Poster Session III
ABSTRACTS - Third International Conference on Malignant Lymphoma, Lugano

P1 CLINICOPATHOLOGIC CORRELATIONS AND PROGNOSTIC RELEVANCE OF BONE MARROW AND PERIPHERAL BLOOD INVOLVEMENT IN ADULT NON-HODGKIN'S LYMPHOMAS. A MULTIVARIATE ANALYSIS OF 172 CASES.


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 (LGLM), 30% (20/67) for intermediate grade (IGLM), and 25% (11/44) for high grade malignant lymphomas (HGLM). 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 LGLM; 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 32/172 or 13% (25% of LGLM, 5% of IGLM, 7% of HGLM) and correlated significantly with BM+, low grade histology, hepatosplenomegaly and bulky disease. A further 27 cases developed a leukaemic phase during the course of the disease, after a median time from diagnosis of 12 mos. Regarding prognosis: the presence of BM+ per se does not affect survival (while lymph node histology and tumour bulk are the most important prognostic factors); peripheral blood involvement, both at diagnosis and during the course of the disease, carries a worse prognosis in the IGLM and HGLM, while in LGLM only the late leukemic spread significantly affects survival, heralding a rapid change to a more aggressive disease. In fact, a less differentiated histology was documented in all LGLM who had repeat lymph node biopsy at the time of secondary leukaemic conversion.

P2 MULTIVARIATE ANALYSIS OF RESPONSE AND SURVIVAL IN NON-HODGKIN'S LYMPHOMAS (NHL). Study on patients treated with the 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 of these predictors were associated with poor response [i.e., presence of systemic symptoms, and increased LDH values] and 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. Similarly 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 of covariates at the event time was calculated to derive the 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. The assessment of such a small number of pre-treatment variables can allow the identification of the best prognostic cut-off point, which in turn can represent a non-adquate treatment. These patients should consequently be considered as candidates for new treatment approaches since the time of diagnosis.

P3 PROGNOSTIC MODEL FOR DIFFUSE HISTIOCYTIC LYMPHOMA (DHL).

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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 Daniell et al. (Cancer Res 1986; 46:2572-2579). Factors studied included: age, sex, Ann Arbor stage, prior therapy, B symptoms, serum lactate 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) from the following mutually exclusive groups: i) peripheral lymph node (PLN) (including Waldeyer ring involvement, spleen); ii) extranodal disease (ES) = PLN; iii) supradiaphragmatic lymph nodes (RLN) = PLN; iv) bulky mediastinal disease (MED) = any other disease; v) ES with RLN. Ann Arbor Staging failed to dissect patient groups differing significantly in prognosis. As in Daniell 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 (based on Daniell 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 ES (43% alive); stage III = high LDH, PLN and/or ES or medium LDH, RLN + PLN + ES and/or MED (25% alive), stage IV = high LDH, RLN + PLN + ES 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.

P4 IDENTIFICATION OF MAJOR PROGNOSTIC SUBGROUPS OF PATIENTS WITH LARGE CELL LYMPHOMA TREATED WITH M-ABCD or M-ABACO. N. Shipp, M. Klatt, B. Yapp, D. Harrington, N. Jochelson, D. Rosenbthal, A. Karlic, G. Canollis, Dana-Farber Cancer Institute and Brigham and Women's Hospital, Boston, Massachusetts, USA.

We recently evaluated 121 diffuse large cell lymphomas (DLCL) patients treated with M-ABCD or M-ABACO between 1976 and 1983 for pre-treatment characteristics predictive of response and survival. In univariate analysis, several variables associated with decreased response rate and shortened survival were identified. Characteristics that retained significance in a multivariate analysis of survival (MOSA) 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 DLC patients treated with M-ABACO have been off therapy for at least two years. Therefore, we re-evaluated an expanded group of 169 DLC patients for predictive pre-treatment characteristics. In a multivariate analysis of the expanded group, each clinical characteristic previously identified as being associated with response and survival (performance status, B symptoms, stage, splenic involvement, pleural effusion, number of extranodal sites, and LDH) was significant as is one new feature, bone marrow involvement. In MOSA of the expanded group, the two factors of major significance in the original study, PS and mass size, retain significance. However, LDH, a feature of borderline significance in the original study, loses significance and two additional features, stage and LSI, retain significance. We used the four features which retained significance in the MOSA of the expanded group (PS, stage, LSI and LDH) to construct a new model containing 16 categories of patients at increasing risk for relapse and shortened survival. These categories can be broadened to three groups with respective predicted five-year survivals of 95%, 75%, and 42%. The identification of the patient groups with respective five-year survival rates of 95%, 75%, and 42% has important implications both from the design of randomized therapeutic trials and the determination of optimal therapy for individual patients.
P 5 PROGNOSTIC VARIABLES AFTER "F-MACHO" IN ADVANCED AGGRESSIVE LYMPHOMAS
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From 1,800 to 12,840 eighty-one old patients (pts) with advanced stages (II-IV) of diffuse large lymphoma were treated with six courses of an innovative chemotherapy program combing prednimustine with six cell cycle active drugs (vinristine, cyclophosphamide, 5-fluorouracil, high-dose cytoxan arabinoside, vincristine, 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 70% and a 75% 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 from this study were analyzed by uni- and multivariate analysis. We examined the following variables: age, sex, histologic subtypes (Working Formulation), stage, B-symptoms of extranodal involvement, number 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-variability analysis the only factor which adversely affected both the CR rate and DFS was the presence of bulky disease. Also B-symptoms adversely affected CR but did not influence 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 number of courses to CR. These results indicate that F-MACHO 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. L. Dubich, W.D. Emswier, and B. Semmich
University of Michigan, K.S. Zuckerman, R.H. Wheeler, and A.F. LoBuglio, University of Alabama

