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45 Expression, Sharing and Remodeling of Idiotypes in Follicular Lymphoma
R. Levy, Stanford Univ. Med. Center, Stanford, California, USA

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 immunoglobulin 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 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-idiotypic antibody reagents. Therapeutic application of such monoclonal antibodies has shown a high degree of tumor responsiveness but ultimate escape of idiotypic negative variant cells. Active immunization can result in an immune response by patients directed against the idioype 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 (14;18) CHROMOSOMAL BREAKPOINTS BY POLYMERASE CHAIN REACTION AND DIRECT DNA SEQUENCING IN B-CELL LYMPHOMA
M. Krebs1, S. Eick1, J. Wittgenstein1, Ch. Post1, I. Bolz2, M. Berghold2, H. Herbst3, H. Suhl1, G. Klinger1, 1 Dept. of Hematology and Oncology, Division of Internal Medicine, 2 Dept. of Pathology, University Clinic Göttingen, and 3 Dept. of Pathology, Klinikum Steigltz, Free University Berlin, FRG

We have examined 148 B-cell non-Hodgkin’s lymphomas for rearrangements of the (14;18) major breakpoint region by Southern analysis of genomic DNA and by polymerase chain reaction (PCR) with direct sequencing of amplified bcl-2/V_{\alpha} fragments. The lymphomas were categorized according to the Kiel classification (35 CC-CB; 37 CB; 24 FC; 6 FL; 19 CC, 17 CLL; 3 LB; 2 MI-2; 2 hairy cell leukemia and 5 plasmocytes). With use of relatively long PCR-primer (Oligo MK 28: 5'-GAGGAGGCTCTTCCGCAGAGT-3', inverse complementary to the consensus V_{\alpha}5 sequence and Oligo MK 3: 5'-GAATTCCGC-AGTTATTATGTCATGTTACGAGG-3'), for bcl-2 primer annealing and extension were carried out within 30 s per cycle at 94°C The specificity of the procedure allowed visual identification of the bcl-2/V_{\alpha} PCR-products in ethidium bromide stained agarose gels after 40 PCR cycles. In 17 cases a 6/2/4 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 subtypes: 9/0/6 % CC-CB; 3/27/0 % CB and 1/24 CC (4 %). Because three of the bcl-5/2, 4 CC-CB lymphomas contained areas of conversion to CB lymphomas it can be speculated, that the three diffuse CH NHL with bcl-2/V_{\alpha} may have originated from CC-CB NHL. Direct DNA sequencing of 15 PCR-amplified, previously uncharacterised (14;18) (4/5) regions, clearly provided corroborating evidence for the specificity of our assay. Together with the variations in the (14;18) breakpoint sequence flanking both chromosomal 18 and chromosome 14 sites, the junctional region N-segments (length 2-45 bp) create highly clone-specific target sequences for tumor-cell specific PCR (T-FCR) or in situ hybridisation and aid in reducing the threat of false positive results inherent to PCR.
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47 Expression of Growth-related Genes and Drug-resistance Genes in HTLV-I-positive and HTLV-I-negative Post-thymic T Cell Malignancies I.J. Su, MD, PhD., A.L. Cheng, MD, T.C. Chang, MD, Department of Pathology and Hematology/Oncology, National Taiwan University Hospital, Taipei, Taiwan, R.O.C.

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-I-positive and 23 HTLV-I-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 sequences of oncogenes and growth-related genes. The expression of onco-genes such as c-myc, c-fos, and c-ras were restricted to a small proportion of cases, including those with poor prognosis. The expression of growth-related genes in the HTLV-I-related cases was also compared to those in HTLV-I-negative cases.

48 PROGNOSTIC SIGNIFICANCE OF PROLIFERATIVE ACTIVITY IN NON-HODGKIN'S LYMPHOMA. H. Grulich, T. Wodriff, D. Portis, J. Armitage, and D. Weisenburger for the Nebraska Lymphoma Study Group, University of Nebraska Medical Center, Omaha, NE, USA

Non-Hodgkin's lymphoma (NHL) is composed of a heterogeneous group of tumors which exhibit diverse biological behavior. Characterization of NHL using flow cytometry has been shown to predict outcome following therapy. The development of techniques for extracting nucleases from paraffin-embedded tissues (J. Histochem. Cytochem. 31:1333, 1983) has permitted retrospective studies of the role of cellular proliferative activity (PA) in NHL. We have developed a method for determining PA in tissue sections using antibodies specific for proliferating cell nuclear antigen (PCNA) and antibody specific for proliferating cell nuclear antigen (PCNA). We have applied this method to a series of 116 patients with NHL, and have found that PA is independently associated with patient outcome.

