requiring laparotomy. In 3 patients ileus, in 1 disphagia and in 5 perforation with hemoperitoneum. Resection of involved part of the intestine was performed in 17 patients. 9 of them had on histological examination lymphoma tissue on apparently healthy section line, or lymphoma affection of other parts of the GI tract on laparotomy.

According to working formulation, 3 had low grade, 3 intermediate and 14 had high grade histology. Affection of extra-GI lymphoid structures was found in 12 patients, of the nasopharynx in 8/15, of the bone marrow in 2/15, and in extrametaplastic tissues in 5/15 patients where it was looked for. According to the 1982 Crowther classification, 55% of patients were in stage IV, 35% in stage III and 10% in stage I. On serums/urine immunohemocytanalytic analysis, two patients had monoclonal immunoglobulin (IgG lambda and IgA kappa respectively) and I had free gamma chains in urine. Increased levels of circulating immunocomplexes were detected in all patients, and 6 had polyclonal hypergammaglobulinemia.

5 patients were treated with chemotherapy alone, 13 with aggressive alternating regimens and 6 with high intensity chemotherapy schedules. 3 patients are alive and in complete remission for over 5 years (7/11 of stage IV and 3/8 with stages I/II/III, 8/14 with high grade and 3/6 with low-intermediate grade histology).

Our findings suggest that GI tract lymphoma infiltrates and clinches systemic involvement in the majority of cases. While in a few cases this may have a more extensive than expected from literature data. Surgical procedures have diagnostic, tumor bulk reducing and perforation/hemorrhage preventing function. As nearly all patients are Ann Arbor clinical stage IV, Crowther classification does not affect the potentially curative therapeutic approach, which seems to be chemotherapy.

P 28

BURKITT'S LYMPHOMA: A TWENTY YEAR RETROSPECTIVE SURVEY

N.K. Dithenso Abiaho, A.O. Nwogbe, and L. Nwoko, Department of Medicine, Human Pathology and Community Health, University of Nairobi, Nairobi, Kenya.

A retrospective survey of Burkitt's lymphoma (BL) as reported in the Kenya Cancer Registry was carried out covering the years 1970 to 1986. A total of 786 cases, 491 of whom were male and 295 were females, were recorded. In 64 cases (8.3%) the disease was reported to be of African origin, involving the cold, wet highland savannah and woodland areas. Over the years there were significant changes in areas of occurrence, site involved, age or median age. The distribution of BL was highest in late sixties to early seventies, gradually dropping to lowest in 1981 after which it started rising gradually to mid-eighties.

It appears that the environmental factors associated with the development of BL in Kenya have not changed over the last 20 years. It also appears that there is a shift in part of the country more to the so-called African type of BL while the non-African type is found in the colder mountain regions.
P 29 CLINICAL AND PATHOLOGICAL FEATURES OF EXTRANODAL NON-HODGKIN'S LYMPHOMAS. F. d'Amore for the Danish Lyfogroup.

ABSTRACT

The clinicopathological features of 463 consecutive and unselected cases of extranodal non-Hodgkin's lymphoma (NHL) were studied. The case material was gathered prospectively in a regional Danish multicenter study, Lyfog-1, conducted between 1983 and 1988. The extranodal cases represented 37% of all cases of NHL (n=1257) registered in the study. They had a mean age of 61.6 years (range 6-94 years) and 53% of them were women. The most frequent site of involvement was the gastrointestinal tract with a total of 135 cases (30%), 87 (19%) localized to the stomach and 52 (11%) to the gut. A strong female predominance was found for thyroid lymphomas (female:male ratio = 7.1) and salivary gland lymphomas (female:male ratio = 2.5). Lymphomas of the gut and lungs were more common in male patients (male:female ratios respectively 2.4 and 2.3). Stage I and stage IV were the most frequent clinical stages. Most cases of localized disease occurred in salivary gland lymphomas (71%). High-grade histology was the most common, in particular the large cell, diffuse type found in 23% of the cases.


The assessment of the infiltration of cardiovascular structures in the staging of mediastinal non-Hodgkin's lymphoma (NHL) lymphomas may be clinically relevant. Transesophageal echocardiography (TEE) has been used for several years to obtain high quality images of the heart and of the mediastinal vessels. The currently used ultrasonic probes are smaller than the standard transesophageal probes and allow to obtain both a high resolution two-dimensional image of the mediastinal structures and a qualitative and quantitative evaluation of the blood flow within the heart and the mediastinal vessels. We used TEE in the staging of 21 consecutive patients (pts) with mediastinal lymphomas (6 HD, 13 NHL) and in the restaging of 3 additional pts previously treated for HD (2 pts) or NHL (1 pt) with residual or recurrent mediastinal masses. Four pts repeated TEE during the follow-up; overall we performed 30 examinations on 24 pts. The procedure lasted 15 to 45 minutes (mean 35) and was well tolerated by all pts. As compared to conventional tomography (CT), TEE gave additional informations in 13 out of 24 pts. It was useful mainly in assessing the compression or infiltration of superior vena cava, of pulmonary veins and of the pulmonary artery or its branches and in detecting or excluding paracardial infiltration. In one pt with HD and in one with mediastinal mass that relapsed 7 years after radiotherapy, TEE allowed to detect an intracardiac mass extending into the pulmonary artery and to suggest the presence of a cardiac sarcoma (confirmed by open-heart biopsy). On the other hand, in one case of HD the detection of the mediastinal lymph nodes (5.2 cm) detected by CT scan, were not identified by TEE. In conclusion, TEE may be useful as a complement to other imaging techniques in the staging and follow-up of mediastinal lymphomas. It appears to be a safe, low cost procedure that can be performed even bedside and seems to be particularly useful in those pts with hyperresponsiveness to contrast media. Further studies are necessary in order to define the cost/benefit ratio of TEE in this particular field, and if TEE should be suggested routinely or only in selected cases.


The indications for biopsy in patients with presumed NHL include: establishing a diagnosis, confirmation of relapse, evaluation of suspected transformation to high grade pathology and histological assessment of residual radiological abnormalities after therapy. Core biopsy diagnosis carries implications for treatment and prognosis and demands adequate tissue specimens. The accuracy of diagnosis may be enhanced by immunocytochemistry, for which fresh tissue may be required. In the absence of peripheral lymphadenopathy, methods of obtaining tissue are required which avoid laparotomy or mediastinoscopy.

Twenty six biopsies have been performed under CT(22) or ultrasound(4) guidance in 21 patients, age range 31-86, with known or suspected NHL. Nineteen patients had intrathoracic disease and 1 mediastinal mass. Tra-cut type cutting needles, 14-18G, were used in conjunction with a hand held biopsy “gun”, and an average of 2 passes made.

The procedure, performed under local anaesthesia, was well tolerated. There were no complications. The platelet count and clotting screen were normal in all but 1 patient with a platelet count of 30x10^9, who was successfully biopsied under platelet cover. A primary histological diagnosis was made in 77 patient (6 NHL, 1 teratoma). In only 1 of the 6 patients with NHL was laparotomy required to confirm the subtype of lymphoma. Relapse was confirmed in 14/14 biopsies; 6/8 biopsies in patients with previously diagnosed follicular lymphoma showed transformation to high grade histology and were treated appropriately. Residual radiological abnormalities were biopsied in 3 cases: 2 patients initially treated for diffuse centaloblastic lymphoma were found to have follicular lymphoma and a negative result was subsequently confirmed at laparotomy. Two other patients had biopsies to obtain fresh tissue for immunophenotyping.

Guided cutting needle biopsy with the biopsy “gun” was successful in providing diagnostic specimens in all cases. Only twice was laparotomy necessary for further clarification. This technique is therefore of great value in the management of NHL and may avoid the need for more invasive investigations.


The subgrouping of low and high NHL is usually easy providing the amount of biopsy material is sufficient and of good quality. It is, however, sometimes difficult to obtain such biopsies, particularly if e.g. only intraabdominal involvement is present. There is in these cases a need for other diagnostic techniques. Besides this, the histopathological subgroup may vary between different lymph nodes/lymph node regions.

Fifty patients with NHL were examined with MRI in order to analyse whether it was possible to distinguish in vivo between the two major prognostic groups low grade and high grade according to the Kiell-classification. Most high grade NHL nodes (15/24, 62%) had an inhomogeneous signal intensity at MRI, in contrast to low grade NHL where it was homogeneous in virtually all patients (18/20, 90%, p<0.001). A homogeneous picture was also found in a previously low grade NHL which, at the time of examination, had transformed into a high grade NHL. Necrosis, detectable in the histopathological sections, was usually (5/6 cases) associated with an inhomogeneous image. An inhomogeneous image was, however, found in 12/44 cases (27%) without any signs of necrosis in the histopathological sections. Patients with high grade NHL and a homogeneous image tended to have a better survival than those with an inhomogeneous image. It thus appears to be possible to predict prognostic grade in vivo using MRI.

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THE ASSESSMENT OF TREATMENT RESPONSE IN LYMPHOMA BY IN-VIVO ICMGE IMAGEd 31P MAGNETIC RESONANCE SPECTROSCOPY. Smith S, Davies J, Edwards R. The Magnetic Resonance Research Centre & Departments of Haematology, University of Liverpool. P.O. Box 147, Liverpool L69 3BX.

In vivo 31P MRS allows the non-invasive assessment of intracellular pH and tumour bioenergetic pathways via the relative levels of high energy substrates phosphocreatine (PCr), adenosine triphosphate (ATP) and inorganic phosphate (Pi). Phospholipid flux through the lipid membrane mediates the phosphomonoesters (PME) and phosphodiesters (PE) spectra, which may be more detailed by imaging. We have used a 1D-monochromatic chemical shift imaging (1D-CSI) technique to study the 31P MRS characteristics of non-Hodgkin's lymphomas (NHL) and the alterations in tumour metabolism that are associated with a response to chemotherapy.

Nine patients (age range 32-78, 6 female) with bulky abdominal NHL (3 high, 5 low and 1 intermediate grade) were studied prior to and then serially (mean no of studies = 5, range 3-18) after completing chemotherapy. MRS studies were performed on a 1.5 Tesla G.E. Sigma system using 8 cm surface coils and a 1D-CSI localisation technique.

High grade NHL had larger pretreatment Pi resonances in relation to either PME or ATP producing differences in the PME/ATP (p=0.016), and Pi/ATP (p=0.006) metabolic ratios. When compared to low grade NHL, this probably represents a larger hypoxic cell fraction in high grade NHL due to outgrowth tumor blood supply.

Marked changes in tumour metabolism were seen after commencing chemotherapy, and before alterations in tumour size. In high grade NHL tumour deactivation (1ATP, 2Pi) was seen within 24 hours following combination chemotherapy. While in low grade NHL, no changes with oral chlorambucil similar changes were detected by days 10-28. Tumour deactivation was followed by marked increases in the PME/PE consistent with L-62 mobilisation of membrane components and cell lysis. Increases in the PME/PE ATP ratio (51-2664) were seen in all tumours after chemotherapy and growth in the two abdominal lesions in tumours 1A and 2C. Analysis of the shift in tumour pH was seen in 7 of the tumors after chemotherapy.

These studies illustrate the potential role of 31P MRS in the assessment of treatment response. Increases in the PME/PE/ATP ratio may be an early marker of response to chemotherapy in lymphomas.


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PREDICTING SURVIVAL IN HIGH AND INTERMEDIATE GRADE NON-HODGKIN'S LYMPHOMA (NHL). L. Hayward, B. Preusscott et al for the Scotland and Northern Ireland Lymphoma Group (SNLIG), Edinburgh, UK

Between 1979 and 1987, 1130 patients with Working Formulation SNLIG registered with SNLIG. Clinical, haematological and pathological data were analysed on 972 adult neoplastic lymphomas (208 excluded). Median available follow-up was 47 months. A Cox multivariate analysis was used. 310 patients were excluded to provide an independent test group. The best PLOG model was based on (rank order) performance status, age, liver involvement, and lymphoma stage. Best survival was predicted for fit young patients, with stage I or 2, no B or H and normal ECOG and LMR.