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 high dose combination: Adriamycin 120 mg/m^2 IV on Day 1, Vinristine 2 mg IV on Day 1 and Prednisone 50 mg PO Days 1 to 14 (8 cycles). CR was achieved in 21 days for 3 courses followed by 3 courses of Cyclophosphamide 800 mg/m^2 IV Day 1 and Cytoxan 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, II A 5, I A 9, and I B 5. Two failed to enter remission. Three died during induction, one due to toxicity, one due to her second malignant infarction and one due to hepatitis. There were two CNS relapses, one at 4 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 6 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 non-related causes 16% (2 during induction and 2 interstitial). The median survival of the other patients is 6 months. It is of interest that one patient with diffuse mixed lymphoma relapsed as poorly differentiated lymphoma. The lymphoma in PDL is then in an eradicated large but not small cleaned cells. One patient with PDL was 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 aggressive chemotherapy has produced a better relapse free survival in patients with large cell lymphoma than conventional dosages, 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 patients 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, with a total of 37 years of reported homosexual relations, and one was infected by a blood transfusion. Five patients had high malignant (4 IWF 1, 1 IWF J) and 2 intermediate (IWF 0) non-Hodgkin's lymphomas. At the 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 total T4/A8 ratio (0.18) 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 1 month 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 III A, histologically T-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 the AIDS patient (classification IX D). While the overall 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 1.65 (95% CI: 0.40-5.85), which is significantly higher than the incidence of 0.01-0.1/100,000 in the general population. The incidence of malignant lymphoma in our anti-HIV-positive patient population is 1.65 (95% CI: 0.40-5.85), which is significantly higher than the incidence of 0.01-0.1/100,000 in the general population, and the incidence of malignant lymphoma (15/100,000) in Switzerland, that the incidence of NHL in patients with AIDS (follow up 3 years) is more than 30 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 localization are frequent in patients with acquired immunodeficiency 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 DESIGNED CHEMOTHERAPY REGIMENS IN 65 PATIENTS (P50). V. Zaffaroni, U. Cerrini, F. Gatta, A. Silvagni, A. Carbone, S. Gandolfi, Centro di Riferimento Oncologico, Aviano, Italy

Elderly patients (70 years old or older) with Non-Hodgkin's lymphoma are usually not considered for aggressive chemotherapy regimens because of high risk for serious complications.

Between August 1979 and September 1989, 65 patients aged 70 or older (median 75 years) with NHL entered two consecutive trials. One with MTX, 100 mg/m² p.m. for 9 days every 21 days (32 pts). Forty-five patients were previously untreated, 21 were previously treated. Forty patients were intermediate and high-grade cases according to the Working formulation. 16 patients were cases with systemic disease; 27 patients were stages I-III, and 9 patients were stages I and II. The median performance status was 70 (range 0-10). Response and survival are reported in the table:

<table>
<thead>
<tr>
<th>No. of evaluable pts</th>
<th>Response</th>
<th>3-year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/PR</td>
<td>Overall Disease-free CR</td>
<td></td>
</tr>
<tr>
<td>No. of total pts</td>
<td>60</td>
<td>30%</td>
</tr>
<tr>
<td>No. of pts with CR/PR</td>
<td>42</td>
<td>20%</td>
</tr>
<tr>
<td>No. of pts with CR/PR</td>
<td>18</td>
<td>12%</td>
</tr>
</tbody>
</table>

There are no significant differences in response and survival as far as stage, histology, prior treatment and performance status are concerned. Overall toxicity was mild. Severe toxicity (grades 3 and 4) estimated according to WHO criteria was observed only in 16/65 courses of therapy (one with one toxic death (grade III febrile). 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 comparable 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. B. Hoerni (1), J. Sott (2), H. Egba (3), M. Jost (4), J. Reug (4), 1) Foundation Berghofer, Bordeaux and 2) University Hospital, Grenoble, France.

