Poster Session III

STUDIES IN NHL

P 1

DIFFUSE SMALL LYMPHOCYTIC LYMPHOMA (DSL): CLINICAL FEATURES AND NATURAL HISTORY OBSERVATIONS FOR 156 PATIENTS (PTS).

P. McLaughlin, W. Pugh, W.S. Velasquez, F.B. Hagemeister, B. Huyhn, F. Swan, F. Cabanillas. U.T. M.D. Anderson Cancer Center, Houston, Texas 77030 U.S.A.

DSL has features in common with the low grade follicular lymphomas, and with chronic lymphocytic leukemia (CLL). We assessed the clinical features of 156 pts with DSL, including pts with the following subtypes or variants: plasmacytoid; paraimmunoblastic; accelerated phase; and centrocytic. We included pts with absolute lymphocyte counts (ALC) up to 15,000 per cu mm (15K). Initial management ranged from observation only without therapy (Rx), for 49 pts, to combined chemotherapy and radiation. The median age was 58 yr (range 25-95). There were 98 males and 58 females. Distribution by Ann Arbor Stage was: I, 7; IE, 10; II, 3; IIE, 8; III, 8; IIIE, 1; IV, 119. For pts with stage I-II DSL, extranodal (E) sites most commonly included Waldeyer's ring (7) and stomach (5). Stage IV was on the basis of involvement of bone marrow (BM) ± peripheral blood (PB) only in 88; other E sites in 7; and BM with other E sites in 24. The overall survival was 58% at 5 yr and 21% at 10 yr. The median failure-free survival for those who received initial Rx was 3 yrs. For patients selected for observation without Rx, the median time to institution of Rx was 21 mo. for 31 pts who have required Rx; another 18 pts remain untreated for a median of 27 mo (range 3-82). The survival of this subset of pts was 64% at 5 yr. Most deaths (76%) were directly or indirectly attributed to DSL; a large number of unrelated deaths were due to second malignant neoplasms, which occurred overall in 21 pts. Thus, the natural history of DSL includes: 1) a high frequency of extranodal involvement in pts with stage I-III disease; 2) common involvement of the BM, with or without PB involvement; 3) frequent association with other malignancies; 4) an indolent yet ultimately fatal course.

P 2

CHLORAMBUCIL/PREDNISON (ChP) VERSUS CHOP IN SYMPTOMATIC LOW GRADE LYMPHOMAS.

E. Kimby & H. Mellstedt for the Lymphoma Group of Central Sweden (LGCS)*. Dept.of Medicine, Division of Hematology, Danderyd hospital and Dept.of Oncology, Karolinska hospital S-104 01 Stockholm, Sweden.

Low grade non-Hodgkin lymphomas (NHL) are heterogenous diseases with a highly variable prognosis. The therapy of choice has not been clearly defined.
In a randomized study comparing ChP (Chlorambucil 0.4mg/kg day 1 p.o. and prednison 75mg day 1-3, every 2nd week) and CHOP (Cyclophosphamide 750mg/m², Doxorubicin 50mg/m², Vincristine 2mg day 1 and Prednison 50mg/m² day 1-5, every fourth week), 258 untreated patients with low grade NHL stage III and IV with symptomatic disease were included (April 1982 to February 1988).
The Kiel classification was used for histological subgrouping. Half of the patients (53%) were leukemic (lymphocytes ≥ 5.0x10⁹/l) with the highest frequency (82%) in the CLL and the lowest (10%) in the follicular & diffuse CB/CC group.
Time from diagnosis to randomization (time with asymptomatic disease) was longer than 1 year in half of the patients; mean time ranging from 8 months in patients with foll.CB/CC to 20 months in the CLL group.

Distribution of patients (numbers) in histological groups according to therapy:

Therapy	CLL	IC	CC	foll.CB/CC	f&diff.CB/CC	NUD
ChP	41	24	10	26	15	16
CHOP	43	21	6	20	18	18

The therapeutic strategy was to achieve an asymptomatic state in the ChP group, while in patients allocated to CHOP, the intention was complete remission (CR). As expected, a higher remission rate (CR+PR) was seen in the CHOP group. However, no significant difference was noted in total survival between the two regimens. Nor in the CLL group, any significant survival advantage could be seen with CHOP. In the other histological subgroups there are insufficient numbers of patients to make a critical evaluation.
Leukemic and non-leukemic patients did not differ regarding response rate or total survival.
Conclusion: Our results at present do no support the use of aggressive chemotherapy as first line therapy in symptomatic CLL and other low grade NHL.

*LGCS Members: M. Björkholm, , G. Gahrton, B. Glimelius, H. Hagberg, B. Johansson, G. Juliusson, M. Järnemark, E. Löfvenberg, A. Killander, R. Lerner, C. Lindemalm, U. Pettersson, K-H. Robért, B. Simonsson, A-M. Stalfelt, E. Svedmyr, A-M. Udén, B. Wadman, A. Wahlin, P. Biberfeldt, C. Sundström, Å. Öst,

P 3

STAGE IV LOW GRADE LYMPHOMA (LGL): MAINTENANCE α-INTERFERON (IFN) PROLONGS REMISSION.

P. McLaughlin, F. Cabanillas, F. Hagemeister, F. Swan, J. Romaguera, S. Taylor, A. Rodriguez, W. Velasquez, J. Redman, and J. Gutterman. M.D. Anderson Cancer Center, Houston, Texas 77030 U.S.A.

Stage IV LGL is usually associated with a continuous relapse pattern following therapy (Rx), and thus is considered incurable with currently available Rx. With a variety of chemotherapy approaches ranging from single alkylating agents to combination regimens, there are fairly consistent reports of median failure-free survival (FFS) of about 3 yr, and median survival of 7-8 yr. From 1982-88, 127 patients (pts) with stage IV LGL received a program of sequential α-IFN (Wellferon) x 8 wk (good risk pts only) ⟶ CHOP-Bleo x 12-18 mo (all pts) ⟶ α-IFN maintenance (maint) x 2 yr for complete responders (CRs). Results were compared with 96 control pts treated from 1974-81 with CHOP-Bleo alone. Forty-nine pts received the initial 8 wk phase of IFN ($3x10^6$ u/m²/d), with 2% CR, 11% partial remission (PR), and 37% minor response (still responding at initiation of CHOP-Bleo). CHOP-Bleo was well tolerated following IFN. With a median follow-up of 34 mo, FFS was significantly longer for pts receiving CHOP-Bleo plus IFN than for those treated with CHOP-Bleo alone:

	CR%	PR%	SURVIVAL	5-YR RESULTS (%) FFS-ALL PTS	FFS CRs: MAINT IFN vs NONE
Study	72	24	67	41 }p=0.08	56 }p=0.01
Control	77	20	62	28	37

Tolerance of IFN was generally good, although 36% required dose reductions or early discontinuation of maint IFN, mainly for fatigue. Thus: 1) we confirm the activity of α-IFN as a single agent in low grade lymphoma; 2) α-IFN maint Rx prolongs remission duration; 3) the integration of α-IFN and chemotherapy is feasible and effective. New strategies are needed to improve overall CR rates and to improve the tolerance and efficacy of maint Rx. (Supported in part by a grant from the Burroughs Wellcome Co.)

P 4

Non Hodgkin lymphoma stage I, with 10 year of follow up Report of the EORTC trial 20751

J.M.V. Burgers, M. van Glabbeke, Ch. de Wolf-Peeters, on behalf of the EORTC Lymphoma Group
The Netherlands Cancer Institute, Amsterdam

During the period 1975-1980 the EORTC cooperative lymphoma group executed trial 20751 for all stages of Non Hodgkin lymphoma of nodal origin for patients (pts) between 15-70 years of age. Of the 566 patients (pts) registered, 117 pts were in stage I. Staging was according to clinical examination, hematologic and liver function tests, chest X ray, lymphangiogram, bone marrow biopsy. Laparotomy was advised for pts < 60 yrs. Histological material was centrally reviewed according to the Kiel and Rappaport classification and the International Working Formulation. All stage I pts were treated with regional irradiation (mantlefield without mediastinum, or inverted Y) to a dose of 40 Gy in 4 weeks, followed by randomisation for adjuvant therapy, to either CVP (Cyclophosphamide [CF], 300 mg/m² day [d] 1,2,3 and 4, Vincristine [VCR] 1,4 mg/m² d 1, Prednisone [PR] 40 mg/m² d 1,2,3,4,5) (arm 1: 37 pts); or VCP (CF 300 mg/m² d 2,3,4,5, VCR 1,4 mg/m² d 1, PR 40 mg/m² d 2,3,4,5) (arm 2: 39 pts) or control (radiotherapy only) (arm 3: 41 pts).
In total 117 pts were randomised, 60% were male, 35 pts were < 40 yr, 46 were 40-60 yr, 31 were > 60 yr. 20 pts had Waldeyer's ring localisation, 54 pts neck, 31 pts inguinal, 8 pts axilla and 1 mediastinum. Size of the gland was not reported.
Histology: 30 pts had a follicular pattern (ptn), 7 a mixed and 43 a diffuse ptn. Follicular cell ptn was more frequent between 40 and 60 yr. Inguinal localisations were more often follicular. Clinical and histological characteristics were evenly divided over the 3 treatment arms, but arm 3 (RT only) contained more pts with diffuse cell ptn.
For the whole group the 10 yr survival (S) is 74% and disease free survival (DFS) 66%; there are no differences between the 3 treatment arms after adjustment for histology. For S the CVP arm seemed marginally better than the VCP arm, but DFS was equal.
For follicular and mixed ptn, the 10 yr S is 85% and DFS 66%; for diffuse ptn S 63% and DFS 63%. For inguinal localisation the 10 yr S is 96% and DFS 65%; for neck and Waldeyer's ring S is resp. 64% and 48%, and DFS 68% and 50%.
Causes of death in the 26 pts who died were malignant disease in 12 pts, chronic disease in 7 pts, other causes and unknown 7 pts.
Conclusion: the prognosis of stage I folliculair non Hodgkin lymphoma, and of inguinal localisations is excellent after treatment with regional radiotherapy. In patients with diffuse histology 10 year survival was 63% and adjuvant chemotherapy did not improve prognosis.

P 5 BNLI TRIAL OF CHOP vs CHLORAMBUCIL IN AGGRESSIVE LOW GRADE STAGE III / IV NON HODGKINS LYMPHOMA : A PRELIMINARY REPORT.

G VAUGHAN-HUDSON BNLI, Sir Jules Thorn Building, Middlesex Hospital, London W I, UK.