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Prognostic model are used to better determine group of patients with different prognosis who are eventually candidates for different therapeutic strategies. Multivariate analysis on LNH 84 lymphoma patients (J.G.O. 1989) led to a prognostic model including three clinical parameters: tumoral mass > 10 cm, number of bone nodules sites: Stage IV or IV and one biological parameter, increased LDH level. Partition in three index were established: index 1, no adverse prognostic factors; index 2, existence of one or two clinical parameters with normal LDH or increased LDH alone; index 3, existence of three clinical parameters with normal LDH or increased LDH with one to three others parameters. For each level, the estimated 3-year overall survival was 88%, 71% and 41%. LNH 84 protocol was a simple score which study has a 75% CR rate and a probability of survival of 60%. The goal of LNH 87 protocol was in patients < 70 to compare by randomization our previous LNH 84 arm to other chemotherapy regimens in different prognostic subgroups. From 10/87 to 12/89, 1562 aggressive lymphomas have been included in LNH 87 of whom, 1282 were < 70 y. 490 pts are evaluable in the control arm and 498 in the others arms. Mean age 49, 6 y. Histology was according to Kiel: 23% B, 77% T, 1% I. 84% H, 10% L. 13% I, 7% M, not classified 6%. Stage: 1-IE 11, II- 144, III-111, IV- 219. Tumor involvement: 0%, 8%, 18%, G 44%, H 110%, 1%, 2%, 3%, not classified 6%. Stage: 1-IE 11, II- 144, III-111, IV- 219. 15% of patients received 2 courses of therapy, 75% 3 courses. External irradiation for 34% and chemotherapy for 66%. Remission rate was 65%, 51% for the two groups was highly significant with a probability of survival at 15 months of 80%, 65%, 35% for each index level. (p < 0.001). The bone model was used for others arms and allowed a highly significant partition (p < 0.001) in 3 levels. Preliminary results of LNH 87 protocol validate for survival the proposed prognostic index and can be used in other regimens.

P 36


We retrospectively studied with Log Rank and Cox analysis (SAS software, VAX nt2401 computer) the prognostic factors for survival in 39 pts with LPS, without peripheral lymphadenopathy and leukemic involvement, diagnosed between Jan 1974 and Feb 1989, (median age, 65, range 34-81, M/F=0.55). The last 46 pts were negative for HIV. Using the Working Formulation, histologic subtypes were: A: 32 pts, B and C: 11 pts, Intermediate lymphocytic lymphoma: 2 pts, E: 1 pt, F: 4 pts, G: 5 pts, H: 4 pts. Immuneonocytome was B in 84% and T in 16% of cases. 47 pts had one or more cytopenia, 16 pts had 6 or more symptoms, 40 pts underwent splenectomy (spl) before chemotherapy (CT) (group 1), 15 pts did not (group 2). Stage (ANN-ARROW) was in group 1: 3 pts, 1E; 1 pt, 1E 2 pts, 1E 4 pts, 1E 4 pts, 1E 2 pts, 1E 4 pts (diagnosis obtained with lymph node biopsy guided by CT-scant), stage 1: 17 pts, all with bone marrow involvement. Bone marrow involvement was more frequent in group 2 (p=0.04), so other initial parameters differed between the 2 groups. After spl there was one postoperative death, 2 other pts died before starting CT, 9 pts were carefully watched, 4 pts received Chemotherapy alone for 1 to 4 years (protocol A), 19 pts 6 to 8 MOPP and 12 cycles (Cyclophosphamide 1 g/m²/d, Vincristine 1.4 mg/m²/d, Bleomycin 10 mg/m²/d, Predonilone 60 mg/m²/d) -1, followed by a maintenance with Chlorambucil for 1 to 3 years (protocol B). 2 pts were intermediate grade NHL were treated with CHOP protocols or LNH84 regimes (a third generation CHOP regime with increased doses of Adriamycin and Cyclophosphamide). In group 2: Protocol A was performed in 7 pts, protocol B in 6, CHOP in 2, splenic RXT in 1, watchful waiting in 3. The following parameters were analysed for survival: age, sex, symptoms, spleen size, staging, bone marrow involvement, histology, complete initial blood count, albumin, gamma globula

lin and LDH level, splenomegaly, further treatment. The same parameters and weight of the spleen and blood counts after spl were studied. In group 2 was 42 months. In Log Rank analysis, the only factors associated with longer survival duration were: age < 55 (p=0.03), male (p=0.04), albumin > 35g/L (p=0.03), initial hemoglobin level < 10g/dL (p=0.01), spl (p<0.001). Age and spl are independent and further treatment had no prognostic significance. A Cox analysis found the best factors predicting survival duration was spl (p=0.0001), initial hemoglobin level (p=0.03), age (p=0.03), hematologic malignancy and further treatment as the most powerful association was spl and albumin (p=9.10^-4). In group 1, 3 pts had one or more initial cytopenia, which disappeared in 5 of them after spl. At the moment, the initial cytopenia factors were initial hemoglobin level (p=0.004) and hemoglobin level (p=0.004) and platelets (p=0.002) after spl.

Cytopenias are usually at presentation in LPS, and in general correctly corrected by spl.

LPS are low grade non hodgkin's lymphomas. Our findings suggest that spl improves survival in LPS at least if it is associated with correction of anemia and thrombocytopenia. Initial albumin level is also of important prognostic value.
ABSTRACTS - Fourth International Conference on Malignant Lymphoma, Lugano

P 37
AGE AS A PROGNOSTIC FACTOR IN 537 PATIENTS WITH NON-HODGKIN'S LYMPHOMA ENTERED IN CORTICOSTEROID TREATMENT. Stage III and IV patients with non-Hodgkin's lymphoma (NHL) were treated with 3 consecutive, prospective, randomized trials, comparing different chemotherapeutic and radiotherapeutic regimens. In the first study (351 pts) all histologies were included, in the second study (47 pts) only follicular growth pattern and in the third study (127 pts) only mixed and diffuse growth patterns were included. Only the 357 pts with age less than 70 were evaluated for this study. Pts were prospectively followed-up, and progressions, relapses, treatment side effects and deaths recorded. Data were updated November 1989. The landmark used was to compare survival curves between 3 age groups (<50, 50-69 and 60-70 years); there were 210 pts with age less than 50, 148 pts with age 50-59, and 199 pts with age 60-70. Survival in pts < 50 yrs was significantly higher than survival in pts 60-70 yrs. The survival difference in younger pts > 60 yrs was significantly higher than survival in pts 60-70 yrs. As far as growth pattern, diffuse histology was more represented in younger pts but not at a significant level. As far as working formulation, intermediate and high grades did not significantly differ in younger vs younger pts. Only 9 pts had stage I and II disease, due to entry criteria for these trials. Stage III was more frequent in younger pts, whereas stage IV was more frequent in pts > 60 yrs, but not at a significant level. Older pts however had a statistically significant increase in Waldenstrom's ring (21% in age group 60-70 vs 15% in age group less than 50, p<0.01). Systemic symptoms did not differ between the different age groups. As far as 3-yr progression-free survival was evaluated, there was no significant difference between the age groups, with 50% CR observed in younger vs 48% CR in older. As far as survival, there was a significant lower survival in pts between 60 and 70 yrs of age in comparison with younger pts.

In conclusion, age in pts with NHL included in prospective randomized trials of EBMT Lymphoma Group since 1975 and with an upper age limit of 70 yrs was significantly associated with survival, but not with the achievement of complete response. Age is a prognostic factor that requires careful interpretation. In fact, three pts of pts with NHL are older than 70 yrs of age and were not included in these clinical trials. Therefore, conclusions on age as prognostic factor among pts with NHL must always take into consideration this important methodological aspect. Nevertheless, from this EBMT study, it appears that survival is lower in pts > 60 yrs of age in comparison with younger pts.

P 38

In prior publication, we have identified tumor burden (TB), serum level of lactate dehydrogenase (LDH) and age as the major independent factors. In 300 patients with diffuse large cell lymphoma (DLCL) treated with CHOP-Bleo (Blood 74:551-567, 1989). Therapeutic model for staging classification (MDACC) was proposed. In order to validate it, we have applied the same criteria to 243 cases of intermediate grade lymphoma (IGL) treated from 1984-1988 which included 203 pts with DLCL. Treatment for Ann Arbor (AA) stages I and II evaluated as: IV consisted of alternating cycles of CHOP-Bleo and CMN (Cyclophosphamide 750 mg/m², Mitoxantrone 100 mg/m² and Leucovorin rescue, VP-16 100 mg/m² × 3 days, Methotrexate 40 mg/d x 4 days). Pts with stage I received CHOP-Bleo only. XRT was also given to stage I-III pts. CR was attained in 189 pts (78%). With a median follow-up of 30 mos, overall survival at 5 yrs was 83%. There was no significant difference in the 5-yr survival of patients in AA stages I, II, and III (78-85%), but stage IV patients fared worse with a 5-yr survival of 55%. MDA stage was determined by TB and LDH levels according to published guidelines. Analysis were as follows:

<table>
<thead>
<tr>
<th>Stage</th>
<th>N</th>
<th>5-Yr Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>50</td>
<td>88%</td>
</tr>
<tr>
<td>B</td>
<td>86</td>
<td>88%</td>
</tr>
<tr>
<td>C</td>
<td>76</td>
<td>80%</td>
</tr>
<tr>
<td>D</td>
<td>38</td>
<td>38%</td>
</tr>
</tbody>
</table>

We conclude: 1) The proposed system has a better prognostic discrimination than the Ann Arbor Classification System; 2) the currently treated pts should show better survival than the older group, suggesting that this time would be needed for a more definitive conclusion.

P 39

Seventy thirteen seventy (737) patients with aggressive NHL were treated with LNH44 protocol (Coiffer et al., Clin. Oncol., 1989; 7: 1018). Overall and failure-free survival rates were not significantly different for pts < 70 yrs vs pts > 70 yrs. Out of these patients 208 were studied after failure: 137 were in relapse after complete response (CR) and 71 were in first progression after partial response (PR) (36% of the eligible patients). For these 208 pts, the failure-free survival (FFS) from the failure was 15 % and 3-yr probability of failure free survival (FFS) is 8 %.

Treatment was given in 191 patients, with radiotherapy alone in 18 patients.

A second complete remission was obtained in 44 patients (23%) and a second partial remission in 65 patients (34%). Three-year probability of 5 and FFS after 2 CR was 51 % and 32 % respectively. Intensive chemotherapy given by bone marrow transplantation (BMT) was performed in 34 patients (1 syngeneic, 5 allogeneic, 28 autologous). BMT was given either after second CR (14), second PR (11) or failure (9).

Three-year probability of 5 and FFS after BMT were 30% and 26% respectively.

Prognosis factors for 5 after failure are immunology (T better than B), Working formulation (intermediate-high), stage (AB), stage (II-III-IV) performance status (PS) (0-1/2), number of extranodal sites (0-1/2), FAB score (0-1/2), CD34+ cell number (0-1/2), CD3+ level, relapse (on or off therapy). The same prognostic factors are found for FFS but, in addition, BMT is significantly worse than no-BMT.

A multivariate analysis performed in 163 patients by COX model shows that only PS (p = 0.0019), LDH initial level (p = 0.0026) and BMT (p = 0.0009) remain independent prognostic factors. The benefit of BMT persists if we analyse only patients under 60 years of age (p = 0.002) or only CR2 and PR2 patients (p = 0.0094).

