MANTLE CELL Lymphoma (MCL) CONCOMITANT TO NON-HEMATOPOETIC MALIGNANCIES
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The detection of two concomitant malignancies in a single patient is a rare event. Some cases of asymptomatic NHL concomitant to other malignancies have been observed, but no MCL cases were reported in this context. In a series of 24 pts with MCL, 3 cases of common type MCL (CT-MCL) concomitant to other malignancy and one case of CT-MCL as second neoplasm were observed (17%).

Case 1: A 50-year-old male with diagnosis of MCN type I (pancreatic adenocarcinoma metastatic to the liver and parathyroid hyperplasia) and CT-MCL, stage IV-A disease. To date, MCL has never been treated. He is alive with evident lymphoma 49 months of follow-up.

Case 2: A 68-year-old male was submitted to prostatectomy and pelvic lymphadenectomy for an adenocarcinoma of the prostate. CT-MCL, stage IV-A, was diagnosed on pelvic lymph nodes. Treatment with CHOP regimen in progress with PR after 7 months of follow-up.

Case 3: A 73-year-old male with pancreatic adenocarcinoma was submitted to laparotomy and gastric and mesentral CT-MCL, stage IV-A, was diagnosed after resection. Pt has been treated only for pancreatic tumor. He is alive with evident lymphoma after 6 months of F-UMP.

Case 4: A 64-year-old female developed a MCL stage IV-A, 4 years later than a resection of adenocarcinoma of rectum. However, small retroperitoneal adenopathies had been observed and regarded as related to the first neoplasm. Racial tumor relapsed after 27 months, but CR was obtained with CTM. Treatment for MCL with chlorambucil is in progress. Pt is alive with evident disease after 8 months from diagnosis of MCL.

Common features shared by these pts were a concomitant disease, A-stage, good PS WHO 0-1, idiopathic anemia and intermediate international prognostic index. No elevated LDH or β2-microglobulin levels, lymphocytosis, thrombocytopenia nor hypogammaglobulinemia were observed in these cases.

Other than increasing evidence of MCL as 2nd neoplasm, current findings suggest that diagnosis in asymptomatic phase as concomitant malignancy could have a prognostic significance. As previously described, early diagnosis of MCL seems to be associated with an improved survival, higher CR and prolonged TTF and OS. As suggested by case history n° 4, MCL has a prolonged proleptic phase, and earlier diagnosis in pts with splenic anemia, chronic lymphocytosis or lymphadenopathy seems feasible. Therefore, this would allow for a timely and more intensive treatment which could significantly improve outcome.

Expression of P53, BCL-2 and Ki-67 in MANTLE CELL LYMPHOMA
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Mantle Cell Lymphoma (MCL) is an uncommon type of non-Hodgkin lymphoma recently recognized as a distinct entity, with a typical clinical, histological, immunophenotypic and molecular genetics (6;11;14) features. We analyze 5 case of MCL diagnosed based on conventional histology subclassifying as mantle zone or diffuse pattern, the presence of proliferation centers and positivity to CDS in immunofluorescence flow-cytometry and immunocytochemistry.

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Every case is CDS +, C-case, HP-histologic pattern, PC-proliferative centers, * BM-bone marrow, m-months, + - alive
p53 have been study in lymphoid malignancies and mutations, deletions and rearrangements were documented and associated to bad prognosis.
Bcl-2 expression characteristic of follicular lymphomas, have not been sought in nodular MCL, but was identified in lymphomatous polypsis the digestive counterpart of MCL. Our positive case had a short survival, and its significance in MCL will be studied. Ki-67 was not associated with clinical or laboratory features of MCL in our cases.
MANTLE CELL LYMPHOMA (MCL), A STUDY OF CLINICAL FEATURES AND PROGNOSTIC FACTORS.

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We report the results of a retrospective study of 81 histologically confirmed patients with mantle cell lymphoma (MCL) diagnosed during 1980-1994. Clinical characteristics at diagnosis, treatment, and response to treatment were recorded, and the disease progression was given to clarify if the International Prognostic Index (IPI) (Shipp et al, N Engl J Med 1993) is a useful tool for predicting prognosis in MCL. The median age was 65 years (range 24-97) and 72% of the patients were over 60 years old. The ratio of males to females was 3:2. Although most of the patients were in an advanced stage (72% had stage III or IV disease) at the time of diagnosis, performance status was usually good (WHO 0-1 in 86%), and only 30% of the patients had B-symptoms. Bone marrow involvement was found in 38 cases (57%) and overt leukemia in 9 patients (11%). Involvement of gastrointestinal tract was detected in 17 (21%), Waldayer's ring in 16 (19%) and eye in 6 (8%) patients. Lactic acid dehydrogenase (LDH) and lymdneykinase (TK) levels were elevated in 28/71 (41%) and 24/38 (63%) cases, respectively. IPI was determined in 71 cases: 22 (31%), 18 (18%), 19 (27%), and 17 (24%) patients were in groups 1, 2, 3, and 4, respectively. Anthracycline-containing regimens were given as a first-line therapy to 92 patients, and 18 of them (37%) achieved complete remission (CR), but only 3 of 16 patients (19%) who received chlorambucil or a combination of cyclophosphamide, vincristine and prednisone achieved CR. The prognostic features of the groups were however not comparable. All together 65% of 75 patients whose treatment was evaluable achieved CR with first line or second line treatments. The median duration of remission was 28 months and the median time to treatment failure (TTF) was 23 months. Median survival as a disease was 63 months (95% CI: TTF curve: 95%). Age, performance status, stage, B-symptoms, IPI and leukocytosis were significantly associated with CR rate, TTF and survival. In addition, LDH had a significant prognostic value on the survival and together with TK on the CR rate.
MODIFIED ProMACe REGIMEN IN THE TREATMENT OF PATIENTS WITH CENTROBLASTIC LYMPHOMA

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According to some literature data efficacy of Etoposide is dose and treatment duration dependent. In standard ProMACe regimen (Fischer et al. Proc. Amer. Soc. Clin. Oncol. 3. 1984.), Etoposide was administered in dose 120 mg/m² only on day 1. The aim of the study was to analyze efficacy and toxicity of ProMACe regimen with modification of Etoposide and Cyclophosphamide doses and days of administration. All patients were treated with following regimen: Doxorubicin 30 mg/m² day 1., Cyclophosphamide 650 mg/m² days 1-2, Etoposide 120 mg/m² days 1-3, Prednisolone 40 mg/m² days 1-8, and Metotrexate 200 mg/m² day 8. From September 1990. to September 1995. 44 patients (22 males and 22 females), median age 45 (range 20-69) with centroblastic lymphoma stage IIB/IV entered to the study. Centroblastic lymphoma was chosen as a model for this study, because it is a borderline NHL type between high and intermediate grade NHL (high grade according to Kiel classification, intermediate grade according to Working formulation). Total number of administered cycles was 188, median 5 per patient. All patients are evaluable both for activity and toxicity. Overall response was 75% with 50% CR (22 patients) and 25% PR (11 patients). Main observed toxicity was haematological with leukopenia and granulocytopenia grade III/IV in 33/44 patients. Trombocytopenia grade III/IV was less frequent 17/44 patients. There was no haemorrhage and treatment related deaths. During the observation period 4/22 patients in CR, progressed, 4 patients in PR had additional radiotherapy and 2 achieved CR, 7 were treated with secondary chemotherapy regimen, 2 entered in CR and 5 had further progression of disease. In comparison to literature data no difference in response rate between standard and modified ProMACe regimen was observed.

MANTLE CELL LYMPHOMA (MCL). A CLINICAL STUDY OF 17 PATIENTS.

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MCL has recently been recognized as a separate clinical and histologic entity. Although it is classified in the low or intermediate grade non-Hodgkin lymphomas (NHL), its biologic behaviour is more aggressive and the response to treatment is poor. The present study aimed to: (i) the sensitization of hematologists and pathologists to this new entity; (ii) the comparison of the efficacy between anthracycline containing chemotherapy (CT) regimen and other regimens and (iii) the identification of PT for response to treatment. We analyzed 17 MCL pts with a median age of 65 years (38-77) and a male to female ratio of 1.0/1. Three pts had the blastic variant of MCL. Thirteen of 17 pts (76%) had clinical stages III and IV and 9/17 (53%) B-symptoms. Lymphadenopathy was present in 15/17 pts (88%), splenomegaly in 5/17 (29%) and hepatomegaly in 9/17 (53%). Four pts had extranodal disease. All of the stage IV pts (66%) had bone marrow involvement, while 5/17 (29%) had a leukemic picture. Anthracycline containing regimens were administered to 6 pts (CHOP 3, ProMACe-CyTOPHAG 4, M-ECAD C1), who were classified as Group A. Group B included 9 pts who received CT without anthracycline (Cembranovic 2, COP 4, COP 5). Complete remission (CR) was achieved in 6/17 pts (35%). CR rates were 50% (4/8) for group A and 22% (2/9) for group B (one pt surgically treated for small intesstine involvement). CR rates were related to stage (100% for stages I/II but not to age, gender and histologic subtype). Median survival was 28.5 months for the whole pts population, 27 months for group A and 23 months for group B. MCL seems to be a very aggressive form of NHL. CR rates are probably higher when anthracycline containing regimens are used, but a positive effect of this increased CR rate on survival has not been demonstrated.

PILOT STUDY WITH AN INTENSIFIED HIGH-DOSE SEQUENTIAL (HDS) CHEMOTHERAPY PROGRAM IN 9 PATIENTS WITH MANTLE CELL LYMPHOMA.


Conventional chemotherapy offers poor results in patients with mantle cell lymphoma. Feasibility and efficacy of an aggressive approach was thus evaluated using an intensified HDS regimen with G-CSF support in patients at disease onset. Diagnosis of mantle cell lymphoma was made by morphological and immunophenotypic criteria. So far, 9 pts have been enrolled, all with stage IV disease and 6 with tumor-related symptoms. Treatment included an intensive debulking (2 full-dose APO courses along with 2 DHAP courses), followed by sequential administration of VP16 (2 g/s), MTX (8 g/s), doxamustine, CTX (7 g/s) and PBVc host: mitoxantron (60 mg/s)+L-PAM (180 mg/s) were then delivered with PBPC autologous. One patient is currently under treatment, 8 are evaluable. There was no treatment-related death; 3 pts did not undergo autograft due to a) persistence of overt marrow disease; b) patient refusal; c) advanced age (66 y-o.). Overall CR was achieved in 7 patients (77%); the only patient in PR for marrow disease persistence was rescued by autologous transplantation. There was 1 relapse requiring salvage treatment and 1 with only minimal marrow involvement; the remaining pts are in CCR between 1 and 5 years. Molecular analysis using Ig-H gene rearrangement as tumor marker showed persistence of PCR-detectable minimal residual disease in 5 out of 6 autografted pts. Nevertheless, all patients are currently alive at a median follow up of 2.8 years. The results suggest that the high-dose approach in mantle cell lymphoma: i) is feasible; ii) can not guarantee disease eradication; iii) may improve life-expectancies compared to conventionally treated patients.

MANTLE CELL LYMPHOMA (MCL): IMMUNOIOHISTOCHEMICAL AND GENOTYPIC STUDY OF 22 CASES

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The N11/14 (01/32) chromosomal translocation, involving the bcl-1/PRAD-1 locus, is detected in about half of mantle-cell lymphomas (MCL); the same genetic lesion has been sporadically detected in cases of CLL, PLL and multiple myeloma. The histopathologic classification of MCL on histopathologic criteria is difficult. The purpose of the study was to compare a combined morphologic and immunohistochernical analysis with the genotypic profile of 22 cases of MCL in an attempt to assess the value of bcl-1 proto-oncogene's rearrangements in the differential diagnosis of MCL from other non-Hodgkin's lymphomas (NHL).

Materials-Methods: Patient samples obtained both at diagnosis (71) and at relapse (5) included: lymph nodes (17), spleens (2), orbit (1), salivary gland (1) and small intestine (1). Fresh biopsy material was analyzed: (i) morphologically (22/22 cases); (ii) immunohistochemically (22/22 cases), on both crystal and paraffin sections, with a broad spectrum of antibodies specific for lymphoid tissue antigens; (iii) genotypically (16/22 cases) with a semi-nested polymerase chain reaction (RCH), using primers specific for the major translation cluster (MTC) region of the bcl-1 proto-oncogene. PCR products were run on a 1.5% agarose gel, transferred onto nylon membranes and hybridized with a bcl-1 specific oligonucleotide, internal to the primers used for DNA amplification.

