45 Expression, Sharing and Remodeling of Idiotypes in Follicular Lymphoma

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Human follicular lymphoma can be viewed as a malignancy in evolution. Since this disease is composed of a clonal population of B lymphocytes all expressing a given immunuglobulin light chain and heavy chain, it seems likely that the transforming event, the rearrangement of the BCL-2 gene occurs in a cell already committed to the expression of a particular VH and VL gene. The selection of VH genes expressed by follicular lymphoma tumors appears to represent that of the normal B cell repertoire . A panel of antibodies has been assembled which define a set of idiotypes expressed repeatedly by B cell lymphomas. The structural basis of shared idiotypes is now being sought. A number of lines of evidence suggest that this tumor is under normal regulatory controls. Interaction of the expanding malignant B cell clone with the host is evident in the pattern of growth which is highly organized in follicles with particular apposition to follicular dendritic cells and heavy infiltration with CD4 positive T cells. Interaction with host T cells can induce the proliferation of the follicular lymphoma cells. This tumor eventually evolves into a diffuse large cell lymphoma which is highly aggressive and lethal. It is now clear that the malignant progression occurs from a single cell within the expanding follicular lymphoma clone. This is based on immunoglobulin variable region gene sequences in the transformed lymphomas in comparison to their antecedent follicular tumors. The entire evolution of the follicular lymphoma clone to the large cell lymphoma is accompanied by extensive somatic point mutation scattered throughout the VH and VL genes. This results in variability in the tumor cell population with respect to activity with monoclonal anti-idiotype antibody reagents. Therapeutic application of such monoclonal antibodies has shown a high degree of tumor responsiveness but ultimate escape of idiotype negative variant cells. Active immunization can result in an immune response by patients directed against the idiotype expressed on their own B cell tumors. It is anticipated that such immune responses will be polyclonal and better able to deal with the problem of tumor heterogeneity due to somatic mutation.

46 ANALYSIS OF t(14;18) CHROMOSOMAL BREAKPOINTS BY POLYMERASE CHAIN REACTION AND DIRECT DNA SEQUENCING IN B-CELL LYMPHOMA.

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We have exmined 146 B-cell non Hodgkin's lymphoma for rearrangements of the t(14;18) major breakpoint region by Southern analysis of genomic DNA and by polymerase chain reaction (PCR) with direct sequencing of amplified bcl-2/J_H-fragments. The lymphoma were categorized according to the Kiel classification (35 CC-CB; 37 CB; 24 IC; 8 IB; 13 CC; 17 CLL; 3 LB; 2 Ki-1; 2 hairy cell leukemia and 5 plasmocytoma). With use of relatively long PCR-primers (Oligo MK 28 : 5' GGTGACCAGGGTCCCTTGGCCCCAG 3' inverse complementary to the consensus J_H sequence and Oligo MK 3 : 5' GCAATTCCC-GATTTAATTCATGGTATTCAGGAT 3' for bcl-2) primer annealing and extension were carried out within 30 s per cycle at 65°C. The specificity of the procedure allowed visual identification of the bcl-2/J_H PCR-products in ethidium bromide stained agarose gels after 40 PCR cycles.

In 17 cases a bcl-2/J_H fusion gene could be amplified by PCR. In two cases with bcl-2 rearrangement on Southern analysis the fusion gene was not amplifiable with our assay. A bcl-2 rearrangement was only found in three lymphoma subgroups: 15/35 (42 %) CC-CB; 3/37 (8 %) CB and 1/24 IC (4 %). Because three of the bcl-2/J_H CC-CB lymphoma contained areas of conversion to CB lymphomas it can be speculated, that the three diffuse CB NHL with bcl-2/J_H may have originated from CC-CB NHL. Direct DNA sequencing of 15 PCR-amplified, previously uncharacterized t(14;18) junctional regions, clearly provided corroborating evidence for the specificity of our assay.

Together with the variations in t(14;18) breakpoint sequences flanking both chromosomal 18 and chromosomal 14 sites, the junctional region N-segments (length: 2-45 bp) create highly clone-specific target sequences for tumor-cell specific PCR (N-PCR) or in situ hybridisation and aids in reducing the threat of false positive results interent to PCR.

47 Expression of Growth-related Genes and Drug-resistance Genes in HTLV-1-positive and HTLV-1-negative Post-thymic T Cell Malignancies

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This study was designed to investigate the molecular basis of the rapid clinical course and poor prognosis of high grade post-thymic T-cell lymphomas. Total cellular RNAs were extracted from 5 HTLV-1-positive and 23 HTLV-1-negative peripheral T-cell lymphomas and cell lines, including 5 paired specimens biopsied at early and late stages of diseases in 5 patients. Slot blot and northern blot hybridization were prepared and investigated for homology with cloned DNA probes specific for proliferation- or growth-related genes (IL-2R , TGF-beta, PDGF, laminin receptor, and topoisomerase I and II) and multiple drug resistance gene (MDR-1). Our results showed that tumor cells associated with high grade HTLV-1-positive ATL and large cell morphology (T-immunoblastic lymphoma) had enhanced expression of IL-2R, TGF-beta, laminin receptor, and Top-I and II, as compared to the low grade malignancies such as mycosis fungoides and Sezary syndrome. The expression of MDR-1 gene is negligible in fresh cases of ATL and high grade or low grade T-cell neoplasms, comparable to that of B-cell lymphoma. Clinical progression or relapsing after chemotherapy, however, was frequently (3 in 5 paired specimens) associated with overexpression of MDR-1 gene, in addition to the enhanced expression of growth-related genes. We therefore conclude that the poor prognosis of high grade T-cell lymphoma and ATL may result mainly from the high-level expression of proliferation- or growth-related genes, resulting in rapid tumor growth. Tumor relapsing is further complicated by the development of drug resistance. Our observations are consistent with the current data that peripheral T-cell lymphoma should be initially treated with an intensive regimens of drugs to avoid tumor relapsing.

48 PROGNOSTIC SIGNIFICANCE OF PROLIFERATIVE ACTIVITY IN NON-HODGKIN'S LYMPHOMA.

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Non-Hodgkin's lymphoma (NHL) is composed of a heterogeneous group of tumors which exhibit diverse biological behavior. Characteristics which have been shown to predict outcome following therapy include the histologic type and stage of disease at diagnosis. The development of techniques for extracting nuclei from paraffin-embedded tissues (J. Histochem. Cytochem. 31:1333, 1983) has permitted retrospective studies of the role of cellular proliferative activity (PA) and DNA content as prognostic factors in NHL. We recently reported that low PA was associated with a favorable prognosis in patients with diffuse mixed cell and diffuse large cell NHL (Cancer Res. 48:6608, 1988). We have since expanded the above study and present the results herein. Paraffin-embedded biopsies of tumor tissue obtained at the time of initial diagnosis from 116 patients with NHL were processed and analyzed by flow cytometry. All patients were uniformly staged, and treated with cyclophosphamide, doxorubicin, procarbazine, bleomycin, vincristine, and prednisone (CAP-BOP). Statistical analyses were performed using the Chi-square test for frequency of complete remission (CR), and the log rank test for survival and duration of CR. We evaluated the effects of three cutoff levels for determining low versus high PA: GOGI<80%=high PA (PA80), GOGI<85%=high PA (PA85), and GOGI<90%=high PA (PA90). In addition to PA, we also evaluated the prognostic significance of age, sex, stage of disease, tumor size and symptom status. Results from all 116 patients showed that low PA (PA80, $p<0.03$) and age (<60 years, $p<0.005$) predicted a favorable survival. We then evaluated the tumors by histologic subtype. Ninety-two patients with high grade tumors (diffuse mixed cell and diffuse large cell NHL) were studied, and an increased frequency of CR and longer survival ($p<0.02$ and $p<0.05$, respectively) were associated with low PA (PA80). However, using PA90, we also found that high PA predicted a longer duration of CR ($p<0.04$). Twenty-two patients with low grade NHL (follicular, diffuse intermediate and diffuse small cleaved cell NHL) were also evaluated, and duration of CR was greater in those with low PA (PA80, $p<0.03$). When only B-cell tumors (95 total, 75 high grade) were evaluated, we found no statistical association of PA with the frequency or duration of CR, or survival. Data from the 11 peripheral T-cell NHL in this study suggested a favorable influence of low PA (PA85) on survival and duration of CR. This is in agreement with our recent study of 31 non-uniformly treated patients with peripheral T-cell NHL, wherein we found that low PA (PA90) was associated with longer survival and duration of CR. The results of our studies indicate that the histologic and immunologic subtypes of NHL must be considered when evaluating the prognostic significance of PA in NHL. This work was supported in part by Nebraska Department of Health Grant LB-506.

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CLINICAL RELEVANCE OF MYELOMONOCYTIC ANTIGEN CD13 (aminopeptidase N) EXPRESSION IN B-CELL CHRONIC LYMPHOCYTIC LEUKEMIA (B-CLL). A.Pinto, V.Zagonel, A.Carbone, S.Monfardini, A.Colombatti, L.Del Vecchio*. Leukemia Unit, C.R.O., 33081, Aviano, Italy, *Immunohematology Centre 'A.Cardarelli' Hospital, Naples, Italy.

Ectopic expression of myelomonocytic antigens (MyAg) on lymphoid leukemia cells has several important biological and clinical implications. In particular the expression of the cell surface peptidase, recognized by anti-CD13 monoclonal antibodies (MY7, MCS-2), is associated with a lower remission rate, poor clinical outcome and a shortened survival in acute lymphoblastic leukemia (ALL) and multiple myeloma (MM). We first reported that CD13 is also expressed, on a subset of B-CLLs°. To further investigate this phenomenon we prospectively studied 70 consecutive B-CLL patients (pts) for MyAg expression. The cytofluorimetric analysis revealed that CD13 and CD14-MY4 antigens were expressed on B cells from 34 and 59%, of pts respectively whereas CD15 and CD33 have been detected only in 7 and 13.5% of samples. 28% of pts displayed a multiple MyAg expression (CD13+CD14, CD14+CD33, CD13+CD14+CD33, CD13+CD14+CD15).
No significant differences were observed between MyAg+ and MyAg- B-CLLs as far as CD5 expression and SIg brightness are concerned. The coexpression of myeloid and B-associated antigens (CD19,CD20,CD24) on the same B cell, was confirmed by double labelling flow cytometric experiments and immunohistochemistry on lymphnode frozen sections. We found a very strong association ($p < 0.0001$) between CD13 expression and a "diffuse" pattern of bone marrow infiltration. A trend for the "diffuse" pattern association with multiple MyAg was also apparent. CD13+ cases were never observed among pts with disease limited to peripheral and marrow lymphocytosis (RAI 0) but no significative differences in CD13 expression were found when comparing pts of higher RAI stages (I-II vs III-IV). This phenomenon is less evident with the Binet staging system (A vs C, p=0.04), probably owing to the inclusion in the group A of some pts with lymphnodal and/or parenchimal disease. These results are of particular clinical importance since the pattern of bone marrow infiltration represents one of the most important single prognostic factors to date available in B-CLL. Our study demonstrates for the first time that, in analogy with early B cell diseases (ALL) and mature plasma cell disorders (MM), also in intermediate B cell neoplasms, such as B-CLL, the expression of the CD13 antigen represents a highly unfavourable prognostic factor. These results suggest a critical role of the Aminopeptidase N/CD13 in the ontogeny of B lymphocytes and in mediating relationships of B cell subpopulations with bone marrow and lymphnode microenvironment.
°Pinto et al. Blood 70, 1450, 1987.
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THE ROLE OF GROWTH FACTORS IN HAEMOPOIESIS: BIOLOGICAL AND CLINICAL IMPLICATIONS. T.M. Dexter. Department of Experimental haematology, Paterson Institute for Cancer Research, Christie Hospital & Holt Radium Institute, Manchester M20 9BX, UK

The growth and differentiation of haemopoietic cells in the bone marrow occurs in association with stromal cells that provide specific microenvironments. Within these microenvironments, haemopoiesis is regulated by a complex network of adhesion molecules, extracellular matrix components and growth stimulatory and inhibitory factors. Many of these growth factors have been molecularly cloned, purified to homogeneity and their receptors characterised. Furthermore, the multipotential stem cells and their differentiated progeny can now be obtained free of contaminating accessory cells and their direct response to growth factors determined in serum-free culture conditions. From analysis of these systems, a general model for regulation of haemopoiesis has been developed which suggests that self-renewal and differentiation of stem cells is regulated by the range and concentration of growth factors to which the cells are expressed - and that combination of growth factors can be selectively used to modulate both self-renewal and the choice of lineage-options taken by stem cells. Some of the growth factors have already entered clinical trials, with obvious beneficial results: other growth factors are currently being examined for the modulatory effects upon haemopoiesis in animal model systems and data will be reported on such studies. The role of haemopoietic growth factors in leukaemogenesis will also be examined.