In conclusion, failure patients after treatment with LNH44 protocol have an extremely poor prognosis. The best way to improve these results is to obtain a second response and to perform IC + BMT.

P 40
PROGNOSTIC VARIABLES IN THE TREATMENT OF NON-HODGKIN'S LYMPHOMA IN ELDERLY PATIENTS. S.H. Ansell, E. Falkson and A.A. Alberts, Department of Medical Oncology, University of Pretoria, Pretoria, Republic of South Africa

Non-Hodgkin's lymphoma (NHL) frequently occurs in patients older than 65 yrs. Most studies exclude elderly patients, if not by virtue of age, then by virtue of concomitant disease. To assess the long-term outcome of these elderly patients, an analysis of prognostic factors was performed on a series of elderly patients with NHL, age > 65 yrs,

When the whole group was considered, the factors associated with prolonged survival were a good performance status (PS), age > 65 yrs and a favourable histology. For patients > 65 yrs, however, the factors of prognostic importance were female sex, a longer time to dose limiting toxicity (DLT), a favourable histology and a good PS. It appears therefore, that elderly patients have similar prognostic factors compared with younger patients with NHL, older than 65 yrs.

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ABSTRACTS - Fourth International Conference on Malignant Lymphoma, Lugano


From June 1984 to March 1989, 180 pts with advanced stage DLC were treated with MACOPB. The median age was 44 yrs (range 15-68). 58% were large cell (G) and 42% immunoblastic type (H). 24% had tumor bulk, 31% E lesions and 59% a LDH >500. 43% were advanced stage I, 24% stage II, 30% stage III, and 10% stage IV. 10% had Bone Marrow involvement (BM inv). 71% achieved a CR, 12% a PR, 13% a HR while 4% died due to toxicity. With a median follow up of 22 months, 2-yr survival (S) for all 180 pts was 59% and 2-yr disease-free survival (DFS) for the 127 CRs was 70%. Overall toxicity was acceptable with mucositis being the most frequent severe side effect. All pts were evaluated for pretreatment characteristics predictive for CR, DFS and S. Factors studied included: age, performance status (PS), stage, B symptoms, tumor bulk, LDH, Histologic subtype (HS), BM inv and tumor burden (TB) assessed as proposed by M.DMH. In univariate analysis variables significant for response and survival were: LDH, TB, HS, PS, stage and BM inv. A regression tree model with survival as endpoint was then used to subdivide pts in different risk groups. In this model BM inv emerged as the major predictor of shortened survival. In BM negative pts LDH (< or >500) was the most important factor for predicting survival. Both in pts with LDH <500 and in those with LDH >500 TB and HS were found to be significant. We used these 4 simple pretreatment clinical features (BM, LDH, TB and HS) to construct a model with 3 groups at increasing risk for shortened survival:

A BM neg, LDH <500 +/- TB high or HS H 84 80 80
B BM neg, LDH >500 + TB high and HS H 71 63 55
or BM neg, LDH >500 +/- TB high or HS H
C BM pos or LDH >500 + TB high and HS H 23 13 8

This study confirm the effectiveness of MACOPB in DLC, but poor-risk subsets of pts still exist and they need a different more aggressive therapy.
Poster Session II

HODGKIN'S DISEASE
P 1 HETEROGENEITY IN THE RELATIONSHIP BETWEEN THE HIGH GRADE MALIGANT LYMPHOMA AND THE CHRONIC LYMPHOCYTIC LEUKEMIA IN PATIENTS WITH RICHTER'S SYNDROME

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Richter's syndrome is defined as a large cell malignant non-Hodgkin lymphoma (NHL) supervening in the course of chronic lymphocytic leukemia (CLL). Based on the presence of identical immunoglobulin (lg) heavy and light chains on the surface of CLL and NHL cells in patients with Richter's syndrome, it was concluded that Richter's syndrome may represent transformation or progression of the CLL clone to the B-NHL clone. However, the presence of identical lg heavy and light chains is not synonymous with clonality, since most B-CLL and B-NHL carry the same heavy chain and the statistical likelihood of two independent B cell clones having the same light chain is more than 50%. Southern blot analysis of the lg genes is an accurate method to prove or exclude the clonal origin of two B cell populations. We studied three cases of Richter's syndrome by Southern blot analysis.

In our first case of Richter's syndrome with different lg light chain expression on the CLL cells and centroblastic NHL cells we demonstrated different lg heavy and light chain gene rearrangements and concluded that in this case the NHL most likely should be considered as a second independent malignancy (Blood 1994;84:371-5).

In our second case of Richter's syndrome the CLL and centroblastic NHL cells were found to express the same m and k lg chains and appeared to have identical lg heavy chain gene rearrangements. This indicates that the NHL cells in this patient represent a clonal progression of the CLL cells (Leukemia 1989;2:199-24).

In our third case of Richter's syndrome the CLL was followed by an immunoblastic NHL and subsequent acute macroglonulomatisa with hypercinosis syndrome. The CLL and immunoblastic NHL and bone marrow plasma cells expressed the same lg heavy and lg light chains (igm-4). The lg heavy chain gene rearrangements of the NHL and bone marrow plasma cells were identical but differed from the CLL cells. Identical results were obtained by lg gene analyses. This indicates that the CLL and the immunoblastic NHL with subsequent progression to acute macroglonulomatisa represent two independent malignancies.

Our observations indicate that the immunologic and molecular genetic features of Richter's syndrome appear to be more heterogeneous than assumed from the clinical picture. Systematic and prospective studies using the combined morphologic, immunologic and molecular approaches have to elucidate the clinical relevance of this heterogeneity in Richter's syndrome.

P 2 EFFICACY OF LOW-DOSE RECOMBINANT INTERFERON-α IN THE TREATMENT OF HAIRY CELL LEUKEMIA

M. Abegg-Weser, J. Reemkes, M. Bogman, R. De Paese, C. Haenen, Dept. of Hematology and Pathology, University Hospital Nijmegen, Nijmegen, The Netherlands.

Treatment with recombinant interferon-α (rIFN-α) has become a standard treatment in hairy cell leukemia (HCL). Both in splenectomy as well as in non-splenectomized patients remission rates up to 10% have been reported, although a complete remission is obtained in only c.10% of the patients. The optimal dose regimen has not been identified as yet. We report here the results of a Dutch multicentre study in 40 consecutive patients with HCL treated in the period 1987-1991. In 27 patients a histologically confirmed diagnosis of HCL (clinical review by one of us, M.K.) was obtained. Twenty-one patients had been treated with splenectomy in the past. None of the patients had received prior interferon treatment. Treatment indication consisted of one or more of the following criteria: hemoglobin < 9 mmol/l, platelets ≤ 70x10^9/l, granulocytes ≤ 0.5x10^9/l or symptomatic splenomegaly. The first 19 patients received 5x10^6 U rIFN-α2b daily s.c. for 12 weeks followed by maintenance treatment with 3x10^6 U rIFN-α2b twice weekly (group A). The second group of 6 patients received 3x10^6 U rIFN-α2b three weekly s.c. (group B) and the remaining 15 patients received 1.5x10^6 U rIFN-α2b three weekly s.c. (group C). Treatment response criteria were defined as follows: complete remission (CR): normalization of all abnormal parameters including reduction of hairy cells in the bone marrow biopsy to <5%; hemoglobin remission (HR): <10% but with persistent hairy cells in the bone marrow biopsy <5% and at least 50% reduction in hairy cells in the bone marrow biopsy; minor response (MR): normalization of one of the hematologic parameters.

There were 6 females and 34 male patients with a median age of 53 years, not significantly different between the 3 groups of patients. Pancytopenia was present in 11 patients (27%). Seven of these patients were treated with group C, with the lowest dose of IFN-α. Two patients experienced early death within one month due to infectious complications (group A, male, n=1; group B, n=1). After 3 months of treatment, the overall response rate was 90% (CR+HR 28%, MR 62%). The response rate increased to 93% after 6 months of treatment between the 3 treatment regimens: after 6 months CR+HR 78% in group A, 80% in group B and 60% in group C (p=0.03). The time to recovery of hemoglobin and platelet counts did not differ significantly between the 3 groups (median values 4 months and 3 weeks respectively). Splenomegaly, if present, resolved within 3 months in all patients. However, recovery of granulocytes ≥ 1.5 x10^9/l was delayed in group C as compared to group A: 5 ± 2 versus months. In spite of the slower recovery of granulocytes, no increased frequency or severity of infectious complications was encountered in group C. Toxicity was substantially reduced in group C, especially chronic fatigue grade 1/II occurring in only 27% in group C vs. 61% in group A (0.05≤p≤0.1). These data highlight the efficacy of rIFN-α in patients with fairly advanced stages of HCL and allow at least early dose adjustments. The lowest dose regimen is substantially better tolerated than the higher dose protocols.

P 3 IMMUNOLOGY OF LYMPH NODE ASPIRATES FROM PATIENTS WITH MALIGANT LYMPHOMAS. J. Dertel, B. Dertel, D.R. Klitholm, W. Wirth-Gentzen, Charitons Altorf Freien Universitaet Berlin, 1000 Berlin 19, Germany

Lymph node aspirates from 137 patients with malignant lymphomas were analyzed. Cytological and immunocytological studies were performed on cytocentrifuged preparations using alkaline phosphatase-antialkaline phosphatase (APAAP) method with a panel of monoclonal antibodies (CD3, CD4, CD8, CD19, CD30, CD45, CD21). The cytological diagnosis was confirmed by histological investigation. 62 aspirates from patients with non-Hodgkin's lymphoma of low malignancy were investigated. 61 cases were monoclonal with respect to their light chain determinants. 35 aspirates were obtained from patients with B-non-Hodgkin's lymphoma of high malignancy. 34 patients showed light chain restriction and a high (≥40%) percentage of CD71^+ cells. 18 malignancies were considered to be of T-cell origin. Nine lymph node aspirates from patients with T-immunoblastic lymphoma, angiocentric histiocytic and pleomorphic small cell lymphoma were included. Eight cases were monoclonal with respect to their lg heavy chain determinants. 35 aspirates were obtained from patients with B-immunoblastic lymphoma, pleomorphic large cell type and large cell anaplastic type. Nine lymph node aspirates from patients with T-immunoblastic lymphoma showed a positive staining for CD45, CD45RO and CD45RO^+. The presence of CD45^+ cells has the morphology of Sternberg-Reed cells. These findings indicate that the immunocytological method is applicable in case of monoclonal lymphoma. The presence of CD45^+ and CD45RO^+ cells indicates the presence of Sternberg-Reed cells, which are known to be an indicator of a poor prognosis. In 22 cases of Hodgkin's disease there were 17 correct cytological diagnoses. A significant number of CD30^+ and CD45^+ cells having the morphology of Sternberg-Reed cells supports the hypothesis that these cells are able to be used in the diagnosis of lymphoma.

P 4 B-CELL STRUCTURE IN HODGKIN'S DISEASE OTHER THAN LYMPHOCYTE DOMINANCE, NODULAR TYPE. M.J. Alavaikko, M.-L. Hansmann, M.R. Parwaresch, K. Lennert. Department of Pathology, University of Kiel, 2300 Kiel, FRG.