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 and the other at a university hospital) put together two series including 1300 patients (pts) with NHL observed during the past 15 years. Among them, 70 (5.8%) were diagnosed after the age of 80 years. 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 (PS) was determined in 52 pts: 6 pts with PS 0 and 60 pts in 15, 10 pts had severe associated visceral deficiencies, mainly cardiovascular, 40 pts had low grade NHL (following FCL classification: 1 lymphocytic, 8 lympho-hamatoic, 25 follicular) and 30 high grade NHL (7 lymphocytic, 6 immunoblastic, 17 unclassifiable). Clinical staging was often incomplete (25 pts had abdominoc-tail 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 9 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, tumor extension and performance status. 47 pts were given chemotherapy (12 with one or two drugs, including corticosteroids, 26 with CHOP (cyclophosphamide, vincristine, doxorubicin, prednisone), 9 with heavier chemotherapy including an anthraclycline). 37 pts were given radiotherapy (27 radical, 9 palliative). 15 pts had surgery, 17 treatment was considered as ideal in younger pts, in 12 pts, good in 34 pts, limited in 24 pts. Toxicity was minimal (grade 1 or 2) in 62 pts, grade 3-4 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), 3 in partial remission, 5 in stabilization and 2 as failures. A response was seen in 51 patients. CR was seen in 23 of 60 CR. 37 of 70 patients were alive more than 5 years. In conclusion, NHL are frequent among older patients, presenting itself as a result of many metastatic and non-typical presentations. These patients are difficult to treat and to follow up.


From 1981 to 1984, 11 patients (pts) with NHL were treated with an induction regimen of Cyclophosphamide (CYC) 400 mg/kg/day 1 and 8, Vinristine (VTR) 1.4 mg/m²/day 1 and 5, Prednisone (P) 80 mg/m²/day 1 to 4 (PCP) randomly associated to Adriamycin (ADR) 20 mg/m² day 1 and 8 (PCPo). 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 Chlorambucil (10 mg/m² p.o. d 1 or CV). The histopathological distribution was diffuse well differentiaed 12 pts, nodular lymphocytic 7 pts, nodular mixed 3 pts, stage distribution was stage I: 8 pts with bulky abdominal masses, stage II: 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 regimens. 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 Adriamycin. Complete response to treatment was the only significant factor (p = 0.01, Cox’s model) in longening the freedom from progression time. In case of relapse, median of second induction was 8 months. At the moment of introduction of Adriamycin in prognostically favorable NHL did not appear to modify the response and survival of NHL, and the induction program of 6 months observation even after several months increases survival without progression and long term survival.

P 11 LOW GRADE LYMPHOCYTIC LYMPHOMA - THE UNIVERSITY OF CHICAGO EXPERIENCE. B. Samuels, J. Ultsman, C. Barker, M. Pearson, S. Williams, and S. Watson. University of Chicago, Chicago, IL 60637, USA.

We retrospectively evaluated 159 patients (pts) with low grade lymphoma seen and treated at the University of Chicago. The majority were non-Hodgkin, poorly differentiated lymphoma (PDL: N); 26% had PDL: N with areas of diffuse disease (PDL:N/D); 10% had nodular, mixed cell lymphoma (MC:HL); and 6% had nodular, mixed cell lymphoma (NCL). Most pts had extensive disease at presentation (84% stage III/IV) and 63% had received prior treatment. There was no association between histological group (IG) and stage at presentation. 42 pts had no therapy within 1 month of staging workup (no initial therapy). 76 pts had initial radiotherapy (RT) or oral chemotherapy (initial palliative therapy). 42 pts had initial aggressive therapy (AT). We examined change in therapy over time by evaluating overall therapy gds: 12 of the NIT pts did not require any therapy (never treated), 31 NIT pts eventually received therapy, 33% of all pts received overall aggressive therapy only (AT), 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 ITP 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 ITP). Only 43% of pts with NIT who had OAT and 25% with ORP achieved CR. For NCL, disease free survival (DFS) was 38 mo for ORP, and 51 mo for CR in pts of ORP. In comparison, DFS was 135 mo for CR pts with ITP. Median survival (MS) for all 159 pts was 90 mo (147 mo for CR and 54 mo for non-CR pts). Median survival (MS) for NIT pts who received OAT, and achieved CR was 92 mo, compared with 147 mo for ITP pts with CR. MS for NIT pts who never required therapy was not reached at 11 mo. OAT (p = 0.008) and achievement of CR (p = 0.0001) were associated with longer survival in treated pts. DFS and MS were significantly lower for age <60 years (p = 0.007), absence of 8 symptoms at presentation (p = 0.004), and number of initial sites of disease (p = 0.009). No clinical parameters at presentation were associated with a change in therapy, or for need for eventual therapy in NIT pts. For ORP, PDL: N/D, and ITP, there was no difference in survival by initial therapy, but pts who had ORP were superior to pts with ITP. For MC: HL, pts who had IAT or OAT survived significantly longer than pts with NIT, ITP, or RT. Asymptomatic pts with favorable lymphomas can be observed for a considerable time. However, the subset of NIT pts who do eventually require therapy have a worse prognosis than pts treated initially. MC: HL pts may benefit from aggressive therapy at diagnosis.


Fractionated TBI was used at the RAI 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, 13 pts were in stage II, 6 patients stage II, 11, 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 unfavorable (unfav), and pts with low grade as favorable (fav).

Results

TBI 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 278 vs 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 71% for unfav pts, with a median duration of resp. 7 and 4 months. Second Line was given to 24 pts (168 for fav. 648 unfav). third line to 12 pts (8% for fav. 12 unfav) and fourth line to 2 pts (8% for fav. 12 unfav).

Median duration of response rate was always shorter for unfav pts.