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Ectopic expression of nyellomonocytic antigens (Nya) on lymphoid leukemia cells has several important biological and clinical implications. In particular, the expression of the cell surface peptide, recognized by anti-CD13 monoclonal antibodies (M7, M5S-2), is associated with a lower relapse 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 Nya expression. The cytotoxicity analysis revealed that CD13 and CD14-Nya antigens were expressed on B cells from 34 and 59% of pts respectively whereas CD15 and CD33 have been detected only in 7 and 15% of samples. 38% of pts displayed a multiple Nya expression (CD13-CD14, CD14-CD33, CD13-CD14-CD33), CD13-CD14-CD33). No significant differences were observed between Nya+ and Nya- B-CLLs as far as CD5 expression and BZ brightness is concerned. The expression of myeloid and B-associated antigens (CD19, CD50, 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 Nya was also apparent. CD13 cases were never observed among pts with disease limited to peripheral and multiple myeloma (RAI 0) but no significant 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 Blum staging system (A vs C, p=0.04), probably owing to the inclusion of the group A of some pts with lymphoma and chronic B-CLL. 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, high expression of the CD13 antigen represents a highly unfavourable prognostic factor. These results suggest a critical role of the Antiproteasase N/CD13 in the ontogeny of B lymphocytes and in mediating relationships of B cell subpopulations with bone marrow and lymphnode microenvironment.

Supported by the A.I.R.C.


The growth and differentiation of hematopoietic cells in the bone marrow occurs in association with stromal cells that provide specific microenvironments. Within these microenvironments, hematopoiesis 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 multipotent 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 hematopoiesis 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 exposed - and that combination of growth factors can be selectively used to modulate both self-renewal and the choice of lineage-0ptions 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 hematopoiesis in animal model systems and data will be reported on such studies. The role of hematopoietic growth factors in leukaemogenesis will also be examined.
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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 Lymphomas. J.O. Armitage, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, NE, USA

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 lymphomas and immunoblastic lymphomas. 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. Early 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, INH-B, Procarbazine-Cytostar, CVP-BOP, CVH-ELAM, 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 lymphomas but also for the less common aggressive non-Hodgkin lymphomas such as lymphoblastic lymphomas, small non-cleaved cell lymphomas, and immunoblastic lymphomas. At the present time, this is the most promising approach to improving therapeutic results.
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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), 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 mononuclear large cells, with 4 subgroups: <10%, 10% - 30%; 10% - 50%; 10% - 50%; 10% - 50%. (b) The degree of folliculity assessed either by the presence of an intracellular pattern of proliferation (absence, minority or majority of follicles); or by the importance of diffuse areas: <25%, 25% - 50%, 50% - 75%, >75%. Two of these parameters were highly correlated (p<0.01). (c) Mitotic rate, maximum grade from 1 + to 4 + . (d) The histologic evidence of fibrosis graded from 0 to 4 + . Mitotic rate is correlated with the percentage of large cells (p<0.01) and the degree of folliculity (p<0.05). Fibrosis is correlated with the percentage of large cells (p<0.05). 80% of pts reached CR and 47% of them relapsed. Median survival is 11 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<0.05) and tumor mass >10 cm (p<0.05).

A high mitotic rate is correlated with a low response rate (p<0.05) and a high histologic progression rate (p<0.01) but not with survival. An increased fibrosis is correlated with a longer overall survival (p=0.01), FFR (p<0.01) or FFP (p<0.01). 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 intracellular pattern of proliferation is significantly associated with a better outcome (p<0.005).

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 lymphomas. 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 lymphomas is probably best determined by clinical or biological parameters as in diffuse lymphomas, i.e., stage, tumor 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 (RT). P. McLaughlin, L. Fuller, J. Hagemeister, J. Redman, E. Dutt, L. Holmes, W. Volokes, D. Swan, T. Baken, Anderson Cancer Center, Houston, TX 77030, U.S.A.

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 with subtotal 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 or CS I-II pts is a consideration but it has substantial morbidity. Between 1984-89, we explored IF + CT in combination with relatively mild CT, cyclophosphamide, vincristine, prednisone, and bleomycin (CPP-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 >65 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, 1 of intercurrent disease, and 1 of myelodysplasia attributed to the COH+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 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 alone (Cancer 1986;58: 1556), the FFS is significantly better (p<0.01) with COH+Bleo+XT. The potentially cured fraction of pts has risen from 45% to 73%.
INTERFERON-α2b (IFN-α2b) 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-α2b (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-α2b (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-α2b), 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 much more frequent with CB+IFN-α2b (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-α2b. 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. 9 months for NT, p<.014). Fewer relapses have been seen in patients who received IFN-α2b in both phases of the study. Accrual to the trial continues; this preliminary analysis indicates that M-IFN may extend remission duration in FL.