The presence of large numbers of follicular dendritic cells in lymphocyte predominance, nodular type (LPN) of Hodgkin's disease (HD) or nodular paragranuloma is well known. This and other findings has led to the hypothesis of a B-cell nature of LPN. In the present study a monoclonal antibody detecting follicular dendritic cells in peraffin sections (Ki-1/Bip) was used to investigate nodular sclerosis (NS, n = 31) and mixed cellularity (MC, n = 16) type of HD. Follicular dendritic cell networks, occupied by Sternberg-Reed and/or lacunar cells, could be demonstrated in approximately 50% of NS and approximately 10% of MC cases. They were accompanied by clusters and/or strands of B cells. These findings indicate that a portion of the NS and MC types also comprise a B-cell microenvironment with a close association to the morphologically specific cells of HD.
ABSTRACTS - Fourth International Conference on Malignant Lymphoma, Lugano

P5 Hodgkin-Associated Soluble CD30 Antigen (CD30A) in the Serum of Patients with Hodgkin's Disease (HD): A Prognostic Factor. A. Gassner, C. Pohl, A. Tschiersch, R. Schmitt, V. Bechtle, M. Friedrich. Medizinische Universität-Institut, University of Cologne, Cologne 41, F.R. Germany

We detected a TRF soluble CD30 (CD30A) antigen released into the supernatant of Hodgkin's derived cell lines in vitro by a recently developed ELISA using the monoclonal antibodies HRS-3 and HRS-2 which were developed by immunisation with the Hodgkin's derived cell lines L428 and L540. HRS-1 and HRS-2 detect two different epitopes of the 125 kd membrane-bound CD30 antigen. Tracer cells CD30A were also detected in the serum of 21/100 patients (21%) with newly diagnosed Hodgkin's disease in 8/10 (80%) with HDV+ HDL-T (Hv+). In all cases, CD30A disappeared after successful therapy. No CD30A antigen was detected in 100 other hematological malignancies (ALL, ANLL, CGL, CML, plasmacytoma), 50 solid tumors (breast, lung, ovarian, colorectal, stomach, carcina), 50 immunological disorders (SLE, RA), and 100 healthy controls. Of 20 hepatitis B and 80 viral infections (EBV, CMV, HSV, HIV), only 8/10 with acute infectious mononucleosis (anti-EBV-IgM) were positive. Thus, CD30A is a valuable and highly specific marker for disease activity in Hodgkin's lymphoma, certain types of NHL and adult T-ALL (HTLV-1+). Of 87 pts. with HD evaluable for response, 65 (75%) achieved complete remission (CR). The CR rate was significantly lower (p<0.001) for 20 CD30* (10/20 = 50%) compared to 67 CD30* pts. (50/67 = 75%). Disease-free survival was better in CD30+ pts. (12/27 = 89%) vs. CD30- pts. (44/14 = 31%) after a median follow-up of 21 months. The curves for freedom from treatment failure (FFTF) were significantly different (p<0.001). We conclude that the presence of CD30A in the pretreatment serum of pts. with HD has prognostic significance for CR rate and FFTF.

Supported by BMBF and DFG


The mechanisms responsible for the systemic symptomatology in Hodgkin's disease (HD) are still unclear. However, since the neoprotegative effect of the disease is regulated by the hypomelanosomes, it is probable that the systemic symptoms may depend on an action at hypomelanotic sites. Moreover, because of the documented influence of cytokines on hypomelanotic neurotransmitter content, it is possible to hypothesise that the alteration of the hypomelanotic function may be due at least in part to a direct central action of cytokines abnormally produced by transformed lymphoid cells. On the basis of the fact that the possible existence of a functional hypomelanotic damage can be indirectly documented by the relief of changes in pituitary hormone secretion, the present study was carried out to evaluate the hypomelanotic-pituitary-interactions in patients (pts) affected by HD with or without systemic symptoms. The study included 24 untreated pts. of whom without and with systemic symptoms. For endocrine detection, venous blood samples were collected during the month before the start of therapy. In each blood sample, the serum levels of the pituitary hormone melatonin (MLT) and those of betaendorphin (BEP) were measured with the RIA method. The results were compared with those obtained in a group of 42 age-matched healthy subjects. Abnormally high concentrations of melatonin were found in 8/24 (33.33%) of HD patients and in 9/42 (21.42%) of healthy controls. MLT levels were higher in pts without than in those with systemic symptoms (Z = 0.44, p < 0.05). On the contrary, hypomelanotic systemic symptoms had higher concentrations of endorphin than those without symptoms (Z = 0.44, p < 0.05). However, none of these differences was statistically significant. These results, which have been confirmed on a greater number of patients, would suggest the existence of differences in the function of the pineal gland and the optical system in HD between pts with and without systemic symptoms. Further studies will be required to better define which relation exists between neuroendocrine secretion and systemic symptomatology in HD.


It is well recognised that in some patients a residual mediastinal mass (RMM) following initial radiation therapy for Hodgkin's Disease (HD) indicates residual active disease whilst in others an abnormal CT or CR scan may persist for many years without evidence of relapse. Thus there exists the need for a reliable non-invasive technique to demonstrate residual disease. In this study we evaluated Gallium (Ga) scanning in 69 patients with biopsy proven HD in an attempt to determine the place of this procedure in monitoring disease activity and in particular within the mediastinum. Patients were scanned following an injection of 390 MBq Ga-67 citrate using triple height pulse analysis. 48 had a Ga avid WM at presentation and were re-scanned following the completion of planned therapy. The mean age was 36 years and there were 23 males and 18 females. Post treatment results and disease status with a mean follow of 39 months is as shown:

<table>
<thead>
<tr>
<th>All Patients</th>
<th>Ga positive</th>
<th>Ga negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>63 (1 new CR)</td>
<td>31 (50%)</td>
<td>32 (50%)</td>
</tr>
<tr>
<td>6 (1 new CR)</td>
<td>3 (50%)</td>
<td>3 (50%)</td>
</tr>
<tr>
<td>1 CR</td>
<td>1 (100%)</td>
<td>0</td>
</tr>
<tr>
<td>4 relapse</td>
<td>1 (25%)</td>
<td>3 (75%)</td>
</tr>
</tbody>
</table>

Residual WM

<table>
<thead>
<tr>
<th>6 (1 new CR)</th>
<th>3 relapse (now CR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 (50%)</td>
<td>3 (50%)</td>
</tr>
</tbody>
</table>

MWM

<table>
<thead>
<tr>
<th>5 deaths</th>
<th>10 CR</th>
</tr>
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<tbody>
<tr>
<td>2 CR</td>
<td>1 relapse (new CR)</td>
</tr>
<tr>
<td>1 death</td>
<td>**</td>
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</table>

The results were as follows: 1) 63 pts. (94%) with only 2 patients now in CR. The predictive value of a positive Ga scan was 60% with only 4 patients studied too soon after the completion of chemotherapy (< 6 weeks) and 2 others who had undergone late relapses (4 & 6 Years).

Therefore Ga scanning is an accurate non-invasive diagnostic indicator of outcome after initial therapy for mediastinal HD independent of a WM. A positive scan is a particularly bad prognostic factor and may indicate the need for further/alternate therapy.

P8 A Numerical Prognostic Index for Clinical Use in the Identification of Poor Risk Patients of NHL and HD who Die at Diagnosis. Proctor S. J., Taylor P., Donnan P., Boys B., Lennard A., Prescott R., with members of the Scotland and Newcastle Lymphoma Group (SNEG). The Lymphoma Centre, Immunological and Pathology Working Party. Department of Haematology, Royal Victoria Infirmary, Newcastle upon Tyne, NE1 4LP; Department of Mathematics (Statistics), The University of Newcastle upon Tyne, Merz Court, Newcastle upon Tyne, NE1 7RU.

The aim of this study was to assess the feasibility of using objective data obtained at diagnosis of Hodgkin’s disease to predict those patients who were likely to die of progressive disease within four years of diagnosis.

Ninety-two consecutive patients from one centre (Newcastle upon Tyne), were used to construct a numerical index based on disease stage (Ann Arbor), age, haemoglobin and absolute lymphocyte count. Weight was assigned according to a predictive value in univariate and multivariate analyses based on survival. The index was then tested on a separate patient set (95%) from other centres within the Scotland and Newcastle Lymphoma Group (SNEG) on whom the same prospective information was available. The index produced a useful separation of those patients destined to die of disease. In 101 patients index *0.65 (61.9%) were dead at four years, whereas with index 0.65 (61.9%) of 336 patients were dead at four years. The index includes Ann Arbor stage but possesses additional prognostic value which allow identification of patients with early stage destined to die of disease. Of 149 patients with Stage I and II disease, 15 patients (10.1%) had index <0.65, whereas the remaining patients had survival of 95% and 85% respectively.

This numerical index is applicable to all patients at diagnosis and in the SNEG population gives better predictive survival at four years than stage alone, and provides a basis for selecting patients for more aggressive therapy.
ABSTRACTS - Fourth International Conference on Malignant Lymphoma, Lugano

P 9

RADIOTHERAPY VERSUS CHEMOTHERAPY IN PATIENTS WITH EARLY STAGE HODGKIN'S DISEASE (PATIL STAGE I-IIIA). A PERSPECTIVE RANDOMIZED TRIAL. REPORT AFTER 6.5 YEARS OF FOLLOW-UP.


University and Hospital of Florence: Departments of Radiotherapy (*) and Haematology (**).

University of Rome: Departments of Radiotherapy (+) and Haematology (+).

The authors present the updated results of the randomized trial comparing MOPP chemotherapy (CT) with extended field radiotherapy (RT) in early stage (patil stage I-IIIA) patients. The results of this trial (HODGE Conference) have been confirmed. In particular, a trend in favor of CT was observed despite the fact that RT was given at 65% vs. 65% of the patients treated with CT. The difference in survival was confirmed in the RT arm. At the 6.5 years follow-up, no difference in survival was observed between the two arms. The long-term follow-up of these patients is ongoing.

P 10

RESULTS OF TREATMENT OF CLINICAL STAGES (CT) II A TO III A HODGKIN'S DISEASE. THE BEI PROTOCOL.


University of Paris: Department of Hematology.

The authors present the results of the BEI protocol, a large-scale, multicenter, randomized trial comparing MOPP chemotherapy (CT) with extended field radiotherapy (RT) in patients with early stage (CT II A to III A) Hodgkin's disease. The protocol was designed to assess the efficacy and tolerability of the two treatment arms in a large cohort of patients.

P 11

RESULTS OF THE PDF 87/12 TRIAL FOR HODGKIN'S DISEASE, CLINICAL STAGES (CS) I + II A. A randomized, double-blind, placebo-controlled, multicenter trial.

From 1.10.87 to 30.09.88, 274 patients (pts) with CS I + II A prospectively treated according to the PDF M 87/12 protocol. Low symptomatic blood collection was performed in all 2 pts. No laparotomysplenectomy was performed except in 2 cases for diagnostic purpose. Initial characteristics of the pts were: Sex: M 143, F 131; age: mean 32.9, range 15-65; histology: LD 21, NS 180, MC 52, LD +, ND 17, CS:IR 57, IIR 143, IB 10, IIB 6, IIIB 4, IIIC 1; Ann Arbor: Stages I 15, II 26, III 44, IV 19; laboratory: 15% of the pts had a bulky tumor of the mediastinal widening (less than 4). As of December 1988, median FU was 48 months.

Results of this protocol are summarized in the table:

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<tbody>
<tr>
<td>CT</td>
<td>CR (%) 82</td>
<td>87 0.001 86</td>
<td>99.2 91</td>
</tr>
<tr>
<td>RT</td>
<td>CR (%) 86</td>
<td>90 0.001 89</td>
<td>99.2 91</td>
</tr>
<tr>
<td>SV (%) 94</td>
<td>95 0.96</td>
<td>96 96</td>
<td>96 96</td>
</tr>
<tr>
<td>FF (%) 90</td>
<td>91 0.001 92</td>
<td>97 97</td>
<td>97 97</td>
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(CT: post chemotherapy; RT: post radiotherapy; SV: 5-year survival; FF: Freedom from progression).

P 12

COMBINED MODALITY TREATMENT OF "BULKY" HODGKIN'S DISEASE. REPORT OF 65 CASES.


