Poster Session III

ABSTRACTS - Third International Conference on Malignant Lymphoma, Lugano

P 1 CLINICOPATHOLOGIC CORRELATIONS AND PROGNOSTIC RELEVANCE OF BONE MARROW AND PERIPHERAL BLOOD INVOLVEMENT IN ADULT NON-HODGKIN'S LYMPHOMAS. A MULTIVARIATE ANALYSIS OF 172 CASES.

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In 172 patients affected by non-Hodgkin's lymphoma and classified according to the Working Formulation (WF) we correlated the presence and the degree of bone marrow (BM) and peripheral blood involvement with 33 variables including the main clinical and pathological parameters of the disease. The overall incidence of BM involvement (BM+) at diagnosis was 39% (67/172). The frequencies of BM+ in the three major prognostic groups of the WF were: 59% (36/61) for low grade (LGML), 30% (20/67) for intermediate grade (IGML), and 25% (11/44) for high grade malignant lymphomas (HGML). The multivariate analysis of all cases showed that the features most significantly correlated with the presence of BM+ are, in order of decreasing importance: 1) the grade of histological malignancy, with BM+ more frequent in LGML; 2) the degree of splenomegaly; 3) high values of LDH; 4) absence of extranodal disease. The application of the analysis only to case BM+ showed that the extent of BM+ was correlated with: 1) non-focal pattern of BM disease, 2) presence of blood involvement at diagnosis, 3) degree of BM fibrosis, 4) diffuse lymph node histology.

A peripheral blood involvement was present at diagnosis in 22/172 or 13% (25% of LGML, 6% of IGML, 7% of HGML), and correlated significantly with BM+, low grade histology, hepatosplenomegaly and bulky disease. A further 27 cases developed a leukemic phase during the course of the disease, after a median time from diagnosis of 12 mos.

Regarding prognosis: 1) the presence of BM+ per se does not affect survival (while lymph node histology and tumour bulk are the most important prognostic factors); 2) peripheral blood involvement, both at diagnosis and during the course of the disease, carries a worse prognosis in the IGML and HGML, while in LGML only the late leukemic spread significantly affects survival, heralding a rapid change to a more aggressive disease. In fact, a shift to a less differentiated histology was documented in all LGML who had repeat lymph node biopsy at the time of secondary leukemic conversion.

P 2 MULTIVARIATE ANALYSIS OF RESPONSE AND SURVIVAL IN NON-HODGKIN'S LYMPHOMAS (NHL). Study on omogeneous series treated with the CHOP combination plus irradiation.

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Multivariate analysis of factors affecting response and survival was conducted on 90 patients with NHL all treated by 6-cycle CHOP combination plus 40 Gy radiotherapy to nodal and extranodal major initial tumor deposits, as consolidation in complete responders. A logistic regression equation has been obtained for response prediction. Two pertinent variables associated with poor response (i.e. presence of systemic symptoms, and increased LDH values) can be used to predict the probability of complete remission (CR). The regression equation was applied to calculate the probability of CR for each patient in the study; these predictions have been matched with the observed responses. Similarity between observed and predicted response rates suggests that this model reliably fits for the given set of data. Using the Cox's stepwise regression, serum LDH value, symptom status and bulkiness were found to be the most important factors for predicting survival, in this order. The proportional hazard estimate for the mean covariate vector has been converted to the survival probability for different covariate patterns. Survival curves have been plotted, indicating that the model was able to distinguish prognostic levels based on all possible combinations of values of the three variables in the regression equation.
Careful assessment of such a small number of pretreatment variables can allow the identification of groups of patients for whom the CHOP + radiotherapy combination represents a non-adequate treatment. These patients should consequently be considered as candidates for new treatment approaches since the time of diagnosis.

P 3 PROGNOSTIC MODEL FOR DIFFUSE HISTIOCYTIC LYMPHOMA (DHL). Koziner B, Danieu L, Wong G, Chapman D, Clarkson B. Memorial Sloan-Kettering Cancer Center, New York, NY, USA.

One hundred and fifty-two consecutive patients with Ann Arbor stage II-IV DHL, who completed treatment between 1973 and 1986 in one of four different Memorial Hospital combination chemotherapy protocols, were reviewed to verify the validity of a predictive model for treatment response and survival in advanced DHL previously proposed by Danieu et al (Cancer Res 1986; 46:5372-5379). Factors studied included: age, sex, Ann Arbor stage, prior therapy, B symptoms, serum lactic dehydrogenase (LDH), sites of initial disease and tumor bulk. LDH was grouped accordingly: low < 225 U/L, medium 225-500 U/L, high >500 U/L. Patients were assigned an overall level of site involvement (LSI) fromthe following mutually exclusive groups: I) peripheral lymph node (PLN) (including ± Waldeyer ring involvement, ± spleen); II) extranodal disease (En) ± PLN: III) retroperitoneal lymph node (RLN) ± PLN; IV) bulky mediastinal disease (MED) ± any other disease; V) En with RLN ± PLN. Ann Arbor Staging failed to dissect patient groups differing significantly in prognosis. As in Danieu et al, serum LDH, LSI and age were the important factors for predicting response and survival after multivariate logistic regression and Cox regression. Also, the four tentative stages proposed by Danieu et al were verified and the survival at 48 months updated: Stage I = low LDH, any LSI (78% alive); stage II = medium LDH, PLN and/or En (43% alive); stage III = high LDH, PLN and/or En or medium LDH, RLN ± PLN ± En and/or MED (25% alive), stage IV = high LDH, RLN ± PLN ± En and/or MED (13% alive). Furthermore, the updated study suggests that it is feasible to collapse stage III and stage IV to yield a 23% survival proportion at 48 months. Identification of prognostic stages based on LDH level and LSI will allow more accurate comparison of clinical trials for DHL patients.

P 4 IDENTIFICATION OF MAJOR PROGNOSTIC SUBGROUPS OF PATIENTS WITH LARGE CELL LYMPHOMA TREATED WITH m-BACOD OR M-BACOD. M. Shipp, M. Klatt, B. Yeap, D. Harrington, M. Jochelson, D. Rosenthal, A. Skarin, G. Canellos. Dana-Farber Cancer Institute and Brigham and Women's Hospital, Boston, Massachusetts, USA.

We recently evaluated 121 diffuse large cell lymphoma (DLCL) patients treated with M- or m-BACOD between 1976 and 1983 for pre-treatment characteristics predictive for response and survival. In univariate analysis, several characteristics associated with decreased response rate and shortened survival were identified. Characteristics that retained significance in a multivariate analysis of survival (MVAS) were used to construct a model to predict an individual patient's risk for relapse and shortened survival.

Since our original analysis, an additional 48 DLCL patients treated with m-BACOD have been off therapy for at least two years. We have, therefore, re-evaluated an expanded group of 169 DLCL patients for predictive pre-treatment characteristics. In a univariate analysis of the expanded group, each clinical characteristic previously identified as being associated with response and survival (performance status (PS), B symptoms, stage, splenic involvement, pleural effusion, number of extranodal sites (# ENS), mass size, and LDH) is significant as is one new feature, bone marrow involvement. In MVAS of the expanded group, the two features of major significance in the original study, PS and mass size, retain significance. However, # ENS, a feature of borderline significance in the original study, loses significance and two additional features, stage and LDH, retain significance. We used the four features which retained significance in the MVAS of the expanded group (PS, mass size, stage and LDH) to construct a new model containing 16 categories of patients at increasing risk for relapse and shortened survival. These categories can be divided into three broad groups with respective predicted five-year survivals of 95%, 72%, and 42%. The identification of the patient groups with respective five-year survival rates of 95%, 72%, and 42% has important implications both from the design of randomized therapeutic trials and the determination of optimal therapy for individual patients.

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P 5 PROGNOSTIC VARIABLES AFTER "F-MACHOP" IN ADVANCED AGGRESSIVE LYMPHOMAS

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From 1.80 to 12.84 eighty-one adult patients (pts) with advanced stages (II-III-IV) of diffuse mixed, large cell or undifferentiated lymphoma were treated with six courses of an innovative chemotherapy program combining prednisone with six cell cycle active drugs (vincristine, cyclophosphamide, 5-fluorouracil, high-dose cytosine arabinoside, adriamycin, intermediate-dose methotrexate) administered sequentially over three days to maximize tumor cytoreduction. Courses were repeated every 3-4 weeks and no further treatment was given to pts in complete remission (CR) after 6 cycles. Despite a CR rate of 78% and a 77% actuarial disease-free survival (DFS) a significant fraction of these pts either relapse or are refractory to this effective regimen. In order to identify those pts requiring new therapeutic approaches, prognostic variables for CR rate and DFS were determined by uni- and multi-variate analysis. We examined the following variables: age, sex, histologic subtypes (Working Formulation), stage, B-symptoms, sites of extranodal involvement, no. of extranodal sites, tumor bulk (diameter of largest tumor mass), sites of bulky disease (>7 cm), response after three courses (complete vs. partial). In uni-variate analysis the only factor which adversely affected both the CR rate and DFS was the presence of bulky disease. Also B-symptoms adversely affected the CR rate, but they did not affect the DFS. Actuarial DFS was also significantly better for pts in CR after 3 courses as opposed to late CRs. In multivariate analysis both bulky disease and B-symptoms proved to be independent prognostic factors on CR rate, while the only independent prognostic factor on DFS was the no. of courses to CR. These results indicate that pts failing CR after 3 courses of F-MACHOP should be considered for alternative treatment approaches.