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


A first-generation CHOP-like cyclic combination chemotherapy (CT) using cyclophosphamide 600 mg/m^2 IV d1, hydroxyurea 50 mg/m^2 IV d1, vincristine 1.4 mg/m^2 IV d1, and prednisone 60 mg/m^2 PO d1-5 was challenged by a second-generation combination adding vinblastine 6 mg/m^2 IV/IM at mid interval (d15) to the former drugs and bleomycin 6 mg/m^2 IV/IM in the treatment of aggressive NHL. From April 1980 to 1.1986, 162 eligible patients with stage III-IV unfavorable histologies (Working Formulation B, F, G, H and I except T lymphoblastic NHL) entered this EORTC randomized trial, in both arms all had chemotherapy (20 Gy) EORTC randomized trial. In both arms identical radiotherapy (20 Gy) was given to bulky or residual disease. Patients who achieved a CR underwent a second randomization for monthly maintenance CHOP during 1 year.

In all patients subsets the outcome favored the second generation regimen. The difference was even larger in patients with Diffuse Large B-cell Lymphoma (DLCL). At 4 years, overall freedom from progression was 72% versus 44% (p = 0.001) and survival 61% versus 42% (p = 0.015). 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 vinblastine and bleomycin. This was not the case for CT maintenance CT had conversely provided no detectable improvement on either RFS or survival.

The trial demonstrates a clear benefit for aggressive NHL 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.

Keywords: Non Hodgkin lymphoma, intermediate grade, high grade, aggressive, chemotherapy, first generation, second generation, CHOP, CHOP + V, adriamycin, maintenance, randomized study.
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57 PROSPECTIVE MULTICENTER TRIAL FOR THE RESPONSE-ADAPTED TREATMENT OF HIGH-GRADE MALIGNANT NON-HODGKIN LYMHPHOMAS: UPDATED RESULTS OF THE COP-EBLAM/IPH-16 PROTOCOL WITH RANDOMIZED ADJUVANT RADIOTHERAPY.


In a prospective multicenter therapeutic trial the remission (CR) inducing efficiency of the response-adapted COP-EBLAM/IPH-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-EBLAM followed by two cycles of IPH-16 in 1 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 IPH-16 regimen (2 to 5 courses) immediately. Patients reaching CR in the 2nd RS after completing chemotherapy were then randomized to adjuvant radiotherapy (40 Gy) or no follow-up observation only with regular RS evaluations every 3 months for patients in both groups. Of 505 evaluable patients 33% presented with stage I, 25% with stage II, 22% with stage III, and 10% with stage IV disease; median age was 56 (range 17 to 75) years. Of all cases 52%, 17% and 14% were classified as the centroblastic, immunoblastic and lymphoblastic subtype of NHL, respectively. 8% were 

58 TREATMENT OF INTERMEDIATE AND HIGH GRADE NON-HODGKIN'S LYMHPHOMS WITH THIRD GENERATION CHEMOTHERAPY REGIMENS: RESULTS OF THE 3GCGO Peek II STUDIES.

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Between July, 1984 and May, 1986, 5803 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 3-6 years, this abstract updates the results of those clinical trials and analyzes the prospective impact of dose intensity on complete remission (CR), disease-free survival (DFS), and overall survival of all patients (OS). Little et al. (SMCG 9410), Procarcy-Cytadim (SMCG 9503), and MACOP-B (SMCG 8508) were each administered entirely as initially described except that the dose of vincristine was capped at 2 mg in the latter two studies. There were 78 evaluable patients on SMCG 9410, 78 on SMCG 9503, and 110 on SMCG 8508 respectively. CR rates were 57%, 69%, and 65% for Procarcy-Cytadim and 65% for MACOP-B. The 49% CR rate for MACOP-B was significantly lower (p = 0.03). Moreover, DFS has not been achieved: DFS at 3 years varies from 64-72% (p = 0.70). OS at 3 years also varies from 50-63% 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 calculated as the average of the RDI's for each drug in a given protocol. The mean RDI for each study was 0.8, 0.8, and 0.8. Age, performance status, and B symptoms were each inversely correlated with RDI. Higher RDI was associated with improved survival in a univariate analysis (p = 0.01). However, after adjustment for age or performance status in a Cox regression model, RDI was no longer statistically significant.

A significant RDI could be achieved with each of the three third generation chemotherapy regimens. The study resulted in the design of randomized Phase III comparison of CECR vs. 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.
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CHEMOTHERAPY (CT) FOR ELDERLY PATIENTS WITH ADVANCED STAGE LARGE CELL LYMPHOMA - A LITTLE GOES A LONG WAY  
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 1985 and August 1989, 128 pts were treated sequentially at our institution with different regimens: from 1985 to 1986, 44 pts had low dose methotrexate 75 mg/m² IV, 70 mg/m² PO daily x 10; from 1987 to 1989, 32 pts had the MOPP (Procarbazine, Oncovin, Prednisone, Cyclophosphamide) regimen; and 36 pts had MOPP and VAD (Vincristine, Adriamycin, dexamethasone) and MOPP and VAD and CHOP (Cyclophosphamide, Oncovin, Prednisone, Procarbazine) regimens. The effect of treatment was evaluated by response, duration of response, time to progression, and survival. The median age of the patients was 70 years (range, 59-79). The overall complete response rate was 46% (95% CI: 35-57%). The median survival of the patients was 27 months (range, 0.1-54). No side effects were noted except for nausea and vomiting, which were seen in 28% of patients. The results of this study indicate that low-dose methotrexate is a safe and effective regimen for elderly patients with advanced stage large cell lymphoma.  