Conclusion

TBI 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 TBI did not compromise subsequent chemotherapy.


The value of consolidative radiotherapy (RT) in patients with advanced (Stages III and IV) lymphocytic lymphoma after induction chemotherapy (CVP) consisting of vincristine, prednisolone, and cyclophosphamide 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 analyses the results attained in patients with a nodular histologic pattern (low-grade malignancy in the International Classification). Ninety-five 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 achieved 5-year survival (p = 0.0014) for those who received RT and 36% for those receiving maintenance CT only. The 5-year survival from the time of initial RT and the 5-year survival at that time whether RT had been administered or not. In subgroups with poorer prognosis (lymphocytic lymphoma mixed nodular diffuse histologic pattern) there was advantage to receiving the RT (p = 0.031) for Stage IV patients, 25 vs 11% for patients with nodular plus diffuse pattern, but there were no differences in any of the subgroups analyzed with respect to overall survival at 5 years from the date of randomization.


Centrocytic lymphoma (CCL) is a unique histopathologically by the Kiel classification of non-Hodgkin's lymphomas (NHL), has to be classified as a separate entity of low-grade malignancy NHL also by clinical and prognostic criteria. As shown by the results of a prospective active control group the International Lymphoma Study Group, these criteria include predeterminant of male sex, tendency to early generalisation, insufficiency of the response achieved by the treatment and the suddenness of progression, unexpected steep, continuous decline of survival curves resulting in short median (30 months) and overall (5 years) survival times. In order to improve the therapeutic approach to advanced NHL we performed a randomized multicenter trial. The study was carried out in the clinical department of the Ann Arbor classification (2 pts presenting stage I, 8 pts stage II, 32 pts stage IV disease). Of 71 pts with stage I-IV disease, 56 fulfilled the randomisation criteria. In both chemotherapy groups the initial pathological and performance status criteria (presence of B symptoms, increased serum LDH activity, sex distribution) did not differ significantly. Complete remissions (CR) were achieved in 15/23 (65%) of pts treated with CHP and 11/29 (38%) of pts with CVP. The median survival probability in CR achieved in pts treated with CHP was 37 months, 17 months, respectively. None of the observed differences were statistically significant. Compared to the strategy followed in the aforementioned previous study early initiation of chemotherapy offers a slight prognostic advantage, but the manifestation of the disease does not influence the risk and stability of CR or the median or overall survival probabilities. Also, neither CVP nor the CHP regimen can be considered a curative treatment approach to advanced CCL.

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.H. McWilliam, J.M. Jones, I. Tyson, D. Gough, Department of Pathology, Department of Histopathology, Ydept. 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 randomised with combined maintenance chemotherapy with cyclophosphamide, vincristine, and prednisolone (CVP) followed by radiotherapy to sites of previous bulk disease. Each patient was 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 that factors that predicted complete response and the achievement of a CR (p = 0.0001) female sex (p = 0.0008), absence of bulky 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 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 = 0.002) 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 39% of patients, mainly because of progression of disease and the induction of side effects. A total of 52% of patients were still alive at 5 years, and 12% of the median RFS by 38 months and it may therefore have a role in the management of low grade NHL.

TREATMENT RESULTS WITH RADIATION THERAPY OF EXTRANODAL LYMPHOMA OF THE HEAD AND NECK AREA. N. Masaki, I. Ikeda, Department of Radiology, Osaka University Hospital, Osaka, 1-1-50, Fukushima, fukushika-ku, Osaka, Japan

To determine possible effects of induction chemotherapy, long-term effects of treatment as well as the causes of failure, have been carried out in the Department of Radiology, Osaka University Hospital. Grouping according to the site of involvement was to be the following order: Waldeyer's ring 104(11.4), Stage I 28, and stage II 36, thyroid 21(15%), paranasal sinus 17(9%), oral cavity 17(9%), orbit 10(5%), nasal cavity 6(3%), and neck 4(3%). Histopathological distribution was 55% DM, 26% GPOG, 9% UGM and 6% others. All patients received a definitive course of radiotherapy(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 field. There was a marginal recurrence in chemotherapy combined group. In Stage I disease a 5-year disease-free survival rate was 71% by radiation therapy alone, and 91% by chemotherapy combined. Patients with Stage II disease had much poorer results: 5% of 5-year disease-free survival rate by radiotherapy alone, and 84% by chemotherapy combined. Patients with Stage III disease in the absence of orbit, 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 were Waldeyer's ring, lymph nodes in the abdomen and GI tract, in the cases of paranasal sinus, and oral cavity sites of relapse were rather widespread; breast, 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-IRRADIOTHERAPY FOR STAGE III AND IV NON-HODGKIN’S LYMPHOMAS OF FAVOURABLE HISTOLOGY: J.H. Neurath, P. Cornes, M.J.V. Burgers, M. Monnendahl, J. Thomas, A. Tanyzy, R. Sorensa on behalf of the EORTC Lymphoma Cooperative Group

Between July 1980 and November 1985 a cooperative clinical trial was run by the EORTC Lymphoma Group to investigate whether a short course of total body irradiation (TBI, 2.5 Gv in 25 fractions, 3 times a week) had the same survival results as combination chemotherapy (CHOP, cyclophosphamide, Adriamycin, prednisone, 8 courses) with chemotherapy. 93 Patients were entered, 10 patients were non-evaluable, mainly because of the same ineligibility based on histology. 65 Patients are evaluable for response: TBI CR 334, PR 37%. CHOP CR 564, PR 13%. No difference in response rate for stage III and 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 75% 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 chemotherapy-radiotherapy.