Since 1985, 148 patients presenting with stage III / IV low grade non Hodgkins lymphoma which was either symptomatic, progressing rapidly or causing critical organ impairment were randomised to receive either chlorambucil or CHOP. Chlorambucil was given at a daily dose of 0.2 mg/kg (max. 10 mg) for 3 months beyond attainment of complete remission (CR) with a treatment period of a minimum of 6 months. Patients progressing on chlorambucil or showing no response on this therapy could be transferred to alternative therapy. CHOP consisted of cyclophosphamide 750 mg/m^2 day 1 & 8, hydroxydaunorubicin 25 mg/m^2 day 1 & 8, vincristine 1.4 mg/m^2 (max 2mg) day 1 & 8 and prednisolone 50 mg/m^2 day 1 to 8, repeated every 28 days until three courses after attaining CR with a minimum of 6 courses. 72 patients received chlorambucil at diagnosis and 76 CHOP. The two groups were well matched for age, stage and histology. There was a preponderance of males in the CHOP arm (59 % vs 43 %). Of the currently evaluable patients there is a higher clinical response in those patients being treated initially with CHOP (53 % vs 35 %) ($0.05 < p < 0.1$). The disease free survival beyond 2 years is however similar in both arms (20 % in the CHOP arm and 24 % in the chlorambucil arm). The actuarial overall survival is identical in both arms being 60 % at 3 years. Of the 16 deaths in the chlorambucil arm 1 was due to heart failure in remission, 2 to infection with disease still present and 13 to progressive lymphoma. In the CHOP arm only 8 of the 17 deaths were due primarily to progressive lymphoma although lymphoma was still present in 8 of the 9 remaining deaths; one death due to myocardial infarction occurred in remission. In aggressive low grade NHL initial CHOP therapy does not appear advantageous to survival compared to chlorambucil. The initial response to CHOP therapy however is probably greater and it may be appropriate to try and maintain the higher incidence of remissions with biological response modifiers.

P 6 PREDICTION OF OVERALL AND SYMPTOM-FREE SURVIVAL IN LOW GRADE NON-HODGKIN LYMPHOMAS.

U. Martinsson, B. Glimelius, H. Hagberg, C. Sundström. Depts of Oncology and Pathology, University Hospital, S-751 85 Uppsala, Sweden.

In a consecutive series of 168 cases of low grade NHL stages II-IV diagnosed at the Depts of Oncology and Internal Medicine 1979-85, 76 pts (45 %) were initially asymptomatic, 19 (11 %) had "local" symptoms, and 73 (44 %) had "general" symptoms. The mean age was 61 years and the male:female ratio was 1.7:1. The ability to predict overall survival was tested for four serum markers (S-thymidine kinase = S-TK, S-LDH, S-haptoglobin and S-orosomucoid), histopathological subgroup (Kiel classification), stage and the presence or absence of "initial symptoms". In univariate analyses, all seven variables could predict survival ($p<0.05$). In a multivariate analysis, "initial symptoms" was the best predictor ($p=0.000$), additional independent information given by S-TK (increased p-value = 0.007), S-haptoglobin (incr. $p=0.034$) and histopathological subgroup (incr. $p=0.042$).

Of the 76 initially asymptomatic patients, 64 had therapy deferred until symtoms occurred. In this group, those becoming symptomatic within 6 months had as poor survival as those who were initially symptomatic (median 41 mo.). The same parameters as above were tested regarding their abilities to predict the symptom-free survival. Histopathological subgroup was the best predictor ($p=0.0002$). Within the "intermediate grade" groups (LP-immunocytoma, follicular and diffuse centroblastic-centrocytic = fdCBCC and small cell centrocytic), S-TK allowed the identification of patients who will become symptomatic within a short time (6-8 months) after diagnosis, something which was not possible in the more favourable subgroups.

Elevated levels of S-TK and S-LDH can also predict progressive disease in patients still asymptomatic and, in CBCC lymphomas, also transformation to a high grade lymphoma.

P 7 PRIMARY NON HODGKIN LYMPHOMAS OF THE UTERINE CERVIX.

C.Graiff°, M.Amichetti°, D.Aldovini*, L.Bolego* and P.Dal Ri"
°Oncology Center, *Department of Morbid Anatomy and Pathology, "Division of Medicine, S.Chiara Hospital, 38100 Trento, Italy.

Secondary involvement of the female genital tract by generalized Non Hodgkin Lymphomas (NHL) is well recognized. However, the occurrence of a NHL primarily localized in the uterine cervix is uncommon. In fact, primary lymphomas of the uterine cervix are extimated to represent less than 1 % of all extranodal NHL. Only 33 well documented cases of primary cervical NHL have been reported up to now in the English literature. The majority of patients present with abnormal vaginal bleeding and diagnosis is made on cervical biopsies. The management of this rare disease is not well standardized and a remarkable treatment heterogeneity, which usually include radiotherapy and chemotherapy, is reported. Prognosis appears to be generally favourable. From January 1979 to December 1988, four cases of true primary NHL of the uterine cervix were observed at the Oncology Center, S.Chiara Hospital, Trento, Italy. There were 4 female patients with age ranging between 38 and 82 years. Pathologic specimens have been reviewed. All the cases were NHL of unfavourable histology. Clinical staging was performed as follows: all the patients had a physical examination, chest Xray, hematological and biochemical tests, total body CT scan; 3 had a linphangiogram; 3 had bone marrow biopsy. The stage according to FIGO was: Ib, IIa, IIb, IIb. Three patients received chemotherapy followed by radiotherapy on the entire pelvis. The oldest patient was treated with radiotherapy alone. All the patients had a complete remission. Three of them are alive and free of relapse after 125, 24 and 22 months respectively. The last patient developed a widespreade disease after 7 months; performance status, age and associated unrelated diseases contraindicated further therapies: she died after 9 months without evidence of local recurrence. Our results seems to confirm the literature data regarding the favourable prognosis of cervical NHL in spite of the fact that the optimal treatment and work-up have to be defined.

P 8 PRIMARY CHEMOTHERAPY FOR LOCALIZED NON-HODGKIN'S LYMPHOMA OF UNFAVORABLE TYPE ARISING FROM WALDEYER'S RING.

K. Sampi, T. Takagi, M. Hattori. Division of Hematology, Saitama Cancer Center and Chiba Cancer Center, Japan

Forty-six patients with localized stage of non-Hodgkin's lymphoma (NHL) of unfavorable type arising from Waldeyer's ring were prospectively treated with primary chemotherapy consisting of anthracycline-based combination chemotherapy with (20 patients) or without (26 patients) regional radiotherapy. Patients with stage I and with stage II were eligible for this study. There were 25 men and 21 women, ranging in age from 20 to 84 years with a median age of 62 years. Eleven patients were aged over 70 and 5 over 80. The primary chemotherapy consisted of 650 mg/m^2 of cyclophosphamide on day 1, 45 mg/m^2 of adriamycin on day 1, 2.0 mg/m^2 of vindesine on day 1 and 40 mg/m^2 of prednisolone on day 1 to 5. 60 mg/m^2 of epirubicin was mainly used in patients over 70 years in stead of ADM. This combination chemotherapy was repeated every 4 weeks and given 10 cycles. There were 4 cases of stage I disease and 42 cases of stage II disease. Histology was classified by the use of Lymphoma Study Group in Japan which is almost similar to the Working Formulation. Histologic subtypes were diffuse large (38), diffuse mixed (4), diffuse medium (3), and true histiocytic (1) lymphoma. Four patients had a bulky tumor of more than 10 cm in diameter. The surface marker of tumors was examined in 5 cases, of which 2 were T-cell lymphoma. A complete response induced by primary chemotherapy was obtained in 42 (91 %) of the 46 patients. Two of four patients who did not attain the complete response were expired. The average course of anthracycline-based combination chemotherapy in complete responders was 10 (range 2-10). Of the 42 responders, only 5 recurred. Twenty patients received radiotherapy of the involved field, of whose 2 recurred. The complete response was well sustained with an actuarial relapse-free survival of 84 % at 5 years. To date 9 patients expired; five of these died after a recurrence, two under complete remission and the remaining two without attaining the CR. The survival curve of all patients became flat at 71 months and was well sustained with an actuarial survival of 75 %. Primary chemotherapy is highly effective treatment strategy for patients with clinically apparent localized NHL arising from Waldeyer's ring.

P 9 **PRIMARY GASTROINTESTINAL LYMPHOMAS: A RETROSPECTIVE ANALYSIS OF 70 PATIENTS.**

L.Tedeschi, G.Dallavalle, M.Vinci, E.Arnoldi, D.Tabiadon, G.Luporini - Medical Oncology Dept., S.Carlo B. Hospital - Milan / Italy.

From 1973, 90 patients (pts) affected by gastrointestinal lymphoma were observed in our Istitution. 20 pts are not evaluated for disease diffusion to periferal lymphonodes, bone marrow, liver or spleen, according to the criteria of Dawson et al. (1961). Then the characteristics of 70 pts with primary gastrointestinal lymphomas were analyzed. There were 35 male and 35 female with a median age of 59 years (range 21+87). 30 pts were in stage I E and 40 in stage II E. When available, the pathology slides were examined and classified according to the Rappaport classification and the International Working Formulation. We had 11 pts with low grade, 33 pts with intermediate and 19 pts with high grade malignancy lymphomas, 7 pts were not classified. The primary site of disease was: stomach = 63 pts, colon = 4 pts, small bowel = 3 pts. The median follow-up is 25 mounths.
3 pts were treated only with chemotherapy: one is dead and two are alive with disease. 67 pts underwent surgical procedures, of these 52 were treated with chemotherapy too: in the '70s mostly with CVP or COP regimen, more recently with CHOP or B-CHOP regimen. 73% of the pts who had a complete and pathologic resection, 50% of the pts with microscopic residual (positive resection margin) and 0% of those who underwent only exploratory laparotomy with biopsy, are alive and free of disease 5 years after treatment. 12 pts,mostly stage I E and low intermediate grade histology,were treated only with surgery: their 5 years survival is 89%. 3 pts were treated with radiation therapy after surgery.
There is a statistically significant difference between pts treated with CVP or COP and CHOP or B-CHOP both plus radical surgery (52% vs. 100% survival at 4 years). The relapse rate after complete resection was 4% in stage I E and 20% in stage II E.
It will be discussed the importance of an omogeneous therapeutic approach to this potentially curable disease, based on some prognostic factors affecting survival. There are conflicting reports in the literature about prognostic factors, but this is due to the difficulties to compare different series: variations in number of pts, long term analysis (over 20 years), different treatment. It is necessary to identify the subgroups of pts who must be treated after surgical approach and the best treatment now available.

P 10 MULTIMODAL THERAPY OF GASTRIC NON-HODGKIN'S LYMPHOMA (NHL).

M. Vovk, M. Jenko, G. Petrič, A. Vodnik, B. Zakotnik. The Institute of Oncology, Zaloška 2, 61105 Ljubljana, Yugoslavia

The efficacy of multimodal treatment of gastric lymphoma (GL) was examined in a retrospective study (1984-1989) of 46 patients. Only patients meeting the criteria of Dawson et al. (Br J Surg 49: 80-89, 1961) for primary GL were included. Kiel classification for NHL and staging according to Musshoff (Strahltherapie 153: 218-221, 1977) for GL was used. Patients with lymphoblastic lymphoma were excluded.
The principal treatment plan: The majority of patients were operated on (partial, seldom total resection), later chemotherapy (ChT) and/ /or radiotherapy (RT) were given according to the persistence of residual disease and histologic type of NHL:

A) no residual disease - low grade NHL (LGNHL) - no more treatment
Resection - high grade NHL (HGNHL) - ChT

B) microscopic residual disease at the resection line and/or St II_1 or II_2 and/or serosal penetration — LGNHL - RT; HGNHL - ChT + RT

LGNHL patients without resection - RT; HGNHL with inoperable GL with bulk disease were treated by ChT+RT. In most patients RT field was the upper part of the abdomen; RT dose 20-30 Gy. ChT was mostly CHOP given at 14-day intervals - 6 cycles.
Results: The medium follow up of 46 patients with GL was 3 yrs (range 1-70 mos); 6-year disease-free survival was 95%. Only 2/46 patients died because of lymphoma: the first one with primary inoperable bulky disease had local progress, whereas the second patient had distal metastases. 6-year DFS in the group of LGNHL patients treated only by resection (4/46) or resection + RT (6/46) was 100%; in the group of HGNHL patients treated by resection + ChT it was 100%, whereas those treated by resection + ChT + RT had 97% DFS.
Conclusion: The results suggest that we are on the right way with our treatment plan. Although our patients had no treatment-related toxic side effects, our future plan is a less toxic therapy, i.e. lower RT dose and smaller RT field, and shorter ChT.