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NON HODGKIN'S LYMPHOMAS (NHL) ASSOCIATED WITH HUMAN IMMUNODEFICIENCY VIRUS (H.I.V.) :  
For CELAC-PEGICAT Cooporative inser-CNS study  
Hopital Saint-Louis - PARIS 75010 - FRANCE  

NHL HIV patients have a poor prognosis related to lymphomas 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 a performance status (<7.0) and no opportunistic infection were treated by LNH 84 regimen (J.C. 06/89) and CNS prophylaxis with radiotherapy. Six patients were administered during the consolidation phase. In group B with >7.0, 3 or 4 patients received a low dose chemotherapy program with Cyclophosphamide 300 mg/m² d1, Adriamycin 25 mg/m² d1, VM26 30 mg/m² d1, Vinristine 15 mg/m² d15, Prednisone 10 mg/m² d15 and Prednison. AAST 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, and a 60 pts, stage distribution was : I 13 pts, II-EIB 15 pts, III-IV 32 pts, B symptoms 28 pts, Bulky tumor 16 pts. Extraneal involvement 11 pts, Bone marrow 12 pts, liver 13 pts, meningeal 11 pts. LDH > normal value 29 pts. After induction, 38 pts (72%) were in CR. Hemotoxicity with neutropenia < 5000/µl and 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 PS and no O.I., LNH 84 regimen achieved a CR rate similar to standard NHL.


227 patients with advanced B cell lymphomas from 3 centers were treated in a 3 years 6 months period in the LMB 03A (See SFOP report this conference). 14% of the CR patients (ie 26/184) did relapse. CNS along (6 cases) 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. 2/13 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 aggressive (and good ?) protocol can be cured with BMT. The respective role of harvesting in CR or purging marrow after relapse will be discussed.

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 aggressive strategy was obvious. Without BMT relapse will conduct to death in 100% of the cases.

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

AUTOGOSOUS BONE MARROW TRANSPLANTATION (ABMT) FOR ADULT LYMPHOMA (AdL) IN FIRST COMPLETE REMISSION. A PILOT STUDY OF THE NON-HODGKIN'S LYMPHOMA CO-OPERATIVE STUDY GROUP (NHLCCSG).

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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 occur during maintenance chemotherapy, the quality of patients life is poor. Due to these reasons we 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-C (70-100 x 10^6/kg) 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 pts. (20%) 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 10/16 pts. are in CR 1 to 56- mos. (median 43), with a DFS probability of 70%: 4 relapsed and died 3.5,5.5,9 mos after ABMT. The procedure was not associated with major complications. The hematological recovery was good, except in 9 purged cases raising 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.
ABSTRACTS - Fourth International Conference on Malignant Lymphoma, Lugano

63 AUTOLLOGOUS BONE MARROW TRANSPLANTATION FOR INCURABLE ADVANCED STAGE B CELL NON-HODGKIN'S LYMPHOMA IN FIRST REMISSION. A. Friedman, J. Rios, T. Takvorian, S. Rubenow, K. Anderson, P. Masch, R. Soffer, K. Blake, L. Nadler. Dana-Farber Cancer Institute, Boston, MA, USA.

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 high disease-free survival (DFS) in 20-40% of patients (pts) who are relapsed and 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 determine 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 treatment ABMT in either 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 at time of BM harvest. 12 of the int/high grade pts were in CR. Lymphomas of BM were present in 6 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 180 cGy x 3), no acute in-hospital toxic deaths occurred. Hematologic engraftment was achieved in all pts within 21 days. Seventeen pts participated in the study of intensive treatment for pts with relapsed NHL. All pts were treated with CHOP at time of BM harvest. At the time of BM harvest, 12 of the int/high grade pts were in CR. Lymphomas of BM were present in 6 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 180 cGy x 3), no acute in-hospital toxic deaths occurred. Hematologic engraftment was achieved in all pts within 21 days. Seventeen pts achieved >500 PMN/mm3, and 21 days to achieve >40,000 platelets/mm3. Culture-negative neutropenic fever was seen in 6 of the low grade pts, while 15 of the int/high grade pts had fever with 3 associated positive blood cultures. One late pulmonary complication was observed in a patient with non-fatal bacterial pneumonia at 6 months, and 4 pts with localized dermatomal herpes zoster. One pt with int/high grade NHL relapsed at 6 months in a site of prior bulk disease. Of the 23 pts remaining, 23 are in remission with a median follow-up of 12 months. Of 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 that high dose chemoradiotherapy 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-B (TGF-B). Michael B. Sporn and Anita B. Roberts, National Cancer Institute, Bethesda, Maryland 20892, U.S.A.