Results: (i) Morphology: (a) common variant of MCL: 11/22 cases; (b) blastic variant of MCL: 3/22; (c) areas of common variant involving with areas of blastic variant: 6; (d) Immunophenotype: (a) CD19+, CD20+, CD22+, CD5+, CD10+, SigA+; 19/22; (f) SigA+ (b) CD10+ ; 16/22; (f) CD11c+; 6/22; (c) DNA ploidy (c) Genotypic Analysis 9/18 were PCR-positive for bcl-1 (MTC)/IGH gene rearrangements.

Conclusions: Our results confirm earlier observations that bcl-1 rearrangements are not detectable by the PCR technique in a significant proportion of MCL cases, and, suggest that, in the identification of MCL from other NHLs, a combined morphologic and immunohistochernical approach may be more sensitive, specific and easy to perform than a genotypic analysis.
IDENTIFICATION AND CHARACTERIZATION OF MCL AMONG NON HODGKIN’S LYMPHOMA PREVIOUSLY CLASSIFIED AS LYMPHOCYTIC LYMPHOMAS OF INTERMEDIATE DIFFERENTIATION OR DIFFUSE CENTROCYTIC LYMPHOMAS


All patients (pts) treated at the Institut Gustave Roussy between 1978 and 1995 and diagnosed as lymphocytic lymphomas of intermediate differentiation (LLI) or as diffuse small cleaved lymphomas were reviewed. According to the European Lymphoma Task Force (1), diagnosis of typical mantle cell lymphoma (MCL) was established on typical cytological criteria (small to medium-sized cells with irregular nuclei and rare or absent large cells) and/or on complete and typical characteristic immunophenotype CD 20 + CD 5 + CD 10 - CD 23 -. 77 cases were reviewed and 46 were considered as MCL. For 41 pts, we disposed of tissue biopsy material. For 5 patients, the diagnosis was established on peripheral blood cells and bone marrow aspirates and immunophenotyping was done by flow cytometry. A diagnosis of typical MCL was done in 42 cases (22 typical cytology alone, 11 atypical cytology and typical immunophenotype and 9 of both typical cytology and phenotype). Architecture pattern was diffuse in 35 cases, nodular and diffuse in 4 and nodular in 2 cases. Residual germinal centers were detected in 23 % and network of follicular dendritic recellular matrix was 44 %. Mosaic Index was low: 4 cases were considered as variant MCL because of the presence of large blastic cells (2 cases) or of a predominance of small to medium-sized round cells (2 cases) with CD 3 negative. Large blastic cells were observed in 7 cases. All cases were of B lineage. Complete immunophenotyping was done in 28 cases and among them, 20 were typical and 8 atypical (7 CD 5 + CD 10 - CD 23 -). Bcl-2 protein was highly expressed (30/32). Light chain restriction (9 α, 8 λ and 4 both negative on 24 cases) or heavy chain restriction (7 IgH, 3 IgD + Igλ and 2 both negative) were detected. Cytopathic study was done in 19 cases: typical (11/13)(11/13) was found in 7 cases and one patient had a (11/13)(8)(11/13) + (6) (11/13)(14/14). In conclusion, based on morphological and immunohistopathological characteristics, 77 LLI and diffuse centrocytic lymphomas were considered as MCL. We distinguish a majority of typical forms and only 4 variant types. In this study, histological features were similar to those described in the literature. It was not possible to precise in this way the pronostic value of variant MCL and large cells MCL.


MANTLE CELL LYMPHOMA: CLINICAL FEATURES AND HISTORY OF 46 CASES DIAGNOSED AT THE INSTITUT GUSTAVE ROUSSY


According to the European Lymphoma Task Force (1), 46 cases of Mantle cell lymphoma (MCL) were diagnosed at the Institut Gustave Roussy between 1978 and 1995. Patients' characteristics were: median age 60 years (29-76), Male/Female ratio 3.6, B symptoms in 39 % and PS 0-1 for 45 cases. The disease was stage I-II for 6 pts, stage III for 9 and IV for 31 (67 %). Nodal involvement was found for 44 pts (with 26 of them with more than 2 areas). Waldenyer's ring involvement in 9 cases and spleen abnormalities in 10 pts. Extralocalization included bone marrow (29 pts) with circulating lymphomatous cells in 10 cases, liver (5 pts), stomach (4) and lung (2 pts); initial neuro- meningeal involvement was never detected. Bulky tumor (> 10 cm) was noted in 9 pts. Biologic characteristics were: elevated LDH in 6/78 pts (17 %), albumin < 40 g/L in 13/33 and elevated β2-microglobulin in 11/22 cases. According to the international index, 44 % of pts were classified as low risk, 20 % to intermediate, 31 % intermediate to high and 5 % to high risk.

Treatment was heterogeneous as expected. 2 pts with localized disease received X-Radiotherapy (X-RT). All other pts were treated by chemotherapy which was an anthracycline-based regimen in 31 cases and Chloramphenicol or low dose chemotherapy in 7 pts received X-RT after chemotherapy on initial involved fields or on residual masses. The median follow-up was 36 months. 40 pts evaluated for response to therapy; 25 achieved a complete response (CR) (61 %) and 13 a partial response (32 %) for pts in CR, 17 relapsed with a median of 12 months (2-84). Features of relapse did not significantly differ from initial presentation. Overall survival was 90 and 37 % at 2 and 5 years respectively; disease free survival was 45 and 26 % at 2 and 5 years.

In conclusion, MCL tend to be an advanced disease at initial presentation with multiple nodal involvement and bone marrow localization and predominate in old pts with high frequency of relapse. This malignancy behaves as low grade lymphoma; however, the low disease free survival suggests the need for new therapeutic approaches in the management of MCL.


MANTLE CELL LYMPHOMA (MCL): A DISTINCTIVE CLINICAL-PROGNOSTIC ENTITY AMONG B-CELL LYMPHOMAS

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MCL shows peculiar morphologic, immunophenotypic and genetic features among indolent Non-Hodgkin's Lymphoma (NHL). We reviewed the published clinical features and outcome of 54 pts with MCL (previous morphologic diagnosis: centrocytic NHL, diffuse small cleaved NHL, intermediate cell NHL, and MCL). Initial characteristics were: median age 58 yrs. (30-77); IF 34/200; ECOG-PS 0-1 42 pts (78%); stage I-II 11 pts (20%); III-IV 43 pts (80%); B symptoms in 19 (24%); bone marrow involvement at diagnosis in 37 (68%) and during course in 6; peripheral blood leukemia at onset in 13 (24%), and during course in additional B; splenomegaly in 24 (44%), hepatomegaly in 9 (17%), non-narrow extranodal sites in 19 (35%); high LDH in 13 (24%). The breakdown according to answer to group risk of the Intercontinental Prognostic Index (IP) was as follows: low 20 pts (37%), low-intermediate 17 (32%), high-intermediate 12 (22%), high 9 (17%). Treatment: RT alone in 2 pts (4%), mono-CHT in 11 (20%), CVP in 16 (30%), CHOP or CNDP in 25 (46%). Overall, 43 pts (80%) responded, with 14 CR (26%) and 29 PR (54%). Most pts (37/43) relapsed or progressed. At a median F-U of 40 mos (12-146 mos), 32 have died (29 of NHL). Progression-free survival (PFS) was: 50% at 2 yrs, 27% at 5 yrs, 24% at 10 yrs. Overall survival (OS) was: 67% at 2 yrs, 41% at 5 yrs, 26% at 10 yrs (median 38 mos). The 11 stage I-II pts showed 100% CR rate and better OS (p=0.02) compared to advanced stage pts: 6/11 are alive in 1st CR at 29-138 mos from diagnosis. Among 43 advanced-stage pts, CR rate was 7%; the type of chemotherapy (CVP vs CHOP or CNDP) did not affect OS or PFS. Considering all pts, the low risk category of the IPI system identified pts with favorable OS and PFS (p=0.01). In conclusion, only the small fraction of pts with localized MCL can achieve prolonged survival. Advanced stage pts show a continuous pattern of progression over time typical of other indolent NHL, but survival is substantially shorter and seems unaffected by the type of chemotherapy. For these patients innovative therapeutic approaches are needed.

Intermediate Lymphocytic (Mantle Cell) Lymphoma: A Clinicopathologic Entity?

ABSTRACT:
Purpose: The authors present a clinical, immunologic and pathogenic retrospective study of intermediate lymphocytic lymphoma (ILL) mantle cell lymphoma (MCL), with emphasis on natural history.

Background: ILLMCL is an uncommon non-Hodgkin's malignant lymphoma (NHL) of B-lymphocyte lineage that is not classified in the Working Formulation for NHL. This inability to categorize has clouded clinical therapeutic decisions for ILLMCL.

Materials and Methods: 57 consecutive cases, since 1983 were reviewed. Hematoxylin & eosin stained sections, flow cytometric analysis were performed on fresh tissue. Clinical history, stage and symptoms were documented. Follow-up, survival from diagnosis to treatment were reviewed.

Results/Conclusions: 30% of the cases had mantle zone pattern; 70% had diffuse histologic architecture. The tumor cells were of B lineage (CD19 and CD20) and commonly expressed surface IgM (75%), along with IgD (45%). 80% of ILLMCL cells expressed CDS. The mean age was 63 years. Generalized lymphadenopathy, advanced stage (70%) and bone marrow involvement (57%) typified presentation. The mean survival was 45 months. "B" symptoms were present in 40%; a statistically significant variable associated with shortened survival, independent of stage (p=0.01). Unusual clinical presentations, including CNS and leukemic phase were associated with shortened survival, 7 and 13 months, respectively.

Complete clinical remissions (p<0.05; remission duration 23 months) did not offer statistically superior survival relative to nonresponses (p=0.27). Initiation of chemotherapy within one month of diagnosis was not associated with better survival (p=0.58) relative to patients treated later in the course of their disease. The optimal therapeutic approach remains undefined. The authors maintain that ILLMCL inherently more aggressive than low grade NHLs. Early therapeutic intervention with combination chemotherapy be initiated in patients with "B" symptoms, bone marrow, leukemic or CNS involvement.
PROGNOSTIC FACTORS IN MANTLE CELL LYMPHOMAS (MCL): A CLINICOPATHOLOGIC ANALYSIS OF 47 PATIENTS (PTS) INCLUDED IN THE LMB95 AND GELF06 TRIALS

P Mouton, B Scudiero, P Broc, Y Bazian, C Haber, H Tikhomiroff, F Merceur, M Laporte, B Pignon, Ph Colombat, F Beaulieu, Ph Scat-Coligny, G Gressin, N Brousse, A GEIA study, CHU Lille, France.

Although clinical characteristics of MCL have been identified, their prognostic factors have not been so well-characterized. Histopathologic review of NHL included in the GELF95 (586 pts) and the LNH97 trials (2651 pts) identified 47 pts with MCL (median age 57, MF=4:2). The GELF06 trial evaluated an adriamycin-containing chemotherapy alone or associated with intensive in follicular lymphoma with high tumor burden (15 pts), whereas pts with low tumor burden received no initial therapy (6 pts) or single agent chemotherapy (3 pts). 21 pts included in the LNH97 trial, received an adriamycin and cyclophosphamide containing induction regimen. Histologic subtype was nodular with parasitic germinal centers in 21 pts, nodular and infiltrating in 8, diffuse in 17 (always confirmed by immunohistochemistry), gastrointestinal lymphomatous polyposis in 1, Ann Arbor stage III (6 pts), IV (41), 27 pts had 2 or more extranodal sites (ENS). ENS involved included bone marrow (28 pts), spleen (21), liver (7), upper aerodigestive tract (6), spleen (4), one or more gastrointestinal sites (2), skin (3), lung (3), scrotum (1), kidney (1). Leukemic lymphoma cells were found in 27.7% of pts. Abnormal LDH level, tumor mass > 7 cm, B symptoms, WHO performance status > 1 were found in 41%, 40%, 19%, 4% of pts respectively. 6 pts had platelet count < 100x10^9/L, 6 hemoglobin level < 10 g/dL, and 53% of pts had beta-2-microglobulin > 3 mg/L. Response was observed in 71% of treated pts (complete response in 25%). Responding pts were younger than other pts (p=0.04). 23 of the 39 treated pts relapsed or progressed. Their median event free survival (EFS) was 20 months (95% CI 13.3-26), only adversely influenced by hepatomegaly (p=0.01). With a median follow-up of 31 months, 9 of 47 pts were alive in first response, 6 in second response, 5 with progressive disease, and 27 pts have died. The median overall survival was 50 months (95% CI 30-77), 22 pts were 2 or more ENS (p=0.002), splenomegaly (p=0.01), and the presence of leukemic cells (p=0.02). Histopathologic characteristics did not have a prognostic impact. In a Cox model for survival, only the presence of 2 or more ENS retained an independent prognostic value. The international index for aggressive NHL and the Rai staging system for chronic lymphocytic leukemia had both a prognostic value for survival at the p<0.05 level. The 8 pts with initial therapy progressed 1 to 14 months (median 9) later. Their overall survival was not different from that of treated pts. Initial treatment arm did not influence outcome. The median duration of survival after progression was 10 months and was not influenced by initial response and the previous duration of disease. We conclude that most MCL pts have a disseminated disease, their survival is mainly influenced by the number of ENS. Initial therapy cannot be withheld for a long time.