P 11 CHEMOTHERAPY OF NON-ENDEMIC BURKITT'S LYMPHOMA.

R. Kath, K. Höffken, K. Günzel, C.U. Anders, M.R. Nowrousian, K. Donhuijsen, and C.G. Schmidt. Innere Klinik und Poliklinik (Tumorforschung), Universitätsklinikum Essen, Hufelandstraße 55, 4300 Essen 1, F.R.G.

The prognosis of non-African Burkitt's lymphoma (high-grade malignant lymphoblastic non-Hodgkin's lymphoma of B-cell-type) is equivocal. Strategies vary as to the type and intensity of chemotherapy. Between 1978 and 1989, 24 patients (19 men and 5 women; age 14-77 years) with histologically proven and immunohistochemically confirmed diagnosis of lymphoblastic Burkitt's lymphoma received primary combination chemotherapy. Fourteen patients were treated with the B-NHL regimen, a protocol originally developed for lymphoma in children (Müller-Weihrich et al, Klin. Pädiat. 196: 135-142, 1984). Seven patients received the COMP regimen (Moxley et al, Cancer Res. 27, 1258-63, 1967) and three patients were treated with three other regimens. Ten patients (42%) died. One patient was lost to follow up. All patients alive (n=13) are in CR with a medium relapse-free survival time of 36 months. Patients treated with the B-NHL-protocol (n=14) achieved a CR-rate of 100% (14/14), and a long term CR-rate of 71% (10/14) with a median relapse-free-survival of 32.5 months. Patients treated according to the COMP-protocol (n=7) achieved a CR-rate of 57.1% (4/7) and a long term CR-rate 43% (3/7). Of three patients treated with other protocols one achieved a short term CR (4 months). Long-term remission rates were stage dependent. All relapses occurred within the first 9 months after initiation of chemotherapy. Side effects of the B-NHL therapy were myelotoxicity, which was reversible in every case. One tumor-lysis-syndrome occurred. In summary, the B-NHL protocol seems to produce remarkable results in adults with non-endemic lymphoblastic Burkitt's lymphoma. The present results, however, do not yet allow to conclude that B-NHL therapy has a statistically significant advantage over other combination chemotherapies.

P 12 **LYMPHOBLASTIC LYMPHOMA IN ADULT PATIENTS: PROGNOSIS AND TREATMENT.**

P. Morel[1], E. Lepage[2], P. Brice[2], B. Dupriez[1], P. Fenaux[1], MF. d'Agay[2], C. Gisselbrecht[2], F. Bauters[1]. [2]Institut d'Hématologie, Hopital Saint-Louis, Paris and [1]Service des Maladies du Sang, CHR, Lille, France.

Eighty patients (pts) (54 males, 26 females) older than 14 years with lymphoblastic lymphoma (LBL) were treated from 1979 to 1989 by 3 successive chemotherapy (CT)protocols: 1) CHOP protocol (21 pts) consisting of 6 monthly cycles of Cyclophosphamide (C) 750 mg/m², Adriamycin (H) 50 mg/m², Vincristine (O) 1.5 mg/m² and Prednisone (P) 60 mg/m², followed by one year maintenance therapy; 2) LNH84 protocol (30 pts) with 3 to 4 cycles of reinforced CHOP with increased doses of C 1200 mg/m² and H 75 mg/m² over 3 months, followed by consolidation therapy during 6 months; 3) acute lymphoblastic leukemia protocol (29 pts) with Daunorubicin (D) 50 mg/m² d1-3, O 1.5 mg/m² d1,8,15,22, C 600 mg/m² d1,8, P 60 mg/m² d1-22 followed by 3 cycles of consolidation and maintenance therapy for 24 months. CNS prophylaxis was performed in all patients. 7 pts underwent an autologous or allogenic bone marrow transplantation (BMT) in 1st complete remission (CR). Median age was 30 years (15-75 y). 5 pts were stage I, 18 pts stage II, 2 pts stage III, 55 pts stage IV (including 37 bone marrow, 5 CNS involvement). 26 pts had leukemic LBL (marrow blast cells > 25% or presence of circulating blasts without pancytopenia). 34 pts had B symptoms, 50 pts mediastinal mass, 26 pts abdominal adenopathies. Immunophenotype was T in 85%, null in 15%. Complete response rate was not different according to treatment groups (76%, 84%, 93% respectively in groups 1 to 3). Higher CR rate was associated with younger age (p <.001), absence of B symptoms (p=.07) of abdominal adenopathies (p=.01), normal LDH level (p=.002). Median CR duration was 20 months. Only 1 relapse occurred in 1st CR patients with BMT. Median overall survival duration was 30 months, survival was estimated to 46% at 60 months. Factors associated with shorter overall survival were : increased LDH (p<.0001), weight loss (p=.004), CNS involvement (p=.01), B symptoms (p=.07). Bone marrow involvement and treatment did not influence CR duration and survival.

Use of intensive non hodgkin's lymphoma regimens yield similar results than ALL protocols in LBL. The role of autologous or allogenic bone marrow transplantation needs to be confirmed.

P 13 HIV-ASSOCIATED HIGH GRADE NON HODGKIN'S LYMPHOMA (NHL): CLINICAL PATTERNS AND OUTCOME. THE EXPERIENCE OF THE FRENCH REGISTRY OF HIV ASSOCIATED TUMORS. JM Tourani. S. Roithmann. M. Toledano, JM Andrieu. Oncology-Hematology. Laennec Hospital. 42 rue de Sèvres. 75340. Paris. CEDEX 07. France.

From 1/87 to 5/89. 126 cases of high-grade NHL were recorded by the registry. There were 45 diffuse small non cleaved cell Burkitt like lymphomas (BL), 31 immunoblastic lymphomas (IL) and 50 diffuse large cell or predominantly large cell lymphomas (LCL). There were 98 males and 7 females with a mean age of 40 years (min 19 - max 73). 57% of patients were homosexuals. 12% IVDA. 4% both and 27% had other risk factor for AIDS. BL and IL/LCL have different clinical presentations. Extra-nodal presentation was less frequent ($p<0.0001$) in BL (2/45) than in IL (15/30) and LCL (16/48). In the later two groups. central nervous system was the main site of isolated extra-nodal involvement (20/31). Other extra-nodal sites as oral cavity. anorectal area. and uterine cervix were less frequently involved. Among patients with disseminated disease (stade IV). bone marrow involvement was more frequent in BL (23/31) than in IL (5/14) and LCL (5/19) ($p<0.01$). 88% of BL patients had no previous manifestations of AIDS. whereas 40% of IL and LCL occured in patients with full blown AIDS ($p<0.01$). CD4 cell count was higher in BL (285) than in LCL (224) and IL (137 cells/µl). Treatment was chemotherapy (CHOP or CHOP-like). frequently associated with radiotherapy for localized disease and chemotherapy only for disseminated disease. Most patients with extra-nodal disease received isolated radiotherapy. 53% of stages I/II and 34% of stages III/IV achieved complete remission (CR). Overall median survival was 5 months (0-32). There was no difference in CR and actuarial 2-year survival rate according to histological subtypes. The two-year survival was 19% and 10% for stages I/II and III/IV. and 23% and 0% for asymptomatic/PGL and ARC/AIDS groups respectively ($p<0.001$). The cause of death was mostly tumor progression. The prognosis of these tumors is still very bad. Main prognostic features are the underlaying status of HIV infection and the extension of NHL. (Supported by AREMAS and Ligue Nationale Contre le Cancer).

P 14 MACOP-B REGIMEN IN ELDERLY PATIENTS: A MULTICENTER ITALIAN STUDY. B. Comotti, P. Viero, C. Tarella, E. Gallo, N. Carlesso, M. Bertini, U. Vitolo, A. Levis, G. Todeschini, A.M. Gatti, D. Rota Scalabrini, A. Pileri, L. Resegotti, G. Perona and T. Barbui. MRSGNHL c/o Department of Haematology, Ospedali Riuniti, Bergamo, Italy.

Forty elderly patients (pts) (median age 63 years, range 59-68) with advanced large cell non Hodgkin lymphoma seen from 1985 to 1989 were treated with MACOP-B. Seventeen had B symptoms, 17 bulky disease, 16 extranodal involvement and 7 showed bone marrow infiltration. The stages at diagnosis were: advanced stage II (bulky and/or E lesion) 9 patients; stage III 13 and stage IV 18 patients.
Twentynine received MACOP-B according to the timing and doses as originally reported by Klimo and Connors, whereas in 11 cases the program had to be interrupted due to: cardiac failure (2 pts), systemic bacterial or fungine infection (6 pts), neurological problems (1 pt), severe mucositis (1 pt) or disease progression (1 pt). Complete remission (CR) was obtained in 20 cases (55%), partial remission in 8 and resistant desease was ascertained in 5. Four deaths were due to systemic infection and one to organ failure related to drugs. Only 3 out of 11 pts with bad performance status and one of 7 with bone marrow involvement achieved CR. E lesions, B symptoms and bulky disease did not influence the response.
The median survival from diagnosis was 8.4 months, whereas the median relapse free survival of the 20 remitters has not yet been reached after median follow up of 8.7 months; 60 % of these patients is projected to be in CR at 4 years.
In conclusion, the majority of pts with age ranging from 59 to 68 years can undergo MACOP-B traetment and the results appear comparable to those obtained in the younger population.

P 15 MACOP-B in the Treatment of High-grade Malignant Non-Hodgkin Lymphomas: H.Hagberg, E.Cavallin-Ståhl. For the Swedish Lymphoma Study Group.

In a national Swedish study, 100 patients with high-grade malignant NHL were treated with MACOP-B. Inclusion in the study started in September 1986 and was completed in June 1988. The mean age was 47 years (range 17-78). The patients were in the following stages: I 7 (all bulky), II 26 (11 bulky), III-IV 63. All but 5 patients could be included among the "Large-cell NHL" (Kiel classification CB 45, IB 15, LB 7, Anaplastic 2, NUD 26). During the first year of the study, no antibiotic profylaxis was administered and prednisone was given intermittently. Thereafter, MACOP-B was given exactly as described by Klimo in Ann Int Med 1985.

Results: The complete remission rate was 72/100 (72%). Twenty-seven patients have relapsed during an observation time of 12-36 months (median 21) after stopping treatment. The relapse-free survival is thus 45/100 (45%). The most common severe side-effect was mucositis. Bone-marrow toxicity was not a major problem. Toxic death occurred in 9 patients. Four died of pulmonary toxicity (2 pneumocystis carinae) during the period when antibiotic profylaxis was not administered. Three patients died of sepsis, 1 of gastro-intestinal bleeding and 1 of tumor necrosis.