Transforming growth factor-B (TGF-B) is a homodimeric peptide, with a molecular weight of 25,000 daltons, that exists in several isoforms. TGF-B is synthesized by almost all mammalian cells and essentially all cells have functional receptors for this peptide. TGF-B 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-B on both T- and B- cells are very potent, since picogram levels of TGF-B can suppress DNA synthesis and immunoglobulin synthesis in these cells. Furthermore, TGF-B 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-B would appear to be an important negative autocrine growth factor for the control of lymphocyte differentiation and function.

Recent work by F. Ruscelli and colleagues has shown that there are no detectable receptors for TGF-B in several T-cell and B-cell lymphomas, as well as in the acute promyelocytic leukemia cell line, HL-60; and it has been suggested that this may contribute to the uncontrolled growth of these tumor cells. Moreover, Ruscelli and colleagues have also shown that phorbol ester and retinoic acid, agents which can induce differentiation in HL-60 cells, cause the re-appearance of TGF-B receptors in these cells. It is believed that the development of the negative autocrine loop mediated by TGF-B is reponsible in part for the arrest of growth induced in HL-60 cells by retinoic acid. Thus, TGF-B receptors in HL-60 cells may be useful for the treatment of acute promyelocytic leukemia. Whether retinoic acid or other differentiating agents can mediate the reappearance of TGF-B receptors and lymphomas remains to be determined.
THE BIOLOGY OF INTERLEUKIN 6: THE ROLE IN PLASMA CELL DISEASES

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Interleukin 6 (IL-6) is a pleiotropic 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 predominant 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 inhibit IL-6 receptors have made it possible to accurately assess the role of IL-6 in a wide range of diseases including plasma cell disorders. 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 tularinant myeloma. Separation and purification studies have shown that the predominant source of IL-6 is paracortical 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 and IL-6 antibodies, clinical studies utilizing antibodies have been initiated. Preliminary studies (Klein et al Blood Abst 74(1): 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.

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 (Bland 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/m² 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/m²) without resort to autologous bone marrow transplantation (ABMT). In this study the period of granulocytopenia (<500/μl x10⁹/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.
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 COPP or NOVP 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.

RECOMBINANT HUMAN GM-CSF AND MITOXANTRONE/HIGH-DOSE ARA-C IN THE TREATMENT OF REFRACTIVE NON-HODGKIN-LYMPHOMA
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Previous study from our group has shown that the combination of mitoxantrone (Novantron, NO) and Ara-C (AC) (NDAC) 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 NDAC chemotherapy in patients with refractory NHL. Mitoxantrone was applied at a dosage of 10 mg/m²/day on days 2 and 3 and Ara-C at 3 g/m²/day on days 1 and 2. rhGM-CSF was administered at 250 μg/m²/day as a continuous IV infusion from Day 6 onwards until the neutrophils were > 3.0/ni 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/ni) 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/ni) 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 3 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 (rG-CSF) VS PLACEBO FOR NEUTROPENIA INDUCED BY CHEMOTHERAPY IN PATIENTS (PTS) WITH NON-HODGKIN LYMPHOMA. (NHL). M. Ogawa, T. Hasegawa, H. Mizoguchi, F. Takaku, M. Nakajima, T. Ikaida, and M. Shimoyama. Cancer Chemotherapy Center, Center for Adult Disease, Tokyo Women's Medical College, Tokyo University, Hamamatsu University, Komagome Hospital, National Cancer Center.

rG-CSF stimulates proliferation and differentiation of granulocytes precursors, efflux of mature granulocytes from bone marrow to peripheral blood and activity of granulocytes.

In order to study the role of rG-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/mm3 in the first course of chemotherapy were randomly allocated to receive either rG-CSF at a dose of 75 μg/body sc or a placebo sc. A dose of 75 μg was determined to be an optimal dose in previous phase 1-11 trials. Both started 3 days after completion of the second course of chemotherapy and continued for 16 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 1,893/mm3 for G-CSF and 493/mm3 for placebo, respectively (p=0.0005). A median days needed for the recovery of neutropenia until 2,000/mm3 from the nadir was 8.3 days for G-CSF and 20.9 days for placebo, respectively (p=0.0000). Toxicities observed were discomfort on chest, rash and pts fever and lumbar discomfort in one each received G-CSF while rash in 2 pts on G-CSF and a patient on placebo developed grade 3 neutropenic fever.

The overall effective rate judged by the response review committee was 49.3% for G-CSF and 13.1% for placebo. The result indicates that G-CSF accelerate recovery of neutropenia and therefore is useful for prevention of infections during chemotherapy.

70 ASSOCIATION OF LYMPHOCYTE HORMING RECEPTOR EXPRESSION AND STAINING INTENSITY WITH S-PHASE FRACTION, STAGE, AND PROGNOSIS IN NON-HODGKIN'S LYMPHOMA. M. Joensuu, P.J. Klemi, K.-O. Söderström, and S. Jalkanen. Depts. of Radiotherapy and Pathology, Turku University Central Hospital, and Depts. of Medical Microbiology and Pathology, Turku University, Turku, Finland.