MANTLE CELL LYMPHOMA: RETROSPECTIVE EVALUATION OF WORKING FORMULATION GROUP E PATIENTS, INCLUDED IN GILS CONTROLLED STUDIES


As first step of a study on Mantle Cell Lymphomas (MCL), we retrospectively evaluated clinical features and outcome of patients classified in group E according to the Working Formulation (WF), since in the past MCL were mainly included in this category. Out of 1614 cases included in GILS controlled trials, 46 patients (2.8%) with E histotype had the following presenting features: 35 males, mean age 56 yrs (19-74), stage III/IV 85%, B symptoms in 48%, bone marrow involvement in 43%, extranodal lesion in 37% (10 liver, 6 GI, 3 Waldayer ring, 1 lung), performance status > 2 in 20%, abnormal LDH in 69%. The distribution performance status = 2 patients, was: 13 cases low (L), 18 low-intermediate (LI), 11 high-patients, was: 13 cases low (L), 18 low-intermediate (LI), 11 high-patients, was: 13 cases low (L), 18 low-intermediate (LI), 11 high-patients, was: 13 cases low (L), 18 low-intermediate (LI), 11 high-patients, was: 13 cases low (L), 18 low-intermediate (LI), 11 high-patients, was: 13 cases low (L), 18 low-intermediate (LI), 11 high-patients, was: 13 cases low (L), 18 low-intermediate (LI), 11 high-patients, was: 13 cases low (L), 18 low-intermediate (LI), 11 high-patients, was: 13 cases low (L), 18 low-intermediate (LI), 11 high-patients, was: 13 cases low (L), 18 low-intermediate (LI), 11 high-patients, was: 13 cases low (L), 18 low-intermediate (LI), 11 high-patients, was: 13 cases low (L), 18 low-intermediate (LI), 11 high-patients, was: 13 cases low (L), 18 low-intermediate (LI), 11 high-patients, was: 13 cases low (L), 18 low-intermediate (LI), 11 high-patients, was: 13 cases low (L), 18 low-intermediate (LI), 11 high-patients, was: 13 cases low (L), 18 low-intermediate (LI), 11 high-patients, was: 13 cases low (L), 18 low-intermediate (LI), 11 high-patients, was: 13 cases low (L), 18 low-intermediate (LI), 11 high-patients, was: 13 cases low (L), 18 low-intermediate (LI), 11 high-patients, was: 13 cases low (L), 18 low-intermediate (LI), 11 high-patients, was: 13 cases low (L), 18 low-intermediate (LI), 11 high-patients, was: 13 cases low (L), 18 low-intermediate (LI), 11 high-patients, was: 13 cases low (L), 18 low-intermediate (LI), 11 high-patients, was: 13 cases low (L), 18 low-intermediate (LI), 11 high-patients, was: 13 cases low (L), 18 low-intermediate (LI), 11 high-patients, was: 13 cases low (L), 18 low-intermediate (LI), 11 high-patients, was: 13 cases low (L), 18 low-intermediate (LI), 11 high-patients, was: 13 cases low (L), 18 low-intermediate (LI), 11 high-patients, was: 13 cases low (L), 18 low-intermediate (LI), 11 high-patients, was: 13 cases low (L), 18 low-intermediate (LI), 11 high-patients, was: 13 cases low (L), 18 low-intermediate (LI), 11 high-patients, was: 13 cases low (L), 18 low-intermediate (LI), 11 high-patients, was: 13 cases low (L), 18 low-intermediate (LI), 11 high-patients, was: 13 cases low (L), 18 low-intermediate (LI), 11 high-patients, was: 13 cases low (L), 18 low-intermediate (LI), 11 high-patients, was: 13 cases low (L), 18 low-intermediate (LI), 11 high-patients, was: 13 cases low (L), 18 low-intermediate (LI), 11 high-patients, was: 13 cases low (L), 18 low-intermediate (LI).
CARBAMAZEPINE AND NON-HODGKIN LYMPHOMA: POSSIBLE CORRELATION IN TWO CASES.

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INTRODUCTION. The use of carbamazepine (CBZ), whose efficacy has been proven both in epilepsy as anticonvulsant and in trigeminal neuralgia, is associated with a variety of adverse effects, ranging from cutaneous reactions to lymphoproliferative disorders mimicking non-Hodgkin lymphomas (NHL). A possible correlation between CBZ long-term treatment and NHL onset has been proposed in several reports, but no definitive conclusions have emerged owing to limited case series.

CASE REPORTS. We found two reports describing two cases of NHL in association with long term CBZ therapy. Case 1: a 65 years old male who had been taking CBZ 200-400 mg daily as to trigeminal neuralgia since 1985, was diagnosed as having stage IVB low-grade NHL (W.F. C) in 1993. He refused stopping CBZ and underwent CHPX, achieving complete remission. Maintenance chemotherapy with CHLB followed. Disease relapsed after 4 months and Mitoxantrone plus VP16 and radiotherapy (RT) were given. He is still alive with progressive disease being treated with RT. Case 2: a 58 years old male who had been taking CBZ 1200 mg daily as to epilepsy since 1982, was diagnosed as having stage II A large cell NHL (Ki-1+) in 1994. He was given CHOPX and had partial remission; subsequently he received mantle field RT (30 Gy). Disease relapsed in subcostal lymph nodes after 1 month. Mitoxantrone plus high dose dasametasone was unsuccessfully administered and the patient died after 20 days.

DISCUSSION AND CONCLUSIONS. The so-called pseudolymphoma and the angioimmunoblastic lymphadenopathy are uncommon but very well recognized adenoplastic adverse reactions to CBZ, whose history is dominated by an immunological reaction affecting the T-zone of the node with expanded pleomorphic infiltration of blasts cells, plasma cells and s.o. The distinction between lymphoma and pseudolymphoma may be impossible on the pure basis of morpho-immunopathological analysis alone. These alterations are to be reviewed at the light of the Working Formulation or the REAL classification.

WHY ARE LYMPHOMA PATIENTS NOT ENTERED ONTO CLINICAL TRIALS. BW Henchock, PC Langan, M Aitken, C Radstone and G Vaughan Hudson, YCIRC Department of Clinical Oncology, Weston Park Hospital, Sheffield and British National Lymphoma Investigation, The Middlesex Hospital, Mortimer Street, London, UK.

Multicentre controlled clinical trials, by standardisation of treatment, offer higher survival rates particularly for less common cancers. However, new oncology patients are entered into clinical trials despite the fact that patients are generally willing to take part in such research. Since 1981, Sheffield Lymphoma Group (SLG) has collaborated fully with the British National Lymphoma Investigation (BNLI) in multicentre trials. We have examined the frequency of enrolment of patients into clinical trials between 1981 and 1992 inclusive.

During this time 2092 patients were diagnosed as having lymphoma in North Trent and 1927 were referred to SLG. Of these, 1813 were accepted as lymphoma after histological review. 822 (45%) patients were enrolled into BNLI studies. 697 (38%) patients were not eligible for ongoing studies, in the majority of cases they were excluded because of age and/or poor performance status. In 133 (7%) patients there was a clinical decision made not to enter patients into a trial and a further 4 patients refused to be randomised. 50 (3%) patients of patients were "missed" although they would have been eligible. In 68 (4%) patients the history was felt to not be lymphoma and in a further 39 (2%) there was disagreement on the type of lymphoma.

In 1982 (a typical year), 114 patients with lymphomas were registered with the SLG. 62 (54%) patients were entered into BNLI trials, of whom 32 (52%) were alive at 12 years follow up. Only 8 of the 32 (15%) not entered into trials were still alive at 12 years, this included 5 cases of Hodgkin's disease. 60% of the patients in the non-trial group were 65 years of age or greater compared with 17% in the trial group.

Patients are often not entered in trials for genuine reasons. Such selection may be an important factor in determining the different outcome between patients enrolled in trials and those not enrolled. Patients not enrolled on clinical trials should still be registered with the trial centre and their clinical details recorded.

GLOBAL HEALTH STATUS AND TREATMENT OF ELDERLY WITH MALIGNANT LYMPHOMAS IN TWO ITALIAN NATIONAL CANCER INSTITUTES

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Multidimensional Geriatric Assessment has been widely used in several diseases, but not in oncological patients (pal). A multidimensional assessment protocol for cancer in the elderly (MACDE) was created and validated at our Institutes to collect information on demographics, social-economic status, depression and disability. Between November '94 and December '95 55 consecutive patients, all aged > 65 years (median 75 years, range 65-88), with malignant lymphomas (46 NHL and 7 HD), were enrolled before chemotherapy and/or radiotherapy. Twenty-seven were males and 28 females. Median PS was 1 (range 0-4).

Mental status was measured by the 30 items Folstein Mini Mental State Evaluation (MMSE), depressive symptoms by the short form (15 items) of the Geriatric Depression Scale (GDS), and physical functioning by the IMS/ADL scale. Both MACDE and IMS/ADL were completed by a trained investigator of Activities of Daily Living. All these parameters were compared with the normal values, which are rarely reached in the general population of hospitalized geriatric patients. Results were as follows:

<table>
<thead>
<tr>
<th>TEST</th>
<th>NORMAL RANGE</th>
<th>65-79 yrs</th>
<th>&gt; 80 yrs</th>
<th>T-TEST (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>24-30</td>
<td>21.9</td>
<td>1.9</td>
<td>0.19</td>
</tr>
<tr>
<td>GDS</td>
<td>&lt; 5</td>
<td>5.2</td>
<td>4.8</td>
<td>0.74</td>
</tr>
<tr>
<td>ADL</td>
<td>5</td>
<td>5.5</td>
<td>5.5</td>
<td>0.91</td>
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<tr>
<td>IADL</td>
<td>6</td>
<td>5.2</td>
<td>0.44</td>
<td></td>
</tr>
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</table>

The mean MMSE showed a relatively high level of cognitive functioning with a statistically significant difference, as in the other parameters, between the group > 80 yrs and the group < 80. Only a minimal degree of ADL and IADL impairment was observed. GDS values showed minimal depression.

In conclusion, all Institutes only elderly and very elderly (80 yrs) selected pts with moderate disability and sufficient level of cognitive function compared with those of the general older population could be entered in chemotherapy and radiotherapy treatment protocols. (This work was supported by grants from the Italian Association for Cancer Research - AIRC, and from the National Research Council - CNR.)

Non-Hodgkin's lymphoma and prior medical conditions

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Conditions that imply some kind of disturbance or intensified activity of the immune system have in several studies been associated with development of non-Hodgkin's lymphoma. However, no general agreement has been reached about a specific pattern of disease to be involved in the genesis of this malignancy. In a large register-based case-control study we evaluated the importance of a variety of different medical conditions with prominent immunologic characteristics belonging to disease categories such as autoimmune diseases, allergic conditions and infections. From the Danish Cancer Registry we selected 7162 cases which were matched as non-Hodgkin's lymphoma cases. Between 1977 and 1991. Four times as many controls matched on sex and age were randomly selected from the Central Population Register. Cases and controls were linked to the Hospital Discharge Register, and all medical diagnoses recorded from 1977 through 1991 were extracted. Preliminary analyses revealed that non-Hodgkin's lymphoma is not generally associated with immunologic conditions but is associated with specific disease entities. There seems to be common features for some conditions strongly correlated with this lymphoproliferative malignancy.
SEmen cryopreservation and posttherapeutic late gonadal dysfunction in non Hodkin’s lymphoma. (Experience at the Institute Gustave-Roussy from 1981 to 1993)

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More than 50% of patients (pts) with non Hodgkin’s lymphoma (NHL) are long-term survivors. We have retrospectively analyzed the indication of semen cryopreservation and late gonadal toxicity for 213 young male pts consecutively treated at the Gustave Roussy Institute from 1980 to 1993 for NHL. The mean age was 30 years (15-42), 43% of them were unmarried, 54% had no children; all received chemotherapy with or without radiotherapy. Histology was of high or intermediate grade in 85% of the cases. Initial characteristics were: 45% stage III-IV, 37% of analyzed LDH above normal values, 33% performance status 2. The 10-years overall survival was 68%.