Conclusion: MACOP-B is a highly toxic regime and an antibiotic profylaxis seems to be important. In this phase II study MACOP-B had a slightly higher complete remission rate and relapse-free survival than our previous studies with CHOP. The mean age in the CHOP study was, however, 65 years compared with 47 years in this study. A randomized study between MACOP-B and CHOP has therefore been started.

P 16 INFECTIONS IN PATIENTS WITH AGGRESSIVE NHL TREATED WITH MACOP-B REGIMEN. A MULTICENTER ITALIAN STUDY. G.Todeschini, V.Meneghini, M.Bertini, E.Brusamolino, B.Comotti, F.Ficara, A.Gallamini, E.Gallo, R.Ghio, G.Luxi, A.Novarino, L.Orsucci, C.Tarella, P.Viero, U.Vitolo, T.Barbui, C.Bernasconi, G.Perona, A.Pileri and L.Resegotti. MRSGNHL c/o Cattedra di Ematologia, Verona University, Verona, Italy.

Between June 1986 and March 1989, 203 consecutive patients with NHL (histologic subtypes: F, G, H according to the Working Formulation) were treated with MACOP-B regimen (Klimo and Connors 1985) in an Italian cooperative study. The mean age of all 203 pts was 44 yrs (15-68). Eighty-seven of 203 pts (43%) underwent 139 infectious episodes, the majority of which were clinically or microbiologically documented. The infections were: Candida mucositis (36), pneumonia (24), mucositis (not due to Candida) (16), viral infections (15; Varicella-Zoster 10/15); upper respiratory tract infections (11), soft tissue infections (8); urinary tract infections (6), bacteremia alone (3); Gastro-Intestinal Tract infections (3); FUO or other infections (17). The overall mortality was 62/203 (30%). Of the 59 evaluable patients, 9 (15%) died because of infection, 41 (70%) due to the progression of lymphoma and 9 (15%) due to other causes. Infection-related mortality was 9/203 (4%). Pneumonia was the most severe infection (8/24 pts died). The fatal pneumonias were due to Aspergillus (4), bacteria (3), Pneumocystis carinii (1). The incidence of infection and the infectious mortality during the first month of chemotherapy (CT) were respectively 28% and 0%; during the second month 40% and 9%; during the third month 26% and 0%; after the third month 5% and 71%. Among the viral infections, 10/15 were observed during the second month of CT.
The mean age of the 87 infected pts was 50 yrs (19-68). It was 56 yrs (39-67) in the 9 pts who died because of infection. Because of infection, CT was delayed in 35 (17%) and definitively interrupted in 9/203 (4 %) of pts. The mean lenght of delay was 19 days (7-120). We observed only one episode of interstitial pneumonia due to Pneumocystis carinii.
Conclusions
1) the infection-related mortality was limited and it occurred mainly in older pts 2) the infectious morbidity was high and CT had to be often delayed 3) the second month of CT was a critical period for infections; 4) the infections which occurred after the third month of CT were few but severe. 5) the cotrimoxazole prohylaxis of Pneumocystis carinii pneumonia seemed to be adequate.

P 17 INTENSIVE WEEKLY CHEMOTHERAPY FOR THE INITIAL TREATMENT OF ADVANCED INTERMEDIATE AND HIGH GRADE NON-HODGKIN'S LYMPHOMA (NHL).

J.W. Sweetenham, G.M. Mead and J.M.A. Whitehouse. CRC Wessex Medical Oncology Unit, Southampton General Hospital, Tremona Road, Southampton SO9 4XY, U.K.

High response and overall survival rates have been reported for MACOP-B chemotherapy for the treatment of advanced intermediate and high grade NHL. We have developed a similar regimen, with lower dose methotrexate, but with the addition of etoposide in an attempt to reduce toxicity but maintain the apparent efficacy of this regimen. From 1/6/86 to 31/10/89, 62 patients have entered this study.

Eligibility Age:15-69. Histology (WF): FLC, DSC, DM, DLC, DLCI, DSNC. Stages: stage II >10cm bulk or >2E lesions, stages III and IV. No prior RT except for stage I disease.

Chemotherapy A = doxorubicin 35mm/m² iv, cyclophosphamide 300mg/m² iv, etoposide 150mg/m² iv. B = methotrexate 100mg/m² iv with leucovorin rescue, vincristine 1.4mg/m² iv, bleomycin 10mg/m² iv. Alternating cycles of A and B are given for a total of 12 cycles. Prednisolone 50mg daily weeks 1 to 4, alternate days weeks 5 to 12, + prophylactic co-trimoxazole.

Patient characteristics 62 patients entered. Median age = 58 (23-69). Histology: DLC - 43, DM - 10, DSC - 1, FLC - 4, DLCI - 3, DSNC - 1. Stages: II - 7, III - 20, IV - 35. B symptoms - 36, extranodal disease - 15, BM+ - 13, >10cm bulk - 14. 56 patients are currently evaluable.

Results CR - 32 (57%), PR - 17 (30%), PD - 2 (4%). Treatment related deaths - 5 (9%). Median FU - 16 months. Actuarial overall survival at 41 months - 48%. RFS for those achieving CR = 78%. Residual abdominal masses were observed without further therapy. 18 patients had residual masses after 12 weeks. 8 have regressed completely (no relapses), 2 remain stable, 8 patients have PD (7 at the same site, 1 at a distant site.

Toxicity Dose limiting toxicity - mucositis. Haematological toxicity - 12 episodes of neutropenic fever, 3 septic deaths.

Conclusion This regimen has produced an overall response rate of 87% in a group of patients with more adverse prognostic factors than those reported for the MACOP-B regimen. Toxicity is much less severe than MACOP-B.

P 18 ALTERNATING NON-CROSS RESISTANT MULTI-DRUG CHEMOTHERAPY (CAMBO-VIP) FOR NON HODGKIN'S LYMPHOMA OF INTERMEDIATE AND HIGH GRADE MALIGNANCY; A PILOT STUDY.

M. Hirano, M. Okamoto, F. Maruyama, K. Ezaki. Department of medicine, Fujita Health University, Toyoake 470-11, Japan

Early exposure to multiple dose-intensely administered non-cross resistant drugs has been associated with an improved disease-free survival in advanced stage non Hodgkin's lymphoma of aggressive histology. We have treated 33 patients (pts) by a pilot 8 drug CAMBO-VIP chemotherapy consisting of weekly alternate administration of myelosuppressive and non-myelosuppressive agents for 12 weeks. Doxorubicin 40mg/m² was given in combination with either cyclophosphamide 600mg/m², or etoposide 70mg/m² qd x 4 or ifosphamide 1000mg/m² qd x 4, in turn on weeks 1, 3, 5, 7, 9, and 11. Vincristine 1mg/m² was used with either methotrexate 200mg/m² with leucovorin rescue or bleomycin 10mg/m² on weeks 2, 4, 6, 8, 10, and 12. Prednisolone 40mg/m²/day was administered for the first and the last 4 weeks. Co-trimoxazole and amphotericin B syrup administered for prevention of opportunistic infections throughout the treatment. The sites of previously present bulky mass received 40 Gy irradiation in CR pts. Pt characteristics are as follows: age, 13-80 (52); stage II/III/IV, 10/13/10; B/T, 20/10; PS 0,1/2-4, 25/8; intermediate/high grade, 25/8.
30 completed the chemotherapy with maximal delay of 3 weeks. 2 pts aged 63 and 69 had incomplete trial; treatment discontinued in 6 and 5 weeks because of liver toxicity and cerebral thrombosis, respectively. Another 80 year old pt received reduced doses. All the pts studied were evaluated. 29 (87.9%) had CR and 4 (12.1%) PR. Overall survival is 2.5+ to 26+ (10+) mos, and disease-free survival 2+ to 25+ (8.5+) mos, and their Kaplan-Myer estimates at 2 years are 93.7% and 83.9%, respectively. 3 relapses occurred after 4, 7 and 9.5 mos of CR. Myelosuppression was severe with nadir neutrophil 200 in 68.8%. Incidence of infection, however, was surprisingly low; oral ulceration, liver damage, excoriation of palms and/or soles, alopecia occurred, causing delay of treatment in some pts; treatment-related death was not observed. Thus, CAMBO-VIP chemotherapy could be administered with an acceptable toxicity. Whether results of this regimen surpass those of currently used standard regimens needs further follow-up, especially, for the longevity of the disease-free survival.

P 19 Randomized comparison of weekly chemotherapy with standard cyclical chemotherapy for high-grade lymphoma.

Stuart NSA[1], Blackledge GR[1], Childs JA[2], Bessel EM[3], Cullen MH[1], Grieve RJ[4], Simmons AV[5], Fletcher J[6], Sykes V[1]. [1]Queen Elizabeth Hospital, Birmingham. [2]General Infirmary, Leeds. [3]General Hospital, Nottingham. [4]Walsgrave Hospital, Coventry. [5]St James' Hospital, Leeds. [6]City Hospital, Nottingham. U.K.

Cyclical chemotherapy of the CHOP type has been used for many years in the treatment of high-grade lymphoma. Other, more complex regimens have been reported, in phase II studies, as producing superior results and most recently Klimo and Connors have reported high response rates with weekly chemotherapy. In order to define whether such regimens have any benefit over standard chemotherapy we have undertaken a randomized trial. Patients entered have not received previous chemotherapy, have disease that is considered incurable with radiotherapy and are of any age as long as they are suitable for chemotherapy given with curative intent.

The weekly regimen (CAPOMEt, regimen A) comprises - Day 1: Cyclophosphamide (CYC) 400 mg/m², doxorubicin (DOX) 50 mg/m² both i.v. Day 8: vincristine (VCR) 2 mg i.v. Day 1-5: prednisolone (PDN) 60 mg/m² orally. Day 15: methotrexate (MTX) 250 mg/m² with Na bicarbonate and folinic acid rescue, etoposide (ETP)100 mg/m² both i.v. Day 16-17: ETP 50 mg tds orally. Day 22: same as day 8. This regimen repeats each 28 days for 13 weeks ending with CYC and DOX. If patients are slow to achieve CR treatment may continue for 17 weeks. The cyclical regimen (CHOP-MTX, regimen B) comprises - Day 1: CYC 750 mg/m², DOX 50 mg/m², VCR 2 mg, all i.v. Day 1-7: PDN 40 mg/m²/day² orally. Day 15: MTX 250 mg/m² i.v. with Na Bicarbonate orally and folinic acid rescue. Treatment continues to CR plus 3 cycles (min 5, max 8).

At the time of analysis 330 patients have been randomized and data is available on 166 who have completed treatment. The distribution of clinical stages for group A are: stage I, 12 (15%); stage II, 24 (29%); stage III, 15 (18%); stage IV, 21 (39%); for group B: stage I, 15 (19%); stage II, 17 (22%); stage III, 20 (25%); stage IV, 27 (34%). Pre-treatment levels of bilirubin, albumin, creatinine and LDH were similar for the two groups as were bulk of disease and age (median age group A =59, group B =57).

Neutropenia below 0.5 x 10^9/l was recorded, at some point, significantly more often during the cyclical regimen (63% vs 36%, p=0.001), largely because of greater cumulative toxicity. Neuropathy of any grade occurred more often with the weekly regimen (33% vs 19%, p=0.04) but was rarely severe in either (2% overall). Thrombocytopenia and mucositis were infrequent and occurred equally with the two treatments. The number of infections requiring i.v. antibiotics and the number of units of blood transfused during treatment were also similar. Toxicity contributed to 9 deaths during standard therapy (32% of deaths, 11% of patients) and 7 deaths during weekly therapy (19% of deaths, 8% of patients).