Of the 270 patients affected by Hodgkin's disease, 90% have been diagnosed over the last 15 years. 56% of the patients presented with a bulky disease, mostly (80%) in the mediastinum. The median age at diagnosis was 46 years (range 10-74). They were staged as follows: stage I 17%, II 31%, III 33%, and IV 29%. The most common at nodal disease (80%) was the cervical nodes, followed by the mediastinum (60%) and the spleen (50%). Other sites of involvement were the liver, the bone marrow, and the skin.

Treatments: 48/55 patients were treated with chemotherapy, on average 6 cycles of MOPP (40% of patients) or Alternating MOPP/ABVD (30% of patients) or plus radiotherapy (17% of patients). Other treatments included 3 patients with high-dose chemotherapy (HDCT) and 2 patients treated with radiotherapy alone.

Results: Overall CR was obtained in 51/55 patients (92.7%), relapse occurred in 7/51 cases (13.7%), in four of seven in the site of bulky. At present 43/51 patients (84%) are in continuous complete remission and two patients showed a freedom from survival curve showing a 10-year plateau of 73% and 83%, respectively. The cure rate was 78%. Of the 48 patients treated with chemotherapy plus radiotherapy, 44.44% (91.74%) obtained CR.

Conclusions: The present bulky mass is currently considered a poor prognostic factor in Hodgkin's disease and needs a more aggressive treatment. Combination therapy including MOPP/ABVD plus radiotherapy appears effective in achieving complete remission and preventing relapse.
P 13 HODGKIN’S DISEASE WITH BULKY MEDIASTINAL INVOLVEMENT: EARLY RESPONSE TO CHEMOTHERAPY DELINITATES HIGH-RISK PATIENTS.
F. Tillet-Tissandier, C. Heulin, A. Lavandier, O. Pelt, J.P. Lebougres, P. Tillet, B. Bugué, Hôpital Lariboisière Montparnasse 92710 Colombes and Hôpital Henri Mondor 94010 Créteil, France.
Between 1977 and 1985 a series of 38 patients with localized bulky mediastinal Hodgkin’s disease were clinically staged and received combined modality treatment. All patients had mediastinal tumours measuring at least 1/3 of the width of the maximum thoracic diameter. Treatment consisted of three courses of MOPP followed by sub-T Sheffield radiotherapy (mantle, lumbro-aortic and spiscic fields). This series included 1 patient with Stage I, 27 patients with Stage II and 10 with Stage III (Stage III was defined as subdiaphragmatic disease restricted to the spleen and/or upper aortic nodes). B symptoms were present in 23 (60.5%) cases. The Nez at time was 1/1 and the median age was 29 years (range 15-60). The histological subtypes were nodular sclerosing in 30 cases (79%), mixed cellular in 7 (18%) and lymphocytic depleted in 1. Complete response after the three initial courses of chemotherapy was referred to as CR5, and an initial CR2 if achieved after completion of the combined modality treatment. Analysis was performed in December 1984.

The C5 rate was 47% and the CR rate 67%. 54.5% of CR patients had reached CR2. The overall B & Y-survival and disease-free survival (DFS) were 64% and 79%, respectively. 5 non-CR patients failed to respond to combined modality treatment, 4 of whom died. 6 CR patients relapsed, 5 of whom were non-CR patients, and 4 died despite salvage treatment. Median time to relapse was 29 months. Failures and relapses were limited to above the diaphragm. 1 CR patient died from acute leukaemia without evidence of recurrent Hodgkin’s disease. Thus, among the 9 non-surviving patients, 4 died from failure and 4 from relapse. Among the 11 patients with unresponsive Hodgkin’s disease (i.e. 5 failures and 6 relapses), 10 were non-CR. Finally, B & Y-survival was better for CR than for non-CR patients: 100% vs 78% (p < 0.001). DFS rates also differ between CR and non-CR patients: 87% vs 55% (p < 0.02). Survival and DFS rates were not affected by other factors such as age, stage, B symptoms and histology.

On the basis of these results a new strategy was devised in which non-CR patients were treated with three courses of chemotherapy (cytophosphamide, methot-GAM, etoposide, mithracin) interspersed with three courses of 15 Gy mantle radiotherapy over a period of 3 months, followed by lumbro-aortic and spiscic irradiation. CR patients were treated as previously. The results on 40 patients treated in this way since 1986 will be presented.

From January 1982 to June 1989 a series of 100 patients were clinically staged as II B or III B Hodgkin’s disease and were consecutively enrolled in the following non-randomized treatment programs: * until December 1985 (45 patients): 6 MOPP plus extended field radiotherapy 36 Gy (subtotal for stage II and TMI for stage III). ** from January 1986 (55 patients): a minimun of 6 courses of 1/2 MOPP - 1/2 ABVD (MA/HA) followed by radiotherapy limited to bulky areas.

Median age was 35 years (range 14-74). No statistical difference was seen between the two consecutive series for median age (38 vs. 39), male sex (49% vs. 58%), stage II (42% vs. 34%), E involvement (18% vs. 16%), bulky mediastinal mass (40% vs. 35%), advanced histology (MC/AL: 35% vs. 31%), more than two B symptoms (31% vs. 32%) and presence of fever (71% vs. 81%).

Results are as follows:
MOPP+RT MA/HA p value
C.R. after 3 cycles 52% 75% 0.06
Final complete remission 77% 93% 0.003
Disease free survival 78% 87% 0.54
Overall survival 67% 83% 0.14
Event free survival 56% 69% 0.15

Treatment program variations due to bad compliance or toxicity were more frequent in patients planned to be treated with MOPP+RT than in patients entered the MA/HA protocol.

Results of combined modality therapy with MOPP+RT were worse than those of MA/HA in terms of tolerance, final remission rate and overall survival. So far disease-free survival of patients achieving final complete remission is not different between the two groups.

P 15 THE RESULTS OF THE TREATMENT OF 538 HODGKIN’S DISEASE PATIENTS WITH MOPP OVER 19 YEARS - THE BEL Feature.
Between 1970 - 1983, 538 patients with advanced Hodgkin’s disease (89% Stage III/IV) were entered into the MOPP randomized trials and studies and treated with MOPP. MOPP consisted of Mustine 6 mg/m² (max 15 mg) i.v. day 1 & 8, Vinristine 1.4 mg/m² (max 2 mg) i.v. day 1 & 8, Procarbazine 100 mg/m² orally daily for 10 days, Prednisone (or Predniisolone) 25 mg/m² (max 60 mg) orally daily for 14 days. Repeated every 28 days.

The results for the series of 538 patients were as follows: the CR rate was 61%; the disease-free survival (DFS) was 28% at 15 years: the relapse-free survival of patients achieving complete remission was 48% at 15 years: and the overall survival was 48% at 15 years.

The series included an appreciable number of patients who failed to receive 6 courses of MOPP, due to lack of response without or with progression of disease and early death. A further group of ‘slow responders’ in the series received more than 6 courses, the DFS of those who received more than 8 courses being less than 30%.

The DFS of those patients who received second line treatment was less than 25% at 15 years from time of start of Second line treatment. The overall survival of those patients who failed to achieve CR from their Second line treatment was less than 30% at 14 years.

The major prognostic factor for overall survival was age at presentation. However many of the deaths occurred in patients in CR, and appear unrelated to it.


Two-hundred-and-forty-four consecutive patients (pts) in stages of IIB (20 pts) or PS (69 pts) IIIb (48 pts), IVA (32 pts) and IVB (97 pts) received 3 double cycles of alternating COPP+ABVD. Patients in complete remission (CR) were then randomized to receive either IF radiotherapy (1.8 Gy per fraction for a total of 42 Gy) or further double cycle of COPP+ABVD. Pts not to CR after 3 x (COPP+ABVD) received salvage radiotherapy for persistent nodular or CEVD chemotherapy (Frenschnikach et al., 71/220, 1987) for persistent diffuse or organ involvement. The CR rate after 3 x COPP+ABVD was 58% and the overall CR rate including salvage therapy was 76% (HIB 79%, IVA 72%, IVB 72%). There were three treatment related and one intercurrent death. Twenty-seven pts (10% proximately) progressed. Fifty-two pts in CR after 3x (COPP+ABVD) were randomized for IF radiotherapy and fifty-three for a fourth double cycle of COPP+ABVD. Freedom from treatment failure (FFTF; median time of observation 33 months) events show no difference between the two arms. Relapse-free survival (median time of observation 21 months) was 81% in the chemoradiotherapy arm (10 relapses) and 87% in the chemotherapy-only arm (7 relapses). Analysis of subgroups according to initial stage or site of involvement showed no differences between the two arms, either. We therefore conclude that for patients with stage IIB/IV Hodgkin’s lymphoma, IF radiotherapy and chemotherapy are equally effective for the consolidation of remission achieved after 3 double cycles of COPP+ABVD.

Supported by BRMT 012529/A0/
ABSTRACTS - Fourth International Conference on Malignant Lymphoma, Lugano

P 17 RESULTS OF COMBINED MODALITY TREATMENT FOR STAGES IE-IV MCDONNELL's DISEASE AT SAINT-LOUIS HOSPITAL. THE H11 PROTOCOL.

From January 1982 to December 1984 74 patients (pts.) with advanced HD were treated according to the H11 protocol consisting of 4 cycles of chemotherapy (CHOP) versus MOPP/ABV. The HD patients were classified according to response and stage. Of the 74 patients, 68 pts. were completely staged, and one was evaluated after laparotomy. 63 were in stage IIE, and 3 in stage IIIE. 12 extranodal lesions were present in 6 stages IIIE and II, and a bone marrow involvement in 3 cases. 70 pts. received 4 cycles of CHOP and 7 of MOPP. The CHOP regimen consisted of vincristine 1.4 mg/m² iv q3w, cyclophosphamide 750 mg/m² iv q3w, prednisone 40 mg qd po, and Adriamycin 30 mg/m² iv q3w. 7 pts. received 2 cycles of CHOP. All but one patient achieved a CR after 2-10 cycles. The 3-yr overall survival rate was 93% (CI 88-100%). The 3-yr relapse-free survival rate was 81% (CI 73-88%). The 3-yr disease-specific survival rate was 95% (CI 90-98%). The 3-yr cause-specific survival rate was 95% (CI 90-98%). The 3-yr event-free survival rate was 83% (CI 75-89%). The 3-yr overall survival rate of stage III patients was 93% (CI 88-100%). The 3-yr relapse-free survival rate of stage III patients was 72% (CI 65-78%). The 3-yr disease-specific survival rate of stage III patients was 93% (CI 88-100%). The 3-yr cause-specific survival rate of stage III patients was 93% (CI 88-100%). The 3-yr event-free survival rate of stage III patients was 72% (CI 65-78%). The 3-yr overall survival rate of stage IV patients was 70% (CI 55-83%). The 3-yr relapse-free survival rate of stage IV patients was 55% (CI 40-69%). The 3-yr disease-specific survival rate of stage IV patients was 71% (CI 56-82%). The 3-yr cause-specific survival rate of stage IV patients was 71% (CI 56-82%). The 3-yr event-free survival rate of stage IV patients was 55% (CI 40-69%).

P 18 PROLONGED FOLLOW-UP OF A RANDOMIZED TRIAL COMPARING MOPP/ABVD/RT TO MOPP/ABVD/RT IN MCDONNELL'S DISEASE (HD) WITH PROGNOSTIC FACTORS.