The percentage of pts benefiting of semen cryopreservation was 6% from 1980 to 1988, 13% from 1988 to 1991 and 47% from 1991 to 1992. During the same periods the proportions of pts with Hodgkin’s disease benefiting of semen cryopreservation were respectively 26%, 43% and 67%. Initial spermograms and cryopreservation of semen were achieved in only 24 pts with NHL. Spermogram characteristics were as follows: 11 normal, 13 abnormal with oligospermia (n=7), asthenospermia (n=7), and teratospermia (n=8). No relation was found between the pretherapeutic status and the semen sample quality.

Cryopreservation was considered for only 22 pts and among them 16 were long term survivor. Two have undergone incesation (successfully in one case) and the remaining 14 are maintaining their cryopreserved semen samples.

Long-term gonadal toxicity was assessed on posttherapeutic spermograms of 9 pts: 3 of them had evidence of return to pretherapeutic status. FSH levels were also assessed for 44 pts: 24 were normal and 24 elevated (in 2 groups the mean interval between the end of therapy and dosage was 45 months); a threshold of 8 ng/ml of cyclophosphamide (cumulated dose), 86% of pts had elevated values (p=10^-6). Cumulated doxorubicin doses were not correlated with FSH elevation. Five pts had had children after treatment.

In conclusion: chemotherapy for NHL seems to induce an intermediate level of gonadal toxicity which is between that of MOPP and ABVD. Complete information about gonadal toxicity of chemotherapy is warranted for young male pts who are to receive chemotherapy and semen cryopreservation should be proposed to this population.

HEPATITIS C VIRUS (HCV) INFECTION IN PATIENTS AFFECTED BY MALIGNANT LYMPHOMA (ML)

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HCV is involved in B lymphocyte expansion during essential mixed cryoglobulinemia type II. Data about prevalence of HCV infection in ML is still incomplete and usually derived from retrospective studies. Moreover, up to now, there are no conclusive data about the role of HCV in the pathogenesis of such disorders. We have prospectively evaluated 176 consecutive patients with HCV acute or chronic infection in the HD series. After an exclusive period of 14 days post infection was made available to the elisa method. Of 119 pts with NHL, all HCV negative, 17 (14.2%) showed HCV infection (confirmed by Ribai and HCV amplification, RNA), whereas only one patient (0.5%) revealed HCV positive in the HD series. Characteristics of HCV pts were: median age 58 years (range 27-79), M/F ratio: 10/6; histology according to Working Formulation (WF): low gradeNALT association 4 pts (23.5%), intermediate-high grade 12 pts (70.5%), comapositiv A1 with nodular sclerosis HD. Stage I: 5 pts, stage II: 3 pts, stage III: 2 pts, stage IV: 8 pts. Primary extranodal involvement was frequent (spleen in 4 cases; liver in 4; stomach in 5; skin in 3; lung in 2; major salvary glands in 2; vaginal, central nervous system and urogenital tract in one case). Primary lymphoma involvement was present only in six cases (5 NHL, 1 HD). The vast majority of HCV pts presented circulating cryoglobulin and clinical evidence of chronic hepatopathy or liver cirrhosis. All patients received conventional cheemo- and radiotherapy according to the disease stage and histology. We observed 8 complete responses, one partial response (WF) and 2B disease; two pts are yet unevaluated and 3 pts (PR) are still receiving treatment. A putative role of HCV in direct infection of malignant B-cell was investigated in four cases of large NHL, by in situhistochemical and immunohistochemical analysis. In none of the cases malignant B-cells stained HCV-positive (De Vita et al., Blood 1995). In conclusion, our series confirms that prevalence of HCV infection (14.2%) in prospectively evaluated pts affected by ML is higher than expected for healthy controls in our region (2%).

FACORS THAT INFLUENCE ACHIEVEMENT OF COMPLETE REMISSION AND ITS DURATION AFTER POLYCHEMOTHERAPY IN FOLLICULAR NON-HODGKIN’S LYMPHOMA


Treatment of follicular non-Hodkin’s lymphoma (NHL) and the achievement of complete remission (CR) remains the subject of much debate. Our co-operative group employs from 1990 CEPO polychemotherapy achieving in 75% (178/234) of patients treated in 1.5 years (range 1.5-2.5) 100% of patients in complete remission with no relapse. Ninety-nine patients with follicular NHL were treated with a median follow-up of 3 years (range 1-6) and 100% of patients were free of disease. Nine patients have completed the 6 projected chemotherapy cycles. Forty-five of these patients and 10 (45%) have achieved a CR and 4 (40%) a partial remission (PR). Univariate analysis showed that stage (p=0.005), absence of neoplastic involvement of the bone marrow (p=0.048), absence of immunosuppression (p=0.004) and sphenoiditis (p=0.02) were the factors relevant to achieving a CR. In contrast, age, sex, performance status, involvement of extraosseous site other than bone marrow and liver by disease, HDL levels, anemia and bulky disease exerted no statistically significant effect. Moreover, there was no statistically significant difference in the number of CR obtained in patients treated as 1st diagnosis and in relapse. The conclusion of remission does not seem to be influenced by the quality of the response. For the 6th CEPO cycle, there was no difference in the disease free survival of CR and PR patients. In contrast, high pretherapy HDL levels (p=0.002) and anemia (p=0.002) were predictors of short remission.

Indolent lymphoma
The chromosomal translocation t(14;18)(q32;q21) is the most frequent karyotypic abnormality characterizing the majority of follicular and some diffuse B-cell non-Hodgkin lymphomas. The focusing of the t(14;18)(q32;q21) chromosomal breakpoints within clustered regions and the high sequence homology among the 3′ portion of each of the six JHI segments, makes the bcl-2/JHI fusion gene suited for the in vitro amplification by PCR. With this purpose we screened 37 unselected cases, which were subdivided into the different groups of the update working formulation, for the presence of mbr bcl-2 rearrangement by PCR. Each of the amplified mbr bcl-2/JHI fusion chromosome junction were hybridized with specific 3′ labeled internal bcl-2 oligonucleotide probe Dig-dUTP. The bcl-2/JHI gene fusion was detected in 5/18 (29.9%) low grade lymphomas (follicular type), 8/18 (44.4%) intermediate grade lymphomas and none of 2 high grade lymphomas. In 10 of the bone marrow (BM) samples assessed, 5 were PCR-bcl-2 positive which correlates with the blood finding, and one of the negative BM samples was positive in blood. Patients without BM infiltration morphologically detected had evidence of BM infiltration when assessed by PCR (54%). Of 24 patients who were PCR negative, 20 (83%) achieved remission with a median progress free interval (PFI) of 11 months. In contrast, of 13 patients who had positive PCR bcl-2/JHI, 4 (30%) died early during treatment, 2 (15%) had a complete remission, and 8 (61.5%) patients had partial remission with a median PFI of only 4 months. All PCR positive patients who remained positive after treatment relapsed. Detection of PCR bcl-2/JHI translocation positive cells was associated with poorer outcome. The low PCR bcl-2/JHI positive incidence in follicular lymphomas in our series could be consequence of the patient's care once the lymphoma had transformed into a diffused type.

Detection of the minimal involvement in bone marrow from non-Hodgkin's Lymphomas and its clinical significance

By using some molecular biological techniques, we studied the clinical significance of the minimal involvement (MI) in bone marrow (BM) from the patients with non-Hodgkin's lymphomas (NHL). Polymerase chain reaction (PCR) and restriction enzyme analysis of PCR products (REA) were applied for the detection and clinical gene rearrangements of IgH and TCRβ for detecting MI in BM. BM samples from 35 patients with NHL were examined by PCR and REA techniques. The total positive rate of IgH (and/or TCRβ) was 59.4% (21/35), the positive rate in IgH group was 51.4% (18/35), and in TCRβ group was 48.5% (17/35). The positive rate of both IgH and TCRβ was 36.5% (12/33), while the positive rate of BM involvement detected by BM smear was only 26.7% (9/35). Both tumour markers of gene rearrangements of IgH and TCRβ were examined at the same time; the positive rate of MI increased by 21-17% compared with that examined separately and was 2.5 times as much as that of the BM smear. It was observed that not only majority of patients with NHL in this group but also 50% of patients in stage I or II had MI in their BM, so it indicated that MI is a systemic disease. It was discussed that the relationship between MI in BM from NHL and pathological subtype, stage, symptoms of B type, response to treatment, mortality and recurrence rate. The results showed that the MI in BM influences the prognosis of NHL and those patients with both positive tumour markers may have worse prognosis.

Combined immunophenotyping, restriction fragment and PCR analysis for detection of bone marrow infiltration in B-cell Non-Hodgkin lymphomas.


In Non-Hodgkin lymphomas the decision whether the bone marrow is infiltrated or not is essential for staging and the subsequent therapeutic proceeding. Therefore in 35 sequential patients with B-cell lymphomas bone marrow histology, the molecular genetic methods of restriction fragment analysis of the IgH gene and PCR analysis to translocation as well as flow cytometric analysis of B and T-fusions genes by PCR analysis in 69% of cases, too, in flow cytometry an imbalance of B- and T-lymphocytes in favour of B-cells was detected in 78% of cases. In contrast to histology, the latter three methods could not definitively exclude contamination with peripheral blood. The molecular genetic methods, although detecting infiltration at the same frequency only matched in 44% since in some cases in which the tumor did not carry the translocation still a rearranged light gene was detectable by Southern blot analysis whereas the PCR was more sensitive in cases with low numbers of translocation positive infiltrating cells. Flow cytometry, on the other hand, was capable to detect a prevalence of B-lymphocytes, indicative of clonal tumor cells, even in cases with as low as 1-5% total bone marrow lymphocytes. In all cases with discordant PCR and flow cytometry results infiltration was confirmed either by histology or by Southern blot analysis. Thus, although flow cytometry by itself cannot prove the malignant nature of the B-cells, it showed the highest sensitivity and might therefore be recommendable as a rapid and easy screening method in the search for bone marrow infiltration in lymphomas.
SERUM CA-125 LEVELS IN THE EVALUATION OF MALIGNANT LYMPHOMAS.

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We evaluated serum CA-125 levels in 127 pts with lymphoma (47 HD and 80 NHL); 81 at diagnosis, 25 in CR and 21 in relapse or progression. Of 81 pts evaluated at diagnosis (26 HD and 55 NHL), 35 (43%) had CA-125 levels above 35 IU/ml, with a range from 40 to 681 IU/mL, (mean value 157; 95% CI 96-219). High CA-125 levels were found at diagnosis in 38% of HD pts and in 45% of NHL pts with no significant difference between early-stage (41%) and advanced-stage disease (46%), and between pts with low-grade (26%) and intermediate/high-grade (53%) NHL. In univariate analysis, high levels of CA-125 were significantly associated with bulky disease (24/36 vs 11/45, p=0.0002), and with mediastinal and/or abdominal nodal involvement vs peripheral adenopathy (29/51 vs 6/30, p=0.001). All pts (77%) with pericardial, pleural or abdominal effusion had high CA-125 levels (mean value 401 IU/mL). Among pts with NHL, those with more extranodal sites tended to have higher values. The 5 pts with primary mediastinal B-cell lymphoma all had high levels at diagnosis (mean 205 IU/mL). Only a partial correlation was observed between CA-125 levels, LDH and β-2 microglobulin levels. Of 27 pts with abnormal CA-125 levels at diagnosis evaluated at the end of treatment, 12 or 63% (18 levels at diagnosis) showed a normalization of CA-125 level and no responders were observed. Ten pts (8 responders and 2 NR) showed a partial decrease in CA-125 level and 4 of them progressed with a rebound of CA-125. Of 42 pts (23 HD and 19 NHL) evaluated from 3 to 120 mos after CR (17 followed from diagnosis, and 25 examined only during follow-up), all showed normal CA-125 levels (7 35%) showed elevated CA-125 levels with a mean value of 74 (95% CI 38-110). In conclusion, CA-125 seems an additional biological marker useful in the staging and restaging of NHL. High levels are correlated with the tumor mass, mediastinal or abdominal involvement, and presence of effusions. Serial CA-125 measurements may be useful, in conjunction with other markers, for monitoring response to treatment and for revealing relapses.