51 MANAGEMENT OF FOLLICULAR LYMPHOMA

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The management of people with follicular lymphoma is determined by the bulk and distribution of the disease at the time. There is a general feeling that an expectant policy is appropriate for those who are well, without evidence of progression. Many attempts have been made to influence the natural history, either with single agent chemotherapy, radiotherapy or combinations of varying intensity, even to the extent of bone marrow ablative therapy with autologous bone marrow rescue. Experience gained to date, and the studies in progress will be presented.

52 THE PRESENT STATUS OF THERAPY FOR PATIENTS WITH AGGRESSIVE NON-HODGKIN LYMPHOMA.

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The aggressive non-Hodgkin lymphomas include some of the malignancies most frequently cured with chemotherapy. However, not all patients are cured and the best treatment approach remains uncertain. The most common aggressive non-Hodgkin lymphomas are diffuse large cell lymphoma and immunoblastic lymphoma. Most recent studies suggest no useful difference in distinguishing between these two groups in the Working Formulation. When these tumors present in a localized manner they are highly curable. Earlier studies showed that radiotherapy alone had a high relapse rate. Chemotherapy alone has been found to have an excellent cure rate, but when followed by radiotherapy, the amount of chemotherapy can be reduced with the same good result. The best chemotherapy regimen for patients with disseminated large cell lymphoma is uncertain. A number of aggressive regimens have been shown to be able to cure approximately 50% of patients. Several are now included in a randomized study ongoing in the United States to see if one is superior. At present, it seems that a number of regimens including m-BACOD, MACOP-B, LNH-84, ProMACE-CytaBOM, CAP-BOP, COP-BLAM, F-MACHOP, and perhaps full dose CHOP have about equal results when prognostic factors are taken into account. The most important present area for a clinical research in treating these patients (unless new drugs are found) is in identifying those patients likely to be cured with our present treatments and those patients for whom alternative therapies such as bone marrow transplantation need to be considered as part of the primary treatment. This is true not only for large cell lymphoma but also for the less common aggressive non-Hodgkin lymphoma such as lymphoblastic lymphoma, small non cleaved cell lymphoma, and peripheral T cell lymphoma. At the present time, this is the most promising approach to improving therapeutic results.

53 MORPHOLOGIC PROGNOSTIC FACTORS IN FOLLICULAR LYMPHOMAS. A RETROSPECTIVE STUDY OF 127 PATIENTS.

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The influence of initial morphologic parameters on response to treatment, overall survival, freedom-from-relapse (FFR) survival, freedom-from-progression (FFP) survival and rate of histologic progression was analyzed in 127 patients (pts) with a follicular lymphoma treated from 1975 to 1985. All slides were reviewed. Four histologic parameters were assessed. (a) The percentage of cleaved and noncleaved large cells, with 4 subgroups: <10%, 41 pts; 10 to 30%, 39 pts; 30 to 50%, 11 pts; ≥50%, 30 pts. 6 pts had a mantle-zone lymphoma. This high percentage of pts with large-cell lymphoma is probably explained by the fact that the count was done on follicles with higher large-cell composition in heterogeneous cases, as proposed by many authors. (b) The degree of follicularity assessed either by the presence of an intrafollicular pattern of proliferation (absence, minority or majority of follicles); or by the importance of diffuse areas: <25%, 78 pts; 25 to 50%, 23 pts; >50%, 20 pts. These two parameters are highly correlated ($p<.01$). (c) The mitotic activity graded from + to +++. (d) The histologic evidence of fibrosis graded from 0 to +++. Mitotic rate is correlated with the percentage of large cells ($p<10^{-4}$) and the degree of follicularity ($p<.05$). Fibrosis is correlated with the percentage of large cells ($p<.05$).

80% of pts reached CR and 47% of them relapsed. Median survival is 111 months with a median follow-up of 9 years. Mitotic rate is the only morphologic parameter correlated with clinical or biological parameters: a high mitotic rate is associated with high LDH level ($p<.05$) and tumoral mass ≥10 cm ($p<.05$).

A high mitotic rate is correlated with a low response rate ($p<.05$) and a high histologic progression rate ($p<.01$) but not with survival. An increased fibrosis is correlated with a longer overall ($p<.01$), FFR ($p<.01$) or FFP ($p<.01$) survival. The percentage of large cells is not correlated with response rate, histologic progression rate, or survival; nor is the percentage of diffuse areas. The presence of an intrafollicular proliferation is significantly associated with a better outcome ($p<.005$).

The absence of statistical correlation between the percentage of large cells and the outcome could not be explained by a more intensive treatment of pts with large cell lymphoma. It raised the problem of subclassification of follicular lymphomas. The prognostic value of diffuse areas has been discussed: we could not confirm a statistical adverse prognosis of follicular lymphomas with diffuse areas. The prognosis of follicular lymphoma is probably best determined by clinical or biological parameters as in diffuse lymphomas, i.e., stage, tumoral mass, number of extranodal sites, performance status, LDH level, than by morphologic parameters.

54 STAGE I-II LOW-GRADE LYMPHOMAS (LGL): A PROSPECTIVE TRIAL OF COMBINATION CHEMOTHERAPY (CT) AND RADIOTHERAPY (XT).

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Patients (pts) with LGL are diagnosed when their disease is in early stage in only about 15% of cases. There have been several reports of potential curability of pts with stage I-II LGL, including from centers in Toronto, Stanford, Houston, Buffalo, and London. Treatment (Rx) has varied from involved field (IF) to total nodal irradiation (TNI), as well as limited published experience with CT. When IF alone is used, a staging laparotomy is advisable, since about half of clinical stage (CS) I-II pts have occult abdominal disease. TNI for CS I-II pts is a consideration but it has substantial morbidity. Between 1984-89, we explored IF XT in combination with relatively mild CT, cyclophosphamide, vincristine, prednisone, and bleomycin (COP-Bleo), for CS I-II pts. Adriamycin was added for high risk pts (high LDH; extranodal sites; bulky abdominal nodes). Bleomycin was omitted in pts > 60 yrs. Of 44 pts, there were 27 with follicular small cleaved, 13 with follicular mixed, and 4 with diffuse small lymphocytic lymphoma. Six were surgically free of disease (NED) at the outset of therapy. All 38 pts with measurable disease have responded: 37 complete and the other one partial so far, still on Rx. There have been only 3 deaths, 2 of intercurrent disease and 1 of myelodysplasia attributed to the COP-Bleo+XT. There have been only 6 relapses: all but 1 were at previously uninvolved sites (out of field); 3 were in pts who had initial high risk features, and 2 others had initial large peripheral nodes; 1 relapse was in a pt who was stage I NED at the time of initial Rx. At 5 yrs, the failure-free (FFS) and overall survival are 73% and 88%. Compared to past experience with IF XT alone (Cancer 1986;58: 1596), the FFS is significantly better ($p>0.01$) with COP-Bleo+XT. The potentially cured fraction of pts has risen from 40% to 73%.

55 INTERFERON-α_{2b} (IFN-α_{2b}) AS INITIAL THERAPY IN COMBINATION WITH CHLORAMBUCIL (CB) AND AS MAINTENANCE THERAPY IN FOLLICULAR LYMPHOMA (FL).

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Since 1985 the combination of CB (10mg daily; initially for 6 weeks, then alternating fortnights for 12 weeks) and IFN-α_{2b} (Schering-Plough; $2x10^6$ units/m^2 3x weekly subcutaneously continuously for 18 weeks) has been compared in a randomised trial with CB alone (as above) in previously untreated patients with stage III & IV FL. Responding patients have subsequently been randomised to maintenance IFN-α_{2b} (M-IFN) or no further treatment (NT). 111 patients have been treated to date and 104 are evaluable for response (57 CB, 47 CB+IFN-α_{2b}), with a median follow up of 28 months. There was no significant difference in response rate. The major toxicity of the initial therapy was myelosuppression, which was more frequent with CB+IFN-α_{2b} (32 patients (65%) requiring a delay in treatment or dose modification vs. 10 (18%) with CB alone, $p<.01$). 5 patients were intolerant of the systemic toxicity of IFN-α_{2b}. There was no treatment related mortality. Actuarial survival at 3 years is 75% for all patients, regardless of therapy. For the 68 patients who have entered the second phase of the trial, there was a significant difference in remission duration in favour of M-IFN (median not yet reached vs. 9months for NT, $p=.014$). Fewest relapses have been seen in patients who received IFN-α_{2b} in both phases of the study. Accrual to the trial continues; this preliminary analysis indicates that M-IFN may extend remission duration in FL.

56 SUPERIORITY OF SECOND VERSUS FIRST GENERATION CHEMOTHERAPY IN A RANDOMIZED TRIAL FOR STAGE III-IV AGGRESSIVE NON HODGKIN LYMPHOMA (NHL): THE 1980-1985 EORTC TRIAL

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A first-generation CHOP-like cyclic combination chemotherapy (CT) using cyclophosphamide 600 mg/m^2 IV d1, hydroxorubicin 50 mg/m^2 IV d1, VM26 60 mg/m^2 IV d1, prednisone 40 mg/m^2 PO d1-5 was challenged by a second generation combination adding vincristine 1.4 mg/m^2 IV and bleomycin 6 mg/m^2 IM/IV at mid interval (d15) to the former drugs in the treatment of aggressive NHL. From 4.1980 to 1.1986, 142 eligible patients with stage III-IV unfavorable histologies (Working Formulation E, F, G, H and I except T lymphoblastic NHL) entered this EORTC randomized trial. In both arms adjuvant radiotherapy (30 Gy) was given to bulky or residual disease. Patients who achieved a CR underwent a second randomization for monthly maintenance CVP during 1 year.