Complete remission rate (95% confidence intervals) for the two treatments were: regimen A 56% (45% - 67%), regimen B: 66% (55% - 77%), p-value of difference < 0.1. Actuarial survival was similar for the two treatments (Mantel-Cox p = 0.5. Alive at 2 years: A=53%, B=60%) as was freedom from relapse (Mantel-Cox p = 0.3. Relapse free at one year: A=74%, B=85%). Assessment of the 95% confidence intervals shows that the weekly regimen is unlikely to produce a response rate more than 7% better than standard therapy, or a 2-year survival more than 11% better but could also be associated with a 2-year survival 23% worse. Further analysis is awaited which will show whether weekly chemotherapy has a lesser advantage over standard treatment.

P 20 RANDOMIZED STUDY PROMACE/MOPP vs MACOP-B IN NHL: A PRELIMINARY REPORT BY NHLCSG.

T. Chisesi - L. Rancan (VI), M.R. Sertoli (GE), P. Coser (BZ), V. Rizzoli (PR), A. Porcellini (CR), A. Contu (SS), L. Moretti (PS), G. Santini (GE), L. Salvagno (PD), O. Vinante (VE) (ITALY).

In the attempt to assess the real impact of third generation regimens on the outcome of the therapy in high grade NHL, a randomized study has been performed in a large cooperative study group comparing the PROMACE/MOPP regimen versus MACOP-B. From January 1988 up to January 1990 151 pts have been enrolled with 122 pts evaluable untill now for response to therapy. Median age of pts in the entire group is 46 year (range 19-65). According to histology all pts were chategorized as F-G-H of W.F.; 25 pts were in stage II, 31 in stage III and 66 pts in stage IV with 69/122 (49%) presenting bulky of disease above or below diaphragm. The two groups were balanced with respect to age, stage, performance status, B-symptoms, number of extranodal sites. 61 pts were treated with a minimum of 6 cycles of alternating PROMACE/MOPP and 61 with MACOP-B. About 60% of CR has been registered with no differences in response rate obtained in both arms. In 10% of pts we obtained a PR, and 30% of pts didn't responde. As far as the toxicity is concerned we registered an increased evidence in terms of general toxicity (alopecia, nausea and vomiting, dyarrea and mucositis) in MACOP-B arm. The hematologic toxicity resulted lower in PROMACE/MOPP group on the contrary liver toxicity havier in MACOP-B. 14 treatment related death occurred in MACOP-B arm versus 25 in PROMACE/MOPP arm. From these preliminary data we can argue that the two used regimens are not different in terms of response rate and toxicity but we hope that the ongoing randomized trial will draw a more detailed information about the differences in the two regimens in order to improve the approach for these categories of pts.

P 21 "F-MACHOP" SEQUENTIAL COMBINATION CHEMOTHERAPY FOR DIFFUSE LARGE CELL OR UNDIFFERENTIATED LYMPHOMA: SUMMARY OF TEN YEARS EXPERIENCE AT A SINGLE INSTITUTION. C. Guglielmi, S. Amadori, M. Martelli, L. Mantovani, G. Papa, F. Mandelli. Ematologia, Dip. Biopatologia Umana, Univ. "La Sapienza", via Benevento, 6 - 00161 Roma, Italy.

From 1.80 to 12.89 we treated 196 consecutive adult patients (Pts) with newly diagnosed stage II - IV diffuse large cell or undifferentiated lymphoma with an intensive cyclic (1 course x 6 in responders) combination chemotherapy program.The F-MACHOP regimen is based on the rationale that exposure of rapidly proliferating tumor cells to as many cell cycle active drugs administered sequentially throughout the entire duration of the cell cycle will maximize tumor cell kill and significantly reduce tumor burden, thereby decreasing the possibility that resistant clones will arise (Cancer Invest. 5:159, 1987). The overall CR-rate is 79% and the 5 and 10 yrs actuarial relapse-free survival is 81%. In 1984 we first noted that Pts achieving complete response (CR) by the 3rd cycle had a significantly lower relapse rate as compared to those who required more courses to attain CR (Semin. Oncol. 12(suppl3):218, 1985). We then confirmed this observation on a larger series and noted that the probability of long-term event-free survival (EFS) was highly dependent on the disease status after 3 courses of F-MACHOP: 0.91 for CRs and 0.35 for PRs even after stratification of Pts according to poor-risk presenting features such as bulky disease (>7 cm) and systemic B-symptoms (Proc. AACR 29:214, 1988). At the same time it became clear that Pts achieving a PR after 3 courses of F-MACHOP could have during and/or after the following 3 courses, either one of these outcomes: 1. Progression of the disease with no response to intensive salvage treatments (ISTs); 2. Achievement of a better PR or a CR with a high risk of early relapse refractory to ISTs; 3. No apparent change of residual disease without evidence of viable tumor cells after biopsy and a very low risk of relapse. Therefore, from 3.86 to 7.88 an early pathologic response evaluation (EPRE) was attempted in 63 consecutive Pts to identify, among those achieving a PR after 3 courses, those at higher risk of failure when tumor burden is minimal making them ideal candidates for early intensification of treatment (Proc. ASCO 8 : 259, 1989). EPRE has not documented viable tumor cells in 15/23 Pts with a clinical PR after 3 courses of F-MACHOP, these Pts have an actuarial %EFS at 3 yrs similar to that of Pts in CR after the 3rd course. On the other hand the outcome of Pts in pathological PR after EPRE, treated immediately after surgery with ISTs, did not appear to be better as compared to our historical control, previously treated with a total of 6 courses of F-MACHOP. We concluded that the cost of an early accurate evaluation of response, was not balanced by the putative benefit of an early administration of ISTs. From 8.88 we therefore started a cooperative italian randomized study (F-MACHOP vs. MACOP-B) where the clinical persistance of tumor after the completion of 2/3 of planned treatment make the Pts eligible for an early treatment intensification (DHAP vs. BEAC + ABMT). This prospectic study is in progress.

P 22 A MULTICENTER RANDOMIZED STUDY, MACOP-B VERSUS F-MACHOP, IN THE TREATMENT OF HIGH GRADE NON-HODGKIN'S LYMPHOMAS; FIRST REPORT. P. Mazza, S. Tura, S. Pileri, M. Bocchia, F. Gherlinzoni, P.L. Zinzani, C. Guglielmi; M. Martelli, G. Papa, M. Antimi, M.F. Martelli, F. Grignani, B. Falini, F. Calabresi, E. M. Ruggeri, V.M. Lauta, G. Lucarelli, L. Moretti C, F. Mandelli. Istituto di Ematologia "Seràgnoli"-Bologna; Cattedra e Istituto di Ematologia "La Sapienza"-Roma; Cattedra di Ematologia "Tor Vergata"-Roma; Istituto Regina Elena-Roma; Istituto di Clinica Medica-Bari; Cattedra di Ematologia-Perugia; Divisione di Ematologia-Pesaro.

In a multicenter ongoing study we are evaluating two therapeutic schemes (MACOP-B versus F-MACHOP) on high grade malignant lymphomas G, J and H categories according to Working Formulation. From September 1988 to December 1989 125 patients were randomly enroled; 75 pateints are now evaluable for response and toxicity with a minimum follow-up of three months form the end of treatment: 42 patients were assigned to MACOP-B and 33 to F-MACHOP. Mean age, sex, clinical and histological characateristics were similar in both groups: the median follow-up was 9.9 months for the group treated by MACOP-B and 8.0 months for that by F-MACHOP. The remission rate was 68% in both groups but 12% resistance was recorded in the group treated by MACOP-B instead 3% of patients treated by F-MACHOP were, primarily, resistant. A significant difference (P <0.05) has been disclosed in disease-free survival being 50% for the group of MACOP-B and 70% for the group of F-MACHOP. Among bad prognostic factors only bulky presentation influenced negatively remission rate (P <0.05). Two toxic deaths were registered in both groups allowing a risk of less than 5%; however severe hematological toxicity, was recorded in 21% of patients treated by MACOP-B and 60% of patients treated by F-MACHOP. Major side effects were infections and mucositis. In conclusion F-MACHOP seems to be superior in inducing a stable remission, however it appears a more toxic regimen than MACOP-B. Firm conclusion will be drawn in a short period of time.

P 23 PROMACE/MOPP (P/M) THERAPY IN AGGRESSIVE NON HODGKIN'S LYMPHOMAS (NHL). T. Chisesi - L. Rancan (VI), M.R. Sertoli (GE), P. Coser (BZ), V. Rizzoli (PR), A. Porcellini (CR), A. Contu (SS), L. Moretti (PS), G. Santini (GE) for the NHL Cooperative Study Group (NHLCSG) (ITALY).

From January '85 to April '87 93 untreated patients (pts) with diffuse intermediate-high grade NHL stage III-IV, median age 49, were enrolled in a cooperative study from the NHLCSG in order to verify previously reported results of a similar NCI protocol. Pts were treated with at least 6 cycles, up to complete remission (CR), of PROMACE (Cyclophosphamide 650mg/sm iv + Doxorubicin 25mg/sm iv + Etoposide 120mg/sm iv days 1,8, Methotrexate 400mg/sm iv day 14 and Prednisone 60mg/sm os) alternating every 28 days with MOPP (Nitrogen mustard 6mg/sm iv + Vincristine 1,4mg/sm iv days 1,8, Procarbazine 100mg/sm os + Prednisone 40mg/sm os from day 1 to 14). At CR pts received two more cycles of consolidation +/- radiation treatment to the site of previous bulky disease. 11 pts died during therapy and are evaluable only for survival. Out of 82 pts evaluable for response and survival, 54 achieved a CR, 11 a PR, 17 progressed. Toxicity was heavy: 8 toxic deaths were recorded and, aside from expected hematological toxicity, 5 pts suffered cardiac toxicity grade 2-4, 3 pts neurotoxicity grade 3-4, 2 pts hepatic toxicity grade 2-4, 2 pts infections grade 3-4. For the 54 pts achieving CR, Actuarial Survival is 50.5% and DFS 67% at 49 and 40 months respectively. 15 pts relapsed. Median time to relapse was 5 months (range 2-15) from CR. The results obtained in this cooperative study are slightly inferior to those reported from the original single institution trial. On the basis of this study, in January 1987 a randomized trial comparing P/M to a third a third generation regimen (MACOP-B) was started.

P 24 ADRIAMYCIN, VINCRISTINE, PREDNISOLONE AND ETOPOSIDE (HOPE) CHEMOTHERAPY FOR ADVANCED DIFFUSE HIGH-GRADE LYMPHOMA FROM THE SOUTH OF ENGLAND COLLABORATIVE TRIALS GROUP.
A.G. Prentice[1], C.J. Tyrrell[1], S.A.N. Johnson[2], P. Harper[3], M.J. Phillips[2], J.G. Smith[1], H.M. Daly[5], J.S. Murrell[5], M. Richards[3], C.J. Singer[4], J.A. Copplestone[1], P.M. McLeod[1], W. Gregory[3], A. Timothy[6], P. Isaacson[7]. 1. Plymouth, 2. Taunton, 3. Guy's, 4. Bath, 5. Truro, 6. St. Thomas', 7. Middlesex.