EXPRESSION OF ACTIVATION MARKERS CD23 AND CD69 IN B-CELL NON-HODGKIN'S LYMPHOMA.

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CD23 is a multifunctional protein in the lymphocyte development and has been used as a marker for CLL. CD69 is an early activation marker mainly seen on small T-cells in the germinal centre. The idea was to see if the expression of the antigens was associated with a more aggressive disease and if the activation markers were associated with transformation to high grade histology.

In 53 samples of B-cell non-Hodgkin's lymphomas the B-cell expression of CD23 and CD69 was studied by flow cytometric analysis using double staining against CD20. Both activation markers showed a bimodal distribution with almost all or no cells expressing the antigens. Lymph nodes from non-B- cell malignancies or benign cases analysed with the same double staining showed a Gaussian distribution.

Fifteen of 40 LGM and two of 29 HGM lymphomas expressed CD23 (p=0.0036) and for CD69 31 of 40 LGM and 15 of 28 HGM cases expressed the antigen (p=0.038). The expression of both markers was associated with male gender and lambda light chain. CD69 was also associated with advanced stage and a worse prognosis for high grade lymphomas, but no association to transformation was found.

In conclusion CD23 seemed to be a histological marker as it is used in diagnosis of CLL. CD69 seemed to be associated with a more advanced disease and worse prognosis, especially in high grade malignant disease and further studies on an extended material with a longer follow is planned.

HLA-A, B, C, DR ANTIGENES AND DQA-POLYMORPHISM IN NHL PATIENTS.

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46 patients with NHL have been observed. HLA-phenotype by antigens of A, B, DR locus was studied using serological methods. Alleles of DQA locus were identified for 19 patients by means of PCR + SSP. Healthy donors were used as control group: 865 of them were phenotyped by, antigens of I class,412- by DR locus and 118- by DQA. For NHL patients the frequency of appearance of HLA-B14, HLA-B35 (p < 0.01, p < 0.05 in both cases), HLA-Cw4 (p < 0.001, p < 0.05), HLA-DR2 (p < 0.05, p > 0.05) and HLA-DR5 antigens (p < 0.01, p < 0.05), DQA1’0101 (p < 0.05, p < 0.05) and DQA1’0501 alleles (47.4% vs. 36.4%, p > 0.05) was increased. It is of interest that the distribution of some HLA antigens (B35, Cw4) is the same at NHL and acute leukemia and for some antigens (B14 and DR5) it is alternative. It was shown that HLAB14 and B35 appeared only at LG NHL. As for B40 which was little rarer for NHL patients as compared with the control group it appeared exclusively at HG NHL along with other antigens of CREG-7 (HLA-B7-B27-B40-B22). For patients with DQA1’0501 gastro-intestinal involvement of lymphomas was registered more frequently (p < 0.025). To confirm possible relationship of DQA1’0501 allele and gastro-intestinal involvement at malignant NHL further investigation is necessary.
IMMUNE STATUS OF NHL PATIENTS

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Immunological parameters (mononuclear subpopulations in peripheral blood, NK-activity, THF-α serum level TNF-α and IL-10 production in supernatants of mononuclear 24-hours' cultures) have been studied for 49 NHL patients. For NHL patients at I-II stages the decrease of CD8+ lymphocytes number (7.5 ± 0.8 % vs. 17.2 ± 0.95 %, p < 0.05), reliable increase of spontaneous (1.75 ± 0.15 ng/ml vs. 0.55 ± 0.11 ng/ml, p < 0.05) and induced (3.20 ± 0.18 ng/ml vs. 1.30 ± 0.11 ng/ml, p < 0.05) TNF-α production were observed as compared with the control group. For patients with III-IV stages of NHL there was revealed inversion of CD4+/CD8+ lymphocytes ratio, stimulation, inhibition of NK-activity (52.2 ± 3.0 % vs. 76.0 ± 2.7 %, p < 0.01) and decrease of spontaneous and induced TNF-α production (0.35 ± 0.07 ng/ml vs. 0.05 ± 0.03 ng/ml, p < 0.05 respectively) as well as spontaneous and induced IL-10 production (0.09 ± 0.02 ng/ml vs. 0.23 ± 0.01 ng/ml vs. 0.56 ± 0.06 ng/ml and 1.87 ± 0.13 ng/ml, p < 0.05 and p < 0.02 respectively) as compared with the control. The serum level of TNF-α was essentially increased in the groups with B-symptoms (1.67 ± 0.97 ng/ml vs. 0.37 ± 0.13 ng/ml, p < 0.05). Bone marrow involvement was also accompanied by TNF-α increase in serum (2.00 ± 2.26 ng/ml vs. 0.62 ± 0.20 ng/ml, p < 0.02). For patients with CR and PR, the decrease of TNF-α serum level to 0.45 ± 0.09 ng/ml (p < 0.03) and 0.76 ± 0.11 ng/ml (p < 0.05) respectively was examined. If no remission no reliable decrease of TNF-α level was observed. The repeated increase of TNF-α (0.95 ± 0.15 ng/ml) was revealed at relapse.

PCNA AND P53 EXPRESSION IN NON-HODGKIN LYMPHOMAS (CORRELATION WITH DIAGNOSTIC AND CLINICAL PARAMETERS)


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Aim: Study of the nuclear antigen (PCNA) and P53 expression in Non-Hodgkin Lymphomas of low, intermediate and high risk group types in order to evaluate if these two cell proliferation markers have any prognostic significance for the outcome of the disease Material and Methods: We studied 30 patients, 8 low, 14 intermediate and 17 high risk group according to the Working Formulation classification. 1 Statistical analysis of the correlation of PCNA and P53 expression with histologic subtype, stage, tumor burden, serum LDH and disease survival of the patients was performed with the paired t-test.

Results: 1. In immunohistochemistry the nuclear PCNA expression was positive in 71.7%, of NHL high expression was detected in only 5%, of the total specimen and 15%. The P53 expression, was positive in 92% of the total specimen and 25% of the high expression was detected in 35.8%, of them 25%. 2. In Statistical analysis, we had the following data. There was no significant correlation between total expression of P53 and histologic subtype (P>0.05). On the contrary the PCNA expression correlated significantly with the histologic subtype (P<0.001). P53 expression correlated significantly with the stage of the tumor burden, serum LDH, risk group (P<0.001) but PCNA expression was not significant with the above mentioned parameter (P>0.05) except of serum LDH, where PCNA expression was significantly correlated (P<0.0002). PC3 expression was not significantly correlated with disease survival (P>0.005) but PCNA was not (P<0.0275). Conclusion: PCNA expression in NHL could be a predictive marker of aggressive lymphoma. P53 expression has been observed but it is a positive prognostic factor for the disease free survival of patients.

VALUE OF bcl-2 EVALUATION WITH PCR REACTION IN PATIENTS WITH FOLLICULAR LYMPHOMAS UNDERGOING HIGH-DOSE CHEMOTHERAPY AND PURGED AUTOLOGOUS STROMAL STEM CELLS INFUSION:

First-Line Therapy.


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From 01/92 to 03/94, thirty patients with follicular lymphomas and had prognostic factors were included in a prospective trial. Median age was 43 years (range 27-70). Histology was follicular small cleaved in 9 patients, follicular mixed in 19 patients and follicular large cell in 24 patients. A 12 extra-nodal sites involvement was observed in 5 patients. 26 patients were stage IV at diagnosis. Massive spleenomegaly was observed in 5 patients. Serous effusion in 4 patients, and 2 extramedullary site involvement in 7 patients. For patients, serous effusion in 4 patients, and 2 extramedullary site involvement in 7 patients. For patients, serous effusion in 4 patients, and 2 extramedullary site involvement in 7 patients.

Conclusions: The correlation of P53 expression with histologic subtype, stage, tumor burden, serum LDH and disease survival of the patients was performed with the paired t-test.

Results: 1. In immunohistochemistry the nuclear PCNA expression was positive in 71.7%, of NHL high expression was detected in only 5%, of the total specimen and 15%. The P53 expression, was positive in 92% of the total specimen and 25% of the high expression was detected in 35.8%, of them 25%. 2. In Statistical analysis, we had the following data. There was no significant correlation between total expression of P53 and histologic subtype (P>0.05). On the contrary the PCNA expression correlated significantly with the histologic subtype (P<0.001). P53 expression correlated significantly with the stage of the tumor burden, serum LDH, risk group (P<0.001) but PCNA expression was not significant with the above mentioned parameter (P>0.05) except of serum LDH, where PCNA expression was significantly correlated (P<0.0002). PC3 expression was not significantly correlated with disease survival (P>0.005) but PCNA was not (P<0.0275). Conclusion: PCNA expression in NHL could be a predictive marker of aggressive lymphoma. P53 expression has been observed but it is a positive prognostic factor for the disease free survival of patients.

8. Indolent lymphoma
COMPARTMENTALIZED CLASSIFICATION OF PERIPHERAL BLOOD AND BONE MARROW LEUKOCYTES FROM PATIENTS WITH LOW-GRADE NON-HODGKIN’S LYMPHOMAS (NHL) H.-G. Höffken*, G. Schmidtke (†), M. Ungermann (†), P. Meusers (†), G. Bittinger (†), A. Franke * , G. Vale‡(†), *Division of Hematology and Oncology, University of Magdeburg, †Div. of Hematology, University of Essen and ‡Max-Planck-Institut für Biochemie, Germany.

Three-color immunophenotyping provides information on lympho-mononuclear and granulocyte compartments by the FSC/SSC histogram and as by quadrant evaluation of the FL1/FL2, FL2/FL3 and FL1/FL3 histograms. Typically, the percentage lymphocyte frequency of 12 (3×4) quadrants or, in the case of absolute numbers, 24 (2×12) numbers are extracted. This information is not exhaustive since neither fluorescence intensities, fluorescence ratios and relative fluorescence densities, nor mono- and granulocyte staining results are evaluated. Using the CLASSFIT software all latter parameters as well as the relative and absolute cell counts are determined. This method introduces 222 values into a database per one three-color measurement of 1110 database columns per five measurements. CD45/14/20, CD8/43, cCD19/5, λ/CD19/5 and CD10/23/19 list mode data files of blood and bone marrow samples from healthy individuals (15 women / 15 men) and patients with chronic lymphocytic leukemia (CLL) (n=15), hairy cell leukemia (n=8), centroblast-centrocytic lymphoma (n=10), immunocytopia (IC) (n=15) as well as from patients with non-specific leukocytosis (n=12) were investigated. By iteration of list mode files, the CLASSFIT program is able to extract the information of 5 database columns, thereby classifying reference cell populations as well as abnormal cells from patients with various low-grade non-Hodgkin’s lymphomas. Using this type of analysis, individual patient samples were correctly classified in 84-100% of cases. It became possible to differentiate between CLL and IC in 9 out of 10 additional patients in whom the exact diagnosis was not able to be established by conventional methods.

IS SYSTEMATIC FOLLOW-UP USEFUL FOR MALIGNANT LYMPHOMA IN COMPLETE REMISSION?
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The means, the rhythm, and the duration of follow-up after achievement of complete response (CR) for malignant lymphoma are empirical and their impact on early detection of recurrence and on survival have not been established. Six hundred patients with malignant lymphoma were treated at our institution between 1982 and 1994 and followed-up regularly; 351 of them (58.5%) achieved a CR after more than 3 mo. after the hall of treatment. A total of 54 recurrences occurred among these complete responders, and we analyzed the circumstances of their discovery. Follow-up was performed every 3 mo. for 3 yr; then every 6 mo. for 2 yr; then once a yr and included physical examination, chest x-ray, abdominal ultrasonic or CT depending on the initial localization, biochemical tests with a complete blood count, sedimentation rate, and LDH. Initial histology was low grade NHL (19), intermediate grade NHL (15), high grade NHL (8), or Hodgkin’s disease (12). Recurrence was discovered by the patient himself (24 cases, 44%) or by the private physician (7 cases, 13%) between follow-up examinations. The other recurrences were found at follow-up visits by physical examination (9 cases, 17%), radiology (11 cases, 20%), or biology (3 cases of HD, 5%). Analysis as a function of the time of recurrence revealed that the diagnosis was made during the follow-up examination in 91% (53 cases) of early recurrence less than 1 yr after the end of treatment. In 10/15 (63%) cases between 1 and 3 yr, and in only 4/18 (22%) after 3 yr.