In all patients subsets the outcome favored the second generation regimen. The difference was even larger in patients with Diffuse Large Cell Lymphoma (DLCL). At 4 years, overall freedom from progression was 72% versus 48% ($p = 0.001$) and survival 61% versus 42% ($p = 0.025$). This advantage was gained through the achievement of a higher complete remission (CR) rate (74% versus 53%, $p = 0.001$). Indeed, once CR was achieved the relapse free survival (RFS) was not significantly influenced (48% versus 43%).

No toxicity of noticeable importance could be attributed to the addition of vincristine and bleomycin. This was not the case for CVP maintenance CT had conversely provided no detectable improvement on either RFS or survival.

The trial demonstrates a clear benefit for aggressive DHL and particularly for DLCL of intercalating non myelotoxic drugs at mid-cycle intervals with no adverse effect. Maintenance CT is of no use in aggressive NHL and may be harmful.

Key words : Non Hodgkin lymphoma, intermediate grade, high grade, aggressive, chemotherapy, first generation, second generation, CHVMP, CHVMP + VB, adriamycin, maintenance, randomized study.

57 PROSPECTIVE MULTICENTER TRIAL FOR THE RESPONSE-ADAPTED TREATMENT OF HIGH-GRADE MALIGNANT NON-HODGKIN LYMPHOMAS: UPDATED RESULTS OF THE COP-BLAM/IMVP-16 PROTOCOL WITH RANDOMIZED ADJUVANT RADIOTHERAPY.

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In a prospective multicenter therapeutic trial the remission (CR) inducing efficiency of the response-adapted COP-BLAM/IMVP-16 protocol in the treatment of high grade malignant non-Hodgkin lymphomas (NHL) as well as the prognostic value of adjuvant radiotherapy were investigated. Thus, patients with advanced stage II-IV (Ann Arbor) disease were treated with five cycles of COP-BLAM followed by two cycles of IMVP-16 if an early 1. restaging (RS) evaluation after 2 to 3 cycles of therapy proved the achievement of CR or the presence of only minimal residual disease. If only a partial remission was obtained (slow responders) treatment was switched to the IMVP-16 regimen (2 to 5 courses) immediately. Patients reaching CR in the 2. RS after completing chemotherapy were then randomized to adjuvant radiotherapy (40 Gy) or follow-up observation only with regular RS evaluations every 3 months for patients in both groups. Of 505 evaluable patients 33 % presented with stage II, 25 % with stage III and 42 % with stage IV disease; median age was 56 (range 17 to 75) years. Of all cases 52 %, 17 % and 5 % were identified as the centroblastic, immunoblastic and lymphoblastic subtype of NHL, respectively, 8 % were Ki1-lymphomas (LCAL) and 18 % remained 'unclassified'. In 60 % of all patients CR were achieved, 12 % of which were obtained by switching slow responders early to IMVP-16. Median overall survival was not yet reached, relapse-free survival was 71 % at one and 63 % at 2 years after a median follow-up time of 15 months. By multivariate risk factor analysis the early (after 3 therapy cycles) achievement of CR proved to be of predominant prognostic relevance for long term survival. While an elevated serum LDH, bulky disease and/or a reduced performance status constitute the major adverse risk factors, the histological subtype, advanced age or initial stage had only inferior prognostic influence. In the additional analysis of the CR stabilizing potential of adjuvant radiotherapy a significant prognostic advantage of this treatment as compared to the control group was not yet discernable. The combined treatment results of this study emphasize the importance of the rapid achievement of CR and contribute to the design of future therapy trials.

58 TREATMENT OF INTERMEDIATE AND HIGH GRADE NON-HODGKIN'S LYMPHOMAS WITH THIRD GENERATION CHEMOTHERAPY REGIMENS: ANALYSIS OF SOUTHWEST ONCOLOGY GROUP (SWOG) PHASE II STUDIES.

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Between July, 1984 and May, 1986, SWOG conducted three consecutive Phase II studies of the new, intensive third generation chemotherapy programs that had been developed for the treatment of patients with Stages II, III, or IV non-Hodgkin's lymphomas of intermediate or high grade. With a follow-up of 3.5 to 5.4 years, this abstract updates the results of these clinical trials and analyzes the prognostic impact of dose intensity on complete remission (CR), disease free survival of CR patients (DFS), and overall survival of all patients (OS). Little mBACOD (SWOG 8410), ProMACE-CytaBOM (SWOG 8503), and MACOP-B (SWOG 8508) were each administered exactly as initially described except that the dose of vincristine was capped at 2 mg. in the later two studies. There were 78 evaluable patients on SWOG 8508, 78 on SWOG 8503, and 110 on SWOG 8508 respectively. CR rates were 65% for m-BACOD and 65% for ProMACE-CytaBOM; the 49% CR rate for MACOP-B was significantly lower ($p = 0.03$). Median DFS has not been reached; DFS at 3 years varies from 64-72% ($p = 0.70$). OS at 3 years also varies from 50-61% and does not differ statistically between studies ($p = 0.23$). Relative dose intensity (RDI) for each drug was calculated as ratio of actual dose administered to the 100% or full dose; the mean RDI was then calculated as the average of the RDI's for each drug in a given protocol. The mean RDI for each study was 89%, 89%, and 82%. Age, performance status, and B symptoms were each inversely correlated with RDI. Higher RDI was associated with improved survival in a univariate analysis ($p = .01$). However after adjustment for age or performance status in a Cox regression model, RDI was no longer statistically significant.

Thus excellent DFS and OS can be achieved with each of the three third generation chemotherapy regimens. Although RDI was associated with several known clinical prognostic factors, it was not an indepedent prognostic factor. SWOG and ECOG are currently conducting a randomized Phase III comparison of CHOP, m-BACOD, ProMACE-CytaBOM, and MACOP-B. To date, 734 patients have been enrolled. The results of this study will determine the relative efficacy of the first and third generation chemotherapy treatment programs.

59 CHEMOTHERAPY (CT) FOR ELDERLY PATIENTS WITH ADVANCED STAGE LARGE CELL LYMPHOMA - A LITTLE GOES A LONG WAY.

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Elderly patients with advanced stage large cell lymphoma are known to have a poor prognosis and increased treatment toxicity. These problems prompted a search for effective, well-tolerated CT. Between March 1983 and August 1989, 108 pts were treated sequentially with one of three brief regimens: from 1983 to 1985, 40 pts had Low Dose MACOP; from 1985 to 1987, 32 pts had VABE (Proc Amer Soc Clin Oncol, #867,225,1988); from 1987 to 1989, 36 pts had POCE. LDMACOP and VABE comprise 12 weekly treatments; both utilize doxorubicin, vincristine, bleomycin and prednisone; LDMACOP also includes cyclophosphamide; VABE includes etoposide. The newer POCE involves 5 treatments given within 8 wks.

POCE

Drugs				Week 1	2	3	4	5	6	7	8
Epirubicin	50 mg/M^2	IV		x	x					x	x
Vincristine	1.2 mg/M^2**	IV		x			x			x	
Cyclophosphamide	300 mg/M^2	IV		x			x			x	
Etoposide	50 mg/M^2	IV	day 1				x				
	100 mg/M^2	PO	day 2,3,4,5				x				
Cotrimoxazole	1 DS	PO	BID	x----------							
Prednisone	50 mg	PO	daily x 10d*	x----			x----			x----	
Ketoconazole	200 mg	PO	daily x 10d*	x----			x----			x----	
Cimetidine	600 mg	PO	BID*	x----			x----			x----	

** No maximum dose

* prednisone, ketoconazole and cimetidine are given for 10 days beginning day 1 of weeks 1, 4, 7

The first 21 pts received doxorubicin 40 mg/m^2 instead of epirubicin, the next 15 POCE pts were treated with the epirubicin-based POCE and experienced less stomatitis.

Dose Reductions/Adjustments

Etoposide, epirubicin and cyclophosphamide

Granulocytes, on day of treatment	Dose
≥1.000	100%
0.500-0.999	50%
<0.500	delay treatment one week then resume

The data from all 108 advanced stage pts has been combined: median age 73 (65-85), 49 M, 59 F, Stage: I, 5 pts; II, 27 pts (I&II included only if bulk >10 cm; in addition, 28 stage I&II pts had extranodal disease); III, 22 pts; IV, 54 pts; B symptoms, 58 pts.

Combined results: Complete response (CR) 67%, toxic deaths 6%, overall survival (OS) 24% at 6 yrs, failure-free survival (FFS) 31%, (includes 6 deaths from unrelated causes). Disease-specific survival (DSS) 27% (excluding unrelated deaths) at 6 yrs. The follow-up for living pts is 2-81 mo (med 22 mo).

	LDMACOP	VABE	POCE	COMBINED
No. Pts	40	32	36	108
CR	65%	59%	72%	67%
FFS	25%	34%	51%	31%
OS	26%	36%	76%	24%
DSS	28%	45%	66%	27%
Maximum F/Up	6 yrs	4 yrs	2 yrs	6 yrs
TOXICITY				
WHO GRADE 3&4				
Neutrophils	24%	91%	62%	
Platelets	7%	8%	6%	
Toxic deaths	2 pts	2 pts	2 pts	

Separate analysis of these three regimens has not as yet demonstrated any difference in outcome, although follow-up on POCE is short (max 2 yrs). 45% of patients will survive 2 yrs and 27% will achieve long term disease-free survival.

Eight weeks of treatment is better tolerated than 12 weeks and early data suggests it may be as effective. Further follow-up of the POCE regimen will be needed to confirm the established results with LDMACOP and VABE.

60 NON HODGKIN'S LYMPHOMAS (NHL) ASSOCIATED WITH HUMAN IMMUNODEFICIENCY VIRUS (H.I.V.) : TREATMENT BY LNH 84 REGIMEN.

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NHL HIV patients have a poor prognosis related to lymphoma and HIV infection. In order to evaluate if a subset of patients could be treated with intensive chemotherapy, a pilot study was initiated based on a clinical stratification. Patients in group A with performance status (P.S.) < 3 and no opportunistic infection (O.I.) were treated by LNH 84 regimen (J.C.O. 08/89) and CNS prophylaxis with radiotherapy. AZT was administred during the consolidation phase. In group B with PS > 3, or O.I. patients received a low dose chemotherapy program with Cyclophosphamide 300 mg/m^2 d1, Adriamycin 25 mg/m^2 d1, VM26 30 mg/m^2 d1, Vincristine 1, 5 mg/m^2 d15, Bleomycin 10 mg/m^2 d15 and Prednisone. AZT 600 mg was started with chemotherapy. In case of CNS involvement cranial irradiation was used. 100 patients have been included in the study, 73 pts are evaluable. Histology : diffuse large cell 29 pts. Immunoblastic 11 pts, Burkitt 19 pts, unclassified 14 pts. In group A 60 pts, stage distribution was : I-IE 13 pts, II-IIE 15 pts, II-IV 32 pts. B symptoms 28 pts, Bulky tumor 16 pts. Extranodal involvement > 2, 20 pts. Bone marrow 12 pts, liver 13 pts, meningeal 11 pts. LDH > normal value 29 pts. After induction, 38 pts (72 %) were in CR. Hematotoxicity with neutropenia < .5/mm^3 was constant with prolonged cytopenia in 6 pts, 40% experienced infection > grade 2, 13 % died during induction. 75 % of the patients received 100 % of the dose, however mean interval between cycle was 21 d. Disease free survival was 55 % at 15 m, median survival 15 m. 28 patients died within 1 yr, 11 in CR, 14 from NHL, 7 in relapses. Factors influencing the probability of survival were achievement of complete remission and B symptoms. In group B, 13 pts with PS > 3, only 1 pt achieved CR, median survival was 2, 6 m. In patients with good P.S. and no O.I., LNH 84 regimen can achieved a CR rate similar to standard NHL.