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P 6 Long Term Follow-Up of Patients with Unfavorable Histology Lymphoma Treated with High Dose Adriamycin Combination Chemotherapy.

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Because of the controversy whether aggressive, intensive chemotherapy in patients with unfavorable histology lymphoma produces better results, we are reporting a follow-up of patients treated with our high dose combination: Adriamycin 120 mg/M^2 IV on Day I, Vincristine 2 mg IV on Day 1 and Prednisone 50 mg PO Days 1-5 repeated at 21 day intervals for 3 courses followed by 3 courses of Cyclophosphamide 800 mg/M^2 IV Day 1 and Cytosine Arabinoside 3000 mg/M^2 IV over 2 hours on Days 1 and 8 administered at 21 day intervals or when bone marrow recovery was evident. No maintenance therapy was used. The 25 patients with large cell lymphoma included 11 women and 14 men with a median age of 52 years (20-65). The Ann Arbor stages were IIA 6, IIIA 5, IVA 9, and IVB 5. Two failed to enter remission. Three died during induction, one due to toxicity, one due to her second myocardial infarction and one due to hepatitis. There were two CNS relapses, one at 8 months treated successfully with radiotherapy and intrathecal Methotrexate and one at 21 months leading to the death of the patient. There was one systemic relapse in a patient with bone involvement. One patient died in complete remission at 21 months of adenocarcinoma and one at 69 months of myocardial infarction. The other 16 patients show no evidence of disease at 94, 82, 73, 68, 68, 61, 61, 56, 46, 41, 41, 37, 32, and 28 months. In summary, there was progression of disease in 8%, death due to toxicity in 4%, systemic relapse in 4%, death due to CNS relapse 4% (incidence 8%), and to non-related causes 16% (2 during induction and 2 later). The median survival of the other patients is 61 months. It is of interest that one patient with diffuse mixed lymphoma relapsed as poorly diffentiated lymphocytic lymphoma (PDLL), indicating a capability to eradicate large but not small cleaved cells. One patient with PDDL has also relapsed. Eight other patients with B cell disease remain in remission. We had previously concluded that this protocol should not be used for T-cell lymphoblastic lymphoma, since, although there was a complete remission in all patients, this was short-lived in all but one. The results continue to show that agressive chemotherapy has produced a better relapse free survival in patients with large cell lymphoma than conventional doses, but the number of patients with other B-cell disorders is too small to be conclusive.

P 7 MALIGNANT LYMPHOMAS IN ANTI-HIV-POSITIVE PATIENTS.

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Between 1983 and 1986 eight anti-HIV-positive patient treated at our institution developed a malignant lymphoma. Seven patients presented with non-Hodgkin's-lymphoma (NHL) and one with Hodgkin's disease (HD). The median age at time of diagnosis was 38 years (22-73). All were male patients, 4 homosexuals, 3 intravenous drug abusers (2 of them also reported homosexual relations), and one was infected by a blood transfusion. Five patients had high malignant (4 IWF I, 1 IWF J) and 2 intermediate (IWF G) non-Hodgkin's-lymphoma. At time of diagnosis all NHL patients presented stage IV disease. In 2 patients only extranodal disease was found (one with small bowel lymphoma, one with involvement of bone marrow, central nervous system and skin), six had both nodal and extranodal involvement. A low T4/T8 ratio (<0,8) was tested and found in 5 patients.
Six patients with NHL received m-BACOD chemotherapy, one died prior to therapy. Two died after an initial response during treatment, 3 and 6 months after diagnosis. One patient died free of disease 16 months after diagnosis of a heroin overdose. Another patient stopped chemotherapy after 3 m-BACOD cycles, but is still in remission 11 months after diagnosis. The 5th patient is in complete remission 7 months after diagnosis and continues chemotherapy and the 6th is in the first induction phase. Radiotherapy was given to the patient with HD (stage II A, histologically mixed cell type) and the patient is still in complete remission 9 months after onset of therapy. Since this patient did not have a prior opportunistic infection, he cannot be classified as AIDS patient (CDC definition IV D).
With an incidence of 12% (7/60), NHL is frequent in our AIDS patient population. The incidence of malignant lymphoma in our anti-HIV-positive patient population is 1,6% (8/490). We estimate, based on the male incidence for NHL (10/100'000 per year) and malignant lymphoma (15/100'000) in Switzerland, that the incidence for NHL in patients with AIDS (follow up 3 years) is more than 300 fold higher than in the general population. The incidence for malignant lymphoma in anti-HIV-positive patients appears 40 fold higher. High malignancy, advanced stage of the disease at time of diagnosis and extranodal localisation are characteristic in patients with the acquired immuno-deficiency syndrome. Nevertheless complete remissions and prolonged lymphoma-free survival are possible in individual cases.

P 8 NON-HODGKIN'S LYMPHOMA (NHL) IN THE ELDERLY: PROSPECTIVE STUDIES WITH SPECIFICALLY DEVISED CHEMOTHERAPY REGIMENS IN 66 PATIENTS (PTS).

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Elderly patients (70 years or older) with Non-Hodgkin's lymphoma are usually not considered for aggressive chemotherapy regimens because at high risk for serious complications.
Between August 1979 and September 1984, 66 patients aged 70 or older (median, 75 years) with NHL entered two consecutive trials, the former with single agent teniposide 100 mg/m^2 i.v. weekly (41 pts), the latter with etoposide and prednimustine (E+P), both 100 mg/m^2 p.o. for 5 days every 21 days (25 pts). Forty-five patients were previously untreated, 21 were previously treated. Forty-seven patients were intermediate and high-grade groups according to the Working Formulation; 19 patients were of the low-grade but with symptomatic disease; 57 patients were stages III and IV, 9 patients were stages I and II. The median performance status was 70 (range 30-100). Response and survival are reported in the table:

No. of evaluable pts		Response		3 - Year Survival		
		CR	PR	Overall	Disease-free	CRs
No. of total pts	66	38%	15%	21%	12%	40%
No. of pts on teniposide trial	41	32%	20%			
No. of pts on E+P trial	25	48%	8%			
No. of previously untreated pts	45	42%	16%	24%	16%	58%
No. of pts on teniposide trial	27	44%	15%			
No. of pts on E+P trial	18	39%	17%			

There are no significant differences in response and survival as far as stage, histology, prior treatment and performance status are concerned. The overall toxicity was mild. Severe toxicity (grade III and IV according to WHO criteria) was observed only in 16/498 courses (3.2%), with one toxic death (grade IV leucopenia).
We experienced the usefulness of a properly oriented clinical approach to elderly patients with NHL. We suggest that also a conservative approach provide results at least superimposable to aggressive therapy with less toxicity in a large fraction of elderly patients with NHL. Randomized clinical studies are necessary in this setting.

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P 9 NON-HODGKIN'S MALIGNANT LYMPHOMAS (NHL) AFTER 80 YEARS. 70 CASES.

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NHL are often observed in old patients who are excluded from the usual clinical trials. In these patients, many difficulties arise. Analyses of presentation, course and treatment of such patients are scarce. This is why two centers (one in a comprehensive cancer center, the other in a university hospital) put together two series including 1300 patients (pts) with NHL observed during the past 15 years. Among them, 70 (5,4%) were diagnosed after 80 years, well balanced in the two series. There were 44 females and 26 males, 4 over 90 y, 12 between 85 and 90, the 54 others between 80 and 85 y. Performance status (Karnofsky) was $\geq$ 80% in 52 pts, 70% in 8 and $\leq$ 60% in 10. 15 pts had severe associated visceral deficiencies, mainly cardiovascular. 40 pts had low grade NHL (following Kiel classification : 7 lymphocytic, 8 lymphoplasmacytic, 25 follicular) and 30 high grade NHL (7 lymphoblastic, 6 immunoblastic, 17 unclassifiable). Clinical staging was often incomplete (25 pts only had abdominal CT scan and 11 lymphography). The majority of them were classified as stage I (24) or II (18), the other as stage III (16) or IV (12). In 43 pts, NHL involved mainly lymph nodes, in 5 skin, in 4 facial structures, in 4 spleen, in 3 Waldeyer ring, in 3 GI tract and in 8 different other tissues. Treatment varied with grade of NHL, tumoral extension and performance status. 47 pts were given chemotherapy (12 with one or two drugs, including corticosteroids, 26 with CVP (cyclophosphamide, vincristine, prednisone), 9 with heavier chemotherapy including an anthracycline). 37 pts were given radiotherapy (27 radical, 10 partial). 6 pts had surgery. Overall treatment was considered as ideal, as in younger pts, in 12 pts, good in 34 pts, limited in 24 pts. Toxicity was minimal (grade 1 or 2) in 62 pts, treatment-limiting in 2 pts and lethal in 6 pts; among these 6 latter pts, 4 had been treated with heavy radiotherapy or chemotherapy. 37 pts were put in complete remission (CR), 21 in partial remission, 5 experienced a stabilization and 7 were a failure. For all pts median survival (MS) was 18 mo. By contrast with younger pts, malignancy grade has not a significant influence. The only significant parameter is CR (MS of 23 mo in case of CR, of 12 mo in case of no CR; p = 0,02). 57 pts died, 35 due to NHL, 11 from another disease, 6 from toxicity and 5 from unknown cause. In conclusion these very old pts must be treated correctly but carefully. Better tolerated treatments are needed to improve results which are neither poor nor as good as in younger pts.