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Patients (pt) with NHL stage III-IV aged 15-70 years were enrolled in EORTC trials 20751, 20851 and 20852 for multiagent treatment. Induction chemotherapy consisted of CTX 60 mg/m², Cytosine 600 mg/m², Prednison 40 mg/m² x 5 (CHOP); 3 courses q. 3 weeks, or the same with Vincriistine 1.4 mg/m² and Bleomycin 30 mg/m² weekly for 6 courses. IR without adjuvant chemotherapy: IR 25-35 Gy in 3-4 weeks, dose depending on irradiation status, on stage III a lymphode masse > 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. Due to the imbalance between the control of the protocol, a group C (78 pt) existed for whom IR was indicated but not given. For G + 5 pt from participating centres, extent of disease for each lymphode area and administration of IR was retrospectively coded. Characteristics of patient material: stage III 67 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 52 pt, diffuse 82 pt. (24 pt unspecified).

Treatment results expressed as actuarial 5 years survival (s) for different subgroups: LG 67%, HG 45% (p = 0.03), follicular 70% ; stage III 61%, stage IV 51% (p = 0.005) with IR versus 11 without IR 44% (p = 0.04). No lymphode area masses > 5 cm (46 pt) or 1 or 2 areas (73 pt), LG s = 74%, 3 or 4 areas (52 pt), 47% (p = 0.0001). Only LG 11 pt had 5 or more areas with large tumour masses. s5 for the different treatment groups: A 65%, B 654, C 48% (p = 0.012). The difference was most significant for the following subgroups: diffuse cell pattern: B 50%, C 35%, (p = 0.002); large cell/histiocytic: B 5%, C 15% (p = 0.008).; stage III B 70%, C 39% (A 70%). LG IR x 3 cycles: B 62%, C 48% (p = 0.037). If all lymphode area masses < 5 cm, the s5 difference was borderline significant: B 60%, C 50%. In the whole patient group only 10 relapses occurred (2.5%) in LG areas.

Although this was not a randomized study, the findings suggest that irradiation in NHL stage III-IV with large or slightly regressiv tumour masses especially for stage III, for diffuse cell pattern and for high grade histology.


One hundred and seven non-Hodgkin’s lymphomas (NHL) patients were treated with the M-BAECOD regime (Belleau 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). There were 3 stage 1, 3 stage II, 35 stage III and 47 stage IV. Grades were as follows: 77 intermediate grade (19-7, 9-1, 39-1, 19-G) and 30 high grade (11-1, 7-1, 7-2, 5-2). Eight patients received a slight modification of the M-BAECOD regimen. Methotrexate 1.5 mg/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 (13%). Other significant prognostic factors included elevated LDH and pathological grade (1 and 3).

Encouraging results in PR patients may be due to efficacy of salvage protocols. After 4 courses of M-BAECOD, 9 PR were converted to CCR: 4 patients by MME regime; 4 patients by intensive chemotherapy plus autologous bone marrow transplantation; and 1 patient by intensive therapy plus autologous bone marrow transplantation. Results of rescue protocols in cases of no response (3 CCR out of 24 patients) of relapse (3 CCR out of 12 patients) following induction therapy were disappointing.

The toxicity of the M-BAECOD in our series was very low with only 4 treatment-related deaths (4%).

We conclude that M-BAECOD is very efficient in NHL grades D, E, F, G and H.


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 COP (n=34) or the CPM-SLM regimen (n=28) from 1979 to 1985 were analysed retrospectively. The distribution of initial clinical and prognostic parameters was comparable in both groups; the cases with primary CHM disease, present only in the COP group, were excluded from further analysis. Half of the patients received additional radiotherapy. The complete remission rate was significantly higher in the COP treated patients (65% vs. 56%, p=0,0009). The overall survival curve of COP-treated patients declined over a period of 70 months until starting to form a plateau at 20 months. The COP 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 COP- and of only 32 months for COP-SLM-treated patients. These data prompt a randomised trial by the NHL Study Group with the aim of establishing COP-SLM as first line therapy (5 cycles) complemented by 2 cycles of VFP for complete responders or employing an early switch to COP-SLM in poor responders. Response is evaluated early after 3 cycles of COP-SLM and again after completion of all 7 courses by complete restaging. Patients in complete remission are then randomly either to receive adjuvant radiotherapy or to be followed without further treatment. Up to date 10 patients have been included for this prospective trial, of whom 34 have already been followed beyond the first restaging. In a preliminary analysis, it will be shown if the findings of the COP-SLM trial on 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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In the treatment of high-grade malignant non-Hodgkin's lymphoma (NHL) combination chemotherapy with CHOP has been extensively used. It has been advocated that increasing the interval between drug delivery might improve the cure rate. Based on this assumption a Swedish randomized study has been performed on an unsedected group of adult patients with high-grade malignant NHL. Within the period from 1 February 1984 to 1 February 1986, 750 patients (124 men; 87 women; mean age 63 years, range 17-75 years) were randomized between 9 courses of CHOP (cyclophosphamide 500 mg/m², vincristine 2 mg and prednisone 50 mg/m² for 5 days) and 14 courses of CHOP-M (cyclophosphamide 500 mg/m², vincristine 2 mg, prednisone 50 mg/m² for 5 days) every third week and CHOP-M (cyclophosphamide 500 mg/m², vincristine 2 mg, prednisone 50 mg/m² for 5 days) given on day 14 followed by lenograstim (recombinant G-CSF) 300 microg every 12 h for 24 h. Nine patients were not treatable in either regimen. Eight of them (4 in each group) had 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 stage I (2), II (136) III-I (174). The histopathological classification according to the Kiel classification was Centrocitic (large cell) immunoblastic 3, Lymphoblastic 3, diffuse Centrocitic/Blastoid 34, truly histiocytic 4, high-grade NHL 48.