61 TREATMENT OF RELAPSES IN THE SFOP LMB 0384 PROTOCOL. ROLE OF BONE MARROW TRANSPLANTATION AS SALVAGE THERAPY

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Previous results of the French SFOP protocols had demonstrated the very high curability of B cell lymphoma using intensive multiagent therapy even with advanced disease. Relapse is a rare event ie 15 % of the cases (Patte et al J. Clin. Oncol. 1986, 4 : 1219). Controversy still exist about the best rescue protocol strategy after relapses despite very good results previously reported in selected cases (Philip et al. Eur. J. Cancer Clin. Oncol. 1986, 22 : 1015-1026 and Hartmann et al. J. Clin. Oncol. 1986, 4 : 1808).
227 patients with advanced B cell lymphomas from 31 centers were treated in a 3 years 6 months period in the LMB 0384 (See SFOP report this conference). 14 % of the CR patients (ie 26/184) did relapse. CNS alone (6 cases) CNS and bone marrow (1 case), abdominal (9 cases), head and neck (1 case), and multifocal (9 cases) were the recorded sites of relapses. Among the 26 patients :

1) 15/26 ie 58 % were treated with 1 or 2 courses of a rescue protocol (MIME or CYVE) and then received massive therapy and ABMT. 2/15 died in CR from toxicity (13 %). 8 relapsed post BMT and 5 are alive disease free with probable cure for all. **At least 30 % of relapses from a very agressive (and good !) protocol can be cured with BMT. The respective role of harvesting in CR or purging marrow after relapse will be discuss.**

2) 11/26 were not grafted (42 %). They all died from disease. At least two of them should have been grafted and delay in very agressive strategy was obvious. **Without BMT relapse will conduct to death in 100 % of the cases.**

Relapses of B Lymphoma are one of the oncological emergency . Everything should be done in less than 2 months. Strategies to rescue these patients will be reviewed in details.

62 AUTOLOGOUS BONE MARROW TRANSPLANTATION (ABMT) FOR ADULT LYMPHOBLASTIC LYMPHOMA (LBL) IN FIRST COMPLETE REMISSION. A PILOT STUDY OF THE NON-HODGKIN'S LYMPHOMA CO-OPERATIVE STUDY GROUP (NHICSGI).

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Sequential multi-agent chemotherapy (CT) has recently improved the prognosis of adult LBL. However, even if overall results are very good, survival and DFS are markedly modified by age and stage of the disease, with a 3 year DFS of about 20% in patients over 30 years old or in stage IV and with bone marrow involvement. In addition there are some controversial points: chemotherapy is too long (1-3 yrs.), the majority of relapses occurr during maintenance chemotherapy, the quality of patients life is poor. Due to these reasons started our study, with the aim to improve long-term survival for LBL pts. in CR by intensification with high dose CT and TBI followed by ABMT. A modified LSA2-L2 was used as induction regimen (Bone Marrow Transplant 1989,4,399). If a CR was attained 1000-1400cc of BM were cryopreserved at recovery, and purged with ASTA-Z (70-100 μg/ml) if involved at diagnosis. At a median time of 2.5 mos. from CR pts. underwent CY (60mg/Kg) d. 1,2 followed by TBI (10 Gy single dose) d.4 and BM reinfusion d. 5 or 6. Thirty successive pts. entered the study: 18 males and 12 females with a median age of 20 yrs. (range 15-51); one pt. was in stage II bulky, one in stage III and 28 in stage IV; 24 had mediastinal and 19 bone marrow involvement. Twenty-seven are evaluable (1 early death, 2 on therapy): 19 achieved CR (70%), 4 PR (died 7,11,16,20 mos.) and 4 were NR (died 3,3,9,14 mos). Of 19 CR three refused ABMT (1 alive 53+mos., 2 died in relapse 19,28 mos.) and sixteen underwent ABMT. Presently 12/16 pts. are in CR 1+ to 56+ mos. (median 43), with a DFS probability of 73%; 4 relapsed and died 3,5,5,9, mos after ABMT. The procedure was not associated with major complications. The hematological recovery was good, except in 9 purged cases rising a platelet count over 20 x 10^9 /L in median day 35 (range 25-105). These promising results should prompt a randomized study to evaluate the possible superiority of this protocol over conventional chemotherapy.

63 AUTOLOGOUS BONE MARROW TRANSPLANTATION FOR INCURABLE ADVANCED STAGE B CELL NON-HODGKIN'S LYMPHOMA IN FIRST REMISSION.

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Despite significant advances in the treatment of patients with previously untreated advanced stage non-Hodgkin's lymphoma, the majority ultimately relapse. The use of high dose therapy and autologous bone marrow transplantation (ABMT) has led to prolonged disease free survival (DFS) in 20-40% of patients (pts) who are transplanted in sensitive relapse. Unfortunately, the majority of pts with relapsed NHL do not benefit from high dose therapy due to the presence of resistant disease. To circumvent treatment induced resistance, earlier implementation of high dose therapy and ABMT may improve the long term DFS for pts with incurable NHL. Previously untreated pts who were considered to be incurable with conventional therapy yet could attain a minimal disease state were included in this study. The pts selected were considered to have less than a 25% probability of being disease free 2 yrs following conventional combination therapy. Twenty five previously untreated pts with B cell NHL (median age of 39) underwent high dose chemoradiotherapy and anti-B cell monoclonal antibody treated ABMT in either first CR or PR. Seventeen pts had intermediate (int) or high grade NHL, and 8 pts had low grade NHL. The int/high grade pts had poor prognostic features at presentation including 7 pts with bone marrow (BM) involvement, and 12 with extranodal disease other than BM infiltration. All pts were treated with CHOP± methotrexate for 4-6 cycles. At the time of BM harvest, 12 of the int/high grade pts were in a CR while only 1 of the low grade pts were in CR. Lymphomatous BM infiltration was present in 5 of the int/high grade and 6 of the low grade pts at harvest. Following high dose ablative therapy (cyclophosphamide 60 mg/kg x 2, TBI 200 cGy x 6), no acute in-hospital toxic deaths occured. Hematologic engraftment was earlier than observed in relapsed pts, with a median of 21 days to achieve >500 PMN/mm^3, and 21 days to achieve >40,000 platelets/mm^3. Culture negative neutropenic fever was seen in 6 of the low grade pts, while 16 of the int/high grade pts had fever with 3 associated positive blood cultures. One late death was observed at 24 months secondary to toxoplasmosis associated with HIV infection. The late complications have been limited; 1 pt with non-fatal bacterial pneumonia at 8 months, and 4 pts with localized dermatomal H. zoster. One pt with int grade NHL relapsed at 6 months in a site of prior bulk disease. Of the remaining pts, 23 are in unmaintained CR with a median follow-up of 12 months for the int/high grade (7 pts disease free for > 3 yrs) and 8 months for the low grade pts. This pilot study suggests that high dose chemoradiotherapy and ABMT can be performed with exceedingly low treatment associated morbidity and mortality in pts with NHL in first remission. Although follow-up is limited, this study demonstrates high effectiveness in a subset of pts who are unlikely to experience prolonged DFS with conventional therapy. Moreover, this study provides a context within which high dose therapy and ABMT can be undertaken as consolidation therapy for pts with incurable NHL.

64 REGULATION OF NORMAL AND MALIGNANT LYMPHOCYTE DIFFERENTIATION AND FUNCTION BY TRANSFORMING GROWTH FACTOR-β (TGF-β).

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Transforming growth factor-β (TGF-β) is a homodimeric peptide, with a molecular weight of 25,000 daltons, that exists in several isoforms. TGF-β is synthesized by almost all mammalian cells and essentially all cells have functional receptors for this peptide. TGF-β is a typical multifunctional regulatory peptide, and can either enhance or suppress cell replication, depending on the context of its action, particularly the set of other growth factors acting on the cell. The actions of TGF-β on both T- and B-lymphocytes are very potent, since picogram levels of TGF-β can suppress DNA synthesis or immunoglobulin synthesis in these cells. Furthermore, TGF-β controls hematopoiesis in bone marrow culture systems; it suppresses the growth of less mature hematopoietic cell populations which have a high proliferative capacity, while it does not affect the growth of more differentiated cells. Thus, TGF-β would appear to be an important negative autocrine growth factor for the control of lymphocyte differentiation and function. Recent work by F. Ruscetti and colleagues has shown that there are no detectable receptors for TGF-β in several T-cell and B-cell lymphoma lines, as well as in the acute promyelocytic leukemia cell line, HL-60; and it has been suggested that this may contribute to the unregulated growth of these tumor cells. Moreover, Ruscetti and colleagues have also shown that phorbol esters and retinoic acid, agents which can re-induce a differentiated state in HL-60 cells, cause the re-appearance of TGF-β receptors in these cells. It is believed that the restoration of the negative autocrine loop mediated by TGF-β is reponsible in part for the arrest of growth induced in HL-60 cells by retinoic acid. Retinoic acid has been shown to be a clinically useful therapy for acute promyelocytic leukemia. Whether retinoic acid or other differentiating agents can mediate the reappearance of TGF-β receptors in lymphoma cells and can thus lead to a new, clinically useful approach to treatment of lymphoma remains to be determined.

65 THE BIOLOGY OF INTERLEUKIN 6 : THE ROLE IN PLASMA CELL DISEASES

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Interleukin 6 (IL-6) is a pleotropic cytokine with biological activities in lymphocytes (T and B), hepatocytes, fibroblasts, haematopoietic cells and neural cells. It is also produced by a variety of cells, but predominantly by macrophages and fibroblasts. Although it has effects on many cells the most striking effects are upon murine plasmacytomas, B-cell hybridomas and human myeloma cells. Recent studies have demonstrated that IL-6 is the predmoninant growth and differentiation factor for human plasma cells. The availability of recombinant forms of IL-6 and also antibodies which bind to and functionally block IL-6 and/or bind to IL-6 receptors have made it possible to accurately assess the role of Il-6 in a wide range of diseases including plasma cell diseases . Recent observations have included: increased levels of IL-6 in the bone marrow and serum of patients with active myeloma and extremely high serum levels in patients with plasma cell leukaemia and fulminant myeloma. Separation and purification studies have shown that the predominant source of IL6 is paracrine rather than autocrine. In vitro studies have shown striking interactions with other cytokines including IL-3 and GM-CSF, both of which enhance the growth stimulatory effects upon purified myeloma cells and cell lines. Further studies are ongoing to assess the exact functions of the IL-6 receptor, especially the second chain or GP 130 component which appears to trigger the intracellular responses to activation. Based upon in vitro studies using high affinity anti IL-6 antibodies, clinical studies utilising anti IL-6 have been initiated. Preliminary studies (Klein et al Blood Abst 749: Vol 74; 89) have shown dramatic growth inhibitory effects in patients with plasma cell leukaemia. It is to be hoped that further improved understanding of the exact mechanisms of IL-6 stimulation and inhibition will expand the ability to manipulate plasma cell growth in clinically meaningful ways.