For all 351 patients who achieved a CR, follow-up examinations led to diagnosis of recurrence in 23 cases (6.5%). In conclusion: (a) recurrence is diagnosed by the patient himself in nearly 50% of cases; (b) biological surveillance appears as no utility for NHL, (c) follow-up after 3 yr is not very cost-effective as well as for diagnosis of recurrence. Proper information of patients and their family physician should permit self-imposed and less costly diagnosis of the majority of recurrences without any impact on prognosis.

PLACE OF LOW-DOSE TOTAL BODY IRRADIATION IN THE TREATMENT OF LOCALIZED FOLLICULAR NON-HODGKIN’S LYMPHOMA, RESULTS OF A PILOT STUDY.
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From January 1986 through October 1989, 29 patients with localized low-grade non-Hodgkin’s lymphoma have been treated in first intention by low-dose total body irradiation (TBI) followed by radical involved field radiotherapy (IF RT). Patients received two courses of whole body irradiation of 0.75 Gy in 5 fractions and one week separated by a rest period of two weeks. After one month, patients were reevaluated and an involved field radiation therapy was performed (40 Gy in 20 fractions and 4 weeks in initially pathological lymph nodes areas). Eight patients have been excluded from the study; 4 for histologic review (2 centrocytic, 1 lymphoma 1 centroblastic); 4 patients were stage IV with obvious bone marrow involvement. The remaining 21 patients were 10 male and 11 female, 48.3 years old (mean age: 37-53,5), with clinical stage I (9 pts), I (5 pts) and II (7 pts). All patients received the planned treatment. Results: The tolerance was excellent with a mean nadir granulocytes count of 3.8±1.0 (2.1-8.1), a mean nadir haemoglobin of 13.6±2 g/l (10.6-14.5) and a mean nadir platelet count of 112.10^9 (44-216). Twenty out of 21 patients were in complete clinical remission after the LD TBI and before the IF RT. Fifteen patients remain alive without any evidence of disease with a median follow-up of 62.3 months. Five patients relapsed three of them died. The five-year disease free survival is 60%. As delivered, this program of LD TBI give a very high rate of complete clinical remission in localized follicular non-Hodgkin’s lymphoma with a very good tolerance. It remains to prove that this immediate efficacy has an impact on long-term disease free survival in such patients and to understand how the LD TBI works (relationship with 14:18 translocation and overexpression of Bcl2; direct and/or indirect induction of apoptosis). This will be the two aims of a prospective randomized trial comparing LD TBI followed by IF RT versus IF RT alone.
Low dose total body irradiation versus combination chemotherapy for follicular lymphomas, long term results.


Between April 1980 and January 1985 the EORTC Lymphoma Cooperative Group performed a twin study, one for low and one for intermediate/high grade non-Hodgkin's Lymphoma.

For the low grade, follicular, NHL patients were randomised between low dose total body irradiation, 2.5 Gy in 25 fract 3 times a week and booster irradiation, or combination chemotherapy CVP (cyclophosphamide, hydroxuricin, VCR, prednison) 8 courses and ice-berg radiotherapy. 44 patients were entered in the study.

No difference in freedom from progression (FFP) or survival was observed, with a minimum follow up of 10 years. FFP was resp 95% at 10 year with 3/46 and 3/40 patients free from progression in resp the TBI and the chemotherapy group.

Survival at 10 year was 32% and 37% with 13/46 and 14/40 alive.

In conclusion: Combination chemotherapy with an Adriamycin containing regimen did not prove to result in a higher freedom from progression or overall survival compared to low dose total body irradiation.

COMBINED CHEMO- AND RADIOThERAPY IN THE TREATMENT OF LOCALIZED (STAGE I-II) LOW GRADE NON-HODGKIN Lymphomas: A PROSPECTIVE MULTICENTER STUDY OF 103 PATIENTS.


Between June 1987 and June 1991, 103 patients (51 females & 52 males) with a localized (Stage I-II) non-Hodgkin lymphoma (NHL) were included in this trial by 15 French centers belonging to the GOELAMS (Groupe Ouest-Est d'Etudes des Leucémies et Autres Maladies du Sang). Ninety-five patients were evaluable at time of analysis (31st December 1995). Pre-treatment characteristics presented as follows: age ranged from 27 to 86 years (60.6±14.8) according to the Working Formulation, 25(26%) were type A, 22(23%) type B, 31(32%) type C, 3(3%) type D and 14(15%) type E; immunological classification found 5(53%) B-lymphomas and was uncertain in 44 cases, 69(73%) cases were stage 1 and 35(37%) stage II; extra-nodal involvement was present in 25(26%) cases, stage 1b = 14 and 1b = 11.

All patients were treated with chemotherapy, 6 cycles of CEP (Cyclophosphamide 750 mg/m² + Vinrosine 3 mg/m² + D1 and Prednison 50 mg/m² on D1 to D5) in 12 weeks, followed by involved field radiotherapy (20 Gy in 8 cases, 30 Gy in 8 and 40 Gy in 79). Complete remission (CR) was observed after chemotherapy for 68(79%) patients; 13/15 patients in partial remission after chemotherapy reached CR after irradiation; CR rate at the end of treatment reached 94.9±1.5%. Median follow-up was 48 months (6-100), with an overall survival (OS) reaching 81% and EFS 55% at 60 months. Relapses occurred regularly between the 4th and 57th months after the end of treatment without any plateau in survival curves. These relapses occurred outside irradiated fields in all cases, generally with stage-I-II presentation at time of relapse. Among studied prognostic factors, clinical status (ECOG 1 vs 2), LDH level (normal vs abnormal) and sex (F vs M) have a significant impact on OS (p=0.49, 56 vs 35 and 65 vs 44% at 60 months respectively). The obtention of CR after chemotherapy also influenced favorably EFS (36% in non-responders vs 56% in responders, at 60 months). Age, stage, extra-nodal involvement, the presence of a bulky disease and lymph level did not influence EFS or OS. Our trial seems to demonstrate that even in so-called localized diseases, low grade NHL appeared difficult to cure despite the obtention of a high initial clinical CR rate, and behave like generalized low grade lymphomas with a high OS but no true CR.

RETROSPECTIVE EVALUATION OF THE EFFECT OF RADIOTHERAPY TO THE ABDOMEN IN PATIENTS WITH NON-HODGKIN LYMPHOMA

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The purpose of the study was to evaluate the efficacy of radiotherapy to the abdomen (RT) to patients with non-Hodgkin lymphoma who previously were treated with chemotherapy, either as part of the initial treatment or as relapse therapy. The following parameters were measured: age, histology, LDH, tumor size, stage of disease, performance status, treatment prior to radiotherapy, response to chemotherapy, survival, time to relapse and the relapse pattern (inside/outside the radiation field).

Among 72 patients treated, 58 cases received RT as part of the initial treatment. Forty patients were in CR (69%), 14 in PR (24%), 2 in PD (3%) and 2 (3%) were NC before RT. Following RT additionally 7 patients obtained a CR. Five surviving patients reached a plateau. Only 4 out of 58 patients who received RT as part of the initial treatment had disease relapse, and one of them was inside the radiation field.

Fourteen patients were treated for relapsed disease. None were in CR after chemotherapy. Two were in CR after RT. One and 2 years survival rates were 52% and 32%, respectively.

Toxicity were mainly diarrhea, thrombocytopenia and leukopenia leading to postponement of RT in 25% of the patients. Toxicity lasting more than 3 months were 3 cases of venoocclusive disease in the liver and abdominal pain in 1 patient.

Conclusion: Radiotherapy to the abdomen is a safe treatment with acceptable toxicity. It appears to confer a good local tumor control when used as initial treatment. As relapse treatment it might relieve symptoms.

α2b INTERFERON AND CHEOP REGIMEN IN LOW GRADE NON-HODGKIN LYMPHOMA


Background: Previous clinical experiences have indicated that α interfon (IFN) alone (α) is an useful agent in the treatment of low grade non-Hodgkin's lymphomas (LGLH) for inducing a response; 2) may increase the quality of response to conventional chemotherapy and 3) is particularly useful in the phase of "minimal residual disease" to maintain a response. The objectives of our study are to verify these statements. Methods: From 1991 to 12/95, 112 previously untreated patients with LGLH (class A,B,C according to Working Formulation) were randomized to receive (n=55) or (n=57) a 3 months pretratment period with Interon-A at the dose of 3 MU/m² times a week. Thereafter, non responsive patients received 6 courses of CHEOP (Cyclophosphamide 800 mg/m² day 1, Etoposide 60 mg/m² day 1, Vinristine 1.4 mg/m² day 1 and Prednisone 50 mg/m² days 1,2,3,4,5) repeated every 21 days. Progressive patients were treated with the CHEOP regimen at the same time of progression. After 6 CHEOP courses, responding patients stratified according to previous randomizations arms were randomized to receive or not maintenance with Interon-A. Results: As of 12/95, a total of 101/112 patients are evaluable for the 3 months period preceding the CHEOP phase. Of these, 49 were randomized to receive Interon-A and 52 to the control group. Before the initiation of the CHEOP regimen a response was observed in 134/95 (26.5%) Interon-A treated patients and in 132/95 (1.9%) patients in the control group (P<0.01). Among the 88 patients who have completed the 6 courses of CHEOP, a response was observed in 36/44 patients treated with Interon-A and in 36/44 of the control group. This response, was comparable (P=0.44 (43%) patients pretreated with Interon-A and in 11/44 (25%) of the control group (P=NS). As for the maintenance phase it is too early to have some result.

Conclusions: Our preliminary results confirm that IFN alone is capable of inducing a response in newly diagnosed LGLH. Moreover, patients pretreated with IFN before the initiation of CHEOP have a greater possibility of reaching a CR as compared to the patients of the control group. However, a greater number of patients and a longer follow-up is needed to draw conclusions from the maintenance program.

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REGIMEN LVPP FOR TREATMENT ADVANCED LOW- GRADE NHL.

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Treatment of advanced low-grade NHL remains not enough successful. The problem of majority trials is retrieval of more effective regimen of chemotherapy with low toxicity rate.

Aim. To evaluate the efficacy of LVPP regimen in treatment of 46 pts with advanced Low-grade NHL.

Patients: Median age 48 years (range 20-74), 65% of pts were aged above 50. Female - 13, male - 53. Low - grade malignancy (WF) was confirmed histologically in all cases. St. performance less than 2 in gr. (WHO) was registered in 11 pts. 23 pts were untreated, 23 pts were earlier treated. 5 pts had stage III disease, 41 pts had stage IV (Arm-Arbor). 50% pts had more than one extranodal lesions (hepatic, skin, born, GI-tract, pulmonum). CLL leukemic transformation was in 29 pts (63%). 18% of pts had B-symptoms.

Methods: 2-weeks regimen LVPP (leucovorin - 10 mg per os daily 1-14 days, Vbl - 10 mg in 1.8 days, procarbazin - 100 mg/m² daily 1-14 days, prednisone - 40 mg/m² daily 1-14 days) every 4 weeks. 136 cycles were conducted (at least 3 cycles for every patient).

Results: All 46 pts were evaluable for response. Total response (TR) rate was 72%; 13 pts (28%) achieved complete response (CR), 20 pts (43%) achieved partial response (PR). More effective treatment was in group untreated pts; TR 83% in comparison with earlier treated - 81% (p<0.03). Rather effective treatment was established in cases with bone marrow leukemia transformation (TR - 58%, CR - 24% PR - 34%). Tolerance of LVPP was good; III grade of haematological toxicity was registered in 12% pts (duration 10-14 days).

Conclusions: LVPP - regimen is rather effective and tolerable for treatment advanced Low - grade NHL.

The trial is going.

TREATMENT OF DIFFUSE LOW GRADE AND FOLLICULAR NON-HODGKIN LYMPHOMA (NHL) WITH THE DHAP REGIMEN: A REPORT OF 40 CASES

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40 patients aged 32 to 72 (median: 56) with diffuse low grade NHL were treated with the DHAP regimen between 1987 and 1994 at the Centre Léon Bénard in Lyon. Histologic subtypes according to the Working Formulation consisted in 13 type A, 18 B, 6 G, 3 D. 21 patients (15 stage IV with bone marrow involvement, 2 stage III and 1 stage II) received DHAP as first line treatment, 13 at diagnosis and 8 after a median watch-and-wait period of 28 months. 19 patients had resistant or relapsing disease. Patients received a median of 5 (2-7) courses of DHAP - CASSIP (Cyclophosphamide 100mg/m² daily 1, ARAC/T INOSIDE 200mg/m² daily 2-3, desamethasone 1 mg daily 1-4). No hematological growth factors were used except before stem cell harvesting. Median interval between 2 courses was 25 days. Reduction of 33 to 50% of the doses was decided initially for 4 patients because of advanced age and low performance status.