Results: In December 1986 204 patients (104 CHOP; 100 CHOP-M) were evaluable. Complete remission rate was 59/104 (56.5%) in the CHOP group compared to 9/100 (60%) in the CHOP-M group. The relapse rate of 15 patients have 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 of the treatment of high-grade malignant NHL.

P 23
INTENSIVE TWO-PHASE CHEMOTHERAPY (CT) FOR HIGH-GRADE NON-HODGKIN'S LYMPHOMA (NHL). NSA Stuart, GRP Blackledge, JA Child, P Fletcher, KJ Kavanagh, MH Collins, 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, high-dose prednisolone 400mg/m² p.o. day 1, Adriamycin 250mg/m² i.v. day 1, L-Asparaginase 30,000units/m² i.v. day 1) followed by maintenance regime of VAMP (250mg/m² i.v. day 1, 40mg/m² p.o. days 2-9) for 2 more days. Prednisolone 60mg/m² i.v. p.o. days 1, 4, 7 and 10 for 2 days. Followed by further intensive CT (VAMP: vincristine 2mg i.v. day 1, Adriamycin 250mg/m² i.v. day 1, Etoposide 250mg/m² i.v. 150mg/m² p.o. days 1-3) for 28 days. Patients reaching less than 3 courses of CVIPs following CR was given to most pts on an outpatient or day case basis.

110 pts with histologically proven, high-grade (Reit) NHL not previously exposed to CT have been treated with this regime. Median follow-up is 21 months. 3 pts (2.7%) had complications treated. Mean age of pts was 52 years (range 14-78), 44/110 pts were aged over 60. Stage (St) of the pts were as follows: St I = 9 (all with bulky abdominal disease), St II = 23, St III = 20, St IV = 58. 65 pts had B symptoms, 34.109 pts had disease more than 10cm in greatest diameter.

Mean percentages of protocol dose given during VAMP were as follows: Adr, 87%; Vinc, 82%; Meht, 83%; Pred, 95%. Number of pts having less than 75% of protocol dose for each drug were: Adr, 28/110 (25.49); Vinc, 23/110 (20.91); Meht, 89/110 (79.54); Pred, 11/110 (10%). 10/110 pts had no dose modification during VAMP. 60/100 pts had no delay. 21 pts did not receive CVIPs, 17 because they died during VAMP and 4 because of physicians choice. Mean percentages of protocol dose given during CVIPs were as follows: Vinc, 82%; Cyto, 82%; VP-16, 81%; 28/110 pts had no delay. Number of pts having less than 75% of protocol dose for each drug (2 pts no data) were: Vinc, 22/82 (27.08); Cyto, 16/82 (19.51); VP-16, 18/82 (22.05); 28/110 pts had no delay. Mean survival was 12 weeks, median relapse-free duration was 134 weeks. Toxicity was acceptable in both phases of treatment. Neutropenia below 1.5 occurred in 89% of pts during VAMP, 52% during CVIPs. Platelet counts below 50,000/µl occurred in 6% during VAMP, 4% during CVIPs. Moderate or severe mucositis occurred in 25% of patients during VAMP, 32% during CVIPs. Nausea and vomiting occurred in 17/110 (15.4%) and 13/110 (11.8%). 13/110 (11.8%) had grade 2 alopecia. No other grade 3 or 4 toxicities were noted. 73/110 (65.9%) dropped out to treatment consisting, 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 within advanced stage disease. We have commenced a randomised, prospective trial comparing standard CVIPs with this regime in which to be compared with CHOP from VAMP-CVIPs are scheduled on a weekly basis (CAPOMED). Main end-points will be toxicity, remission rate and survival.
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P 25
Treatment of intermediate and high grade malignancy non-Hodgkin's lymphomas (NH) with a platinum containing combination alternating with Methotrexate and B-CHOP. Greek Lymphoma Research Group
Cis-platinum (P) Etoposide (E) and Vindesine (V) have been found active both alone and in combination in various combinations in the treatment of NHL. The combination of PVE plus Methotrexate (MTX) with Leucovorin rescue (LR) was administered in a pilot study to 18 previously untreated patients with NHL in relapse and produced remissions in 35% of the patients with acceptable toxicity. Therefore we initiated a study to evaluate the response rates and duration of previously untreated patients with intermediate and high grade NHL with the following drug combination: P:50 mg/m2 i.v. and V:3 mg/m2 i.v. days 1, 8, 15, MTX:1g/m2 i.v. infusion day 14 with LR, followed by B-CHOP on days 1 and 8. Cycles (PVE-MTX-LR/B-CHOP) were repeated every 49 days to a total of 6 cycles. Thirty-nine patients were 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 I, II, stage III and stage IV disease. Complete remission (CR) was achieved in 77 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 hematologic) 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. Forty-three patients had to moderate myelotoxicity and none nephrotoxicity or hematotoxicity. The estimated probability of survival at 2 years was 72.7% and of disease-free survival 69.3%.