66 THE CLINICAL ROLE OF THE HAEMOPOIETIC GROWTH FACTORS

PROFESSOR DEREK CROWTHER

Since the first publication in 1987 showing that G-CSF given by continuous intravenous infusion ameliorates the neutropenia and reduces the incidence of infection following intermittent combined chemotherapy for cancer (Bronchud et al, 1987), there have been a number of reports indicating beneficial effects in this context using both G and GM-CSF. In our first study the period of neutropenia was significantly shortened (by a median of 80%) and the neutrophil count levels were above normal again by 14 days following chemotherapy. In view of these results a further study was undertaken to examine the possibility of using intensive 2 weekly chemotherapy under cover of G-CSF. Treatment with Doxorubicin at doses of 75, 100, 125 and 150mg/m^2 was followed by infusion of G-CSF for 11 days. Again the neutrophil counts returned to normal within 12-14 days allowing the delivery of up to 3 cycles of high dose chemotherapy at 14 days intervals. These studies demonstrated that intensive chemotherapy with dose limiting myelodepression can be given with increased frequency under cover of G-CSF. Our studies using GM-CSF have also shown that administration by continuous i/v infusion can reduce the period of life threatening neutropenia following high dose Melphalan (120mg/m^2) without resort to autologous bone marrow transplantation (ABMT). In this study the period of granulocytopenia (<500gram x10^9/l) following Melphalan was less than 15 days. This compares favourably with other series using high dose Melphalan followed by ABMT without CSF where the duration of severe neutropenia was prolonged beyond 3 weeks. Enhanced neutrophil recovery has been demonstrated following conventional and high dose chemotherapy allowing the use of accelerated chemotherapy of higher dose intensity than would have been possible without the use of a myelopoietic growth factor.

Improvement in the neutrophil count using G and GM-CSF has been observed in patients with marrow graft failure, bone marrow failure from a variety of causes, myelodysplastic syndrome, AIDS undergoing therapy with AZT, cyclic neutropenia, Kostman's syndrome and in patients undergoing chemotherapy for acute myelogenous leukaemia. To date, most of these studies have involved relatively few patients but major large randomised studies are underway to confirm these findings. Although enhanced platelet recovery has been observed following the use of GM-CSF, these effects have been relatively modest but early trials with IL-3 and the combined use of growth factors are showing more beneficial effects on platelet counts in patients with some forms of bone marrow failure. The administration of haemopoietic growth factors has increased the yield of peripheral blood stem cells allowing the use of these cells as rescue following ablative chemotherapy and it would appear that the combined use of growth factors including IL-3 is likely to further increase the yield.

Proteins and small peptides have been identified which are capable of inhibiting haemopoiesis and their future use in reducing bone marrow toxicity associated with chemotherapy is an exciting prospect. Studies of the possible use of GM-CSF and M-CSF in enhancing host anti-tumour activity are only just beginning. Although continuous i.v. infusion has been accompanied by more pronounced effects than bolus intravenous or subcutaneous administration, optimal routes and schedules of administration have not been established for the various therapeutic indications. The use of combinations of growth factors is only just beginning and a great deal of work is required to optimise the way these are delivered.

67 ROLE OF GM-CSF IN TREATMENT OF MALIGNANT LYMPHOMAS.

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48 patients with newly diagnosed malignant lymphomas (non-Hodgkin lymphoma and Hodgkin's disease) were treated in a phase I/II study with rhGM-CSF.

The patients were previously untreated, and all received standard chemotherapy with CHOP or MOPP respectively.

rhGM-CSF was used in 4 dose levels, 2-4-8 and 16 µg/kg. At each dose level rhGM-CSF was given for 5 days, either continuously i.v. to half of the patients or s.c. twice daily to the other half. Furthermore pharmacokinetic studies were done.

An increase in leucocyte count was observed 24 h. after rhGM-CSF administration. The peak was reached day 2 or 3 and the counts then dropped. All patients showed a leucocyte nadir, but of shorter duration and higher in cycles with rhGM-CSF compared to cycles without rhGM-CSF and historical controls. A significant dose dependent increase in WBC and ANC was observed until a dose of 8 µg/kg. Further increase of the dose led to more side effects.

S.c. administration was compared to continuous i.v. at each dose level and a detailed analysis will be shown together with data concerning recovery after chemotherapy. In cycles with rhGM-CSF recovery was faster and more pronounced that in cycles without rhGM-CSF, and the chemotherapy could be given on time in full dose. In future trials it should be possible to shorten the standard interval between cycles of chemotherapy by using rhGM-CSF.

68 RECOMBINANT HUMAN GM-CSF AND MITOXANTRONE/HIGH-DOSE ARA-C IN THE TREATMENT OF REFRACTORY NON-HODGKIN-LYMPHOMA

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Previous study from our group has shown that the combination of mitoxantrone (Novantrone, NO) and Ara-C (AC) (NOAC) was active in refractory non-Hodgkin's lymphoma (NHL) but myelosuppression was dose-limiting. In this pilot study, we have investigated the effects of recombinant human GM-CSF (rhGM-CSF) after NOAC chemotherapy in patients with refractory NHL. Mitoxantrone was applied at a dosage of 10 mg/m^2/day on Days 2 and 3 and Ara-C at 3 g/m^2/12h on Days 1 and 2. RhGM-CSF was administered at 250 ug/m^2/day as a continuous IV infusion from Day 6 onwards until the neutrophils were > 3.0/nl for 3 consecutive days.

Twenty-three patients from 5 of the 9 participating centers were treated with NOAC chemotherapy plus rhGM-CSF whereas 14 patients from the other 4 centers received chemotherapy alone. With rhGM-CSF, the median duration of severe neutropenia (<0.5/nl) after NOAC was 8.0 days versus a median of 13.0 days without rhGM-CSF ($p = 0.0058$), and that of thrombocytopenia (<20.0/nl) 3.0 days versus 7.0 days ($p > 0.4$, not significant). The rates of infections and stomatitis were 25% and 17% respectively for patients treated with rhGM-CSF as compared to 53% ($p = 0.0547$, n.s.) and 60% ($p = 0.0078$) without rhGM-CSF. The following side effects were associated with the administration of rhGM-CSF: pleural and/or pericardial effusions in 5 patients, thrombosis in 2 patients, bone pain in 2 and respiratory distress syndrome in one patient. A complete remission (CR) was achieved in 9 of the 23 patients treated with NOAC plus rhGM-CSF, and in 2 of the 14 treated with chemotherapy alone. The median survival of patients treated with rhGM-CSF was not reached at 400 days and appeared to be longer than that of patients treated with chemotherapy alone (median 109 days, $p = 0.036$).

The regimen NOAC is therefore active as salvage therapy in advanced and refractory high-grade NHL. RhGM-CSF after chemotherapy can be applied safely to patients with NHL, shorten the period of severe cytopenia and reduce the rates of stomatitis. Above all, rhGM-CSF did not seem to have any adverse effect on the response rate and duration, but was associated with better treatment outcome in poor risk patients.

69 A PROSPECTIVE RANDOMIZED TRIAL COMPARING RECOMBINANT GRANULOCYTE COLONY STIMULATING FACTOR (rhG-CSF) VS PLACEBO FOR NEUTROPENIA INDUCED BY CHEMOTHERAPY IN PATIENTS (PTS) WITH NON-HODGKIN LYMPHOMA (NHL).

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rhG-CSF stimulates proliferation and differentiation of granulocytes precursors, effulux of matured granulocytes from bone marrow to peripheral blood and activity of granulocytes.
In order to study the role of rhG-CSF on neutropenia induced by induction chemotherapy in pts with NHL, we conducted a prospective randomized trial. The same induction chemotherapy was repeated twice and in the first course changes of neutropenia was observed. Pts who had shown neutropenia less than 1,000/cmm in the first course of chemotherapy were randomly allocated to recieve either rhG-CSF at a dose of 75μg/body sc or a placebo sc. A dose of 75 μg was determined to be an optimal dose in previous phase I-II trials. Both started 3 days after completion of the second course of chemotherapy and continued for 14 days. A total of 63 pts entered and 57 (28: G-CSF, 27: placebo) were fully evaluable. Major background factors such as ages, stages and others were well balanced in both groups. A median nadir of neutrophile was 1893/cmm for G-CSF and 493/cmm for placebo, respectively (P=0.0005). A median days needed for the recovery of neutropenia until 2,000/cmm from the nadir was 8.3 days for G-CSF and 20.0 days for placebo, respectively (P=0.0000). Toxicities observed were discomfort on chest, rash and palplitation in one each received G-CSF while rash in 2 pts, fever and lumbar discomfort in one each occured in the placebo group. The overall effective rate judged by the response review comittee was 89.3% for G-CSF and 13.8% for placebo.
The result indicates that G-CSF accelarate recovery of neutropenia and therefore is usefull for prevention of infections during chemotherapy.

70 ASSOCIATION OF LYMPHOCYTE HOMIMG RECEPTOR EXPRESSION AND STAINING INTENSITY WITH S-PHASE FRACTION, STAGE, AND PROGNOSIS IN NON-HODGKIN'S LYMPHOMA.

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Lymphocyte homing receptors (HRs) mediate lymphocyte binding to high endothelial venules, and control lymphocyte circulation between the blood and the lymphoid organs. The prognostic and biological roles of HR expression (HRexp, absence or presence of HRs in staining with a MoAb Hermes-3, graded -, -/+, or +), HR staining intensity with Hermes-3 (HRint, graded -/+, ++, or +++), S-phase fraction (SPF, studied with DNA flow cytometry), and several other factors were investigated from paraffin-embedded tissue of 245 patients with non-Hodgkin's lymphoma. A large SPF was closely associated with a high Working Formulation and Kiel grade ($p < 0.0001$), and its was more strongly associated with poor prognosis ($p=0.0001$) than either of the histological gradings in a univariate analylis. Lymphomas which stained strongly for HR (HRint +++, n=88) had poorer outcome ($p<0.0001$) than those with a moderate (HRint ++, n=80) or a weak staining intensity (HRint - or +, n=77), and they were less often of Ann Arbor stage I ($p=0.005$). Lymphomas with a low staining intensity (HRint -/+) were more often high grade lymphomas than those with a higher staining intensity ($p=0.002$) despite their favourable prognosis. HRint grouping did not correlate with SPF, but lymphomas that did not express HRs (HRexp -, n=24) had higher SPFs than those that expressed HRs ($p=0.0003$). Both SPF and HRint grouping were independent prognostic factors in a multivariate analysis. Hence, favourable prognosis in non-Hodgkin's lymphoma appears to be determined by both a low cellular proliferation rate (low SPF), which is closely associated with low histological grade but not with stage, and absence of homing receptors (HRint weak, HRexp low), which is associated with high histological grade and low stage.