P 10 ROLE OF COMPLETE RESPONSE IN SURVIVAL LENGTHENING IN PROGNOSTICALLY FAVORABLE NON HODGKIN'S LYMPHOMAS (NHL).

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From 1981 to 1984, 113 patients (pts) with NHL were treated with an induction regimen of Cyclophosphamide (CYC) 400 mg/sqm days 1 and 8, Vincristine (VCR) 1,4 mg/sqm days 1 and 8, Procarbazine (P) 80/sqm day 1 to 14, Prednisone (p) 60 mg/sqm day 1 to 5 (PCOp) randomly associated to Adriamycine (ADR) 20 mg/sqm days 1 and 8 (PACOp).
Evaluation of response was performed by complete restaging, including bone marrow biopsy, after 6 cycles carried out at 4 weeks intervals. Maintenance therapy consisted of monthly treatment of Chloraminophene (10 mg/sqm 5 d) or CVP. The histopathology distribution was diffuse well differenciated : 12 pts, nodular lymphocytic : 70 pts, nodular mixed : 31 pts. Stage distribution was stage II : 8 pts with bulky abdominal masses, stage III 17 pts, stage IV : 88 pts including 74 pts with bone marrow infiltration. Complete response (CR) was observed in 49 pts (43%) : 30 after induction treatment and 16 after maintenance therapy. No statistical difference was found between the two induction regimen. By a stepwise logistic regression, stage IV ($p < 0.01$) a number of adenopathies > 5 ($p < 0.05$) were found influencing probability of achieving a response. Estimated median of response without progression was estimated to 44 months without advantage for the regimen containing Adriamycine. Complete response to treatment was the only significant factor ($p = 0.01$, Cox's model) in lengthening the freedom from progression time. In case of relapse, median of second response was 12 months. In conclusion, introduction of Adriamycin in prognostically favorable LNH did not appear to modify response rates and survival without progression. CR obtention even after several months increases survival without progression and long term survival.

P 11 LOW GRADE LYMPHOCYTIC LYMPHOMA - THE UNIVERSITY OF CHICAGO EXPERIENCE.

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We retrospectively evaluated 159 patients (pts) with low grade lymphoma seen and treated at the University of Chicago. 58% had nodular, poorly differentiated lymphoma (PDL-N); 26% had PDL-N with areas of diffuse disease (PDL-N/D); 10% had nodular, mixed cell lymphoma (MC-N); and 6% had well differentiated lymphoma (WDL). Most pts had extensive disease at presentation (84% stage III/IV) and 65% had bone marrow involvement. There was no association between histological group (gp) and stage at presentation. 42 pts had no therapy within 1 month of staging workup (no initial therapy-NIT), 76 had initial local radiotherapy (RT) or oral chemotherapy (initial palliative therapy-IPT), and 41 pts had initial aggressive therapy (IAT). We examined change in therapy over time by evaluating overall therapy gps: 12 of the NIT pts did not require any therapy (never treated), 31 NIT pts eventually received therapy, 33% of all pts received overall palliative therapy only (OPT), and 59% of all pts received [overall] aggressive therapy at some time (OAT). Median time to first therapy for NIT pts was 29 months (mo). 34 IPT pts had local RT as their initial therapy, of whom 8 required no further treatment, and the median time to systemic therapy was 22 mo. Overall, 49% of treated pts achieved CR, (71% of pts receiving IAT). Only 43% of pts with NIT who had OAT and 25% with OPT achieved CR. For these, disease free survival (DFS) was 38 mo for OPT, and 51 mo for OAT pts. In comparison, DFS was 135 mo for CR pts with IAT. Median survival (MS) for all 159 pts was 90 mo (147 mo for CR, and 54 mo for non-CR pts). MS for NIT pts who received OAT, and achieved CR was 92 mo, compared with 147 mo for IAT pts with CR. MS for NIT pts who never required therapy was not reached at 117 mo. OAT (p=0.008) and achievement of CR (p=0.0001) were associated with longer survival in treated pts. Clinical parameters predictive of survival were age <50 years (p=0.007), absence of B symptoms at presentation (p=0.004), and number of initial sites of disease (p=0.009). No clinical parameters at presentation were predictive of a change in therapy gp, or need for eventual therapy in NIT pts. For PDL-N, PDL-N/D, and WDL, there was no difference in survival by initial therapy, but pts who had OPT had prolonged survival. For MC-N, pts who had IAT or OAT survived significantly longer than pts with NIT, IPT or OPT. Asymptomatic pts with favorable lymphomas can be observed for a considerable period before requiring therapy, but the subset of NIT pts who do eventually require therapy have a worse prognosis than pts treated initially. MC-N pts may benefit from aggressive therapy at diagnosis.

P 12 LOW DOSE TOTAL BODY IRRADIATION (LTBI) FOR NON-HODGKIN LYMPHOMAS (NHL), EFFECTIVENESS AND POSSIBILITIES OF SUBSEQUENT TREATMENT IN CASE OF RELAPSE.

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Fractionated LTBI was used at the RRTI as treatment for NHL in the period between 1973 and 1979. 68 Patients (34 male, 34 female, age 22-82) received this treatment. At diagnosis 45 patients had stage IV, 16 patients stage III, 6 patients stage II, and 1 patient stage I. According to current malignancy grading classifications, 19 pts had high grade, 10 intermediate, and 34 low grade NHL. In 5 cases no exact grading was possible. Patients with high or intermediate grade were grouped as unfavourable (unfav), and pts with low grade as favourable (fav).

Results
LTBI induced remissions in 85% of fav and in 40% of the unfav pts. Median duration was resp. 30 months and 10 months. Long lasting RFS was observed only in the fav. group: 27% at 10 years. A wide variety of modalities of treatment was given in case of relapse, including almost always chemotherapy.
First line post-treatment was given to 40 patients. Response Rate (RR) was 73% for fav, and 70% for unfav pts, with a median duration of resp. 7 and 4 months. Second line was given to 24 pts (RR: 88% for fav, 64% unfav), third line to 12 pts (RR: 8/10 for fav, 1/2 unfav), and fourth line to 2 pts (RR: 1/2 for fav). Median duration of response rate was always shorter for unfav pts.

Conclusion
LTBI induced high response rates in fav pts lasting for an extended period of time.
No long-term RFS were observed in case of relapse but RR remained high, indicating that LTBI did not compromise subsequent chemotherapy.

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COMBINED MODALITY TREATMENT OF ADVANCED LOW-GRADE LYMPHOMAS - A CALGB STUDY. H.W. Grünwald, J. Anderson, A.S. Glicksman, T.F. Pajak, N.I. Nissen and A.J. Gottlieb, Jamaica, NY, Boston, MA, Providence, RI, Philadelphia, PA, Copenhagen, DK and Syracuse, NY for Cancer and Leukemia Group B, Brookline, MA, USA.

The value of consolidative radiotherapy (RT) in patients with advanced (Stages III and IV) lymphocytic lymphoma after induction combination chemotherapy (CT) consisting of streptonigrin, vincristine and prednisone was assessed by Cancer and Leukemia Group B. The randomized trial was begun in 1976, and was closed to patient accrual in 1979. This report analyzes the results attained in patients with a nodular histologic pattern (low-grade malignancy in the International Formulation). Ninety of 95 evaluable patients achieved at least a partial response after the induction regimen; 36 of these patients received radiation (30 to 40 Gy) to areas of initial bulky disease prior to initiation of maintenance CT with cyclophosphamide, vincristine and prednisone, 49 received maintenance CT only and 5 did not receive the assigned post-induction therapy. The maintenance CT was continued till relapse or for a maximum of 3 years. Forty-three percent of the patients were Stage III, 57% Stage IV, 36% had "B" symptoms and 30% were under the age of 50; the distribution of these variables was fairly uniform among the 2 random arms of the study. The 5-year failure-free survival (FFS) for the 85 randomly treated patients was 39%; it was 42% for those who received RT and 36% for those receiving maintenance CT only. The 5-year survival from the time of post-induction randomization was 52%, and the same proportion of patients was alive at that time whether RT had been administered or not. In sub-groups with poorer prognosis (Stage IV, "B" symptoms, mixed nodular and diffuse histologic pattern) there was some advantage to receiving the RT (48 vs 19% 5-year FFS for Stage IV patients, 25 vs 0% for patients with symptoms, 29 vs 11% for patients with nodular plus diffuse pattern), but there were no differences in any of the sub-groups analyzed with respect to overall survival at 5 years from the date of randomization.

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MAINTENANCE CHLORAMBUCIL FOLLOWING CVP IN THE MANAGEMENT OF ADVANCED STAGE, LOW GRADE HISTOLOGY NON-HODGKIN'S LYMPHOMA - A RANDOMISED PROSPECTIVE STUDY. W.P.Steward*, L.J. McWilliams#, J.M.Jones¥, D. Crowther*, CRC Dept. of Medical Oncology, #Dept. of Histopathology, ¥Dept. of Radiotherapy, Christie Hospital & Holt Radium Institute, Manchester M20 9BX, U.K.