From 1982 to 1988 165 patients with diffuse large cell non-Hodgkin's Lymphoma were treated with HOPE chemotherapy (H=30 mgs/M^2 D1+15, O=2 mgs D1+15, P= 40 mgs p.o. D1-5, E= 100 mgs/M^2 p.o. D1-5, q 28 D x 6-8). There was no age limit, but doses were reduced for age and day 15 blood count. 124 patients were evaluable at the time of this abstract (Stage II 42, III 31, IV 51). The mean age was 62 years, range 18-85 years. The overall response rate was 89%, 68% CR and 21% PR. Responses by stage, age and histology are shown below.

	OVERALL	STAGE			AGE			HISTOLOGY	
		II	III	IV	<60	60-69	70+	IG	HG
N	124	42	31	51	54	44	26	33	91
CR%	68	78	68	61	78	73	42	60	71
PR%	21	21	19	29	18	23	23	27	19

Median duration of remission and overall survival for all patients have not been reached (median follow-up 3½ years). However, centroblastic/centrocytic tumours (intermediate grade or IG) have a median survival of 3½ years as well as a lower CR rate than high-grade tumours (HG). Overall toxicity was low with 5 early deaths (4 due to septicaemia) and universal alopecia.

Good remission and disease-free survival rates are obtained with this combination and scheduling of drugs despite the omission of an alkylating agent and the comparatively high median age. Alternative treatment for patients with IG lymphomas may be indicated. Data on 165 patients will be available for presentation.

P 25 BRIEF CHEMOTHERAPY (ACOB) AND MODERATE DOSE INVOLVED FIELD (IFRT) IN THE TREATMENT OF LOW STAGE LARGE CELL LYMPHOMA.

N. Voss, R. Klasa, R. Fairey, S. O'Reilly, P. Hoskins, J. Connors. Cancer Control Agency of British Columbia (CCABC) 600 West 10th Avenue, Vancouver, B.C. Canada

From 1985 to 1989, 92 consecutive patients with stage IA and IIA (bulk <10 cm) aggressive lymphoma were prospectively treated with 6 weeks of chemotherapy (ACOB) and moderate dose radiotherapy (RT). Histological subgroups (all diffuse) were: mixed 12, large cleaved 27, large non-cleaved 20, immunoblastic 21, large cell otherwise unclassified 12. Median age was 67 years (25-85) and 37 were over 70 years. Fifty-four were male, 38 female; there were 49 stage IA, 43 IIA; 66 had extranodal disease or extension. Median follow-up was 26 months (1-60).

ACOB consists of doxorubicin 50 mg/m2 IV and cyclophosphamide 350 mg/m2 IV days 1, 15, 29; bleomycin 10 u/m2 IV and vincristine 1.2 mg/m2 IV days 8, 22, 36; prednisone 50 mg po for 4 weeks and taper; cotrimoxazole 1 DS tablet po bid and ketoconazole 200 mg po daily for 6 weeks. IFRT (3000 cGy in 10 treatments or equivalent) is given to sites of original disease 4 weeks after ACOB. Patients with sinus involvement receive intrathecal chemotherapy twice weekly X 6 after RT.

One patient did not respond, 7 relapsed (of these, 3 remain in remission 29 to 32 months after further treatment). Nine died: 4 of lymphoma, 2 of treatment related causes, 3 of unrelated causes.

Actuarial failure free survival was 78%, overall survival 83% and disease specific survival 91%. Three year failure free survival and uncorrected survival, respectively, were: all patients: 86% and 90%; stage IA: 86% and 88%; stage IIA: 86% and 93%; age ≥ 70 years: 78% and 84%.

This regimen is effective and well tolerated by all age groups. It avoids many of the complications of prolonged chemotherapy and/or higher dose extended field RT.

P 26 VIM-Bleo/CHOP IN HIGH GRADE MALIGNANT NON-HODGKIN'S LYMPHOMAS: FINAL RESULTS OF A PROSPECTIVE STUDY.

B. Steinke, K. Bross, H.-M. Reinold et al.
Medizinische Universitätsklinik, D-74 Tübingen, FRG

Between 1986 and 1988, 81 patients (male 35, female 46, median age 57 years) with high grade malignant NHL were treated with the VIM-Bleo/CHOP-regimen: Etoposide 100 mg/m² iv days 1-3, Ifosfamide 1,5 g/m² iv days 1-5 with Mesna for prophylaxis of cystitis, Methotrexate 30 mg/m² iv day 3, Bleomycin 10 mg iv days 8 and 15, Cyclophosphamide 750 mg/m² day 22, Adriamycin 50 mg/m² day 22, Vincristine 1,4 mg/m² day 22, and Prednisolone 100 mg po days 1-5 and 22-26. Cycles were repeated four times beginning on day 43. Regions with bulky disease were irradiated after chemotherapy. According to the Kiel-classification, 38 patients (47 %) had a centroblastic, 22 (27 %) an immunoblastic, 3 (4 %) a lymphoblastic and 18 (22 %) a high grade malignant lymphoma, which could not be further classified. 36 patients (44 %) had stage II, 12 (15 %) stage III and 33 (41 %) stage IV disease. B-symptoms were present in 49 % of patients. Serum-LDH activity was elevated in 53 %. Overall, 59 patients (73%) reached a complete and 14 (17%) a partial remission. 8 (9%) had stable or progressive disease. After a median follow up of 17 months so far, 15 relapses occured. Probability of survival at 24 months is 60%. Toxicity of treatment was very low with leukopenia being the main side effect. Only in 2% of cycles, maior infections were observed with one treatment related death. Other toxicity was minimal. We conclude, that VIM-Bleo/CHOP is a well tolerated regimen with remission rates in the range of other, more toxic regimens. Final results with a minimum follow-up of 20 months will be presented at the meeting.

P 27 VAPEC-B CHEMOTHERAPY FOR DIFFUSE HISTOLOGY NHL - RESULTS OF A COLLABORATIVE TRIAL AND THE VALUE OF SERUM LDH IN PREDICTING RELAPSE AFTER CR IN STAGES III/IV.

J A Radford[1], J Whelan[2], D Deakin[3], T A Lister[4], D Crowther[1]. [1]CRC Dept Medical Oncology and [3]Dept Radiotherapy, Christie Hospital, Manchester, UK and [4]ICRF Dept of Medical Oncology and [2]Dept Radiotherapy, St Bartholomew's Hospital, London, UK.

This collaborative trial between two specialist centres has been active since October 1987. Over 200 pts have so far been entered but interim analysis for the purpose of this abstract is of 115 patients treated at the Christie Hospital.

Median age was 56 years (17-77) and 68 were male and 47 were female. Median KP was 70 (20-90) and median follow-up is 12 mths (3-28). 72 of 115 (63%) were stage IV, 10 (9%) were stage III, 21(18%) were stage II and 11(10%) were stage I. Bulk disease occurred in 56% overall and in 70% of stage IV pts. 63 of 115 (54%) had either centroblastic or high grade unclassified histology. 14 of 115 (12%) were T cell tumours, 11(10%) were lymphoblastic, 9(8%) immunoblastic, 6(5%) CB/CC diffuse, 5(4%) were unclassified and 7(6%) had either lymphoplasmacytoid, centrocytic or lymphocytic histology.

After chemotherapy 76(66%) had acheived CR or equivocal CR (minimal residual abnormality on CXR or CT scan but no palpable disease and BM/biochemistry normal), 16(14%) PR, 7(6%) had progressed and 16(14%) had died. The CR/equivocal CR rate by stage was 92%(I), 86%(II), 90%(III), 53%(IV). Thirteen of 16 deaths on treatment occurred in stage IV patients either from sepsis or probable sepsis (7 pts), disease (4 pts; 2 within 24 hours of starting treatment) or other causes (2 pts; 1 from CVA, 1 from small bowel infarction).

OS for the whole group at 12 mths is 60% (Stages I and II 92%, III 70%, IV 50%) and RFS for 76 pts in CR/equivocal CR is 82% (I 100%, II 95%, III 90%, IV 65%). For stage III/IV pts in CR/equivocal CR after VAPEC-B, serum LDH at presentation is predictive of high, intermediate or low risk of relapse (when LDH ≤500 RFS is 95%; 501-900, 78%; ≥901, 38%). This information may allow selection of pts requiring intensive consolidation following remission induction with VAPEC-B.

VAPEC-B is Adr 35mgs/m² weeks 1,3,5,7,9,11; Cyclo 350mgs/m² i.v. weeks 1,5,9; Etop 100mgs/m² p.o. daily for 5 days weeks 3,7,11; Vinc 1.4mgs/m² weeks 2,4,6,8,10; Bleo 10mgs/m² i.v. weeks 2,6,10 plus prednisolone 50mgs p.o. daily weeks 1-5, 25mgs daily 6-11 then tailed to zero, and prophylactic co-trimoxazole 2 tabs 12 hrly and ketoconazole 200mg 12 hrly, both for 12 weeks.

P 28 SEQUENTIAL VS ALTERNATING CHEMOTHERAPY FOR HIGH GRADE NON HODGKIN'S LYMPHOMAS: A PHASE III MULTI-CENTRE TRIAL.

H. Köppler, K.H. Pflüger, K. Havemann for the study group, Dept. Internal Medicine, Philipps-University, Baldingerstrasse, D-3550 Marburg, FRG

In a multicentre phase III trial 140 previously untreated patients with high grade non-Hodgkin's lymphomas stages II-IV were randomized to receive either four cycles of CHOEP (cyclophosphamide 750 mg/m² iv d 1; doxorubicin 50 mg/m² d 1, vincristine 2 mg iv d 1, etoposide 100 mg/m² iv d 3-5, predenisolone 100 mg po d 1-5) (treatment arm A), or four cycles of chemotherapy with hCHOP (cyclophosphamide 1200 mg/m² iv d 1, doxorubicin 40 mg/m² d 1+2, vincristine 2 mg iv d 1, prednisolone 100 mg po d 1-5) alternating with IVEP (ifosfamide 1500 mg/m² iv d 1-5, vindesine 3 mg/m² iv d 1, etoposide 120 mg/m² iv d 3-5, prednisolone 100 mg po d 1-5) in treatment arm B. After 4 cycles of chemotherapy an involved field irradiation with a total dose of 35 Gy was given to all patients demonstrated to be in complete or partial remission without persisting extranodal disease. Main toxicity of the protocol was chemotherapy induced neutropenia which was mild after CHOEP and IVEP. In treatment arm B haematological toxicity was increased after hCHOP with an increased morbidity due to neutropenia related infections and two deaths in patients > 70 years. Therefore in hCHOP cycles cyclophosphamide and doxorubicin were reduced to 65% in patients > 70 years old. A complete response (CR) was seen in 115/140 patients (82%) with 85% CR in arm A vs 78% in arm B. With a median follow-up of 12 months the overall survival at 36 months is projected to be 72% vs 83% for arm A and B respectively. Response was strongly related to stage at diagnosis and histologic subtype. While patients stage II and III achieved CR rates of 80-100%, patients with stage IV had CR rates of 64% and 56% in arm A and B, respectively. Only 63% of patients with immunoblastic NHL showed a complete response whereas patients with lymphoblastic or centroblastic NHL had CR rates of 78% to 93%. So far, no significant differences are seen in CR, survival and disease-free survival. A longer follow-up will be needed to exclude an advantage for any treatment arm.