71 Secondary B-Cell Lymphomas Developing in Two Patients with Adult T-Cell Leukemia

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Two Japanese patients with adult T-cell leukemia (ATL) of smoldering and chronic type developed secondary B-cell lymphomas of diffuse large cell, non-Burkitt type during the clinical course of ATL. They were seropositive for human T-cell leukemia virus type I (HTLV-I) and Epstein-Barr virus (EBV) but negative for human immunodeficiency virus (HIV). They also suffered from pulmonary tuberculosis, and one from adenovirus type 11-induced hemorrhagic cystitis, indicating immunodeficient states.

Southern blot analysis revealed the following results.
1) Monoclonal integration of HTLV-I provirus in ATL leukemic cells from both patients,
2) One or two rearranged bands of immunoglobulin heavy chain gene (JH) in lymphoma cells from both patients, indicating monoclonal B-cell lymphomas,
3) Clonally rearranged T-cell receptor beta-chain gene (CT beta) and germline configuration of JH in ATL leukemic cells, and germline of CT beta and rearranged JH in lymphoma cells from both patients, showing that the two malignancies have distinct clonal origin,
4) Definite presence of EBV genome in lymphoma cells from one patient,
5) Lack of c-myc gene rearrangement in lymphoma cells from both patients.

This is the first report of secondary B-cell lymphomas developing in patients with ATL. Our data suggest that opportunistic B-cell lymphomas may occur in the terminal or immunodeficient stages of ATL.

72 LARGE CELL ANAPLASTIC Ki-1 POSITIVE LYMPHOMA. A STUDY OF 5 CASES.

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Non-Hodgkin's lymphoma (NHL) expressing the Reed-Sternberg associated antigen Ki-1 (CD 30) represent neoplasms of activated lymphoid cells. These high-grade lymphomas are of heterogenous lineage, the majority being of T-cell origin on phenotypic and genotypic analyses. These neoplasms tend to have a predilection for the younger age group and are said to have a relatively better prognosis than other high grade T-cell lymphomas.

Five cases of large cell anaplastic Ki-1 positive lymphomas, diagnosed over the past 23 months at King Edward Hospital, Durban, South Africa are presented. There were 3 males and 2 females. The ages ranged from 13 to 60 years (mean 30 years; median 26 years). Two patients were less than 20 years of age. The group includes three Blacks, one Indo-Asian and one White.

Lymphadenopathy was the presenting feature in 4 cases. One patient presented with paraplegia due to an extra-dural mass lesion. This association has not been previously described. This patient, a 60 year old Black male also developed skin nodules and lymphadenopathy terminally. This latter phase resembles the clinico-pathological syndrome first described in children.

Another patient, a 26 year old female developed menorrhagia. Features of large cell Ki-1 lymphoma were found on endometrial curettings. This unusual presentation has also not been previously described.

One patient received radiotherapy alone; two chemotherapy alone and two combined modality therapy. Two patients are still alive at 22 and 95 months following diagnosis. Anaemia and peripheral blood lymphopenia appear to be poor prognostic factors.

The histological appearance and the expression of Ki-1 antigen has established a distinct entity for Ki-I lymphomas, which has, therefore, been recently incorporated into updated Kiel classification.

The natural history and optimal therapy of Ki-1 lymphomas has not been established and further studies are essential.

73 MEDIASTINAL LARGE CELL LYMPHOMAS. A HISTOPATHOLOGICAL AND IMMUNOHISTOCHEMICAL STUDY

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Between 1987 (Oct, 1st) and 1989 (May, 30th) 844 cases of aggressive malignant lymphomas were recorded in the French national protocole LNH87 (GELA). Thirty cases of mediastinal large cell lymphoma were recognized representing a frequency of 3.5% of the lymphoma in this serie. One case was unclassifiable for technical reasons and excluded. For the remaining 29 cases a slight predominance in female was observed (sex ration M : F = 11 : 18). The mean age was 38 years ranging from 18 to 67. In 2 cases a susclavicular lymph node was involved and in 2 other the lung. A bone marrow biopsy performed in 17 patients was negative. Twenty six cases were classified as centroblastic malignant lymphoma according to Kiel classification (group G of intermediate grade in the WF). Three cases corresponded to the criteria of the so-called "mediastinal clear cell lymphoma". Seven out of the 26 centroblastic lymphomas comprised areas constituted by large cells with clear cytoplasm. On paraffin section, all cases were positive for 2 or 3 of the pan B markers : LN1, LN2 and particularly MB2 and L26. UCHL1 was only positive on reactive cells. On frozen sections, the tumour cells were positive in most of the cases for CD22, CD19, CD20 but negative for CD21 (C3dR). Surface immunoglobulins were found in only 5 cases on the 11 tested. CD30 was positive only in one of the 8 tested cases. Calla was expressed in only one of the 3 tested cases. Ki67 was studied in 10 cases, demonstrating that 30 to 80% of the cells were engaged in cell division. No difference could be seen between the clear cell type and the centroblastic type with or without a clear cell component.

This group of patients, confirms the existence of an anatomo-clinical entity, the mediastinal large B cell lymphoma. No difference between centroblastic and clear cell type could be demonstrated in clinical symptoms, sex and age distribution or in the phenotype. A comparison with the evolution and the prognosis is under consideration.

74 PRIMARY GASTRIC NON-HODGKIN LYMPHOMAS. DOES THE CONCEPT OF "MUCOSA-ASSOCIATED LYMPHOMA" HAVE ANY CLINICAL RELEVANCE?

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The newly proposed concept of extranodal non-Hodgkin lymphomas (NHL) in the mucosa-associated lymphoid tissue (MALT), i.e. in the gastro-intestinal tract, has been described in the litterature as diseases with clinical features that differ from nodal lymphomas. They are thought to spread to other MALT-organs and regional lymph nodes (LNDs) rather than disseminate to distant LNDs and bone marrow and they are also thought to have a better prognosis.

Patients: To evaluate the clinical relevance of the MALT-entity, we performed a retrospective study of 58 pats, 41 males and 17 females, treated for primary gastric lymphoma at the dept. of Oncology, University Hospital of Lund during the 15-year period 1970-1985. The lymphoma was considered primary in the stomach if the main symptom, leading to medical attention, was upper abdominal distress. Median age at diagnosis was 65 years, range 16-80. A histopathological reevaluation according to the Kiel-classification was performed by one pathologist (MÅ). Special interest was payed to the presence or absence of lympho-epithelial lesions in the mucosa, a characteristic sign of MALT-lymphoma.

Results: Thirteen pats had low-grade malignant NHL (6 cb/cc, 2 cc, 5 ic) and 26 high-grade (21 cb,1 ib, 4 unclass.). There were 9 cases of MALT-low grade and10 cases of MALT-high grade malignant NHL. Staging of the disease according to the Ann Arbor system showed 31 pats with stage IE, 15 with stage IIE, 2 with stage IIES and 10 with stage IV. Localized disease (stage I or II) was found in 69% of pats with low-grade malignant, 84% high-grade, 67% MALT-low and 90% of pats with MALT-high grade NHL. Staging according to the principles of UICC for local invasiveness and regional lymph node spread of gastric carcinoma was possible to perform in the 48/58 cases where a laparotomy had taken place. When correlating to histology, stage T3 or T4 (locally advanced, penetration of the gastric wall) was found in 56% of cases with low-grade, 59% high-grade NHL, 25% MALT-low grade and in 67% of cases with MALT-high grade malignant NHL. None or limited LND spread (N0, N1) was seen in 54% of cases with low-grade, 85% high-grade, 56% MALT-low grade and in 70% of cases with MALT-high grade NHL.

The pats were treated with surgery, radiotherapy or chemotherapy, in varying combinations.

Survival rates in correlation to MALT-characteristics, Kiel subgroups, stage and treatment will be presented.

Conclusion: Primary gastric lymphomas with histological "MALT-characteristics" were not found to be more frequently confined to the stomach and regional lymph nodes than other histological types.

75 PRIMARY GASTRIC LYMPHOMA. CLINICAL AND PROGNOSTIC FEATURES OF 145 CASES.

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Although in recent years primary gastric lymphoma has been investigated in detail with morphological and immunohistochemical techniques, only a few clinical data exist. In this study we investigated 145 cases of early stage of primary gastric lymphoma using gastrectomy specimens. The tumors could be distinguished considering morphology and immunohistochemistry in low-grade B-cell lymphoma of the MALT, including immunocytoma (n=71) and high-grade B-cell lymphoma with evidence of a low-grade (n=25) or without evidence of a low-grade (n=49) component. In the low-grade lymphoma group, lymphoepithelial lesions and residual follicles were the most typical features, which could also be seen in those tumors that showed high-grade transformation. Looking at the infiltration stage, in 43 cases the submucosa, in 24 cases the muscularis propria and in 78 cases all layers of the gastric wall were infiltrated. Most tumors were located in the antrum and presented as ulcers. Eighty patients were biopsied and in 57 of those cases the diagnosis was made during the biopsy. The male to female ratio was 1.4:1. The age ranged from 25 to 82 years (mean: 58.6). Most patients had a history of unhealing gastric ulcers with the leading symptom of epigastric pain. Eighty-eight patients were in stage I and 57 in stage II. Twenty-two patients revealed involvement of adjacent tissue. All patients underwent primary gastrectomy and 65 additionally received adjuvant chemotherapy (n=33), radiotherapy (n=22) or both (n=10). Follow-up ranged from 1 to 179 months (mean follow-up period: 56.6 months). Fourty-two patients relapsed after 1 to 103 months (mean: 24.5 months). There was a statistical difference in the survival of patients with low-grade B-cell lymphoma of the MALT, including immunocytoma and the group of high-grade B-cell lymphoma. Patients in stage I showed a considerably better prognosis than those in stage II.

76 THE PROGNOSTIC SIGNIFICANCE OF HISTOLOGICAL PATTERN IN PRIMARY GASTRIC LYMPHOMA : AN ANALYSIS OF 80 PATIENTS.

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Recent descriptions of primary gastric lymphoma as a malignancy of mucosa associated lymphoid tissue (MALT) and delineation of the histological criteria necessary to establish the diagnosis of MALT lymphoma have prompted us to review all cases of primary stomach lymphomas submitted to the British National Lymphoma Investigation (BNLI) to assess the relative frequency and prognostic significance of this entity. 80 cases of primary gastric lymphoma were accrued between 1970 and 1987. Cases were reviewed by two pathologists (KAM,MHB) in the absence of any clinical information and classified as either MALT lymphoma or non-MALT lymphoma. The following criteria were used to diagnose MALT lymphoma:-

1) The presence of a superficial plasma cell rich infiltrate in the gastric mucosa.
2) A polymorphous B cell infiltrate containing irregular small and medium sized lymphoid cells (termed by some centrocyte-like cells).
3) The occurrence of lymphoepithelial lesions.

MALT lymphomas were further subdivided into low and high grade subtypes: the high grade subtype being recognised by the presence of confluent sheets of large cell cytology.

Non-MALT lymphomas were classified using the BNLI and Kiel classifications. Analysis of actuarial survival curves shows a large and significant difference in favour of the MALT type of gastric lymphoma compared to stomach lymphomas not displaying these histological features.

Subdivision of MALT lymphomas into low and high grade subtypes did not appear to influence survival.