MOPP/ABVD was our standard therapy from April 1981 to June 1984, while ABVD/RT was evaluated in a randomized trial from April 1984 to June 1987. Patients (pts) were randomized (42 pts) to standard MOPP/ABVD/RT every 3 wk for 6 courses (42 pts) or to ABVD/RT every 3 wk for 4 courses followed by radiotherapy. Complete remission was achieved in 25% of pts with MOPP/ABVD/RT and in 75% of pts with ABVD/RT. The 3-yr overall survival rate was 81% (CI 65-94%) for MOPP/ABVD/RT and 83% (CI 68-96%) for ABVD/RT. The 3-yr relapse-free survival rate was 47% (CI 29-63%) for MOPP/ABVD/RT and 57% (CI 39-75%) for ABVD/RT. The 3-yr disease-specific survival rate was 84% (CI 68-95%) for MOPP/ABVD/RT and 86% (CI 70-97%) for ABVD/RT. The 3-yr cause-specific survival rate was 84% (CI 68-95%) for MOPP/ABVD/RT and 86% (CI 70-97%) for ABVD/RT. The 3-yr event-free survival rate was 47% (CI 29-63%) for MOPP/ABVD/RT and 57% (CI 39-75%) for ABVD/RT. The 3-yr overall survival rate of stage I patients was 88% (CI 74-96%) for MOPP/ABVD/RT and 93% (CI 84-98%) for ABVD/RT. The 3-yr relapse-free survival rate of stage I patients was 71% (CI 53-86%) for MOPP/ABVD/RT and 83% (CI 65-94%) for ABVD/RT. The 3-yr disease-specific survival rate of stage I patients was 89% (CI 75-96%) for MOPP/ABVD/RT and 93% (CI 84-98%) for ABVD/RT. The 3-yr cause-specific survival rate of stage I patients was 89% (CI 75-96%) for MOPP/ABVD/RT and 93% (CI 84-98%) for ABVD/RT. The 3-yr event-free survival rate of stage I patients was 71% (CI 53-86%) for MOPP/ABVD/RT and 83% (CI 65-94%) for ABVD/RT. The 3-yr overall survival rate of stage II patients was 70% (CI 47-85%) for MOPP/ABVD/RT and 74% (CI 50-88%) for ABVD/RT. The 3-yr relapse-free survival rate of stage II patients was 38% (CI 19-61%) for MOPP/ABVD/RT and 44% (CI 24-65%) for ABVD/RT. The 3-yr disease-specific survival rate of stage II patients was 68% (CI 45-85%) for MOPP/ABVD/RT and 71% (CI 48-86%) for ABVD/RT. The 3-yr cause-specific survival rate of stage II patients was 68% (CI 45-85%) for MOPP/ABVD/RT and 71% (CI 48-86%) for ABVD/RT. The 3-yr event-free survival rate of stage II patients was 38% (CI 19-61%) for MOPP/ABVD/RT and 44% (CI 24-65%) for ABVD/RT. The 3-yr overall survival rate of stage III patients was 47% (CI 30-63%) for MOPP/ABVD/RT and 53% (CI 37-71%) for ABVD/RT. The 3-yr relapse-free survival rate of stage III patients was 28% (CI 15-43%) for MOPP/ABVD/RT and 33% (CI 20-49%) for ABVD/RT. The 3-yr disease-specific survival rate of stage III patients was 52% (CI 37-67%) for MOPP/ABVD/RT and 58% (CI 42-77%) for ABVD/RT. The 3-yr cause-specific survival rate of stage III patients was 52% (CI 37-67%) for MOPP/ABVD/RT and 58% (CI 42-77%) for ABVD/RT. The 3-yr event-free survival rate of stage III patients was 28% (CI 15-43%) for MOPP/ABVD/RT and 33% (CI 20-49%) for ABVD/RT. The 3-yr overall survival rate of stage IV patients was 26% (CI 14-42%) for MOPP/ABVD/RT and 26% (CI 14-42%) for ABVD/RT. The 3-yr relapse-free survival rate of stage IV patients was 11% (CI 0-30%) for MOPP/ABVD/RT and 11% (CI 0-30%) for ABVD/RT. The 3-yr disease-specific survival rate of stage IV patients was 30% (CI 12-50%) for MOPP/ABVD/RT and 30% (CI 12-50%) for ABVD/RT. The 3-yr cause-specific survival rate of stage IV patients was 30% (CI 12-50%) for MOPP/ABVD/RT and 30% (CI 12-50%) for ABVD/RT. The 3-yr event-free survival rate of stage IV patients was 11% (CI 0-30%) for MOPP/ABVD/RT and 11% (CI 0-30%) for ABVD/RT.
ABSTRACTS - Fourth International Conference on Malignant Lymphoma, Lugano


We retrospectively reviewed 312 patients treated with MOFP/AVBD chemotherapy (RT) and 126 patients treated with MOFP/AVBD/RT. Before 1980 stage II-IV patients with high risk disease due either to presence of symptoms or to bulky disease were treated with MOFP followed by extended-field radiotherapy (RT). After 1980, an introduced ABVD regimen, to be administered alternatively or sequentially to MOFP/RT on bulky disease. Patients have been evaluated after a median of observation 24 months. A minimum follow-up of 4 years. Overall survival of the patients treated with MOFP/AVBD is 85% versus 78% of the patients treated with MOFP/RT (p=0.004). Stage II patients had the same survival (85%) in both groups treated by MOFP or MOFP/AVBD; stage III patients treated with MOFP had an overall survival of 72% versus 85% of patients treated by MOFP/AVBD (p=0.001). MOFP-treated stage IV patients had an overall survival of 45% versus 78% of the other group (p=0.004).

In conclusion combined chemotherapy with 8 drugs (MOFP/AVBD) was more effective in increasing the overall survival of stage III-IV Hodgkin's disease patients, even if it has been associated with lower dose and less extended RT.

P 22 RANDOMIZED STUDY IN ADVANCED STAGE HODGKIN'S DISEASE. COMPARISON BETWEEN MOFP/AVBD, MOFP/AVBD/RT, and MOFP/AVBD/RT.

From May 1983 to our institution there is an ongoing randomized study comparing two advanced stage AH patients randomly allocated to receive: 8 cycles of MOFP followed by extended-field radiotherapy (RT) on days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64 mg/mq/d on days 1-15 of RT; 8 cycles of MOFP followed by extended-field radiotherapy on days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64 mg/mq/d on days 1-15 of RT. The same schedule and chemotherapy given at random assignation between the 2 groups (CR) after chemotherapy are treated with consolidative low-dose chemotherapy (20 Gy total dose) plus salve (4 Gy by total dose). Methylprednisolone, 1 mg/kg/day orally on days 1-21. The main purpose of this study is to improve therapeutic results. Clinical characteristics in MOFP/AVBD and MOFP/AVBD + RT are comparable, no patients are evaluable in MOFP/AVBD + RT.

At present, 84 patients are evaluable in MOFP/AVBD and MOFP/AVBD + RT. The present report includes the clinical data of all patients treated with MOFP/AVBD and MOFP/AVBD + RT. All patients in partial remission (PR) after chemotherapy. Hematologic toxicity has been comparable in two groups whereas the neutropenic toxicity (peripheral neuropathy) has occurred more frequently in MOFP/AVBD + RT patients. Both overall (CR and disease-free survival) and specific survival (1 year, 3 year, 5 year) are 100% in both groups.

In conclusion, chemotherapy combined with radiotherapy is superior to chemotherapy alone. The beneficial effect of combined chemotherapy has been consistently shown to improve the outcome of patients with advanced stage AH. MOFP/AVBD + RT was more effective in increasing the overall survival of stage III-IV Hodgkin's disease patients, even if it has been associated with lower dose and less extended RT.


Between 1/85 and 11/89, 88 patients with Hodgkin's Disease, 41 males and 47 females with a median age of 35 years (range 15-64), were admitted to the study. All the pts underwent staging procedures inclusive of total body CT scan and laparoscopy. Laparoscopic examination was performed only in selected pts (6 cases). Subsequently the pts. were administered chemotherapy followed by radiotherapy. Chemotherapy consisted of 3 to 6 cycles; every cycle was included of half of cycle of MOFP alternated with half of cycle of ABVD. With the exception of the stage IV pts and of 6 other pts, radiotherapy (20 Gy if there was no "residual disease" at the CT scan or 40 Gy in the other cases) was administered after the completion of chemotherapy to all the involved field. In stage I and II pts, radiation was administered also to the paracostal nodes and to the spleen.

Stages were: IIA in 23 (bulky in 18), IIB in 10, IIIA in 18, IIB in 20, IVA in 8, IVB in 13 pts. Until now 73 pts are fully evaluable for response and toxicity; after the combined treatment the complete remission was achieved in 60 pts (82%).

For those pts who completed treatment, the median follow up is 30 months and up to now 6 pts have relapsed and 2 of these (not previously irradiated) obtained prolonged secondary remission after radiotherapy alone.

Main toxicities: one non fatal pneumonia from pneumocystis carinii, one fatal interstitial pneumonia in a non-responsive pt, one myocardial infarction occurring two years after the completion of treatment. This combined program is feasible, but approximately 20% of the pts still await for more effective treatment.

P 24 NOVPI: A NOVEL CHEMOTHERAPY REGIME FOR TREATMENT OF HODGKIN'S DISEASE (HD) WITH MINIMAL TOXICITY.


Treatment of patients (pts) with early stage HD results in high cure rates, with 73-85% of pts relapse-free, and survival rates of 65-85%.

For pts with favorable disease characteristics, radiotherapy (RT) alone provides good results, but also shows a high rate of local relapse, especially in patients with extensive nodal involvement. However, both NOFP and ABVD are associated with various risks of toxicity, both acute (venous, vomiting, alopecia, myelosuppression) and chronic (arterial, cardiac, pulmonary). We developed NOVPI (ifosfamide 10 mg/m2/day 1, Oncovin 2 mg/day 1, vinblastine 60 mg/m2/day 1, Lomustine 100 mg/m2 day 1) given 3 weeks for 3 cycles in an effort to provide effective and minimal toxic chemotherapy without delaying agents prior to XRT for pts with unfavorable presentations of stages IA-IIA and for stage III HD. We have treated 31 pts (16 stage IA-11, 15 stage III) with 3 NovPI XRT. The complete remission and partial remission rates were similar to that obtained with MOFP. Tolerance to therapy has been excellent. Acute problems were minimal. Most pts experienced nausea, grade 1; 1 had phlebitis, grade 1; 2 reported alopecia, grade 1. There had transient paresthesias or myalgias, but all resolved within 7-10 days of onset. Median nadir granulocyte count was 600, with no thrombocytopenia. Duration of neutropenia was short and no pts experienced neutropenic infection or fever. No cardiopulmonary complications have developed. None of the 6 pts studied experienced acute or severe oligopenia following the third dose of NOVPI, but immediately after the third course, sperm counts began to rise. At 3-5 weeks, the median counts of 7 semen motile ml of seminal fluid. At the end of therapy, 3/7 are normospermic and 4/7 are moderately oligospermic. Hematoxicities of NOVPI and NOVPI were compared by examining chromosomes breaks and sister chromatid exchanges (SCEs) in lymphocytes of pts during treatment. In vitro bleomycin treatment was also used to examine single-strand DNA breaks. By contrast, NOVPI induced higher level of chromosome or single-stranded DNA breaks, or SCEs. From these early results, NOVPI was a very well tolerated chemotherapy regimen, with side effects that appear to be less severe than those associated with NOFP or ABVD. Early results of treatment also are comparable to that seen with 2 cycles of MOFP prior to XRT.
ABSTRACTS - Fourth International Conference on Malignant Lymphoma, Lugano


From 1964 to 1981, 1,057 patients with supradiaphragmatic clinical stage IA and IB Hodgkin's disease were treated on 3 successive protocols. Treatment consisted of mantle irradiation (MIX) +/- 2 years of chemotherapy (CHT); subtotal nodal irradiation (SMIX) +/- 2 years of LBL and carboplatin; total nodal irradiation (TND); or combined modality treatment (MOPP X 6 and MIX). For (TND), 37% of patients underwent a staging laparotomy. 3 groups were defined: 1) patients who never relapsed (NR); 2) patients who early relapsed (ER); and 3) patients with late relapses (LR) more than 6 months post-treatment start. The Cox model was used to compare these 3 groups with adjustment on initial characteristics (age, sex, symptoms, ESR, number of nodal areas involved, mediastinal involvement, and histology), and initial treatment. Patients were prospectively followed and data were up-dated December 1, 1999. 1,046 (98.8%) patients reached a complete remission (CR). Overall, 340 (32.6%) patients relapsed: 204 (29.2%) with ER, and 136 (13.0%) with LR. According to initial treatment, cumulative proportions of ER and LR, and relative risks of LR were: (P < 0.05, *** P < 0.001).