P 29 RESULTS OF BNLI STUDIES IN LARGE CELL AND MIXED SMALL AND LARGE CELL NON HODGKINS LYMPHOMAS.

D C Linch, G Vaughan Hudson, MH Bennett, K MacLennan, B Vaughan Hudson. BNLI, Middlesex Hospital, London, UK.

From 1974 to 1984 292 patients with stage III / IV large cell (including immunoblastic) or mixed small and large cell Non Hodgkins lymphoma were treated initially with CHOP combination chemotherapy (cyclophosphamide 750 mg/m^2 day 1 and 8, hydroxydaunorubicin 25 mg/m^2 day 1 and 8, vincristine 1.4 mg/m^2 (max 2 mg) day 1 and 8 and prednisolone 50 mg/m^2 day 1-8) given as 4 weekly cycles until 3 courses beyond complete remission with a minimum of 6 courses. 74 % of patients were aged over 50 years, 62 % were stage IV and 46 % had 'B' symptoms. The complete remission rate was 49 % and the overall disease free survival and overall survival were 27 % and 36 % respectively with no firm evidence of a plateau.
Since November 1987 the efficacy of six 4-weekly cycles of CHOP has been compared with 12 weeks of PACEBOM therapy (cyclophosphamide 300 mg/m^2 hydroxydaunorubicin 35 mg/m^2 , etoposide 150 mg/m^2 every other week alternating with methotrexate 100 mg/m^2 (plus folinic acid rescue) vincristine 1.4 mg/m^2 and bleomycin 10 mg/m^2 , prednisolone 50 mg/m^2 for 4 weeks and then on alternate days for 8 weeks and Co-trimoxazole 1 bd weeks 1-14) in a randomized trial. All patients with stage II to IV disease are eligible. 204 patients have been entered in the first two years. 110 patients are presently evaluable for response to treatment. The results with CHOP are the same as in the previous study. The results with PACEBOM compare favourably with CHOP in all patient categories.

Stage	Response			
	CHOP		PACEBOM	
	No	%CR	No	%CR
II	18	83	14	86
IIIA/IVA	17	65	20	70
IIIB/IVB	17	35	23	61
Overall	53	62	57	70

PACEBOM has been associated with frequent mucositis (methotrexate) but the toxicities otherwise have been comparable. The complete response rate with a 3 month regimen is thus at least as high as with 6 months of CHOP therapy and merits continued study.

P 30 CHEMOTHERAPY FOR PATIENTS WITH STAGE II-III AND IV INTERMEDIATE AND HIGH-GRADE LYMPHOMA, COMPARING CHVmP/VCR-bleo VERSUS ProMACE/MOPP, A RANDOMIZED STUDY.

R. Somers, M. van Glabbeke, U. Tirelli, J. Thomas and P. Carde for the EORTC Lymphoma Cooperative Group. Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX, Amsterdam, The Netherlands.

The results of non-randomized phase II studies on high dose chemotherapy ask for confirmation in randomized trials. In an earlier study of the group we demonstrated a higher CR rate for CHVmP-VCR-bleo in comparison to CHVmP.
In the first regimen vincristine-bleomycin is administered on day 15 between CHVmP courses.
In the EORTC lymphoma cooperative group a randomized phase III study was started in January 1986 for stage II, III, IV, intermediate and high grade lymphoma comparing the group standard regimen CHVmP-VCR-bleo, consisting of cyclophosphamide 600 mg/m2 day 1, VM26 60 mg/m2 day 1, adriamycin 50 mg/m2, day 1, prednisone 40 mg/m2 day 1-5, vincristine 2 mg day 15, bleomycine 10 mg day 15, q 21D x 8 cycles (arm 1) with ProMACE/MOPP consisting of adriamycin 25 mg/m2 day 1, cyclophosphamide 650 mg/m2 day 1, VP16 120 mg/m2 day 1, nitogen mustard 6 mg/m2 day 8, vincristine 1,4 mg/m2 day 8, prednisone 60 mg/m2 day 1-15, procarbazine 100 mg/m2 day 8-15, methotrexate 500 mg/m2 day 15, q 21D x 8 cycles (arm 2).
In this first interim analysis 159 patients were available for response and 222 for toxicity.

The preliminary results may be summarized as follows:

	CR at 8 courses %	Rem. dur. 30 months %	Dis.free surv. 30 months %	Survival 30 months %
CHVmP-VCR-bleo	67	68	59	58
ProMACE/MOPP	63	67	50	66
All	65			

WHO grade III and IV toxicity occurred for WBC in 60%, for platelets in 5%, for G.I. toxicity in 18%, in the CHVmP-VCR-bleo arm; in the ProMACE/MOPP arm the figures were: 70% (p.0.03), 17% (p.0.0064) and 24% respectively.
We found no significant difference in response rate, disease free survival, remission duration and survival between two treatments, while there was more toxicity in the ProMACE/MOPP arm. The earlier results with CHVmP-VCR-bleo were confirmed, the regimen is well tolerated and can be given on an outpatient basis.

P 31 "Improvement of results of treatment of agressive non Hodgkin's lymphoma (NHL) using Epirubicin containing regimen - BECOP".

N. GAD EL MAWLA, H. KHALED, N. HABBOUBI, M.R. HAMZA, Z. ZIKRI, M. EL SERAFI, A. EL KHODARI, R. GAAFAR, H. EL ZAWAHRI, A. ABDEL WARETH, NCI Cairo, FICE Milano.

85% of NHL reporting to NCI, Cairo are of intermediate and high grade types with big tumor burden. Different chemotherapeutic regimens have been tried, with low CR rate and short relapse free intervals. BECOP regimen aims to improve these results: VINCRISTINE 1,4 mg/sqm, Epirubicin 40 mg/sqm, Cyclophosphamide 650 mg/sqm, all I.V. on day 1,8 while Bleomycin was given 5 units/sqm I.V. day 15,22 and Prednisone 40 mg/sqm P.O. day 15-28. Courses repeated every 28 days for 3-6 cycles. 40 patients with stage III, IV have studied, 28 with intermediate and 12 with highgrade. Age ranged 16-65 y., median 40 y., median number of courses 5. Responses were: CR 67,5%, PR 25% and NR 7,5%, an overall RR of 92,5%, at a follow up of 6-35 months, median 22 months, median time to relapse was 15 months, median overall survival 20 months. Previous results with CHOP were overall response of 68% with CR of 40-60% and median time to relapse 8 months, median overall survival 16 months. Using COP combination, overall response 55,7%, CR 47%, median time to relapse 9 months, median overall survival 12 months. BECOP combination increased the CR rate and prolonged the median time to relapse and median overall survival in our cases of agressive NHL.

P 32 DHAP TREATMENT RESULTS IN 24 PATIENTS WITH REFRACTORY OR RECURRENT NON HODGKIN'S LYMPHOMA.

M.Martelli,C.Guglielmi,R.Gastaldi, S.Coluzzi,V.De Santis,L.Mantovani,C.Sgadari, F.Mandelli.Ematologia,Dip.Biopatologia Umana, Università"La Sapienza", via Benevento 6, 00161 Roma, Italy

Cisplatin and Cytosine Arabinoside (ARA-C) are effective drugs for the treatment of refractory non Hodgkin's Lymphomas (NHL), either as single agents or in combination with other drugs. DHAP regimen including Cisplatin, high doses of ARA-C and Dexamethasone was reported by Velasquez et al. to induce a complete response (CR) and partial response (PR) in 33% and 27% of 90 refractory NHL respectively. From January 1987 to March 1989 DHAP regimen was employed as salvage treatment in 24 patients (pts) with relapsing (n=11), refractory (n=6) and partial responding (n=7) NHL observed in our Institute. Each course of DHAP consisted of: Cisplatin (100mg/sqm) infused i.v. over the first 24 hours followed by a 3 hrs infusion of ARA-C(2g/sqm) repeated after 12 hrs and Dexamethasone (40mg) i.v. daily from day 1 to 4. Each course was repeated every 3-4 week up to a maximum of 6 in responding pts.All pts were adults, 15 were males and 9 females, the median age was 46 yrs (range 19-57 yrs). According to the Working Formulation, 2 pts had low grade malignancy, 4 pts intermediate grade and in 18 the histology revealed a high grade NHL. The performance status according WHO was ≤ 2 in all pts, 8 pts had a bulky disease (> 7 cm), LHD levels higher than 2 times the normal values were present in 11 pts. Moreover, 21/24 pts have been previously treated with a first line Adriamycin comprehensive regimen. Response was obtained in 10/24 pts (42%). Of these 7/24 (29%) obtained a CR while 3/24 (13%) obtained a PR. Factors negatively influencing the type of response were: presence of bulky disease, high LDH levels and absence of response to previous first line therapy.The actuarial disease-free survival was 67% while the overall survival was 57% at 20 and 24 months respectively. Toxicity was mainly hematological. No therapy related deaths were observed. In conclusion, in our experience, the DHAP regimen is a useful second line treatment for "non refractory" (relapsing and partial responding) NHL.

P 33 MITOXANTRONE, IFOSFAMIDE AND VP-16 (MIV) COMBINATION CHEMOTHERAPY IN AGGRESSIVE LYMPHOMAS FAILING TO THE LNH 87 PROTOCOL. A GELA STUDY.

R. Herbrecht*, B. Coiffier, C. Gisselbrecht, H. Tilly, C. Haioun, A. Bosly, Y. Devaux, P. Lederlin, M. Blanc, F. Morvan, for the GELA. *Service d'Onco-Hématologie - Hôpital de Hautepierre 67098 Strasbourg, France.

LNH 87 is a prospective ongoing multicenter study for the treatment of aggressive non-Hodgkin's lymphomas. It has been designed after the LHN 84 study. Patients under 70 years are divided in three groups according to their risk factors and are then randomized between LNH 84 regimen (induction with ACVB cycles, see J. Clin. Oncol. 1989, 7 : 1018-1026) and other regimens. Elderly patients (≥ 70 years) are treated with less intensive chemotherapy regimens (CVP or CVP plus THP-adriamycin).
All the patients failing to a LNH 87 induction therapy arm not containing ifosfamide and/or mitoxantrone could be included in the MIV study. Patients who relapsed at any time after induction could also be included.
MIV is a three-drug combination chemotherapy regimen composed of mitoxantrone (10 mg/m2 D1), ifosfamide (1500 mg/m2 D1 to 3) and VP-16 (150 mg/m2 D1 to 3). Courses are repeated every 21 days for a total of 6 to 9 cycles.
Fifty two patients have been included in the MIV study. Forty eight patients are evaluable for response. Most of them (38 patients, 79%) have been previously treated with the ACVB induction arm. The characteristics of the 48 evaluable patients were median age 58 years (range 40-79) ; stage I-IE : 8 %, stage II-IIE : 10 %, stage III : 6 %, stage IV : 75 % ; bone marrow involvement : 43 %. Main histological subtypes are diffuse large cell (42 %) diffuse mixed cell (29 %) and immunoblastic (13 %). Sixteen patients (33 %) achieved a CR. Seven patients (15 %) attained a PR ≥ 75 % and 4 (8 %) a PR ≥ 50 %. Three patients (6 %) died of toxicity and 18 (38 %) progressed. Of the 23 good responders (CR and PR ≥ 75 %) 8 relapsed after 4 to 9 months. One patient died in CR of a mycobacterial infection. Fourteen are still in CR or PR ≥ 75 % after 2 to 19 months. Four of the complete responders received an intensive chemotherapy with autologous bone marrow transplantation after CR was obtained with MIV. One of these patients relapsed 3 months after BMT was performed.
The most common side effect was the hematological toxicity : grade ≥ 2 neutropenia or thrombopenia was recorded in 21 % patients ; infections occured in 11 % of the patients.
In conclusion MIV regimen appears well-tolerated and can provided good responses in patients failing to the LNH 87 protocol.