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 Ki67 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 analysis. 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 - , 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 SPFp 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 cell 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
Kensei Tobinai, Toshiaki Sai, Tomoko Ohtsu, Masaki Hayashi, Kiyoshi Nakai, and Masanori Shimoyama
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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-1) 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 ANEMOPLASTIC Ki-1 POSITIVE LYMPHOMA: A STUDY OF 5 CASES.
C.C. de Bruyn, E.B. Jongsas, K. Cooper, Department of Hematology, King Edward VIII Hospital and University of Natal, Durban, South Africa.

Non-Hodgkin's lymphomas (NHL) expressing the Reed-Sternberg associated antigen Ki-1 (CD30) represent neoplasms of activated lymphoid cells. These high-grade lymphomas are of heterogeneous lineage, the majority being of T-cell origin on phenotypic and genotypic analyses. These neoplasms tend to have a predestination 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 anemoplastic 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-Iranian 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 clinicopathological syndrome first described in children.

Another patient, a 36 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. Anemia and peripheral blood lymphopenias appear to be poor prognostic factors.

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

The natural history and optimal therapy of Ki-1 lymphomas has not been established and further studies are essential.
ABSTRACTS - Fourth International Conference on Malignant Lymphoma, Lugano

73 MEDIALINIAL LARGE CELL LYMPHOMAS: A HISTOPATHOLOGICAL AND IMMUNOHISTOCHEMICAL STUDY
J AUDOUIN*, H F D'AGAY**, P GAULARD***, F BERGER****
J DIEBOLD* and the executive comité of the GEIA
(LNH87) protocol (Hôpital-Dieu, Paris - France).

Between 1987 (Oct. 1st) and 1989 (May, 30th) 844 cases of aggressive malignant lymphoma were recorded in the French national protocol LNH87 (GEIA). Thirty cases of mediastinal large cell lymphoma were recognized, representing a frequency of 3.5% of the lymphomas in this series. 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 subclavicular 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 lymphomas according to the Kiel classification (group B of intermediate grade in the LNH). 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 : L26, L24 and particularly MB2 and MB5. UC191 was only positive on reactive cells. On frozen sections, the tumour cells were positive in most of the cases for CD25, CD45, CD20 and negative for CD1 (CD8). Sialomucins were found in only 5 cases of the 11 tested. CD30 was positive only in one of the 8 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 literature as diseases with clinical features that differ from nodal lymphomas. They are thought to spread diverse to other MALT-organs and regional lymph nodes (LNSs) rather than disseminate to distant LNSs 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 69 patients, 41 males and 17 females, treated for primary gastric lymphoma at the dept. of Oncology, University Hospital of Lund during the 16-year period 1970-1986. 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 66 years, range 16-80. A histopathological reevaluation according to the Kiel-classification was performed by one pathologist (MA). Special interest was paid to the presence or absence of lympho-epithelial lesions in the mucosa, a characteristic sign of MALT-lymphoma.

Results: Thirteen patients had low-grade malignant NHL (6 cbc, 2 co, 5 ic) and 26 high-grade (21 d, 1 b, 4 und). There were 9 cases of MALT-low grade and 10 cases of MALT-high grade malignant NHL. Staging of the disease according to the Ann Arbor system showed 31 cases with stage IE, 16 with stage II, 2 with stage III and 10 with stage IV. Localized disease (stage I or II) was found in 69% of patients with low-grade malignant, 84% high-grade, 67% MALT-low and 90% 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 45/80 cases where a laparotomy had taken place. When correlating to histology, stage 73 or 74 (locally advanced, penetration of the gastric wall) was found in 50% 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 (NO, N1) was seen in 54% of cases with low-grade, 59% high-grade, 66% MALT-low grade and in 70% of cases with MALT-high grade NHL.

The tumors 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.
ABSTRACTS - Fourth International Conference on Malignant Lymphoma, Lugano

75 PRIMARY GASTRIC LYMPHOMA. CLINICAL AND PROGNOSTIC FEATURES OF 145 CASES. S.S. Cogliatti, K.-L. Hansmann U. Schumacher, F. Eckert, U. Schmid, K. Lennert Department of Pathology, University of Kiel, 2300 Kiel, FRG

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 lymphomas using gastrectomy specimens. The tumors could be distinguished considering morphology and immunohistochemistry in low-grade B-cell lymphomas of the MALT, including immunocytoxa (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 received primary gastrectomy and 65 additionally received adjuvant chemotherapy (n=53), radiotherapy (n=22) or both (n=19). Follow-up ranged from 1 to 159 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 lymphomas of the MALT, including immunocytoxa and the group of high-grade B-cell lymphomas. Patients in stage I showed a considerably better prognosis than those in stage II.