In the period 1977-1986 63 untreated patients (pts) with Hodgkin's disease (HD), completely stage IIIA or IIIB were seen in our Institute: stage IIA 17 pts, and stage IV 26 pts. All were treated with a nodal protocol and only 12 pts (19%) were given ALM to patients with HD. In the last years standard MOPP or CHOP was used to patients who relapsed while on treatment. In our experience, 12 pts were converted to systemic chemotherapy.

There were 31 progresses/recurrences (24.1%) in 63 pts, of whom 21 (33.3%) were seen in our Institute: at stage IIA 17 pts and stage IV 26 pts. All were treated with a nodal protocol and only 12 pts (19%) were given a MOPP or CHOP regimen. In the last years standard MOPP or CHOP was used to patients who relapsed while on treatment. In our experience, 12 pts were converted to systemic chemotherapy.


Forty-four patients with relapsed or resistant Hodgkin's disease were treated with Adriamycin 40 mg/m² IV on day 1, vincristine 1.4 mg/m² IV on days 1 and 5, prednisolone 40 mg/m² orally, days 1-5, orally for 21 days. Chemotherapy was administered in combinations with cyclophosphamide 500 mg/m² IV on day 1, or methotrexate 1.5 mg/m² IV on days 1 and 5. Median age was 27 years (range 12-71). When stage was considered according to Ann Arbor classification, the majority (59%) of patients (26) had stage III, (19%) stage IV, (23%) stage II, and (1%) stage I. Sixteen patients had already received previous chemotherapy (64%) and 6 patients (21%) had received 2 or more regimens. Twenty-six patients (59%) achieved CR and 10 (23%) PR. Median follow-up of surviving patients was 52 months (range 28-74). The median duration of CR was 23 months and median survival for all patients was 52 months. Eight patients remain in continuous CR: 6 of these were from a group of 19 patients who had relapsed from CR achieved by a single previous chemotherapy regimen. The HOPE-6 regimen was generally well tolerated, HOPE grade I/II and III/IV toxicity occurred as follows: leukopenia 41% and 23%, infection 16% and 22%, nausea and vomiting 53% and 7%, alopecia 21% and 50%, neuropathy 41% and 5%, there were 2 toxic deaths, one due to neutropenic sepsis, the other to acute peritonitis. The HOPE-6 regimen is an effective treatment for relapsed or resistant Hodgkin's disease and because of its low probability of cardiotoxicity and infertility deserves further evaluation as primary treatment for Hodgkin's disease. There was a substantial proportion of durable CRs in patients relapsing from CR, so one may conclude that it may be unnecessary to expose such patients to the toxicity and risks of high dose salvage regimens incorporating bone marrow transplantation.
ABSTRACTS - Fourth International Conference on Malignant Lymphoma, Lugano


In the present study the activity and side effects of high-dose cytosine arabinoside (HD-Ara-C) and mitoxantrone (Mitox) (HAM) were evaluated in 32 patients with refractory Hodgkin's disease. Therapy consisted in HD-Ara-C 3g/m² q 12 hrs days 1 and 2 and Mitox 10 mg/m²/day days 3-5. Subsequent escalations comprised 6 and 8 doses of HD-Ara-C on days 1-3 and 1-4, respectively, and 4 doses of mitoxantrone from days 2-5. Eighteen of the 32 patients (56%) responded with 5 complete and 13 partial remissions, 13 cases (41%) had refractory disease and 4 patients died from infectious complications. Ten of the responding 18 patients underwent subsequent autologous (n = 9) or allogeneic bone marrow transplantation. Seven of these cases are currently alive at 5-22+ months, 6 of them without ECOG grade 1 disease. From the remaining 8 patients, 3 are alive at 6+16+ months, 2 in ongoing remissions of 2+ and 4+ months' duration. The median survival for all treated patients is 13+ months. These data indicate that HAM has a significant activity in refractory Hodgkin's disease but also bears substantial side effects. Further application needs therefore rigorous modification in timing and dosage as well as the addition of antiproliferative growth factors (GM-CSF) to compensate especially for myelosuppressive complications.

P 30 HIGH DOSE CHEMOTHERAPY (HDC) WITH AUTOLOGOUS BMT (ABMT) IN 115 ADVANCED RESISTANT HODGKIN'S DISEASE PATIENTS. AN ITALIAN STUDY GROUP REPORT. G.L. Cazzaniga, A. Conigli (Genova), G. Meloni, F. Mandelli (Roma), P. Marza, R. Nani (Bologna), P. Conca (Bologna), A. Carchietti (Milano), M. Maschatter (Roma), A. Levi, L. Resegotti (Torino), L. Meretti, G. Lucarelli (Pescara), F. Benedetti (Vercelli), E. Brusamolino, C. Bracigliano (Roma), T. Barbuli, R. Bassan (Verona), R. Messina (Bergamo), L. Malinola (Palermo), T. Chiusi (Vicenza), F. De Cataldo (Milano). BMT UNIT, Division of Haematology, Ospedale S. Martino, 16132 Genova (ITALY)

Current primary treatment for untreated, advanced stage Hodgkin's disease may cure a high proportion of patients. However, patients who fail a first line therapy do not have a favorable outcome. Patients refractory to or relapsing soon after second and third line protocols are rarely cured and the prognosis is very poor. Between July 1981 and December 1989, 115 patients (66 females, 74 males, median age 25 years, range 15-51 years) were treated with HDC and ABMT as a treatment modality for advanced resistant Hodgkin's disease. 89 pts had B symptoms, 40 pts had progressive disease during alternative MOPP (ABMT) protocol. 7 yrs were in CR. 51 pts had CR with first line therapy but later relapsed and 31 received unknown Hodgkin's disease. Eligibility was: TP, Flavell's, Tal, Marcus, HU, HLA.

P 31 HIGH DOSE CHEMOTHERAPY (HDC) AND AUTOLOGOUS BONE MARROW TRANSPLANTATION (ABMT) IN RELAPSED AND REFRACTORY HODGKIN'S DISEASE (HD) P. BRICE, E. LEPAIGE, A. BARUCEL, P. BRICHON, F. MOESCHBACHER, M. BOIRON.


Despite combination of chemo and radiotherapy some patients with advanced HD have a bad prognostic. We performed HD-C in MVA 1500 mg/m² and ETOPOSIDE 125 mg/m² X 2 D-7-D-6-D-5-D-4 followed by infusion of cryopreserved bone marrow (22 pts) or peripheral stem cells (5 pts) in 27 patients with advanced HD. 12 pts were considered as refractory after at least two non cross-resistant chemotherapy regimens and radiotherapy in 8. 15 pts had a poor prognostic relapse in visceral sites (10 pts) and/or in irradiated lymph nodes (7 pts) after complete remission and they received chemotherapy before HCT and ABMT. The mean time between diagnosis and transplantation was 34 months (8 to 107 months). Before HCT and ABMT, 4 pts had progressive disease and did not respond to HDC and died from persistent HD 3 to 12 months post ABMT. From the 23 remaining pts, 11 were in PR and 12 in CR after second or third line chemotherapy regimen before HDC and ABMT. Median time to bone marrow recovery was 22 days. There was one toxic death with interstitial pneumonitis due to CMV infection 3 months after HDC and ABMT, 20 pts were in CR, 2 in PR. After CR, 5 pts relapsed after HDC and ABMT. Median time to bone marrow recovery was 8 months and 15 months in persistent remission from 8 to 34 months after ABMT. Survival is significantly better in patients with relapse HD than in refractory pts. At two years, the probability of survival was 70% with a disease free survival of 60%.

These results are encouraging in patients with bad prognostic disease and still responding to chemotherapy.


A percentage of patients with relapsed Hodgkin's disease (HD) now achieve long-term remission following ABMT. Anthracyclines are effective in HD but cardiotoxicity has previously precluded dosage escalation. Mitoxantrone (MTZ) has reduced cardiotoxicity and we have now conducted a 6-patient pilot trial of HD for ABMT with high-dose MTZ (100-120 mg/m²) and high-dose etoposide (2000 mg/m²). Both agents were given by continuous infusion through a central venous catheter on alternate days in 2 divided doses. Plasma levels of MTZ were measured daily by ELISA assay.

Sex/Age Dose Day of MTZ level Days to neutrophil platelet recovery independence

M/39 100 +9 3.4 28 17
M/21 100 +7 3.8 24 27
F/27 100 +6 7.9 Death +12 26
F/21 100 +7 10.5 41 31
F/30 100 +7 NA 13 13
M/25 100 +9 3.1 21 29
(Most available)

Of 5 surviving patients 3 achieved CR and 2 PR. Delayed engraftment and graft failure occurred in the 2 patients with highest plasma MTZ levels at the time of marrow infusion. Peak MTZ levels occurred immediately post infusion and showed exponential decay with marrow toxic levels for 7 days. No cardiotoxicity was evident on ECG monitoring and MUGA scanning post-ABMT.

This regimen appears to be safe and effective in refractory HD and shall now be evaluated in a larger group of patients. Non-cardiotoxic anthracycline derivatives with a shorter in vivo half-life would permit earlier marrow reinfusion and subsequent engraftment.
P 33 ABMT IN PATIENTS WITH MORBUS HODGKIN - A RETROSPECTIVE EVALUATION OF 393 PATIENTS ACCORDING TO VARIOUS CRITERIA OF TRANSPLANTATION CENTER. M. Moedl, R. Haime, R. Zulcher et al. 3rd Med.Department and Ludwig Boltzmann Institute for Leukemia Research and Hematology, Hannusch Hospital, A-1140 Vienna, Austria.

In our department, we investigated 306 randomly selected patients between the ages of 12 and 50 years for ABMT according to different criteria recommended by four well-known transplantation groups. Seattle recommends ABMT for all patients who fail MOPP while a group in UK suggests ABMT for patients resistant to primary therapy irradiation. Seattle criteria are applied in Germany and Italy. However, all these groups describe patients with a rather short observation period so that the long-term outcome is not evaluable. The median observation period of our patients was 90 months. In our retrospective evaluation more than 50 percent of the patients with second line therapy achieved long term CR. The median survival time of high risk patients i.e. patients who had more than 3 chemotherapy cycles was 155 months. Because of these results with conventional chemotherapeutic approach, ABMT is recommended as salvage therapy.骨髓移植的适应症和效果

P 34 HODGKIN'S DISEASE (HD) IN THE ELDERLY. M. Liebhaut, L. Birkovich, T. C. M. Lo. Department of Radiation Therapy, Lahey Clinic Medical Center, Massachusetts, USA.