162 patients with stages III and IV non-Hodgkin's lymphoma of low grade histology were treated with combination chemotherapy using Cyclophosphamide, Vincristine, and Prednisolone (CVP) followed by radiotherapy to sites of previous bulk disease. The patients were randomised to receive either follow up alone or 'maintenance' chemotherapy with two years of intermittent Chlorambucil. A complete remission was obtained in 56% of patients and the median survival (with a median follow up of 74 months) was 64 months. Multivariate analysis revealed stage ($p<0.0001$), KP ($p=0.021$) and serum bilirubin ($p=0.002$) to predict complete response and the achievement of a CR ($p<0.0001$), female sex ($p=0.008$), the absence of bulk disease ($p=0.038$) and low serum alkaline phosphatase ($p=0.002$) to predict prolonged survival. The median relapse-free survival (RFS) of the complete responders was 41 months. A prolonged RFS was predicted by low stage ($p=0.014$), low serum LDH ($p=0.045$) and ALT ($p=0.046$) levels, and by the administration of maintenance Chlorambucil ($p=0.045$). A prolonged survival of the complete responders was predicted by a low number of nodal sites of involvement with lymphoma at presentation ($p=0.022$) and lack of liver involvement ($p=0.011$). The administration of oral maintenance therapy with Chlorambucil for a full two years was only possible in 38% of patients, mainly because of progression of disease and the induction of thrombocytopenia, but despite this it prolonged the median RFS by 38 months and it may therefore have a role in the management of low grade NHL.

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MULTICENTER RANDOMIZED THERAPEUTIC STUDY FOR ADVANCED CENTROCYTIC LYMPHOMA: ANTHRACYCLINE DOES NOT IMPROVE THE PROGNOSIS. P. Meusers, H. Bartels, T. Binder, M. Engelhard, H.H. Fülle, K. Görg, U. Gunzer, K. Havemann, W. Kayser, E. König, H.J. König, R. Kuse, H. Löffler, W.-D. Ludwig, K. Mainzer, A. Pezzutto, H. Pralle, W.D. Schoppe, H.J. Staiger, H. Theml, K.H. Zurborn, T. Zwingers, K. Lennert, G. Brittinger, Coordination center: Division of Hematology, Dept. of Medicine, University of Essen, 4300 Essen, Germany

Centrocytic lymphoma (CC), as identified histomorphologically by the Kiel classification of non-Hodgkin lymphomas (NHL), has proven to be a separate entity of low-grade malignant NHL also by clinical and prognostic criteria: As shown by the results of a prospective observation study of the Kiel Lymphoma Study Group, these criteria include preponderance of male sex, tendency to early generalisation, instability of remissions achieved by chemotherapy induced only at evidence of progression, unexpected steep, continous decline of survival curves resulting in short median (30 months) and overall survival times. In order to improve the therapeutic approach to advanced CC a prospective randomized multicenter trial was initiated examining the remission-inducing and possibly curative potential of the COP regimen as compared to the more intensive, adriamycin containing CHOP regimen. From 1982 to 1985, 84 of the 91 patients (pts) recruited for the study were evaluable on the basis of histology and complete staging according to the Ann Arbor classification (2 pts presenting stage I, 8 pts stage II, 32 pts stage III, 42 pts stage IV disease). Of 71 pts with stage II-IV disease, 58 fulfilled the randomisation criteria. In both chemotherapy groups the initial parameters (pattern of disease manifestation, performance status, presence of B-symptoms, increased serum LDH activity, sex distribution) did not differ significantly. Complete remissions (CR) were achieved in 15/30 (50 %) of pts treated with COP and in 15/23 (65 %) of pts treated with CHOP, median duration of CR was 12 and 7 months, the relapse rate was 11/15 and 10/15. The median survival probability in COP and CHOP treated pts was 32 and 37 months, the death rate 57 % and 48 %, respectively. None of the observed differences are statistically significant. Compared to the strategy of watchful waiting followed by the aforementioned previous study early initiation of chemotherapy offers a slight prognostic advantage. However, the introduction of anthracycline does not significantly influence the rate and stability of CR or the median or overall survival probabilities. Also, neither the COP nor the CHOP regimen can be considered a curative treatment approach to advanced CC.

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TRETMENT RESULTS WITH RADIATION THERAPY OF EXTRANODAL LYMPHMA OF THE HEAD AND NECK AREA. N. Masaki, H. Ikeda, Department of Radiology, Osaka University Hospital, 1-1-50, Fukushima, fukushima-ku, Osaka, Japan

To determine possible effects of induction chemotherapy, long-term effects of treatment as well as the causes of failure have been reviewed. Between 1971 and 1984, 182 patients(Stage I:85, Stage II:97) with extranodal lymphoma of the head and neck area were treated with radiation therapy in the Department of Radiology, Osaka University Hospital. Grouping according to the site of involvement was in the following order: Waldeyer's ring 104(57%)(Stage I:28, and Stage II:76), thyroid 25(14%), paranasal sinus 17(9%), oral cavity 17(9%), orbit 10(5%), nasal cavity 6(3%), and skin 1. Histological distribution was 59% DH, 26% DPDL, 9% DWDL and 6% others. All patients received a definitive course of radiation therapy(40 - 55 Gy), including 61 patients (34%) in which one or two cycles of chemotherapy were given prior to radiation therapy.

All cases achieved a complete response after radiation therapy, but there were two cases of local recurrence in radiation therapy alone group. There was a marginal recurrence in chemotherapy combined group. In Stage I disease a 5-year desease-free survival rate was 71% by radiation therapy alone, and 91% by chemotherapy combined. Patients with Stage II disease had much poorer results: 57% of 5-year disease-free survival rate by radiotherapy alone, and 64% by chemotherapy combined. Patients with Stage I disease in the area of orbit, nasal cavity, Waldeyer's ring and thyroid had the best prognosis. Patients with disease in paranasal sinus, and oral cavity had the poorest prognosis, and with Stage II disease of Waldeyer's ring was in between. The most common sites of relapse in the cases of Stage II Waldeyer's ring were lymph nodes in the abdomen and GI tract. In the cases of paranasal sinus, and oral cavity sites of relapse were rather unpredictable; braest, testis, bone and skin of distant sites. Additional chemotherapy may be required for those with poor prognosis.

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P 17 TOTAL BODY IRRADIATION VERSUS COMBINATION CHEMO-RADIOTHERAPY FOR STAGE III AND IV NON-HODGKIN'S LYMPHOMAS OF FAVOURABLE HISTOLOGY.

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Between July 1980 and November 1985 a cooperative clinical trial was runned by the EORTC Lymphoma Group to investigate whether a short course of Total Body Irradiation (TBI, 2.5 Gy, in 25 fractions, 3 times a week) had the same survival results as combination chemotherapy (CICS, cytoxan, adriamycin, oncovin, prednison, 8 courses) with iceberg irradiation. 93 Patients were entered, 10 patients were non-evaluable, mainly ineligible based on histology. 65 Patients are evaluable for response; TBI: CR 34%, PR 37%; CICS: CR 56%, PR 13%. No difference in response rate for stage III and stage IV. When corrected for imbalances in stage no statistically significant differences were observed for relapse-free survival and survival between the two treatment arms. Overall survival and RFS were 76% and 34%, resp. at 3 years.
No prognostic factors could be identified for RFS or survival.
In conclusion: the survival results of TBI do not significantly differ from combination chemo-radiotherapy.

P 18 INFLUENCE OF ICEBERG RADIOTHERAPY (IR) ON SURVIVAL OF NON HODGKIN LYMPHOMA (NHL) PATIENTS, STAGE III-IV.

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Patients (pt) with NHL stage III-IV aged 15-70 years were enrolled in OERTC trials 20751, 20801 and 20802 for multimodality treatment. Induction chemotherapy (CT) consisted of Adriamycine 50 mg/m², VM 26 60 mg/m², Cyclofosfamide 600 mg/m², Prednison 40 mg/m² x 5 (CHVP), 8 courses q. 3 weeks, or the same with Vincristine 1,4 mg/m² and Bleiomycine 8 mg/m² on day 10 of each course (in trial 20802). For pt without progression, the protocol prescribed IR, 25-35 Gy in 3-4 weeks, dose depending on remission status, on nodal areas either containing lymphnode masses > 5 cm at onset, or not in complete remission after 3 courses (group B, 87 pt). Group A consisted of 17 pt for whom IR was not indicated. However, due to problems with the interpretation of the protocol, a group C (78 pt) existed for whom IR was indicated but not given.
For 183 pt from 5 participating centres, extent of disease for each lymphnode area and administration of IR was retrospectively coded. Characteristics of patient material: stage III 87 pt, stage IV 96 pt, mean age 52 years, histology according to Kiel: low grade (LG) 105 pt, high grade (HG) 48 pt, (30 pt unspecified); cell pattern follicular 52 pt, mixed 25 pt, diffuse 82 pt, (24 pt unspecified).
Treatment results expressed as actuarial 5 years survival (S_5) for different subgroups: LG 67%, HG 45% (p = 0,03), follicular 70%; stage III 62%, stage IV bonemarrow 72%, stage IV liver 33%, stage IV otherwise 54%. No lymphnode areas with masses > 5 cm (46 pt) or 1 or 2 areas (73 pt), S_5 = 74%, 3 or 4 areas (52 pt), 47% (p = 0,0001). Only 11 pt had 5 or more areas with large tumour masses.
S_5 for the different treatment groups: A 65%, B 65%, C 48% (p = 0,012). The difference was most significant for the following subgroups: diffuse cell pattern: B 63%, C 35%, (A 75%)(p = 0,002); high grade histology: B 57%, C 15% (p = 0,008); stage III: B 70%, C 39% (A 70%) (p = 0,009). Pt in partial remission at 3 cycles: B 62%, C 48% (p = 0,037). If all lymphnode areas were < 5 cm, the S_5 difference was borderline significant: B 80%, C 50%. In the whole patientgroup only 10 relapses occurred in irradiated nodal areas.
Although this was not a randomized study, the findings suggest that iceberg irradiation in NHL stage III-IV with large or slowly regressing nodal masses contributes to survival, especially for stage III, for diffuse cell pattern and for Kiel high grade histology.