Early toxicity was essentially gastrointestinal with 9 grade 3 and 1 grade 4 vomiting despite preventive treatment. 17 patients (42%) had grade 1 or grade 2 toxicity and grade 3 with a major functional part due to dehydration. For 1 patient, DHAP was stopped after three courses because of grade 1 renal toxicity and persistent grade 3 vomiting. Hematologic toxicity consisted in 76% grade 3 or 4 neutropenia (median at day 21: 0.42 grade 3 or 4 or thrombocytopenia (nadir at day 11) and 18% febrile neutropenia. The mean number of hospitalization days between two courses was 2.7 days. Severe acute toxicity was grade 2 body weight increase with dyspnea (1 patient), grade 4 vomiting with severe hypotension (1 patient) and two toxic deaths (5%), one due to delayed acute renal failure and one due to infection during neutropenia. Late toxicity was neuro and ototoxicity with 4 cases of polyneuritis (9 grade 1 and 1 grade 2), 1 case of tinnitus and 2 case of hypoaesthesia.

The overall analysis of response to DHAP shows 36 responses (90%), 21 partial responses (PR) (52.5%) and 15 complete responses (CR) (37.5%). Median time to response was 1.5 months. Median follow-up is 50 months. Median progression free survival (PFS) and overall survival (OS) was 23 and 80 months respectively. From the 41 patients treated to first relapse, 12 PR (29%) and 29 CR (68%). 8 of the responder patients were intensified with autologous bone marrow or peripheral blood stem cell support, 4 PR patients reached CR. Median PFS was 21 months and 5 years OS was 85% (95% and 86% respectively in the intensified group). From the 19 patients with resistant or relapsing disease, 15 responded (79%), 9 PR (47%) and 6 CR (32%). Median PFS was 13 months and 5 year survival of 4 patients resistant to DHAP, 3 had primary resistance to CHOP or COP and 1 was treated in fourth line.

We conclude that the DHAP regimen is an efficient treatment for diffuse low grade and follicular NHLs either as first line or salvage therapy. Further randomized studies are needed to compare DHAP with standard regimen.
Bendamustine, a low toxic nitrogen-mustard derivative with high efficacy in pretreated low-grade malignant non-Hodgkin lymphomas

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Bendamustine is a benzimidazole derivative of nitrogen mustard, which has shown high antineoplastic activity in malignant lymphomas including Hodgkin’s disease and non-Hodgkin lymphomas (NHL). To investigate its efficacy in pretreated low-grade NHL, 50 patients (histologic subtypes: CLL n = 11, LP-IC n = 21, plasmacytoma n = 14, CC n = 2, CB-CC n = 3) at least refractory to the alkylating substances cyclophosphamide, chlorambucil, prednimustine or melphalan (8 patients with additional resistance to anthracyclines and 4 patients to fludarabine) received 5-day-cycles (median 3, V:1-9) of daily short infusions of 50-60 mg bendamustine/lm², q 28-35 d. Responses (CR + PR) have been observed in 41/50 patients (82%) with CR in 8, PR in 33, NC in 6 and PD in 3 patients. Median remission duration is 8 months and median time with freedom from progression is 9 months. Toxicity included mainly myelosuppression, low emetogenicity and some weakness, but no alopecia. In conclusion, bendamustine showed high efficacy and low toxicity in refractory low-grade NHL but no cross-resistance to other alkylating substances, anthracyclines or fludarabine. Randomized studies are warranted comparing bendamustine with other alkylators in untreated and pretreated low-grade NHL patients.

OUT PATIENT INFUSIONAL IFOSFAMIDE AND CYTOSINE ARABINOSIDE FOR RELAPSED AND REFRACTORY LYMPHOMA
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17 patients with relapsed or refractory lymphoma were treated with ifosfamide 3g/m², mesna 3g/m² and cytocide arabinoside 800mg/m² as an intravenous infusion over 4 days, every 3 weeks, as an out patient, via a Wallcomed pump. 15 patients were treated as induction therapy prior to high dose chemotherapy with peripheral stem cell support, the other 2 were previously transplanted. 10 man and 7 women, aged 22 to 62 years (median age, 46 yrs) received a total of 62 courses. 4 patients had Hodgkin’s lymphoma, 13 had Non Hodgkin’s lymphoma. At the time of treatment 9 patients had stage IV, 4 stage III, and 4 patients stage II disease. 11 had B symptoms and 3 had marrow involvement. 7 patients had more than 2 previous chemotherapy regimes. 11 patients had received previous radiotherapy.

2 patients died within the first 21 days from progressive lymphoma. Of the 15 evaluable patients 7 (41%) achieved a partial remission (1 to 18 months), 4 (24%) had a complete remission, giving an overall response rate of 65%. WHO grade IV neutropenia was seen in 69% of courses and grade IV thrombocytopenia in 62% of courses. These were more marked in patients with marrow infiltration. 4 patients experienced WHO grade 3 vomiting and 1 patient had grade 1 peripheral neuropathy. 12 patients required admission to hospital for myelosuppression. Out of 62 courses there were only 5 treatment delays and 7 dose reductions. 3 patients with marrow involvement and pancytopenia at presentation were successfully dose incremented.

Despite marked myelosuppression this out patient combination of infusional ifosfamide-ara-C was well tolerated by patients. Given the high response rate we feel this is suitable for induction therapy prior to transplant.

CID: AN ALL-ORAL COMBINATION CHEMOTHERAPY FOR LOW GRADE NHL: CHLORAMBUCIL, IDARUBICIN AND DEXAMETHASONE; A REPORT ON TOXICITY AND EFFICACY
P R A Taylor, G H Jackson, M J Galloway, M Soukop, B Angus, S J Proctor on behalf of the SHLG, Royal Victoria Infirmary, Newcastle upon Tyne, NE1 4LP, UK

We have treated 62 newly-diagnosed patients with LG NHL (Working Formulation) with: Chlorambucil 20 mg/m² for 3 days (divided doses) for 4 weeks
Idarubicin 10 mg/m² for 3 days for 6 weeks
Dexamethasone 4 mg bd for 5 days for 4 weeks
In addition, 5 patients were treated for compassionate reasons and are included in toxicity analysis. All patients had histology review.

Patient Details - 38M : 24F, median age 54 (range 26-72). Three patients were Stage II, 10 Stage III, 49 Stage IV. 26 had "bility" disease.
Review Histology - Follicular NHL 47, lymphocytic 6, centricytic 5; diffuse CC/IB 2; T-cell, 1 lymphoplasmacytoid.
Prognostic Index - 7 worst index; 39 Intermediate; 16 best.
Response - 49 patients received all 8 courses. 5 patients not assessable; CR,GPR was achieved in 41 patients; PR in 8; 9/57 showed no response.

Toxicity (349 courses)
WHO Grade

Nodular

Tumor

Pancytopenia

Anemia

N & V

CNS

Infections

2

47

4

24

1

0

5

12

4

0

0

0

3

2

1

0

0

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0

4

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0

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0

The combination was well tolerated by both physicians and patients. Survival - At 2 years: EFS for patients is 30%; but overall survival at 2 years is 64%. By prognostic groups, overall survival is 84% (best), 66% (intermediate) and 55% (worst).

8. Indolent lymphoma

THERAPY FOR RESISTANT LOW GRADE NON-HODGKIN’S LYMPHOMA WITH MITOXANTRONE AND PREDNISOLINE AS CYTOREDUCTIVE CHEMOTHERAPY AND MAINTENANCE WITH INTERFERON AND DEXAMETHASONE
Societal Aragonese de Hematologia Intemacional. Speaker: Pilar Giralde.

Purpose: To evaluate the efficacy of mitoxantrone (MTX) and prednisolone (PDM) as induction therapy and 22b interferon (IFN), dexamethasone (DMT) as maintenance in resistant low grade non-Hodgkin’s lymphoma (LDLNHL).

Patients and methods: Type of study: prospective and multicentric. Period of evaluation: March 1991-December 1995. Number of cases: 82. Pathological diagnosis: Working Formulation, Inclusion criteria: a) resistance to previous chemotherapy, b) no therapy in the two previous months. Induction therapy: MTX 4 mg/m² days 1-2 + PDM 100 mg/m² days 1-5 every 4 weeks for 6 - 9 months. Maintenance therapy: a) interferon 9 mL/week = DXM 15 mg/m² days 1-4 repeated every 3 weeks. Statistical evaluation: descriptive and Kaplan-Meier method for survival.

Results: Clinical data: mean age 65.6 (range 36-84), M/F ratio 44/38. Histological types: DLT 53 (64.5%), FL 12 (14.6%), LP 7 (10.9%), T-CL 3 (2.4%), MALT 6 (7.3%). 74 cases (90.2%) showed bone marrow involvement. The previous therapies were: alkylating agents 49 (59.5%) polychemotherapy (PDTQ) alone or plus alkylants 29 (33.3%), radiotherapy alone or plus PDTQ 4 (4.8%). Only 69 cases were evaluable for response, (non evaluable: 3 in 11 on induction therapy and 2 out of protocol). Observed responses were: objective response: 45 (53.6% CR,22; PR,22). Maintenance therapy was started in 23 of 44 patients with objective response. PCST was performed in 3 of the remaining 19 cases; in 7 cases maintenance was not applied because progression detected promptly, and 9 patients refused therapy. The median follow-up for maintenance is 18 months (range 5-56). Progression is observed in 3 cases (12%). Side effects related to IFN therapy were observed in 5 (20%). The remaining 17 patients (62%) are asymptomatic and well. The survival probability from the diagnosis was 80% at 5 years and 65% at 8 years. The Survival probability from the start of therapy was 80% at 3 years. The probability of relapse for treated patients was 50% at 3 years.

Conclusions: 1. In spite of the LDNLH “stasis” of disease, we have obtained an objective response in more than 50% of cases. 2. Maintenance therapy seems to be effective to maintain the response with a projected survival time at 3 years of 80%. 3. Side effects, with disruption of therapy, have been observed in 30% of patients.
SELECTION CRITERIA FOR ASCT IN PATIENTS WITH PO-LYCLINICAL OR HIGH MALIG-NANT NON-HODGKIN'S LYMPHOMA (NH-L): RESULTS OF A SINGLE CENTER EXPERIENCE.


Follicular and high grade NHL comprise a group of patients with chemosensitive disease, but relapse is the most important contributor to mortality. Out of a data base of over 1200 patients with NHL treated at our institution from 1980-1994, we have selected 136 patients with high grade NHL and 81 patients with follicular NHL aged >60 years, that match the 47 patients with NHL undergoing ASCT at the same time with either bone marrow or peripheral blood stem cells.

89/16 patients with high grade NHL and 63/81 patients with follicular NHL had high risk disease (stage 2b2b) at diagnosis. The estimated DFS at 5 years is 39 and 54% without and 75% with ASCT. Regression analysis for risk of relapse showed stage >2b and high malignancy as positive and ASCT as negative risk factors. Notably, age, amount of previous therapy, conditioning or radiation therapy nor in vitro purging had an effect on remission duration after ASCT. Patients transplanted in PR or relapse (n=8) all relapsed ≤6 months post transplant.

Patients transplanted in 2nd CR (n=12) had the same DFS as those transplanted in CR 1, but without ASCT only few patients remained in CR. These results remain unchanged, when the time to ASCT is taken into account.

We conclude, that patients with high risk NHL should undergo ASCT in CR 1, all other patients pally scored should have a median of event-free survival of 28 months. For this reason, we decided to prospectively compare standard therapy (mini-CHOP+paclitaxel) with an intensive therapy approach consisting of 4 courses of CHOP, Cy-VP16+G-CSF followed by asparaginase, and Cy-VP16-IFN (10 Gy) with PBSCT re-infusion in pts ≤60 years (group 2). In pts >60 and ≤70 years (group 3). The experimental arm consisted in 12 courses of fludarabine phosphate (25 mg/m² x 5d monthly for 6 months, then 20 mg/m² x 5d every other month). The primary objective is to assess if these new approaches improve time to treatment failure. The study also includes molecular examination of the bcl-2/JH rearrangement on the MBR breakpoint performed by PCR analysis at diagnosis (in lymph node, bone marrow and blood), then in apheresis sample (group 2) and in blood and bone marrow during the follow-up of pts achieving CR (group 2 and 3). Secondary endpoints are to determine the eventual significance of the persistence of this molecular marker in PBSCT and during follow-up on disease-free and overall survival. The trial started in 07/94 and on 31/12/95, 30 different centers in France and Belgium have yet included 168 pts (107 in group 2 and 60 in group 3). Molecular studies at inclusion were performed in 103 pts (61%). Among 73 pts in which material has been already evaluated, 36 (49%) presented a bcl-2/JH PCR-amplifiable breakpoint at diagnosis and are eligible for molecular follow-up. Updated data on clinical inclusion and molecular and cytogentic registration will be presented.