The overall response rate of 92% with our treatment protocol is encouraging but long follow-up is necessary to access the durability of remission. The toxicity has been acceptable.

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- Thessaloniki Hospital (V. Tsaligou)
- Medical Center of Athens - N. Constantoulakis (Chairman)

P 26
PHASE I/II TRIAL OF HIGH DOSE ETOPOSIDE IN PATIENTS WITH LYMPHOMA. D. C. Cass Jr., B. Gabby, T. J. Blevins, R. Boyd and F. O'Leary, Maine Medical Center, Portland, ME, University of Alabama, Birmingham, AL, Ohio State University, and Adria Laboratories, Columbus OH

Utilizing Adriamycin in high doses (120 mg/m2), significant responses have been seen both as a single agent in refractory lymphoma and in combination with other agents. Analogous to the findings of other workers, we observed complete and sustained granulocytopenia seen with high-dose Adriamycin, which led us to study a new analogue of Adriamycin, epipodophyllotoxin at high doses (250 mg/m2). Adriamycin (Adriamycin) was administered at doses of 150 mg/m2, 180 mg/m2 and 220 mg/m2 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 to Adriamycin in the high dose group.

The dose level was escalated based upon response and toxicity at the previous level. Sixteen of the final ten patients treated received the maximum dose of 220 mg/m2 every 3 weeks (range 1-10). The response rate was independent of the dose levels. Neutropenia was observed with median platelet nadirs of 375,000/mL at all levels. Forty-two percent of patients (8 patients) had fever/nonpneaemia and required antiinfectious therapy. One treatment-related septic death occurred. At the 180 mg/m2 level, the majority of patients failed to have hematologic recovery by the day of next scheduled therapy. Adriamycin (60 mg/m2) fever immediately following treatment (63%); mild/moderate stomatitis (39%), nausea/ vomiting (33%) were the most common hematologic toxicities. No patient developed clinical or laboratory evidence of congestive heart failure. Myocardial infarction occurred in 1 patient. The overall 1 year freedom from progression of the entire group of patients fell from 0.63 to 0.56. A 10% change in the radiographic disease fraction (RD) was noted in 3 patients. A mycophenolate therapy in 1 patient can produce a 50% response rate in previously-treated patients with lymphoma with appropriate supportive care. The recommended dose trials in untreated patients was 180 mg/m2. Cardiac function studies need to be assessed regularly.
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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 bacteraemia, fungal and viral infections, and pneumocystis carinii identified in one pt. prior to the institution of neotrin prophylaxis. In several pts., an interesting pattern of gran positive followed by gram negative bacteraemia was seen.

Neurologic toxicity seen in the pilot pts. (reported ASCO 5:394, 1986) has been totally eliminated by avoiding concomitant administration of intrathecal (IT) and high dose (HD) systemic cytotoxic antibiotic (Arac-D). Details of the protocol follow: Cyclophosphamide 1 g/m² is given x 3; Intrathecal 1.5 g/m² is given x 3; Methylprednisolone (Mtx) 3 g/m² is given x 3 followed by leukovorin rescue; and HD Arac 3 g/m² is given x 2 during initial induction and IT Mtx 6 to 12 mg with HD Mtx courses.

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From 1980 to 1986 thirty two patients with lymphoblastic lymphoma (LBL) were included in two successive chemotherapy protocols. 15 patients were treated by an induction regimen with Cyclophosphamide (C) 600 mg/m² qd. Methylprednisolone (MP) 1.4 mg/kg/day and 5, Adriamycin (A) 45 mg/m² qd days 1 and 4 and Prednisone (P) 40 mg/m² qd. 6 cycles were carried out at 4 weeks intervals. (Protocol A). The other patients were treated by a less intensive modality with increases of scheduling of Cyclophosphamide to 1500 mg/m² qd and Adriamycin 90 mg/m² qd 4 cycles performed at 2 to 3 weeks interval. (Protocol B). Complete responders (CR) received CNS prophylaxis and maintenance therapy during 12 months, essentially by COP associated to Procarbazine 80 mg/qd day 1 to 4. 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 a mediastinal involvement, 49% with bulky disease > 7 cm. Stage distribution was stage I: 1 pt, stage II: 5 pts, stage III: 2 pts, stage IV: 27 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 72% 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 mediastinal involvement are alive without relapse after 24 months. B symptoms was the only factor influencing CR duration (p=0.01). Median survival duration was 22 months with a plateau at 41 months after 25 months. These factors were found lengthening survival duration with sex (p=0.01), B symptoms (p=0.03) and protocol B (p=0.09). In conclusion, use of an intensive induction regimen appears of benefit in this subgroup of high risk non Hodgkin's lymphoma.