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 lymphomas were accrued between 1970 and 1987. Cases were reviewed by two pathologists (JMM,WEB) 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 showed a large and significant difference in favour of the MALT type of gastric lymphomas 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.
77 MALIGNANT LYMPHOMA OF GASTROINTESTINAL TRACT (GIT): ANALYSIS OF CLINICOPATHOLOGICAL FEATURES AND TREATMENT RESULTS. H. Ben-Shahar, E. Epelbaum, N. Bani, Y. Ben-Arie, T. Cohen, and E. Robinson. Departments of Oncology and Pathology, Ramot Medical Center, 53254 Haifa, Israel.

Between 1969-89, 97 patients (pts) with primary GIT lymphoma (48 stomach (S), 40 small intestine (SI) and 9 large intestine (LI)) were referred to the northern Israeli oncology center. Stage of disease (I/II/III/IV) was 38/12/27/13 and SI/I 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 (19 yrs); 22 with SI and 3 with LI.

TREATMENT RESULTS OF 48 PTS WITH GASTRIC LYMPHOMA

<table>
<thead>
<tr>
<th>TREATMENT MODALITY</th>
<th>NO.</th>
<th>STAGE</th>
<th>RECURRENCE RATE</th>
<th>10 YRS SURVIVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resection ± RT</td>
<td>16</td>
<td>13/5/1</td>
<td>R/19</td>
<td>53%</td>
</tr>
<tr>
<td>irritated -</td>
<td>15/19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resection ± CT</td>
<td>16</td>
<td>0/13/3</td>
<td>1/6</td>
<td>79%</td>
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<tr>
<td>No resection</td>
<td>13</td>
<td>2/3/8</td>
<td>B/10</td>
<td>18%</td>
</tr>
</tbody>
</table>

TREATMENT AND RESULTS IN PTS WITH BOWEL LYMPHOMA

Patients with localized bowel involvement responded well to resection or debulking (total 33 pts) and those who did not (16 pts), because of more extensive disease (10 yrs-71%), than those who did not (16 pts), because of more extensive disease (10 yrs-84%). The survival approach and the resectability rate (50.1% R/I) have not changed over the last 20 years. However, outcome of the 27 pts with bowel lymphomas, especially of children, (CR=73%, 10 yrs=77%), has markedly improved in the last decade due to more intensive and effective chemotherapy, compared to the 22 pts, with the same clinical features, treated from 1969-78 (CR=38%, 10 yrs=30%).

We may conclude from our study: (1) Retention of the primary focus in GIT, particularly in stomach, 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.

78 NON-HODGKIN LYMPHOMA OF WALDEYER'S RING LYMPHOMATOUS TISSUE: PRESENTATION AND PROGNOSIS. J. Rauackers, M. Bogman, B. de Pauw, E. Ruten, S. Sijpk

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 chemotherapy 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.
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79 Primary cerebral malignant non-Hodgkin's lymphomas. Histological and immunomorphological findings on stereotactic brain biopsies.
Karl Schwachheimer et al. Dept. of Neuropathology, Inst. of Pathology, University of Freiburg i.B., FRG

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 immunocytological study reports on 10 cases of malignant non-Hodgkin's lymphoma with primary manifestation in the central nervous system. The series comprised 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 UCHL1) 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. UCHL1-positive lymphocytic cells were interpreted as associated non-neoplastic T-lymphocytes. A small and variable number of MAC 387-reactive histiocytoses were observed. A large number of tumors showed regressive alterations with predominance of UCHL1-positive non-neoplastic lymphocytes. In conclusion, our results show that primary cerebral non-Hodgkin's lymphoma can be predominantly 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.
H C Schouten, W G Sanger, D D Weisenburger, J Anderson, J O Armitage, University of Nebraska Medical Center, Omaha, NE, USA, University Hospital Maastricht, the Netherlands.

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 #7 were correlated with a diffuse histology. Patients with a t(11;14)(q13;q21) had an elevated LDH. Skin infiltration was correlated with abnormalities on 2p. Abnormalities involving breakpoints 8q21-24 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=0.0068, 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.
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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 12%. Median followup of all patients is 73 months. Late relapses developed only in high grade NHL (14% in ALL), as well as 9% in IC, 13% in BL/CC and 40% in AILD). The necessity of long term observation in low grade NHL.


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/m2), teniposide (75 mg/m2) and prednisolone (120 mg/m2) with (CTFP) or without (CTP) THP-adriamycin (pirarubicin) (30 mg/m2). Pirarubicin was chosen because of absence of cardiac toxicity in early phase II trials. 176 pts (81 males and 95 females) are evaluable for response, survival and toxicity. Median age was 74 y (pts <75 y, 51 pts >75-80 y, 24 pts >80 y). Histology according to the Working Formulation: D 29%, E 6%, F 13%, G 22%, H 15%, I 1%, J 1%, not classified 8%. 11% 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% homoblastic and 30% mesostatic adenopathies with 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 35% increased LDH level.