GELF-94: A RANDOMIZED PROSPECTIVE TRIAL OF THERAPEUTIC ALTERNATIVES (INTENSIVE THERAPY WITH PBSCT OR FLUDARABINE) IN POOR PROGNOSIS FOLLICULAR LYMPHOMA (FLI) PATIENTS (PTS) WITH MALIGNANT T CELLS (@GELA STUDY).


Stage III or IV FL pts with at least one of the following adverse prognostic factor (elevated LDH or β2-microglobulin levels, presence of B symptoms or ECOG performance status ≥2, large tumor burden [tumoral mass >7 cm, serious effusion, compressive syndrome, symptomatic splenomegaly]) have been previously showed to have a median of event-free survival of 28 months. For this reason, we decided to prospectively compare standard therapy (mini-CHOP x2+IFN) with an intensive therapy approach consisting of 4 courses of CHOP, Cy-VP16+G-CSF followed by asparaginase, and Cy-VP16-IFN (10 Gy) with PBSCT re-infusion in pts ≤60 years (group 2). In pts >60 and ≤70 years (group 3). The experimental arm consisted in 12 courses of fludarabine phosphate (25 mg/m² x 5d monthly for 6 months, then 20 mg/m² x 5d every other month). The primary objective is to assess if these new approaches improve time to treatment failure. The study also includes molecular examination of the bcl-2/JH rearrangement on the MBR breakpoint performed by PCR analysis at diagnosis (in lymph node, bone marrow and blood), then in apheresis sample (group 2) and in blood and bone marrow during the follow-up of pts achieving CR (group 2 and 3). Secondary endpoints are to determine the eventual significance of the persistence of this molecular marker in PBSCT and during follow-up on disease-free and overall survival. The trial started in 07/94 and on 31/12/95, 30 different centers in France and Belgium have yet included 168 pts (107 in group 2 and 60 in group 3). Molecular studies at inclusion were performed in 103 pts (61%). Among 73 pts in which material has been already evaluated, 36 (49%) presented a bcl-2/JH PCR-amplifiable breakpoint at diagnosis and are eligible for molecular follow-up. Updated data on clinical inclusion and molecular and cytogentic registration will be presented.

FLUDARABINE AS A SINGLE AGENT AND IN COMBINATION WITH MITOXANTRONE AND DEXAMETHASONE IN RELAPSED AND REFRACTORY LOW-GRADE NON-HODGKIN LHMPHOMA


1 Department of Hematology and Oncology, University of Göttingen, Göttingen, Germany, for the German Low-Grade Non-Hodgkin's Lymphoma Study Group

Low-grade non-Hodgkin lymphomas (HL) comprise a heterogeneous group of disorders and are in generally known to be incurable. With the development of the new purine analogs fludarabine, phosphate, 2-deoxycoformycin and 2-chlorodeoxyadenosine new perspectives in the therapy of low-grade NHL were provided. Fludarabine has shown to be effective in the treatment of chronic lymphocytic leukemia (CLL) and low-grade NHL. In consecutive multicenter phase II studies the German Low-Grade NHL Study Group investigated fludarabine as single agent and in combination with mitoxantrone and dexamethasone (FMD) in 76 Patients with relapsed or refractory low-grade NHL. 45 cases were treated with fludarabine alone at a dose of 25 mg/m² on 5 consecutive days and from 38 evaluable patients, at a dose of 25 mg/m² on 5 consecutive days and from 38 evaluable patients, at a dose of 25 mg/m² on 5 consecutive days and from 38 evaluable patients. Based on these results a follow-up study was initiated combining fludarabine (25 mg/m²)/day 1-3 with mitoxantrone (10 mg/m²)/day 1 and dexamethasone (20 mg/day) day 1-5 in an attempt to further improve treatment results. 39 patients entered the study, comprising 14 cases with centrocytic-centroblastic NHL, 10 cases with mantle-cell NHL, 13 patients with lymphoplasmacytoid immunocytoma, 1 patient with a T-cell lymphoma and 1 patient with a monocytoid B-cell lymphoma. Patients treated with FMD achieved a higher rate of remissions with a response rate of 39% with 6 (21%) complete and 5 (18%) partial remissions. Although a higher over-all remission rate with FMD was inducible, there was no difference between the event free survival or time to relapse or death in both treatment groups. The treatment with FMD seems not to provide any advantage with respect to overall survival. A recent update of both studies including a follow up of survival will be presented.
FLURDARABINE TREATMENT IN INDOLENT LYMPHOMA PATIENTS: ANALYSIS OF 108 PATIENTS TREATED IN ONE CENTER.


108 patients (pts) treated with fludarabine (25 mg/m²/d x 5 d every month) between 3/91 and 8/95 were reviewed to analyze parameters associated with good outcome. 28 pts had small lymphocytic lymphoma/immunocytoma (SLL/I), 11 Waldenström disease, 18 mantle cell lymphoma (MCL), 5 marginal zone lymphoma, 43 follicular center lymphoma (FCL), and 3 Sézary syndrome. Fludarabine was given as 1st treatment in 43 pts (14 SL/I, 13 MCL, 11 FCL), 2nd line treatment in 36 pts (21 FCL), and 2nd line in 29 pts. Relapsing pts were treated 28 m after 1st treatment (2-160 m) and 23 of them had reached a CR before fludarabine. At time of treatment, 16 pts had poor performance status, 86 bone marrow and 31 blood involvement, 18 bulky tumor, 32 high LDH level, 44 >3 mg/dl microglobulin (B2-m) level, and 14 35 g/dl serum albumin (SA) level. 48 pts received <6 courses because of disease progression or toxicity, 35 pts 6 courses, and 25 pts 7 to 12 courses to reach maximum response. 48 pts had at least one course with >2 grade leukopenia, 40 pts >2 grade thrombocytopenia. 29 pts had infectious episode(s). 13 pts died from adverse events related to treatment, 3 of them from opportunistic infections. Response to treatment was CR in 29 pts (26%), PR in 37 (35%), and stable or progressive disease in 36 pts (33%). 26 pts had high-dose therapy with stem cell support after response. Median freedom-from-progression (FFP) survival was 10 m, 19 m in SL/I pts, 6 m in MCL pts, and 19 m in FCL pts. Median overall survival (OS) was 50 m, 45 m in SL/I pts, 26 m in MCL pts, and was not reached in FCL pts. In all subtypes except MCL, outcome was better in 1st line treatment. High LDH, >3 mg/dl B2m, and <35 g/dl SA levels were associated with a poorer outcome. Relapsing pts intensified after fludarabine had a significantly longer FFP and OS (p<0.0005 and p<0.05 respectively).

In conclusion, fludarabine had significant antitumor activity in SL/I, FCL, and other indolent lymphomas except MCL. Long-term disease-free survival may be reached only after high-dose therapy with PBSCT in responding pts.

Preliminary results of 2-Chlorodeoxyadenosine in 24 follicular lymphoma relapsing or refractory after previous chemotherapy.

In May 1994, the GELA started a phase II multicenter study to evaluate the response and the tolerance of patients with refractory or relapsing follicular lymphomas to ICORDA (ICORDA). Patients and Methods: Patients (pts) were eligible when they had a follicular lymphoma relapsing after previous chemotherapy in a first line autologous or allogeneic containing regimen. Refractory or relapsing was documented by a lymph node biopsy with concordant review (40) in order to include histological progression. Twenty-eight patients were included between December 1993 and 24 patients were evaluated for response. The median age was 57 years (range 38-72); 11 pts were male and 13 female. Complete response in 14 pts (58%), partial response in 6 pts (25%), stable disease in 3 pts (12%), and disease progression in 3 pts (12%). Two of the 3 pts who progressed had a biopsy before the onset of the ICORDA which confirmed the follicular lymphoma in 19 cases and a lymphoid proliferation in one. A new biopsy could not be performed in two. ICORDA was given as 3 h infusion 0.14 mg/kg every 3 consecutive days. Three treatment cycles were given every month. 17 pts have completed the treatment schedule. Six pts have received only two cycles and one patient one cycle because of progression on therapy. Complete remission was defined by the absence of lymphadenopathy and a normal bone marrow on histological evaluation. Partial and minor remissions were defined respectively as <50 or >25% decreasing measurements of the tumor. Results: Overall response rate was 62.5% (5/84); complete remission 3 cases (12.5%), partial remission 10 cases (41.7%) and minor response in 2 cases (8.2%). After a median observation period of 9.2 months (1 to 16 months), response persisted in 13 patients (61, 13, 11, 11, and 3 months respectively. Hematologic toxicity was moderate (see below) as like as the toxicity: one myeloproliferative syndrome, a reactivation of cytomegalovirus infection and two cases of either fever. Liver or renal toxicity was not observed.

VHO 3 and VHO 4 hematological toxicity:

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<th>Grade</th>
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Conclusions: ICORDA is effective in follicular lymphoma relapsing or progressing after chemotherapy containing polychemotherapy. Treatment was well tolerated. This study is still ongoing.

Efficacy of long-term adjuvant bacillus Calmette-Guerin therapy in non-Hodgkin's malignant lymphomas. Results of a randomized trial.


Purpose: Given the significant results of a previous randomized trial in favor of adjuvant bacillus Calmette-Guerin (BCG) therapy in certain forms of non-Hodgkin's malignant lymphomas (NHML) achieving complete remission following chemoradiotherapy, we conducted a randomized trial to compare 1 versus 3 years of this treatment.

Patients and Methods: Between January 1978 and May 1993, patients younger than 65, with stage I or II, mainly high grade NHLM, still in complete remission one year after treatment associating chemotherapy (CHOP or CHOP-derived), radiotherapy and adjuvant BCG were included in this trial. They were randomized, to stop or to continue BCG scarifications up to 3 years.

Results: One hundred forty eight patients were randomized. After pathological and clinical review, 133 patients were available for this analysis including 64 in the 1-year group and 69 in the 3-year group. Toxicity was mild, provoking the cessation of scarifications in only 9 patients. A stepwise Cox's analysis showed that BCG significantly influenced time to relapse (TR) for the whole population (p=0.033). Analysis restricted to the high grade lymphomas, showed significant for TR (p=0.036) and approached significance for overall survival (p=0.067).

Conclusions: Following previous results obtained in our institution and others, BCG appears as a worthwhile adjuvant treatment, well tolerated which may improve time to relapse and overall survival of patients with high grade NHLM. It should be used in further trials to determine its best means of administration.
MONOCLONAL ANTIBODY THERAPY WITH “CAMPATH-1H” IN RELAPSED NON-HODGKIN’S LYMPHOMAS (NHL): A PHASE I/II STUDY IN GERMANY


18 patients (pts.) with B-cell NHL were treated with the humanized monoclonal antibody, CAMPATH-1H (CP-1H). 2 pts. received an escalating dose of CP-1H (up to 240 mg) once weekly and 16 pts. a fixed dose of 30 mg three times weekly. 12 pts. had a low grade NHL, 4 suffered from a mantle cell lymphoma and 2 from a high grade NHL. All pts. had received chemotherapy before and had either relapsed or were refractory to conventional therapy. 6 pts. were withdrawn from the study because of death (2), serious adverse events (2) and progressive disease (2). Out of 12 evaluable pts., 7 achieved a partial remission, 2 showed no change of disease and 3 had progressive disease. All pts. with response to CP-1H had a low grade NHL and achieved a tumor cell reduction in the blood and bone marrow. Common acute adverse events included fever, chills, rigor, urticaria, dyspnea/bronchospasm, nausea, and thrombocytopenia. 14 pts. suffered from bacterial or viral infections; some had recurrent infections (6). The most frequent infections were confined to the respiratory tract (7). We observed bacteremia with Staph. aureus (3) and E. coli (1) as well as Herpes infections (6). 1 pt. died of progressive multiple leukoencephalopathy 3 months after CP-1H therapy was ended. With respect to the relapsed or refractory disease status, CP-1H therapy seems to be beneficial for pts. with low grade NHL, especially with circulating tumor cells and bone marrow infiltration. Acute side effects were tolerable, except for 2 pts. with bronchospasm. Pts. with mantle cell and high grade NHL did not respond to CP-1H therapy.

*CAMPATH-1H is a trademark owned by the Wellcome group of companies.