P 19 EUROPEAN EXPERIENCE OF M-BACOD PROTOCOL IN 107 NON-HODGKIN'S LYMPHOMAS.

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One hundred and seven non-Hodgkin's lymphoma (NHL) patients were treated with the M-BACOD regimen (Skarin *et al.* J. Clin. Oncol. 1983; 1:91). There were 63 males and 44 females ranging in age from 2 to 76 years (mean, 45). Three were stage I, 32 stage II, 25 stage III and 47 stage IV. Grades were as follows : 77 intermediate grade (10-D, 9-E, 39-F, 19-G) and 30 high grade (11-H, 7-I, 7-J, 5-others). Eight patients received a slight modification of the M-BACOD regimen: Methotrexate 1.5 g/m² instead of 3 g/m². Results of treatment were evaluated after 4 courses. There were 56 CR (52%), 24 PR (22%), 24 failures (22%) and 3 non-evaluable cases (3%). The survival curve, established for all 107 patients, showed a plateau occurring at 62% and beginning at thirty months. Twenty-four months after initiating therapy, 36 patients remained alive. Relapse free survival of CR was 72% at thirty months. Survival at thirty months depended on the response to therapy : CR 86%, PR 66%, (CR versus PR : p < 0.025) and failures 12%. Other significant prognostic factors included elevated LDH and pathological grade (I and J).
Encouraging results in PR patients may be due to efficacy of salvage protocols. After 4 courses of M-BACOD, 9 PR were converted into CCR : 4 patients by MIME regimen ; 4 patients by intensive chemotherapy plus autologous bone marrow transplantation ; and 1 patient by intensive therapy plus allogeneic bone marrow transplantation. Results of rescue protocols in cases of no response (3 CCR out of 24 patients) or of relapse (3 CCR out of 12 patients) following induction therapy were disappointing.
The toxicity of the M-BACOD in our series was very low with only 4 treatment-related deaths (4%).
We conclude that M-BACOD is very efficient in NHL grades D, E, F, G and H.

P 20 COP-BLAM AND CHOP CHEMOTHERAPY IN HIGH-GRADE MALIGNANT NON-HODGKIN LYMPHOMAS (NHL) : RETROSPECTIVE COMPARISON. PRELIMINARY RESULTS OF A MULTICENTER PROSPECTIVE RANDOMIZED STUDY USING COP-BLAM/IMVP-16 WITH OR WITHOUT ADJUVANT RADIOTHERAPY.

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To evaluate and to improve concepts of intensive polychemotherapy for high-grade malignant non-Hodgkin lymphomas the clinical course of 62 consecutive patients treated by either the CHOP (n=34) or the COP-BLAM regimen (n=28) from 1979 to 1985 were analyzed retrospectively. The distribution of initial clinical and prognostic parameters was comparable in both groups; the 5 cases with primary CNS disease, present only in the CHOP group, were excluded from further analysis. Half of the patients received additional radiotherapy. The complete remission rate was significantly higher in the COP-BLAM- than in the CHOP-treated patients (85 % vs. 38 %, p=0.0009). The overall survival curve of CHOP-treated patients declined over a period of 70 months until starting to form a plateau at 30 % whereas the COP-BLAM group reached a plateau after 26 months at 70 % survival probability. Relapse-free survival probability was comparable in both groups plateauing at about 70 %, with a mean observation time of 58 months for CHOP- and of only 32 months for COP-BLAM-treated patients.
These data prompted a prospective multicenter randomized trial by the NHL Study Group with the aim of establishing COP-BLAM as first line therapy (5 cycles) complemented by 2 cycles of IMVP-16 for complete responders, or employing an early switch to IMVP-16 in poor responders. Response is evaluated early after 3 cycles of COP-BLAM and again after completion of all 7 courses by complete restaging. Patients in complete remission are then randomized either to receive adjuvant radiotherapy or to be followed without further treatment. Up to date 105 patients have been recruited for this prospective trial, of whom 34 have already been followed beyond the first restaging. In a preliminary analysis it will be determined if the favorable results obtained by COP-BLAM in the retrospective analysis can be confirmed by the prospective trial. In addition, the potential of adjuvant radiotherapy to stabilize the achieved complete remissions is investigated on the basis of randomization.

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P 21 CHOP VERSUS CHOP-M IN THE TREATMENT OF HIGH GRADE MALIGNANT NON-HODGKINS LYMPHOMAS IN ADULTS: A Swedish national randomized study. Hagberg H, Lindemalm C, Cavallin-Ståhl E. For the Swedish Lymphoma Study Group.

In the treatment of high-grade malignant non-Hodgkin's lymphoma (NHL) combination chemotherapy with CHOP has been extensively used. It has been claimed that regimes with more drugs and shorter interval between drug delivery might improve the cure rate. Based on this assumption a prospective national randomized study has been performed on an unselected group of adult patients with high-grade malignant NHL. Within the period March 1983 to February 1986, 221 patients (134 men;87 women; mean age 63 years, range 17-75 years) were randomized between 9 courses of CHOP (cyclophosphamide 750 mg/m², adriamycin 50 mg/m², vincristin 2 mg and prednisone 50 mg/m² for 5 days) every third week and CHOP-M (CHOP + methotrexate 250 mg/m² given on day 14 followed by leucovorine rescue after 24 h). Nine patients were not eligible. Eight of them (4 in each group) had a NHL with a low-grade malignant histopathology while 1 patient had a squamous cell cancer. The remaining 212 patients were in the following stage (Ann Arbor): I (2), II (36) III-IV (174). The histo-pathological distribution according to the Kiel classification was Centrocytic (large cell) 9, Centroblastic 81, Immunoblastic 33, Lymphoblastic 3, diffuse Centroblastic/Centrocytic 34, truly histiocytic 4, high-grade UNS 48.

Results: In December 1986 204 patients (104 CHOP; 100 CHOP-M) were evaluable. The complete remission rate was 59/104 (56%) in the CHOP group compared to 63/100 (63%) in the CHOP-M group. In the CHOP group 15 patients have relapsed with 42/104 (40%) still living in CR compared to 26 relapses in the CHOP-M group with 37/100 (37%) still living in CR. The median follow-up time from end of treatment was 10 months. An analysis of the impact of age and histopathology to prognosis will be discussed.

Conclusion: The addition of 250 mg/m² methotrexate day 14 to CHOP did not improve the result in the treatment of high-grade malignant NHL

P 22 STAGE III-IV NON HODGKIN LYMPHOMAS (NHL) WITH UNFAVORABLE HISTOLOGIES : ROLE OF ADDED NON MYELOTOXIC DRUGS AT MID CHEMOTHERAPY INTERVALS AND ROLE OF MAINTENANCE CHEMOTHERAPY. A RANDOMIZED EORTC STUDY (20802 : 1980-85). P. Carde, J.H. Meerwaldt, R. Somers, M. Monconduit, J. Thomas, R. Nordijk, B. de Pauw, A. Tanguy, B. Caillou, C. de Wolff-Peeters, M. Hayat, M. Van Glabbeke, M. Tubiana. EORTC Lymphoma Cooperative Group - Brussels.

In stage III-IV NHL patients with unfavorable histologies (Working Formulation E, F, G, H and I except T lymphoblastic NHL) it was attempted to improve the results upon a former induction chemotherapy regimen, the so - called CHVmP (Int J Radiat Oncol Biol Phys 9 : 11-15, 1983). The CHVmP regimen included cyclophosphamide 600 mg/m2 IV d_1, hydroxorubicine 50 mg/m2 IV d_1, Vm26 60 mg/m2 IV D_1, prednisone 40 mg/m2 p.o. d_{1-5} and was given for 8 cycles q.3-4 weeks. CHVmP was randomized with the same regimen where vincristine 1.4 mg/m2 IV and bleomycin 6 mg/m2 IM (VB) was added at d_{15}. In both arms adjuvant radiotherapy (30 Gray) was given to "Icebergs". From 4.1980 to 1.1986 141 patients eligible entered the trial. Better results were obtained in the CHVmP + VB arm as compared to CHVmP : 72 % versus 48 % complete remission (CR), p = 0.005 Fisher test ; 50 % versus 35 % freedom from progression at 3 years (FFP), p = 0.051 Kaplan-Meier ; 60 % versus 44 % survival at 3 years, p = 0.025. The induction arm did not influence the relapse free survival in complete responders (CRs). A maintenance chemotherapy with cyclophosphamide, vincristine, prednisone (CVP) was randomly administered to CRs. There was no difference for RFS or survival. A non-myelotoxic VB chemotherapy randomly added ad mid-cycle intervals of myelotoxic CHVmP cycles improved the survival mainly from a higher CR achievement. Maintenance CVP was demonstrated as of no benefit in patients with unfavorable stage III-IV NHL who achieved a CR.