Response to treatment was CR 47%, PR 14%, SD 5%, PD 19% and death 13%. CR rate was 34% for CVP and 60% for CTP (p<0.001). 12% of pts with CVP died during therapy vs 18% with CTP. Median overall survival is 14 months, median PFI survival is not reached with a median follow-up of 8 months. Overall survival is not different in the two treatment arms but CTP pts have better FFP survival (p=0.05) and FPR survival (p=0.05). 27% of the CR pts relapsed, 30% in the CVP arm and 21% in the CTP arm (p=N.S.). Toxicity grade 2 was not the same in the 2 arms. CVP gave 24% neutropenia, 11% infections, 5% thrombocytopenia, 4% mucositis, and 3% cardiac toxicity. CTP gave 38% neutropenia, 16% infections, 9% thrombocytopenia, 3% mucositis, and 1% cardiac toxicity. Results are significantly different only for neutropenia.

High CR rate and longer overall survival and CTP survival are associated with stage I, good PS, <2 extranodal sites, absence of B symptoms, bulky tumor, abdominal adenopathies, bone marrow or skin 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 described in LNH-84 patients has a very good discrimination value in these patients (p=0.002). Better outcome is statistically associated with treatment containing pirarubicin despite a relatively more important toxicity.
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83 ABLATIVE THERAPY WITH AUTOLOGOUS BONE MARROW TRANSPLANTATION AS CONSOLIDATION THERAPY FOR FOLLICULAR LYMPHOMA

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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 rarely 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: 2000Gy 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 45 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. Twelve had residual disease present (<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 six 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 a vascular cause. Two patients died following relapse. Twenty four continue in remission between 2 months and 4+2 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) and platelets (20 x 10^9) 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.

84 TREATMENT OF B-CELL NON-HODGKINS LYMPHOMAS WITH IMMUNOTOXICINS

D. Naredco, 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 asymptomatic 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 molecular of the toxin delivered to the cytoplasm will be lethal for that cell. The issues of single chain, modified toxin 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 ricinFT) which is internalized as efficiently as the whole ricin molecule yet can be specifically targeted since the galactose binding site of the B chain have been neutralized. The anti-CD20(197) mAb was selected because of its specificity for B cells, high affinity, and expression at all stages of normal B cell ontogeny. Anti-B4R is highly toxic, and B lineage restricted. At least 5 logs of oncogenic lymphoma cells are killed after 24 hr culture with 10^9 mls anti-B4R. 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-B20 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 reduced to 50ug/kg/day (MTD=250ug/kg). Nine pts have completed this dose level and have demonstrated 5-20 fold elevation of SGOT/SGPT without other abnormalities. No other significant toxicities have been observed. Even though therapeutic blood levels of anti-B4R were only transiently elevated, no increase in serum levels of IL-6 was observed. Treatment resulted in a total of 11 CR, 2 PRs, and 10 transient or mixed responses were observed. HAMA/HARMA 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 sustained reversible hepatocellular injury as the only major clinical side effect. An attempt to improve efficacy and decrease toxicity, continuous infusion administration of anti-CD20 was evaluated in subhuman primates. In these studies, anti-B4R could be administered continuously for 7 days at total doses between 1000-1500ug/kg without significant hepatotoxicity. A phase I clinical trial of the identical pt population described above was begun administering anti-B4R by constant infusion over 7 days. To date, 18 pts have been treated. Daily doses have been escalated to 40ug/kg x 7d. As observed with bolus infusion, the only significant toxicity thus far observed has been transient elevations (5-10 fold) SGOT/SGPT. Again no other significant side effects were observed. Blood levels are still in the 10^-10M range. At the first 15 pts treated, there has been 1 CR, 3 PR, 4 transient or mixed responses. Six of 15 pts have thus far made HAMAHAMARA. We are presently dose escalating to achieve therapeutic blood levels with tolerable reversible toxicity to define DLT as well as MTD with 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.

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 252-606 mCi 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 1 virus, controlled with Acyclovir, while another had a gram cellitis in a biopsy site which was controlled with antibiotics. Six of seven patients had complete remissions. Patients receiving 1000 rads relapsed 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. R.A. Cowan1, M. Drayson2, H. Sharma3, B. Murty4, S. Owen5, P. Nuttal2, J. Chang6, D. Deskill1, D. Cowan1. 1Dept of Radiotherapy, 2Dept of Haematology, 3Dept of Medical Physics, 4CRC Dept of Medical Oncology, Christie Hospital & Holt Radium Institute, Manchester, 5Dept of Immunology, 6Dept of Medical Biophysics, University of Manchester.

Five patients with advanced diffuse lymphoma lymphocytic (DLL) have been treated with autologous lymphocytes loaded with the β-emitting radionuclide indium 114m (T1/2 = 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 localized 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 pharmacokinetic 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, demonstrating a substantial anti tumour effect in patients with highly resistant disease.