Local nodal involvement was significantly more common in MALT type compared to non-MALT gastric lymphomas but was often subtle and required immunocytochemistry for diagnosis.

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MALIGNANT LYMPHOMA OF GASTROINTESTINAL TRACT (GIT): ANALYSIS OF CLINICOPATHOLOGICAL FEATURES AND TREATMENT RESULTS.

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Between 1969-88, 97 patients (pts) with primary GIT lymphoma (48 stomach (S), 40 small intestine (SI) and 9 large intestine (LI)) were referred to the northern Israel oncology center. Stage of disease (I+II/III+IV) was 36/12, 27/13 and 8/1 in S, SI and LI respectively. Histology according to Working Formulation was 29 intermediate grade, 56 high grade and 12 (10-stomach) low grade. There were 25 children (15 yrs): 22 with SI and 3 with LI.

TREATMENT RESULTS OF 48 PTS WITH GASTRIC LYMPHOMA

TREATMENT MODALITY	NO. PTS	STAGE I/II/III-IV	RECURRENCE RATE	10 YRS SURVIVAL
Resection ± RT	19	13/5/1	8/19	53%
irradiated -	15/19		locoregional -4	P<0.1
Resection + CT	16	0/13/3	1/16	79%
irradiated -	4/16			P<0.01
No resection	13	2/3/8	8/10	18%
(CT alone) irrad-	3/13			

TREATMENT AND RESULTS IN PTS WITH BOWEL LYMPHOMA

Patients with localized bowel lymphoma usually underwent resection or debulking (total 33 pts) and thus had better prognosis (10 yrs-71%), than those who did not (16 pts), because of more extensive disease (10 yrs-42%). The surgical approach and the resectability have not changed over the last 20 years. However, outcome of the 27 pts with bowel lymphoma, especially of children, (CR-79%, 10 yrs-77%), has markedly improved in the last decade due to more intesive and effective chemotherapy, compared to the 22 pts, with the same clinical features, treated from 1968-78 (CR-36%, 10 yrs-30%).

We may conclude from our study: (1) Resection of the primary focus in GIT, particularly in stomach, lymphoma is a significant determinant for long term survival. (2) Chemotherapy following resection is indicated in gastric lymphoma, whereas more intensive regimens produce better survival in bowel lymphoma. (3) The role of radiotherapy in GIT lymphoma is questionable.

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NON-HODGKIN LYMPHOMA OF WALDEYER'S RING LYMPHOID TISSUE: PRESENTATION AND PROGNOSIS.

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From 1978 through 1988, 57 out of 267 (21%) patients with newly diagnosed non-Hodgkin lymphoma (NHL) presented in our hospital with involvement of Waldeyer's ring lymphoid tissue. Staging evaluation included history and physical examination, chest X-ray, abdominal CT-scan (or lymphangiography) and bone marrow biopsy. The median age of the patients was 63 years, significantly older than in the remaining 210 patients (56 years; $p<0.01$). Clinical stage I disease was diagnosed in 22 of the 57 patients (38%), stage II in 16 (28%) and stage III/IV in 19 (33%), resulting in a significantly less disseminated disease as compared to that in the other 210 patients: 23%, 11% and 63% respectively ($p<0.01$). The spleen was involved in 5 and the digestive tract in 2 of the 19 patients with stage III/IV disease. Bone marrow positivity was found in 13 patients. Bulky disease (>5 cm) was present in 24 patients (42%). Histologic classification according to the Working Formulation revealed 26% low-grade, 47 % intermediate and 27% high grade NHL (not significantly different from the pattern in the remaining 210 patients). Treatment modalities consisted of extended field radiotherapy alone in 28 patients (21 of the 22 stage I and 7 of the 16 stage II patients), whereas combined chemo- and radiotherapy was instituted in 29 patients (chemotherapy CHOP-like regimen for intermediate and high grade NHL and COP for low grade). The 5 patients with lymphoblastic NHL received intensive chemotherapy according to an acute lymphoblastic leukemia protocol. After a median observation period of 45 months, 31 (54%) of the patients had died. The calculated median overall survival time was 43 months (stage I not reached, stage II 58 and stage III/IV 35 months). In the group of 21 patients who had received radiotherapy alone, 70% were expected to be relapse-free after a median observation period of 42 months. No consistent relapse pattern has become evident yet, especially no preponderance of gastro-intestinal involvement. These data indicate that NHL of Waldeyer's ring lymphoid tissue occurs at more advanced age and presents more frequently with localised disease than NHL without Waldeyer's ring involvement. The response to treatment does not differ significantly between these 2 groups of patients.

79 Primary cerebral malignant non-Hodgkin's lymphomas. Histological and immunomorphological findings on stereotactic brain biopsies.

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Primary cerebral malignant non-Hodgkin's lymphomas are extremely rare neoplasms of the central nervous system. They often occur in association with immunosuppression.
This retrospective histological and immunocytochemical study reports on 54 cases of malignant non-Hodgkin's lymphomas with primary manifestation in the central nervous system. The serie comprises CT-guided stereotactic brain biopsies between 1982 and 30th June 1989. The diagnoses were done on intraoperatively performed methylene blue stained squash preparations and routinely processed paraffin sections as well. The lymphomas were uniformly classified by one of us (H.K.M-H). As a rule, HE, Giemsa, PAS and reticulin fiber stains were done. To confirm the histological diagnoses by immunomorphological methods, monoclonal antibodies against common leucocyte antigen (CLA, mab T200), human B-lymphocytes (mab L26), human T-lymphocytes (mab UCHL 1) and human myeloid/histiocyte antigen (mab MAC 387) were applied using the Pap-technique on paraffin sections. Our results show that the majority of primary cerebral malignant NHL are blastic lymphomas of high malignancy. Histological diagnosis could be ascertained in each case by positive CLA reaction. The B-cell nature of these neoplasms was documented by positive surface immunoreactivity with the monoclonal antibody L26. UCHL 1-positive lymphocytic cells were interpreted as associated non-neoplastic T-lymphocytes. A small and variable numer of MAC 387-reactive histiocytes were observed. A large number of tumors showed regressive alterations with predominance of UCHL 1-positive non-neoplastic lymphocytes.
In conclusion, our results show that primary cerebral non-Hodgkin's lymphomas can predominantly be classified as high grade blastic B-cell lymphomas. Immunomorphological techniques using monoclonal antibodies are valuable and helpful methods to confirm the histological diagnosis of CNS lymphomas.

80 CHROMOSOMAL ABNORMALITIES IN UNTREATED PATIENTS WITH NON-HODGKIN'S LYMPHOMA HAVE AN INDEPENDENT PROGNOSTIC VALUE FOR TREATMENT OUTCOME.

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We describe the chromosomal abnormalities found in 104 previously untreated patients with non-Hodgkin's lymphoma (NHL) and the correlations of these abnormalities with disease characteristics and treatment outcome. All patients were homogeneously treated according to the protocols of the Nebraska Lymphoma Study Group. The cytogenetic method used was a 24 to 48 hours culture, followed by G-banding. Several significant associations were discovered. A trisomy 3 was correlated with high grade NHL. In the patients with an immunoblastic NHL an abnormal chromosome #3 or #6 was significantly more frequently found. As previously described a t(14;18) was significantly correlated with a follicular growth pattern. Abnormalities on chromosome #17 were correlated with a diffuse histology. Patients with a t(11;14)(q13;q32) had an elevated LDH. Skin infiltration was correlated with abnormalities on 2p. Abnormalities involving breakpoints 6q11-16 were correlated with B symptoms. Patients with abnormalities involving breakpoints 3q21-25 and 13q21-24 had more frequent bulky disease. A shorter survival was correlated with a +5, +6, +18, all abnormalities on chromosome #5 or #17 or involvement of breakpoint 14q11-12. In a multivariate analysis these chromosomal abnormalities, age, B symptoms and elevated LDH appeared to be independent prognostic factors. Based on these factors three groups could be defined. Group I consisted of patients with no B symptoms and a low LDH, group II of patients with no B symptoms and an elevated LDH and group III of patients with B symptoms. In these three groups patients with a +5, +6, +18, breakpoints 14q11-12 or abnormalities on chromosomes #5 or #17 had a significantly poorer outcome than patients without these abnormalities (group I $p=0.0008$, group II $p=0.03$ and group III $p=0.004$). Therefore, we conclude that because of these correlations between certain clinical findings and specific chromosomal abnormalities, cytogenetic analysis of lymph nodes involved with NHL can be of help in unveiling the pathogenetic mechanisms of NHL. Also, because certain chromosomal abnormalities have an independent prognostic value for survival, they can be used for tailoring treatment regimens.

81 LONGTERM FOLLOW UP OF 1520 NHL PATIENTS CLASSIFIED ACCORDING TO THE KIEL CLASSIFICATION - EXPERIENCES OF A SINGLE INSTITUTION.

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1520 NHL patients defined according to the modified Kiel classification and treated at the 3rd Medical Department of Hanusch hospital were analysed respectively with regard to clinical presentation and outcome. Survival of patients with B-cell NHL differed significantly considering the subdivision in low grade malignancy and high grade malignancy according to the Kiel classification (p=0.0001). No such difference was seen in recently defined PTCL (p=0.7). Symptoms at presentation, prognostic factors influencing outcome were evaluated for the various subentities and compared to that of the multicenter trials of the Kiel Lymphoma Study Group. Concerning the subentities of the Kiel classification significant differences were seen. Therapeutic modalities have changed during the observation period. We were not able to improve prognosis by more aggressive therapy in patients with low grade NHL (p=0.5). But prognosis was improved in high grade NHL by early aggressive chemotherapy (p=0.005). But long term observation is still necessary because of a secondary cancer rate of 15%. Median followup of all patients is 73 months. Late relapses, development of secondary high grade NHL (1.4% in CLL, 9% in IC, 11% in CB/CC and 40% in AILD), as well as secondary non lymphatic neoplasias underlined the necessity of long term observation in low grade NHL.

82 TREATMENT OF AGGRESSIVE LYMPHOMAS IN PATIENTS OLDER THAN 69 YEARS. FIRST INTERIM REPORT OF A RANDOMIZED STUDY FROM THE G.E.L.A.

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273 patients (pts) older than 69 years and presenting an aggressive lymphoma were included from 10/1987 to 9/1989 in a prospective study testing chemotherapy with cyclophosphamide (750 mg/m^2), teniposide (75 mg/m^2) and prednisolone (120 mg/m^2) with [CTVP] or without [CVP] THP-adriamycin (pirarubicin) (50 mg/m^2). Pirarubicin was chosen because its absence of cardiac toxicity in early phase II trials. 176 pts (81 males and 93 females) are evaluable for response, survival and toxicity. Median age was 74 y (98 pts <75 y, 51 pts 75-80 y, 24 pts ≥80 y). Histology was according to the Working Formulation: D 2%, E 6%, F 15%, G 52%, H 15%, I 1%, J 1%, not classified 8%. 13% were stage I, 25% stage II, 14% stage III and 48% stage IV. 43% had B symptoms and 31% a low performance status. 24% had mediastinal adenopathies, 45% lomboaortic and 30% mesenteric adenopathies with 29% having a tumoral mass ≥10 cm. Extranodal localizations were spleen 22%, bone marrow 21%, GI tract 16%, head & neck 16%, pleura 14%, liver 13%, lung 11% with 24% having more than one extranodal site. 54% had serum albumin level <35 g/l and 55% increased LDH level.