P 23 INTENSIVE TWO-PHASE CHEMOTHERAPY (CT) FOR HIGH-GRADE NON-HODGKINS LYMPHOMA (NHL). NSA Stuart *, GRP Blackledge, JA Child, J Fletcher, J Kavanagh, MH Cullen, A Simmons, K O'Brien, D Barnard. For The Central Lymphoma Group. Co-ordinating centre, Clinical Trials Unit, Queen Elizabeth Hospital, BIRMINGHAM, UK.

In an attempt to improve complete remission (CR) rate and overall survival of patients (pts) with high-grade NHL we have used a two-phase CT regime beginning with an intensive, 6-week, remission induction regime (VAMP: Vincristine 2mg i.v. day 1 of wks 1 to 6, Adriamycin 50mg/m^2 and Methotrexate 250 mg/m^2 both i.v. day 1 of wks 1,3 and 5 with folinic acid orally for 3 days, Prednisolone 60mg/day wks 1 to 6 reducing over 10 days) followed by further non-cross resistant CT (CViVp: Cyclophosphamide 1gm/m^2, Vindesine 3mg/m^2, Etoposide 125 mg/m^2 all i.v. day 1, Etoposide 250 mg/m^2 p.o. days 2 and 3) given each 21 days. Patients received at least 3 courses of CViVp following CR. CT was given to most pts on an out-patient or day case basis.

110 pts with histologically proven, high-grade (Keil) NHL not previously exposed to CT have been treated with this regime. Median follow-up is 21 months, all pts have completed treatment. Mean age of pts was 52 years (range 14-78), 44/110 pts were aged over 60. Stages (St) of the pts were as follows, St I = 9 (all with bulky or abdominal disease), St II = 23, St III = 20, St IV = 58. 65 pts had B symptoms. 34/109 pts had disease more than 10 cms in greatest diameter.

Mean percentages of protocol dose given during VAMP were as follows; Adr, 87%; Vincr, 82%; Meth, 82%; Pred, 95%. Number of pts having less than 75% of protocol dose for each drug were Adr, 28/110; Vincr, 35/110; Meth, 39/110; Pred, 8/110. 35/110 pts had no dose modification during VAMP, 60/110 pts had no delay. 21 pts did not receive CViVp, 17 because they died during VAMP and 4 because of physicians choice. Mean percentages of protocol dose given during CViVp were as follows: Vind, 82%; Cyclo, 91%; VP-16, 86%. Number of pts having less than 75% of protocol dose for each drug (2 pts no data) were: Vind, 22/87; Cyclo, 16/87; VP-16, 18/87. 39/87 pts had no dose modification during CViVp, 52/87 pts had no delay.

At the end of VAMP 54 pts (49%) were in CR. 66/87 (76%) pts who had CViVp achieved CR (2 no data). 20/38 (53%) pts in PR at the end of VAMP achieved CR during CViVp. Overall best response was CR 75/110 (68%), PR 27/110 (25%), no response 8/110 (7%). Median survival is 129 weeks, median relapse-free duration is 134 weeks. Toxicity was acceptable in both phases of treatment. Neutropaenia below 1.0 x 10^9/l occurred in 36% of patients during VAMP; 52% during CViVp. Platelet counts below 50 x 10^9/l occurred in 6% during VAMP; 4% during CviVp. Moderate or severe neuropathy occured in 25% of patients during VAMP. Septicaemic episodes occured in 17/110 (15%) patients. 16 deaths occured to which treatment contributed, in 9 of these other causes were also involved.

This regime is effective and well tolerated. Results are as good as with any other regime particularly with regard to the large proportion of elderly patients and those with advanced stage disease. We have commenced a randomised, prospective trial comparing standard cyclical chemotherapy with a regime in which the most active drugs from VAMP-CViVp are scheduled on a weekly basis (CAPOMEt). Major end-points will be toxicity, reponse rate and survival.

P 24 ALTERNATING PROMACE/MOPP CHEMOTHERAPY IN ADVANCED DIFFUSE POOR PROGNOSIS NON HODGKIN LYMPHOMA (NHL).A PRELIMINARY REPORT OF THE ITALIAN STUDY GROUP (ILSG). T.Chisesi (Vicenza)*; G.Santini (Genova);V.Rizzoli (Parma); L.Repetto (Genova);A.Contu (Sassari); A.Porcellini (Pesaro);P.Coser (Bolzano);A.Congiu,E.Rossi, D.Scarpati,M.R.Raffo,A.Maiolino,A.Marmont (Genova). *Dept.Haematology, Ospedali Civili, Vicenza, Italy.

Third generation chemotherapy (CT) regimens have recently increased complete remission (CR) rate and disease free survival (DFS) in advanced stages of aggressive lymphoma.

Up to December '86 seventy eight pts. with diffuse, intermediate and high-grade malignancy NHL were treated with the PROMACE/MOPP protocol. Criteria for entry into the study included: no prior therapy. III and IV stage, histological diagnosis of diffuse centroblastic-centrocytic, centroblastic, immunoblastic, T-zone, and histiocytic lymphoma. Chemotherapy was administered alternatively (PROMACE-MOPP-PROMACE.....) and MTX was adjusted at 400mg/mq. All pts. received six courses of chemotherapy at full dose, plus radiotherapy on bulky disease.

At present 54pts., 38 males and 16 females, median age 51yrs. (range 19-66), 16 in stage III and 38 in stage IV, are evaluable. B simptoms (fever, weight loss) were present in 20 pts. (37%), bulky disease (>10cm) in 14 (26%), and splenic involvement in 10 (18.5%). The most common localizations for extranodal disease were gut (18%), liver (17%) and bone marrow (15%). Thirty five out of 54pts. achieved CR (65%), seven PR (13%), eight were NR (15%) and four went into PD (7%).

At a median of six months of remission follow-up (range 2-20 months), progression free pts.'s survival was 71.5%. Ten relapses (18.5%) occurred, in a median time of 4 months (range 2-12) from CR. Twenty pts. (37%) died during therapy due to a worsening of their disease or following relapse.

In conclusion our preliminary results are not in accordance with a more encouraging data reported by others.

This discrepancy is not clear, it could possibly be due to the fact that our pts. are all in an advanced stage (III and IV). This and other problems will be discussed.

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P 25 Treatment of intermediate and high grade malignancy non-Hodgkin's lymphomas (NHL) with a platinum containing combination alternating with Methotrexate and B-CHOP. Greek Lymphoma Research Group (Athens-Greece).*

Cis-platinum (P) Etoposide (E) and Vindesine (V) have been found active both as single agents and in various combinations in the treatment of NHL. The combination of PEV plus Methotrexate (MTX) with leucovorin rescue (LR) was administered in a pilot study to heavily pretreated patients with NHL in relapse and produced remissions in 39% of the patients with acceptable toxicity. We therefore initiated a study to evaluate the response rate and remission duration of previously untreated patients with intermediate and high grade NHL with the following drug combination: P:50 mg/m^2 I.V. and V:3 mg/m^2 I.V. on day 1, E:120 mg/m^2 I.V. days 1-3, MTX:500 mg infusion day 14 with LR, followed by B-CHOP on day 28. Cycles (PEV/MTX-LR/B-CHOP) were repeated every 49 days to a total of 6 cycles.
Thirty nine, of 51 previously untreated patients entering the protocol, completed at least two chemotherapy cycles and are evaluable. Eighteen were males and 21 females and had an age range from 18 to 70 years. Eleven patients had intermediate, and 28 high grade malignancy NHL. Twelve patients had stage II, 8 stage III and 19 stage IV. Complete remission (CR) was achieved in 27 patients (69%) and partial remission (PR) in 9 (23%). Two patients showed no response and one died of myocardial infarction before completion of the 1st cycle. Two patients died of drug related toxicity (renal and haematologic) and three died in relapse after remissions lasting 3,4 and 6 months. The remaining patients are in continuous remission 2 to 14 months after completion of treatment. Forteen patients had mild to moderate myelotoxicity and none nephrotoxicity or hepatotoxicity. The estimated probability of survival at two years is 82.7% and of disease free survival 69.3%.
The overall response rate of 92% with our treatment protocol is encouraging but longer follow-up is necessary to access the durability of remission. The toxicity has been acceptable.

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P 26 PHASE I-II TRIAL OF HIGH-DOSE EPIRUBICIN IN PATIENTS WITH LYMPHOMA.

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Utilizing Adriamycin in high doses (120 mg/M^2), significant responses have been seen both as a single agent in refractory lymphoma as well as in combination therapy. Because of severe mucositis and sustained granulocytopenia seen with high-dose Adriamycin, we elected to study a new analogue of Adriamycin, epirubicin, at high dose. High-dose epirubicin (HD-Epi) was administered at doses of 120 mg/M^2, 150 mg/M^2 and 180 mg/M^2 every 3 weeks (maximum 4 doses) to groups of six patients with previously treated intermediate and high-grade lymphoma. The dose level was escalated based upon response and toxicity at the previous level. Sixteen of the nineteen patients treated in this study had received significant prior therapy with an anthracycline and/or anthracenedione. A response rate of 58% was achieved (56% in those patients receiving prior anthracycline and/or anthracenedione) with a median duration of 5 months (range 1-15+). The response rate was independent of the dose levels. Myelosuppression was severe with median granulocyte nadir <504/mm^3 at all levels. Forty-two percent of patients (8 patients) had fever/neutropenia and required antibiotics; one treatment-related septic death occurred. At the 180/M^2 level, the majority of patients failed to have hematologic recovery by the day of next scheduled therapy. Alopecia (68%), fever immediately following treatment (63%), mild/moderate stomatitis (58%), and nausea/ vomiting (53%) were the most common nonhematolologic toxicities. No patient developed clinical or radiologic evidence of congestive heart failure. The median EF for the entire group of patients fell from 0.63 to 0.56. A 10% change in the radionuclide ejection fraction (EF) was seen in 7 patients. HD-Epi can produce a high response rate in previously-treated patients with lymphoma with appropriate supportive care. The recommended dose trials in untreated patients is 180 mg/M^2. Cardiac function studies need to be assessed regularly.