P 31
NON-HODGKIN'S LYMPHOMA IN TREATED HODGKIN'S DISEASE. THE BML EXPERIENCE. J.K. Henry, Department of Histopathology, Charing Cross and Westminster Medical School, London, SW 1, U.K.

The development of second malignancies following treatment for Hodgkins Disease (HD) is well documented. Acute leukemia 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) trial75 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 leukemias and 48 carcinomas.

The pathlogy 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 40) and all responded completely to treatment. 5 patients developed grade II NHL and 3 grade I NHL. The mean duration of time from treatment of HD to diagnosis of NHL was 9 years (range 0-12 years) in the grade II NHL group and 2.7 years (range 2-5 years) in the grade I NHL. The 5 patients with grade I NHL were all clinical stage 1 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 1 HD, with a mean age of 4 out of 5 of these 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 ALLOGENIC AND AUTOLOGOUS BONE MARROW TRANSPLANTATION IN REMISSION OF NON-HODGKIN'S LYMPHOMA. A.H. Goldstone, J.G. Gibben, P. Ernst, for the EMMT lymphoma group.

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 (EMMT). 220 patients received autologous BMT and 42 patients allogenic 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 and autografts 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 GVHD, 6 out of 11 greater or equal to grade 3 GVHD and all the cause of death of 2 patients. Relapse of disease was the commonest cause of death in the autograft and group and 7 (16%) of the autograft group. Patients transplanted in first CR had a higher chance of remission than patients 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.
ALLOGENEIC BONE MARROW TRANSPLANTATION FOR LYMPHOMA MALIGNANCIES: A.P. Kadmonen, S.J. Foran, P.J. Hummer, M.R. Dunbar, B.S. Szydlo, G.M. Schindl, J.L. Fishel, P.M. Parker, A.S. Stein, J.A. Lipsett, L.G. Blume. Department of Haematology and Bone Marrow Transplantation, City of Hope National Medical Center, Duarte, California

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 16 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 3320 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. The 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 38 group II-pts (12 Hodgkin's disease; 4 diffuse large cell and 1 lymphoblastic lymphoma; 1 lymphocytic 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 Cr, 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 (3 with interstitial pneumonitis and 1 with chronic GVHD/bacterial pneumonia). 4 pts who had achieved only a partial response (as opposed to progressive disease and 2 who were too early for evaluation when they died within 5 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 lymphomas during first complete remission; 2) A significant number of pts with advanced disease (66%) achieve CR, but mortality due to pulmonary complications remains high (6/16 who had received prior radiation therapy to the chest developed fatal pneumonitis); 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.

300 BMF IN ADULTS NH: AT RELAPSE: BACKGROUND FOR AN INTERNATIONAL RANDOMIZED STUDY ON RELAPSED INTERMEDIATE AND HIGH GRADE LYMPHOMA: E. Phillips, J. Armitage, G. Slack, P. Cohen, P. Coleman, P. Goff, C. Carise, J. Zinzani, N. Ylenko, S. Jaganath, T. Huguet, J. French, France autogreffe Study group, Houston-Omaha Lymphoma group. (CMBT) Lymphoma Study group, CMBT ABMT Study group and the protocol writing committee Centre Leon Bertin 28 rue Lorraine 69573 Lyon CE 69 France

In 1986, data from bone marrow transplant centers in Europe and America were pooled to determine the outcomes of autologous BMF 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 (41 patients) or high dose chemotherapy plus total body irradiation (TBI) (59 patients). Thirty-four 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 27 patients had no response or disease progress during remission - RR). 66 patients responded with partial or complete response to salvage chemotherapy (sensitive relapse RR). The actuarial 2-year disease free survival for the entire group was 26% 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 for 66% of CR group, 14% of RR group, and 38% of 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 NR. A multivariate analysis showed that the outcome was not affected by present regimen 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 relapse off therapy. In conclusion, the multivariate analysis showed that response to chemotherapy was the only significant prognostic variable in patients with intermediate or high grade NHL undergoing ABMT.

The international randomized study will begin July 1987 and could be summarized as follows:

- All patients with a intermediate or high grade histology at first diagnosis are eligible (ie transformation of nodular extranodal).
- With the exception 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 response after 2 courses of DCHAP).
- 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 platelet was observed for the majority of CR patients in these data and no maintenance therapy will be given after ABMT. Pre-ABMT involved field radiotherapy on en bloc of initial localization of the relapse will be recommended to 75% of the relapses are local relapses.
- In the chemotherapy arm of this study and in order to avoid any delay in the chemotherapy, involved field radiotherapy will be recommended for non responsive patients at the end of the program.