Response to treatment was CR 47%, PR 14%, SD 5%, PD 19 % and death 15%. CR rate was 34% for CVP and 60% for CTVP (p<.001). 12% of pts with CVP died during therapy vs 18% with CTVP. Median overall survival is 14 months, median FFP survival 7 months and median FFR survival is not reached with a median follow-up of 8 months. Overall survival is not different in the two treatment arms but CTVP pts have better FFP survival (p<.05) and FFR survival (p=.05). 27% of the CR pts relapsed, 30% in the CVP arm and 25% in the CTVP arm (p=NS).

Toxicity ≥grade 2 was not the same in the 2 arms. CVP gave 24% neutropenia, 11% infections, 5% thrombopenia, 4% mucitis, and 3% cardiac toxicity. CTVP gave 38% neutropenia, 16% infections, 9% thrombopenia, 5% mucitis, and 1% cardiac toxicity. Results are significantly different only for neutropenia.

High CR rate and longer overall and FFP survival are associated with stage I, good PS, <2 extranodal sites, absence of B symptoms, bulky tumor, abdominal adenopathies, bone marrow or spleen localizations, high protein or serum albumin levels, normal LDH level. Age did not influence the response to treatment. The prognostic parameters are those described in younger patients. The prognostic index describe in LNH-84 patients has a very good discrimination value in these patients (p=.002). Better outcome is statistically associated with treatment containing pirarubicin despite a relatively more important toxicity.

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ABLATIVE THERAPY WITH AUTOLOGOUS BONE MARROW TRANSPLANTATION AS CONSOLIDATION THERAPY FOR FOLLICULAR LYMPHOMA Rohatiner AZS[1], Price CGA[1], Dorey E[1], Arnott S[2], Amess J[3], Norton A[4], Davis CL[1], Clark P [1],Horton M[1], Lister TA[1]: ICRF Department of Medical Oncology[1], Departments of Radiotherapy[2], Haematology[3] & Histopathology[4] St. Bartholomew's Hospital, London, EC1

The majority of patients with follicular lymphoma die as a consequence of the disease despite responsiveness to both chemotherapy and irradiation. Repeated remissions can usually be achieved but are hardly ever more than temporary, the continuous relapse pattern making death from lymphoma virtually inevitable. A study has been in progress since June 1985 to evaluate the use of bone marrow ablative therapy (Cyclophosphamide: 60mg/kg x 2 and total body irradiation: 200cGy x 6) supported by autologous bone marrow transplantation (Cy + TBI + ABMT) in patients in second or subsequent remission. The marrow mononuclear cell fraction is being treated in vitro with 3 cycles of the monoclonal antibody anti-CD20 (anti-B1, Coulter Immunology) and baby rabbit complement (Pel Freez). Thirty five patients (age range 29-61, median 43 years) have been treated to date. At the time of treatment, 24 patients were in 2nd remission, 8 were in 3rd, and 3 in > 3rd respectively. Twenty three patients were in complete remission, 12 had residual disease present (4 < 10% bone marrow infiltration, 4 lymph nodes < 2cm diameter, 1 gut involvement, 1 skin involvement, 1 splenomegaly and 1, residual disease in both bone marrow and lymph nodes). Twenty nine patients are alive, 6 have died; four of the latter in remission; two as a consequence of the transplant procedure (1 cerebral haemorrhage at 9 days, 1 systemic fungal infection at 3 months), 1 from secondary acute myelogenous leukaemia at 4 years having presented 8 years prior to receiving Cy + TBI + ABMT and another from an unrelated cause. Two patients died following relapse. Twenty four continue in remission between 2 months and 4½ years; a total of 7 have relapsed, 2 with transformation to high grade histology. The mean time to engraftment was 33 days (range 15-90 days) and 32 days (range 15-150 days) for neutrophils (0.5 x 10^9/l) and platelets (20 x 10^9/l) respectively. In the context of the natural history of follicular lymphoma these results are preliminary but encouraging and confirm those of others. It remains to be established whether such intensive therapy prolongs survival.

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TREATMENT OF B-CELL NON-HODGKINS LYMPHOMAS WITH IMMUNOTOXINS. L. Nadler, S.F. Schlossman. Division of Tumor Immunology, Dana Farber Cancer Institute; Boston, Massachusetts, USA.

Since most patients with NHL are capable of achieving a CR with primary or salvage therapy, the major obstacle to cure is residual resistant lymphoma. One approach to the treatment of residual disease is the use of immunotoxins. Immunotoxins combine the specificity of a monoclonal antibody with the lethality of a highly potent toxin. Protein toxins such as ricin, diphtheria toxin, and pseudomonas exotoxin are very potent cell-killing agents since one molecule of a toxin delivered to the cytoplasm will be lethal for that cell. The issues of single chain and modified whole toxin molecules will be discussed.

We and others have treated patients with B cell NHL with immunotoxin therapy and an overview will be presented. Our trial involves the use of a novel toxin [blocked ricin(bR)] which is internalized as efficiently as the whole ricin molecule yet can be specifically targeted since the galactose binding sites of the B chain have been neutralized. The anti-B4(CD19) mAb was selected because of its specificity for B cells, high affinity, and expression at all stages of normal B cell ontogeny. Anti-B4bR is highly toxic and B lineage restricted. At least 5 logs of clonogeneic lymphoma cells are killed after 24 hr culture with 10^{-9}M anti-B4bR.

A phase I clinical trial of daily bolus infusions for 5 days was undertaken in pts whose tumors were resistant to conventional and salvage therapy and expressed the CD19 antigen. Anti-B4bR was administered as a daily 1 hr bolus infusion for 5 consecutive days. Twenty-five pts have been treated. No clinical or laboratory toxicity was observed until the 40ug/kg/day dose when 5-10 fold transient elevation of SGOT/SGPT was observed. At 60ug/kg/day, 2 of 3 pts demonstrated 10-20 fold elevation of SGOT/SGPT. The dose was therefore reduced to 50ug/kg/day (MTD-250ug/kg). Nine pts have completed this dose level and have demonstrated 5-20 times elevation of SGOT/SGPT without other abnormalities. No other significant toxicities have been observed. Even though therapeutic blood levels of anti-B4bR were only transiently(<6 hrs) achieved, in vitro PBL Ig synthesis was inhibited >95%. Of 25 pts treated, 1CR, 2 PRs, and 10 transient or mixed responses were observed. HAMA/HARA was seen in 50% of pts. Although bolus infusions did not achieve sufficient in vivo drug levels to mimic in vitro cytotoxicity, clinical responses have been observed with transient reversible hepatocellular injury as the only major clinical side effect.

In an attempt to improve efficacy and decrease toxicity, continuous infusion administration of anti-B4bR was evaluated in subhuman primates. In these studies, anti-B4bR could be administered continuously for 7 days at total dosages between 1000-1500ug/kg without significant hepatocellular toxicity. A phase I clinical trial of the identical pt population described above was begun administering anti-B4bR by constant infusion over 7 days. To date, 18 pts have been treated. Daily does have been escalated to 40ug/kg x 7d. As observed with bolus infusion, the only significant toxicity thus far observed has been transient elevations (5-10x) SGOT/SGPT. Again no other significant side effects were observed. Blood levels are still in the 10^{-10}M range. Of the first 15pts treated, there has been 1 CR, 3 PR, 4 transient or mixed responses. Six of 15 pts have thus far made HAMA/HARA. We are presently dose escalating to achieve therapeutic blood levels with tolerable reversible toxicity to define DLT as well as MTD for phase II studies of constant infusion.

The challenges of immunotoxin therapy will be to decrease toxicity, inhibit HAMA formation, and to test the efficacy of this form of therapy in patients with only minimal residual disease.

85 RADIO-IMMUNOTHERAPY OF NON-HODGKIN'S LYMPHOMA WITH SINGLE HIGH DOSE I-131 RADIOLABELED ANTIBODIES.

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21 patients with non-Hodgkin's lymphoma have been evaluated as candidates for experimental radio-immunotherapy with single high dose I-131 labeled anti-pan B-cell antibodies. Of these patients, seven have been treated with doses designed to deliver 1000 rads, (3 patients), 1500 rads, (3 patients), and 1675 rads, (1 patient), to normal organs. These radiation doses were estimated from pretherapy quantitative imaging and biodistribution studies. Doses administered to achieve these radiation absorbed doses ranged from 252-608mCi I-131.

Patients receiving 1000 rads to normal organs had severe pancytopenias requiring platelet transfusion. They had spontaneous recovery of bone marrow function. Those patients who received greater than 1500 rads to normal organs had severe prolonged pancytopenias that required reinfusion of previously stored bone marrow. Normal marrow function was recovered in all cases. While cytopenic, one patient had fever associated with herpes simplex type I virus, controlled with Acyclovir, while another had a groin cellulitis in a biopsy site which was controlled with antibiotics. Six of seven patients had compete remissions. Patients receiving 1000 rads relapses at 4, 6 , and 12 months. Of the patients receiving 1500 rads, the two patients with complete remissions, are disease free at 9, and 14 months, while the one patient with partial remission died nine months post treatment. The one patient who received 1675 rads to normal organs, is still in the early post treatment phase. Because of only hematologic toxicity, which is overcome with autologous bone marrow reinfusion, radiation absorbed doses will continue to be escalated in groups of three patients, at 175 rads per patient group.

86 AUTOLOGOUS LYMPHOCYTES AS VECTORS TO TARGET THERAPEUTIC RADIATION IN PATIENTS WITH DIFFUSE LYMPHOMA LYMPHOCYTIC.

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Five patients with advanced diffuse lymphoma lymphocytic (DLL) have been treated with autologous lymphocytes loaded with the ß emitting radionuclide indium 114m (T/2 = 50 days). All patients were heavily pre treated and had progressive lymphoma resistant to conventional chemotherapy and radiotherapy at the time of indium 114m therapy. Following intravenous infusion the labelled cells remain viable for up to 12 hours permitting active migration to lymphoid tissues creating an intense field of localised irradiation along the lymphocyte migration pathway for many weeks. The in vivo distribution of activity was uniform in the 5 patients and concurred with our previous pharmaco kinetic study (1); 75% - 80% of administered activity localised in the spleen and liver with up to 5% deposited within the bone marrow. A clear response was seen in 4 / 5 patients with a marked reduction in peripheral lymphocyte count, and regression in hepatosplenomegaly and bulky adenopathy. Two patients remain free from progressive disease 2 and 6 months post therapy, and two showed an initial response of 4 and 12 months duration, and remain well in partial remission at 11 and 24 months respectively. The non responder died of progressive lymphoma 10 weeks following indium therapy. Indium 114 treatment was associated with myelosuppression, but no subjective toxicity.

This represents a new concept in the administration of therapeutic radiation in lymphoid malignancy, demontrating a substantial anti tumour effect in patients with highly resistant disease.

Hamilton D., Cowan R.A., Sharma H.L., et al.The behaviour of Indium 114m labelled autologous lymphocytes in patients with lymphoid cell malignancy.J. Nucl. Med. 1988, 29, 485 - 493.