P 27 PILOT STUDY OF AN ADRIAMYCINE, ARA-C, ETOPOSIDE, METOTREXATE, L-ASPARAGINASE AND METHYLPREDNISOLONE REGIMEN FOR B-IMMUNOBLASTIC LYMPHOMA,

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The B-immunoblastic lymphoma (Kiel) is a high grade malignancy lymphoma, whose response to different treatement regimens is still debatable. According to the authors experience, with 15 patients with B-immunoblastic lymphoma, neither COOPP/MOPP nor CHOP or BACOP prooved satisfactory (for the whole group CR rate 1/15, PR 3/15, response rate -RR 4/15,11 remaining patients displaying progressive disease). Thus, apilot study of an agressive regimen was started in a group of 2o previously untreated patients in clinical stage IIB-IV, 17 males and 3 females, mean age 48 years, range 16-7o years.
The regimen consisted of 8 induction cycles with monthly intervals consisting of: Adriamycine 6o mg/m^2 iv day 1; Etoposide 15o mg/m^2 /24 h iv days 2-4; Ara-C 12o mg/m^2/24 h iv days 2-6; Metotrexate 25o mg/m^2 day 4 with folinic acid rescue; L-asparaginase 15.ooo E/m^2/24 h iv days 7-1o; Methylprednisolone 2 gr iv Day 7, 1,5 gr iv day 8, 1 gr iv day 9,o,5 gr iv day 1o. Consolidations were carried at three month intervals: A (Vinblastine, 6-Thioguanine, Cyclophosphamide,Methylprednisolone), B (Daunoblastine, Etoposide, Methylprednisolone), C (L--asparaginase, BCNU, Metotrexate, Methylprednisolone), D (Teniposide, Ara-C, Mechlorethamine). Reinductions were performed once yearly, as inductions, Adriamycine omitted. Treatment was supposed to last for 48 months.
11/2o patients (55%) achieved complete remission (CR), 6/2o (3o%) a partial remission, overall response rate (RR) being 85%. 5/11 (45%) of patients achieved CR during I-III induction cycle, 6/11 (55%) achieved CR during IV-VIII cycle. Mean survival for CR is at the moment over 2o months (median 16+months). for PR 1o months (median 6 months), for non-responders 3 months. On both the survival and remission duration curve, a plateau seems to be established from the 12-th months, with at the moment 8 patients being in uninterrupted remission lasting 12+, 13+, 16+, 21+, 31+, 43+, 44+ and 48+ months.
Alopecia gr. II-III was present in all patients. Hematological toxicity was most marked on leucocytes with gr. III-IV in 6o% of patients with 1 therapy related death. The regimen seems very active, with a high RR and a prolonged survival for responders. Remissions are usually achieved after several induction cycles. The regimen bears a considerable hematological toxicity and requires application in a germ-free unit.

P 28 BURKITT'S LYMPHOMA IN LEUKEMIC PHASE: PROGNOSTIC FACTORS IN 14 PATIENTS.

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American Burkitt's lymphoma may have a median survival rate of more than 50% at two years. In leukemic phase median survival is less than 6 months. These observations prompted a study of parameters of Burkitt cells to detect prognostically significant variables. Fourteen patients (PTS)(12 of them untreated) presented with Burkitt's Lymphoma in leukemic phase. L3 blast cell counts in bone marrow (14/14 PTS) and blood (9/14 PTS) were 51-95% and 3-50%, respectively. The white blood cell counts varied from 2.6 to 29.8x10^9/l. Serum LDH ranged from 234 to 9999 U/l. 11/14 PTS had B symptoms. 9/14 PTS had an abnormal amount of DNA in G1 cells of the malignant cell populations. The % cells in S, G2 and M phases of the cell cycle ranged from 15 to 52. The amounts of both cellular and nuclear RNA of G1 cells ranged between 1.6 and 4.9 times that of normal lymphocytes. Although the RNA content was not different in blood and bone marrow, the % of SG2M cells was significantly lower in blood cell populations. 5 PTS had Null, 9 PTS had B surface antigen phenotypes. 6 PTS had kappa light chain excess; 5 had IgM heavy chains. 3/5 Null cell PTS had highly elevated TdT. 10/12 PTS with cytogenetic cell preparations had $\geq$23 analyzable metaphases. The % metaphases with clonal abnormalities ranged from 60-100. The modal numbers of chromosomes (pseudo-, hypo-, hyperdiploid) were paralleled by corresponding findings in DNA content of G1 cells (normal, decreased, increased) in 9 cases. In 1 case, the modal number of chromosomes was pseudodiploid whereas the DNA content of some G1 cells was increased. The characteristic translocations [t(8;22), t(8;14)] were identified in 6 PTS. The t(14;18) abnormality was found in 2 PTS. In two other cases no translocations were found. Treatment reginems included previously published Memorial Hospital protocols L-10, L-17M, and LSA2-L2. Survival times of the 14 PTS ranging from 8-474 days (d), median 118 d, fit exquisitely an exponential curve. The 8 variables potentially useful for predicting survival included abnormal DNA content, aneuploidy, pseudodiploidy, translocation t(8;14), translocations t(8;22) and t(14;18), all translocations, Null and B cell phenotypes. Due to the small number of 14 PTS, two categories, i.e. presence or absence of each variable, were studied univariately for their impact on survival. For each type of variable, the survival times of PTS followed a strictly exponential distribution. A two-sided F-test at significance level .05 determined the presence of a difference between the two catogories. Independent of treatment protocol, median survival was significantly determined by abnormal DNA content (if present: 65±21 d for n=9; if absent: 204±91 d for n=5) and/or pseudodiploidy (if present: 177±72 d for n=6; if absent: 52±30 d for n=4). Moreover, 3 PTS with t(8;14) survived 371-474 d; 5 PTS with other translocations survived 32-100 d from diagnosis.

ABSTRACTS - Third International Conference on Malignant Lymphoma, Lugano

P 29 INTENSIVE, BRIEF CHEMOTHERAPY FOR BURKITT'S LYMPHOMA.

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Between 1984 and 1986 ten patients (pts) with Stage C or D Burkitt's lymphoma or B cell acute lymphoblastic leukemia have completed a two month intensive regimen of chemotherapy. All ten achieved complete remission (CR) status; there have been no toxic deaths. Nine have remained in CR for periods ranging from four months to three years.
Toxicity has been primarily related to neutropenia and immunosuppression, including repetitive bacteremia, fungal and viral infections, and pneumocystis carinii identified in one pt. prior to the institution of Bactrim prophylaxis. In several pts., an interesting pattern of gram positive followed by gram negative bacteremia was seen.
Neurologic toxicity seen in the pilot pts. (reported ASCO 5:194, 1986) has been totally eliminated by avoiding concomitant administration of intrathecal (IT) and high dose (HD) systemic cytosine arabinoside (Ara-C). Details of the protocol follow:
Cyclophosphamide 1 gm/m^2 is given x 3; Vincristine 1.5 mg/m^2 is given x 5; HD Methotrexate (Mtx) 3 gm/m^2 is given x 3 followed by leukovorin rescue; and HD Ara-C 3 gm/m^2 is given q 12 hours x 3 or 4 days x 2 courses. IT Ara-C 40 mg/m^2 is given x 2 during initial induction and IT Mtx 6 to 12 mg with HD Mtx courses.

P 30 TREATMENT OF LYMPHOBLASTIC NON HODGKIN'S LYMPHOMAS IN ADULTS.

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From 1980 to 1986 thirty two patients with lymphoblastic lymphomas (LBL) were included in two successive chemotherapy protocols. 14 patients were treated by an induction regimen with Cyclophosphamide (C) 600 mg/sqm d1. Oncovin (O) 1.4 mg/sqm d1 and 5, Adriamycin (H) 45 mg/sqm d1 and Prednisone (P) 60 mg/sqm d1, 6 cycles were carried out at 4 weeks intervals. (protocol A). The other patients were treated by the same modalities with increasing schedules of Cyclophosphamide to 1500 mg/sqm d1 and Adriamycin 90 mg/sqm d1 4 cycles performed at 2 to 3 weeks intervals (Protocol B). Complete responders (CR) received CNS prophylaxis and maintenance therapy during 12 months, essentially by COP associated to Procarbazine 80 mg/sqm day 1 to 14. Median age was 52 years in group A and 27 years in group B (p=0.01). The male sex predominates in both groups (62.5%). 53% of patients presented with mediastinal involvement, 69% with bulky disease > 7 cm. Stage distribution was stage I : 3 pts, stage II : 5 pts, stage III : 2 pts, stage IV : 22 pts including 14 pts with bone marrow infiltration and 2 pts with CNS involvement. Except age, no initial parameters differ among both protocols. 22 patients achieved CR (69%), 45% in protocol A and 78% in protocol B (p=0.09). Age, sex, stage, bulky disease, B symptoms, number of visceral involvement localizations, leukemic infiltration did not influence likelihood of response but number of patients was weak. 11 of 22 CR relapsed. CR median duration was estimated to 60 months. No difference was observed in CR duration between the two protocol regimen. 4 of 11 complete responders with initial medullary involvement are alived without relapse after 24 months. B symptoms was the only factor influencing CR duration (p=.01). Median survival duration was 22 months with a plateau at 41% after 25 months. Three factors were found lengthening survival duration : male sex (p=.07), B symptoms (p=.05) and protocol B (p=.09). In conclusion, use of an intensive induction regimen appears of benefit in this subgroup of high risk non Hodgkin's lymphoma.