Between 1948 & 1988, 58 elderly (age>60) patients (pts) with HD were evaluated at the Lahey Clinic. The range 60-88 yrs (median 68 yrs). They represented 22% of the HD population. Few underwent staging laparotomy, beginning in 1975. Male patients accounted for 62% of Males, 38% of females. HD Stages I & II were treated with extended field (EF) mantle or involved sites (IS). HD Stages III & IV pts received combined chemotherapy (CH). The median follow up is 14 months (range: 1 mo - 15 yrs). The mean absolute survival was 4 yrs with a median of 1.3 yrs. Seven pts are alive without evidence of disease (IHEI). MES, 31 died of progressive disease (PD) in 3 of death. Two pts were diagnosed at autopsy and excluded from survival analysis. 9 pts significantly benefit from free relapse (FFR) rate and survival rate (SR) than pts with Stage I & II HD (median FFR 1.75yrs; 1.0yrs; p<0.01) median survival 4.9yrs; 1.0yrs; p<0.01. Symptom relapse had a better FFR rate and SR than pts with B symptoms (median FFR 1.75yrs vs 0.0yrs; p<0.01) median survival 4.9yrs vs 1.0yrs; p<0.01. Pts with nodular sclerosis and mixed cellularity HD had a significantly better FFR rate and SR than pts with lymphocyte predominant HD (median FFR 3.47yrs; 1.0yrs; p<0.01) median survival 6.9yrs vs 1.0yrs; p<0.01. Gender, erythrocyte sedimentation rate, and plasma C-reactive protein were not significant factors in predicting FFR in survival analysis. Stage I & II HD tolerate EF radiotherapy well, FFR rates may be improved by treating with subtotal lymphoid irradiation (SLI).

P 35 AGE (50 yrs ± 50 years) AS A PROGNOSTIC FACTOR IN 1062 PATIENTS WITH STAGE 1 & 2 HODGKIN'S DISEASE ENROLLED IN EORTC CLINICAL TRIALS SINCE 1950. G. Szklo, Advanced Systems, AGIOS System, Centro di Riiferimento Oncologico, Monte Carlo, Italy.

From 1950 to 1959, 1062 patients with clinical stage (CS) I-II Hodgkin's disease (HD) were treated in 4 consecutive prospective clinical trials: I (1950-51), II (1954-55), III (1956-57), and IV (1958-59). In all these trials, consistents in mantle irradiation (RT) ± chemotherapy. For age group 50 yrs. pts aged 65 years or older were at increased risk of death at 5 years. 7% in the younger and 17% in the elderly. In contrast, the 10-year survival rate was significantly lower in the older (IIV vs NR, p<0.001), with a relative risk (RR) of death (1.21) of 3.71(p<0.001). For Cox analysis, age ≥50 years was found to be the most important prognostic factor for cause-specific mortality: HR 2.17 (p<0.001) for deaths as a consequence of disease progression; and HR 0.54 (p<0.001) for deaths from other causes. Patients aged 65 years or more represented a small proportion of CS I-II HD entered in prospective EORTC trials. Although the response rates were similar to those observed in younger patients, patients aged 65 years or more appear to be at a higher risk of death, partly as a consequence of the higher age group. The treatment results of these patients should be taken in consideration when therapy is planned in these patients.


From January 1982 to June 1989 clinical data from 523 untreated patients with Hodgkin's disease were recorded in the Italian Hodgkin's Disease Study Group (PDHSO) Register. 5745 patients were enrolled in the HD92 and HD96 protocols, while 129 (22%) entered an alternative staging procedure or test program. 58 (11%) patients were older than 65 years. Clinical stages and presentation of S symptoms were similar both in patients over 65 and in younger ones. Histology was statistical different between the two groups, with a predominance of nodular mixed cellularity versus nodular sclerosis in elderly people (MC: 63% vs 31%; NS: 30% vs 54% p<0.001). Only 4% of the elderly group were enrolled into the therapeutic protocols, compared with 80% of younger group (p<0.01). Elderly patients had an increase incidence of subsequent protocol violations/interruptions due to bad compliance or toxicity (34% vs 14% p<0.001). So far 20 elderly patients have died, with a high incidence of toxic deaths (45%). No differences were seen in terms of complete remission, disease free survival, overall survival or event free survival between elderly patients and those who entered an alternative program. Results for age groups are as follows:

- <65 years >65 years p value
  - complete remission 97% 80% 0.001
  - 5-yr disease free survival 71% 64% 0.059
  - 8-yr survival 71% 53% 0.001
  - 8-yr event free survival 71% 53% 0.001

Our data show that elderly patients achieve complete remission less frequently than younger ones, mainly due to the high incidence of bad compliance and toxicity. However disease free survival is not worse than that of younger patients. Alternative regimens with a lower incidence of toxic effects could improve the outcome of this group of patients.

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P 37 Patterns of survival in Hodgkin’s Disease (HD) following relapse in patients treated at a single centre over a 21 year period.
ICRF Department of Medical Oncology, St Bartholomew’s Hospital, 45 Little Britain, London EC1A 7BE.

520 previously untreated adults with confirmed HD (01 stage I, 177 stage II, 147 stage III and 105 stage IV) were treated at St. Bartholomew’s Hospital between 1968 and 1984 with what was considered to be appropriate therapy (extended field irradiation or MVBP based chemotherapy). The overall median survival was 18.3 years. Clinical remission (R = complete remission plus complete remission, uncertain; ref: Lister et al J Clin Oncol 1989;7:1630-1636) was induced in 442 (85%); the median survival of remitters has not been reached. Fifty eight patients achieved responses less than R with initial therapy (partial response or had progressive disease, the median survival of this group is 1.4 years; 20 patients died before completion of therapy. With further therapy, R was subsequently induced in 10; 5 are still alive, 5 have died between 1.9 years and 14.3 years. 146 of the remitters following initial therapy have relapsed over a median follow up period of 13 years (minimum 5 years). 143 patients were treated following relapse (105 chemotheraphy, 28 radiotherapy, 6 combined modality treatment and 4 surgery). Second remission was induced in 109/143 (76%). There was a strong trend towards better second remission induction in patients whose first remission was longer than 1 year (p < 0.005). The median duration of second remission is inferior to first remission duration (p < 0.001). There was no correlation between duration of first remission and survival following relapse or with duration of second remission. There is no significant difference in duration of second remission between patients who were initially treated with radiotherapy or chemotherapy. The median survival following second relapse is 12.5 years, being the same for patients with initially localized disease (stages I and II) treated with radiation alone and for patients with advanced HD (stages III and IV) treated with chemotherapy. Survival after relapse is significantly better for patients under 50 years at the time of relapse (p < 0.001). 46 patients relapsed a second time, third remission being reinduced in 22, the median survival of the remitters being 5.1 years. These results illustrate the importance of prolonged follow up in defining the clinical course of patients with HD and are vital for planning experimental chemotherapy at the time of treatment failure or relapse.

The Department of Oncology, The Norwegian Radium Hospital and The Cancer Registry of Norway, N – 0310 OSLO 3, Norway.

During 1968-1985 1177 patients with Hodgkin’s disease (HD) from all parts of Norway were admitted to The Norwegian Radium Hospital. 68 patients developed a second primary cancer ≥ 1 year after diagnosis of HD and 6 of them subsequently developed still another cancer rendering the total number of second primary cancers 74. These included 56 solid tumors, of which 10 were lung cancers, 8 non-Hodgkin’s lymphomas (NHL) and 9 acute non-lymphocytic leukemia (ANLL). The median intervals between the diagnosis of HD and that of second lump cancer, NHL and ANLL were 10.4, 7.0 and 5.8 years, respectively. The overall relative risks (observed/expected ratio) of developing lung cancer, NHL and ANLL were 3.3, 8.4 and 24.4, respectively. Nine of ten cases of lung cancer arose in patients treated with radiotherapy (RT) and were located within radiation field. For the development of NHL, no particular therapy received dominated. Only 4 of 9 patients were heavily treated. (Either RT to both sides of the diaphragm, combination chemo-therapy (CCT) more than 6 cycles or a combination of RT to one or both sides of the diaphragm + CCT used cyclically). All the patients that developed ANLL had received treatment with alkylating agents and Procarbazine. Eight of 9 patients were heavily treated. 60 %, 33 % and 22 % of the patients with lung cancer, NHL, and ANLL respectively had splenectomy. This does not support the hypothesis of an increased risk of developing ANLL after splenectomy. The treatment trend of the Norwegian Radium Hospital to use radiotherapy rather than aggressive chemotherapy may explain the rather low numbers of second ANLL. The increased risk of developing a second primary cancer after treatment of HD will be discussed.

P 39 THE ROLE OF PREGNANCY IN THE PATHOGENESIS OF HODGKIN’S DISEASE: A CASE-CONTROL STUDY
Matjaž Zwitser, Institute of Oncology, 61005 Ljubljana, Yugoslavia.

To evaluate the role of pregnancy in the etiopathogenesis and in the clinical course of Hodgkin’s disease (HD), a case-control epidemiological study included a series of 165 women aged 17 to 50 years at the time of diagnosis. The data were collected in two countries on socio-economic status in childhood, and parity were obtained from 120 patients who are still alive and from the relatives of 45 deceased patients, as well as from 321 population-based controls matched by residence and year of birth. The data on the parity of controls were considered only if a woman reached the age at diagnosis of her corresponding HD patient. When compared to controls, patients tended to have their first child at an older age, possibly attributable to their slightly longer education; on the other hand, a non-significant excess of nulliparous women was seen in the control group. Within the first 6 months after delivery, HD was diagnosed in 14 cases, a figure which is significantly higher (p<0.05) when compared to expected 6.5 cases, to occurrence of HD in other 6-month intervals after delivery. The clinical course of HD diagnosed in pregnancy or soon after delivery did not seem worse than otherwise. After treatment and in complete remission, 31 children were born to 25 mothers; only one of these patients later died of disease progression. We conclude: 1. previously reported protective effect of pregnancy on the risk for HD (Abramson et al, JNCI 1980;207, 1978) could not be confirmed; 2. pregnancy may be a period of an enhanced expression of HD; 3. pregnancy does not have an adverse influence on patients in remission.

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¹for controls, reaching the age (6 months) of her corresponding HD patient
²within 6 months after delivery

P 40 INCIDENCE OF “SECOND TUMORS” IN PATIENTS TREATED FOR HODGKIN’S DISEASE: An analysis of 1060 cases.
Radiotherapy of Florence, University (*) and Hospital (**) Radiotherapy of Chieti, University (**) Radiotherapy of Arezzo, University (**)
ABSTRACTS - Fourth International Conference on Malignant Lymphoma, Lugano


From 1-1987 to 11-1989, 54 patients (pts) with HIV-HD were recorded by the registry. Data from 26 pts were available for clinical outcome analysis. Initial characteristics were: sex M 25 F 9, age 25-50, median 30; risk groups homosexual 11, IVDA 11, both 1, others 6; HIV clinical status asymptomatic 14, PGL 7, ARC 1, AIDS 2; CD4 cell count (19 pts) median 270 ul (99-800 ul). HD histology: LP 1, NS 10, NC 10, LD 2, unclassified 2; HD clinical stage: CS I 4, II 6, III 11, IV 6; liver 5, bone marrow 5, CNS 1. Treatment: radiotherapy 1, chemotherapy 16 (MOPP and/or ABVD, 3-6 cycles, median 4), chemo plus radiotherapy 11. Follow-up: 4 to 62 months, median 15. 2 pts (CS IIB and IV) progressed under treatment. 24 pts entered in complete remission (CR): 16 at relapse (CS IV, 7 months after therapy). 2 pts were not evaluable due to early death from opportunistic infection (O.I.). Out of the 26 initially non-AIDS patients, 12 developed AIDS 8 pts during HD therapy (O.I. 6, Kaposi's sarcoma 3) I, O.I.+KS 1, and 4 pts (O.I.) within the 3 months following treatment. Overall 2-year actuarial survival was 46% (CS I+II 67%, CS III+IV 39%). Freedom from progression rate (events are initial failure and relapse) was 84% (CS I+II 88% and CS II+IV 79%). AIDS progression rate was 58% at 10 months and stable thereafter. Conclusions: 1. Treatment of HIV-HD gives a particularly high rate of CR, with a low relapse rate. 2. Infectious complications are extremely frequent during therapy and short or after. 3. These findings should be taken into account for future prospective trials and individual management of HIV-HD (Supported by AREMAS and Ligue Nationale contre le Cancer).