P 31 NON-HODGKINS LYMPHOMA IN TREATED HODGKINS DISEASE. THE BNLI EXPERIENCE.

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The development of second malignancies following treatment for Hodgkins Disease (HD) is well documented. Acute leukaemia and solid malignant tumours have been reported from many centres, and more recently the occurrence of non-Hodgkin's lymphomas (NHL) has been highlighted.

In the British National Lymphoma Investigation (BNLI) trial '75 second malignancies were diagnosed in 2518 patients treated for HD between February 1970 and October 1986. Of these second malignancies, 11 were NHL, 14 were acute leukaemias and 48 carcinomas.

The pathology of the 11 NHL cases was reviewed; two were excluded on the basis that the initial diagnosis of HD was incorrect. and one case was excluded because the diagnosis of NHL was not confirmed. Thus the incidence of NHL in the BNLI series is 8 in 2518 patients (0.3%). Of these 8 patients there were 7 men and 1 female. Their ages ranged from 38-64 years at presentation with HD (mean 49) and all responded completely to treatment. 5 patients developed grade II NHL and 3 grade I NHL. The mean duration of time from treatment to HD to diagnosis of NHL was 9 years (range 6-12 years) in the grade II NHL group and 2.7 years (range 2.2-4 years) in the grade I NHL. The 3 patients with grade I NHL were all clinical stage I HD, with a mean age of 57 years: in each case the NHL was of follicle centre cell origin and all received radiotherapy. In contrast, none of the grade II NHL patients were clinical stage I HD and 4 out of 5 were treated with MOPP; their mean age at representation was 53 years.

The significance of these preliminary results will be discussed and the incidence of NHL in the BNLI series compared to that of other large trials.

P 32 A COMPARATIVE STUDY OF ALLOGENEIC AND AUTOLOGOUS BONE MARROW TRANSPLANTATION IN REMISSION OF DISEASE IN NON-HODGKIN'S LYMPHOMA.

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In October 1986, 262 patients had received bone marrow transplantation (BMT) for non-Hodgkin's lymphoma (NHL) and have been registered with the European Bone Marrow Transplant Group (EBMT). 220 patients received autologous BMT and 42 patients allogeneic BMT. 220/262 (84%) had high grade histology. 78.5% of patients receiving allogeneic BMT were in complete remission (CR) at the time of BMT whereas 87% of patients treated by autologous BMT were treated in relapse. We have therefore compared the outcome of adult patients treated by autologous or allogeneic BMT in remission of disease. 71 patients were transplanted in first or subsequent CR, 27 (38%) by allograft and 44 (62%) by autograft. All the allograft group were conditioned using total body irradiation (TBI) containing regimens but TBI was used in only 12/44 (27%) in the autografts. At the time of analysis 47 patients were alive, 18/27 (67%) allografts at median follow-up of 14 months post BMT and 29/44 (66%) autografts at median follow-up of 16 months post BMT. 3 patients (11%) had procedure-related mortality in the allografts and 3 patients (7%) died during the autograft procedure. 33% of the allografts developed acute graft-versus-host disease of Grade II or greater and was the cause of death of 2 patients. Relapse of disease was the commonest cause of death, accounting for 4 (15%) of deaths in the allograft group and 7 (16%) of the autograft group. Patients transplanted in first CR had a survival advantage over those transplanted in subsequent CR ($p = 0.05$). The source of marrow, whether autologous or allogeneic, was found not to influence overall survival or probability of relapse of disease in these patients.

P 33 ALLOGENEIC BONE MARROW TRANSPLANTATION FOR LYMPHOID MALIGNANCIES.

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To determine the efficacy of allogeneic bone marrow transplantation (BMT) in patients (pts) with poor risk high grade lymphoma (bone marrow, CNS and/or skin involvement) in first remission (group I) and in pts with advanced lymphoid malignancies (group II), we have carried out a study in 6 group I-pts (age range: 18-38 years) and 18 group II-pts (age range: 22-41 years).

The 6 group I pts (5 lymphoblastic and 1 diffuse undifferentiated lymphoma) received a preparatory regimen consisting of 1320 cGy total body irradiation (TBI) and high dose (100 mg/kg) cyclophosphamide (CY) while in first remission. Of these 6 pts, 4 are alive and in complete remission (CR) at 6, 12, 19, and 45 months after BMT. One pt underwent a second BMT after relapsing at 7 months but died 27 months later with recurrent disease. One other pt in group I died with chronic graft-versus-host disease (GVHD) at 34 months; no evidence of lymphoma was found at autopsy.

In a phase I/II study 18 group II-pts (12 Hodgkin's disease; 4 diffuse large cell and 1 lymphoblastic lymphoma; 1 prolymphocytic leukemia) received escalating amounts of single dose TBI (26 cGy/min) on day -7 (5 pts received 300 cGy, 6 pts 500 cGy, 6 pts 650 cGy and 1 pt 750 cGy) and chemotherapy (Etoposide, 60 mg/kg on day -5 and CY, 100 mg/kg on day -3) followed by BMT on day 0. CR was achieved in 12 pts; 6 of these 12 pts are alive for 4 to 23 months after BMT and 6 pts have died (5 with interstitial pneumonia and 1 with chronic GVHD/bacterial pneumonia. 4 pts who had achieved only a partial response succumbed to progressive disease and 2 were too early for evaluation when they died within 3 weeks after BMT with fungal infections.

Conclusion: Our data suggest that 1) BMT is an effective modality and should be considered in pts with poor risk high grade lymphoma during first complete remission; 2) A significant number of pts with advanced disease (66%) achieve CR, but mortality due to pulmonary complications remains high (6/14 who had received prior radiation therapy to the chest developed fatal pneumonias); nevertheless, BMT is a form of therapy with a considerable response rate, and deserves further evaluation in pts in whom the underlying disease is less advanced.

P 34 100 ABMT IN ADULTS NHL AT RELAPSE : BACKGROUND FOR AN INTERNATIONAL RANDOMIZED STUDY ON RELAPSED INTERMEDIATE AND HIGH GRADE LYMPHOMA

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. In 1986, data from bone marrow transplant centers in Europe and America were pooled to determine the outcome of Autologous BMT in adult patients with relapsed diffuse intermediate or high grade NHL (excluding Burkitt lymphoma), and to identify the prognostic significance of response to therapy preceding the bone marrow procedure. One-hundred patients were treated with high dose chemotherapy alone (61 patients) or high dose chemotherapy plus total body irradiation (TBI) (39 patients). Thirtyfour patients had disease that was primarily refractory to chemotherapy (ie never achieved complete remission) and had progressive disease (no CR). Sixty-six patients achieved a complete remission (CR) with primary chemotherapy but later relapsed. After receiving further chemotherapy (salvage) at "traditional" doses 22 patients had no response or disease progression (ie resistant relapse - RR) and 44 patients responded with partial or complete responses to salvage chemotherapy (ie sensitive relapse - SR). The actuarial 2-year disease free survival for the entire group was 20 % with the last death at 31 months and a median observation time of 33 months. Disease free survival was significantly related to previous response to chemotherapy. The two-year disease free survival was 0 %- no CR group, 14 %-RR group, and 38 %- SR group. Patients who had achieved a CR to initial chemotherapy had a superior disease free survival after ABMT when compared to patients never achieving a CR. Patients with SR had a better disease free survival than patients with RR. A multivariate analysis showed that the outcome was not affected by treatment regimens and histologic grade. Whether relapse occurred on or off therapy was also not of significance but the probability to be a SR was significantly higher for relapses off therapy. In conclusion, the multivariate analysis showed prior response to chemotherapy the only significant prognostic variable in patients with intermediate or high grade NHL undergoing ABMT.

. The international randomized study will began July 1st 1987 and could be summarized as follow :

- All patients with a intermediate or high grade histology at first diagnosis are eligible (ie transformation of nodular excluded).
- With the exclusion from the study of patients who never reach a CR in the course of their disease the group of **sensitive relapse** only will be selected for the trial (ie responders after 2 courses of DHAP).
- Purging marrow is not a major issue for this group of patients. The study will concern only selected patients with **normal marrow** and **no purging procedures** will be allowed in the ABMT arm.
- An early plateau was observed for the majority of CCR patients in these data and no maintenance therapy will be given after ABMT. **Pre-ABMT involved field radiotherapy** on iceberg of initial localisation of the relapses will be recommended as 75 % of the relapses are local relapses.
- In the chemotherapy arm of this study and in order to avoid any delay in the chemotherapy timing, involved field radiotherapy will be recommended for non progressing patients at the end of the program.