P 34 IFOSFAMIDE-ETOPOSIDE COMBINATION CHEMOTHERAPY FOLLOWED BY BEAM AND AUBMT AS SALVAGE TREATMENT FOR MALIGNANT LYMPHOMA.

P.C.Huijgens*, G.J.Ossenkoppele*, J.van der Lelie**, L.L.M. Thomas**, M.J.Wijngaarden*** and C.M.Slaper***. Free University Hospital*, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands, Academic Medical Centre** and Central Laboratory of the Netherlands Red Cross Blood Transfusion Service***, Amsterdam, The Netherlands.

Twenty-seven patients with high and intermediate grade malignant lymphoma were treated by ifosfamide-etoposide combinations after failing to respond completely or after relapsing on CHOP-like therapy. Responders to this salvage therapy were subsequently treated with BEAM ablative chemotherapy (BCNU, etoposide, Ara-C and melfalan) and autografted. Of these 27 patients 9 were in relapse, 10 were partial responders to and 8 failed CHOP-like therapy. The salvage treatment (IMVP in 24, MIME in 3 patients) induced 7 complete and 9 partial remissions. Two more patients achieved a partial remission after additional therapy. These 18 patients were autografted after BEAM ablative chemotherapy, together with 1 non-responder. Nine patients are disease free 7 to 62 months after autografting (median 23 months). Of 8 relapsing patients, 1 did 50 months after autografting. There were 3 therapy related deaths: 1 related to MIME and 2 to BEAM therapy. Using one of the best salvage therapy combinations followed by high-dose chemotherapy and autografting is feasible. An appreciable number of patients may be cured by this procedure.

P 35 ALLOGENEIC BONE MARROW TRANSPLANTATION IN MALIGNANT LYMPHOMA. THE EUROPEAN COOPERATIVE BONE MARROW TRANSPLANT GROUP (EBMT) EXPERIENCE.

P. Ernst and E. DeVol. Departments of Oncology and Biostatistics. King Faisal Specialist Hospital and Research Centre, Riyadh 11211, Saudi Arabia.

EBMT has collected and analysed data on allogeneic bone marrow transplantation (BMT) in 112 patients with malignant lymphomas (8 HD and 104 NHL) performed in the period 1978-1989. Material: age: 3-42 (med 24 y), sex: M:77, F:35, 94 of 104 NHL patients had high grade disease. 79 patients were in stage IV at diagnosis. 55 patients had BM involvement and 12 CNS disease. 57% of patients had received 2' line and 25% 3' line therapy before BMT. All but 4 patients received a fully HLA matched graft from a relative. Status at time of BMT was as follows: 1 CR:44, ≥2 CR:30, relapse:38. The conditioning regimen was for 101 patients total body irradiation and chemotherapy, while 11 cases received chemotherapy alone. Results: 99 patients remained in, or obtained, CR after BMT, PR was seen in 2 patients, 6 showed NR and 4 were ineligible for response. Acute GvHD was seen in 52% (grade 3-4:11%), chronic GvHD was seen in 18% (extensive in 6%). Main causes of death: malignant lymphoma:32 patients, interstitial pneumonia:12, GvHD:5, fatal infections were mainly caused by fungi:9. 51 patients are at time of report alive and well (longest follow-up 5½ y), median survival has not yet been reached for best prognostic group, ie. 1 CR patients. Multivariate Cox analysis reveils that 3 factors are of importance for survival namely: status at time of BMT (1 CR best), acute GvHD (bad prognosis) and histology (lymphoblastic best, Burkitt worst). For duration of remission, only histology was found to be of significance. In patients relapsing after BMT, a very strong correlation between site of recurrence and previous involved site was found. Updating of this material will be presented.

P 36 AUTOLOGOUS BONE MARROW TRANSPLANTATION IN LOW GRADE NON-HODGKIN'S LYMPHOMA AT RELAPSE AND FOLLOWING HISTOLOGIC CONVERSION.

A.Freedman, S. Rabinowe, J. Ritz, K. Anderson, T.Takvorian, P. Mauch, R. Soiffer, K.Blake, L. Nadler. Dana-Farber Cancer Institute, Boston, MA. USA.

Advanced stage low grade NHL are incurable diseases albeit with a long natural history. Although the initial response rate to conventional treatment is high, following relapse the durablity of subsequent responses progressively decrease. Moreover, 40-70% of patients (pts) undergo histologic conversion to a more aggressive NHL which has been associated with poor prognosis. Because of the indolent nature of these diseases and the very high frequency of bone marrow involvement with lymphoma, few pts with low grade NHL have undergone high dose therapy and ABMT. Fifty-one pts with low grade NHL in sensitive relapse or incomplete first remission and 18 pts with transformed low grade NHL underwent high dose chemoradiotherapy and anti-B cell monoclonal antibody treated ABMT. Prior to ABMT all pts achieved a minimal disease state with conventional therapy. The median age of this population was 41 years. The majority of the 51 pts with low grade NHL had failed to achieve a CR with conventional combination chemotherapy (28 pts), and had a history of bone marrow (BM) infiltration (39 pts). A history of extranodal disease other than BM infiltration was present in 13 pts. At the time of ABMT, only 20 pts were in CR and 31 attained a minimal disease state. At the time of harvest, 24 pts had histologic evidence of lymphoma infiltrating the marrow. Following high dose ablative therapy, one acute in-hospital toxic death secondary to cerebral hemorrhage, and one late death due to a myelodysplastic syndrome was observed. Of the remaining 49 pts, 34 are in unmaintained CR with a median follow-up of 12.9 months. The majority of relapses (71%) were in sites of previous disease (12 old sites, 3 old and new sites) while 1 occurred in a new site. Seven pts relapsed in the BM, 5 of whom had a prior history of BM infiltration, and all of whom had marrow involvement at BM harvest. In contrast to the low grade pts, the majority of 18 pts with transformed NHL had a prior CR (14 pts) and at the time of ABMT 10 were in CR. A history of BM involvement with NHL (12 pts) as well as BM infiltration at the time of harvest (6 pts) was similar to the relapsed low grade pts. No acute in hospital toxic deaths were seen and only one late death was observed, not due to recurrent NHL. Four of these pts relapsed, 3 in old sites and 1 in an entirely new nodal site. All of the relapsed pts had a prior history of BM involvement with lymphoma, and 3 had BM infiltration at harvest. The morbidity of ABMT for both pt populations was similar; 8 pts with H. zoster, 10 pts with pneumonia (2 P. carinii, 1 CMV, 7 culture negative). Kaplan-Meier actuarial analysis predicts 50% probability of disease free survival at 26 months for the low grade pts and 47 months for the patients with transformed histology. To date, there is no statistically significant difference in DFS between these two groups of pts. Therefore relapsed pts and pts who never achieved a CR with low grade and transformed NHL can undergo ABMT with very low treatment associated mortality and morbidity. Due to the long natural history of patients with low grade lymphoma, longer follow-up will be necessary to determine whether high dose therapy and ABMT has a significant impact on the curability of the disease.

P 37 HIGH-DOSE CHEMOTHERAPY WITH HEMATOPOIETIC RESCUE IN 22 CASES OF LOW GRADE NON HODGKIN'S LYMPHOMAS.

LINASSIER C[1], COLOMBAT Ph[1], BIRON P[2], MISSET JL[3], FAVROT M[2], DESBOIS I[1], LAMAGNERE JP[1], PHILIP T[2].
[1]*Department of hematology, CHU Bretonneau, TOURS.*
[2]*Department of Bone Marrow Transplantation, Centre Léon Bérard, Lyon.* [3] *Department of hematology, Hospital Paul Brousse, Villejuif, France.*

Few data exist about the value of Autologous Bone Marrow Transplantation (ABMT) in the treatment of low grade non Hodgkin's lymphomas (L-NHL), though first results are promissing.
We report results of intensive chemotherapy with hematopoietic rescue in 22 patients with L-NHL. They were 13 men, 9 women (age range 27-61 (mean = 42,3 years)). Histologies included follicular mixed (n=14) and follicular small clived types (n=8). 17 patients were on sensitive relapse (SR), 5 patients in first partial remission (PR). Conditioning regimen prior transplant was either total body irradiation (TBI) plus cyclophosphamide (n=16), or exclusive chemotherapy schedules (BEAM (n=4), BEAC (n=1)). 21 patients were grafted with bone marrow, 1 patient received peripheral blood stem cells. Marrow purging was performed in 15 patients, either with asta-Z (n=11) or with monoclonal antibodies (n=4). 2 patients received GM-CSF. No death occured during aplasia. 1 patient developed a leukoencephalitis and died 10 months after ABMT. 1 patient treated with BEAM developed pulmonary fibrosis. Following transplant, the 3 patients in first PR are alive and free of disease 22 to 40 after ABMT. Among 17 patients on SR (11 in second complete remission (CR), 3 in second PR, 2 in third CR and 1 in third PR) one patient did not achieve CR after transplantation, 1 patient died free of disease, 4 patients relapsed, and 12 are well and alive 2 to 40 months after ABMT. No relapse was observed among the 6 patients treated with TBI and cyclophosphamide.

P 38 AUTOLOGOUS BONE MARROW TRANSPLANTATION (ABMT) IN POOR-PROGNOSIS NON-HODGKIN'S LYMPHOMA (NHL). REPORT OF THE NON-HODGKIN'S LYMPHOMA CO-OPERATIVE STUDY GROUP (NHLCSG).

G. Santini (Genova)*,P.Coser (Bolzano),V.Rizzoli (Parma), T. Chisesi (Vicenza), A. Porcellini (Cremona), R. Sertoli (Genova), A. Contu (Sassari), L. Salvagno (Padova), O. Vinante (Noale),L.Indrizzi (Bassano),M.Congiu,D.Pierluigi,E.Rossi,E.Damasio (Genova). * Dept.of Hematology, Ospedale S. Martino, Genoa, Italy.

Up to December 89, 48 patients with diffuse intermediate and high-grade malignant NHL, 33 males and 15 females with a median age of 30 yrs. (range 12-53) entered a trial consisting of high-dose therapy with ABMT rescue. At the diagnosis 3 pts. were in stage II, 14 in stage III and 31 in stage IV. At the time of ABMT 26 pts. were in 1st, 3 in 2nd and 1 in 3rd complete remission (CR) respectively, 10 in partial remission (PR), 7 in 1st or 2nd relapse and 1 in progression. For the patients transplanted in CR, the median time from CR to ABMT was of 2 months. The majority of patients, 37 out of 48, underwent procedure after a conditioning regimen consisting of Total Body Irradiation (10Gy in a single dose) and Cyclophosphamide (120mg/Kg), while the others were treated with different combinations. The marrows of 15 patients, involved at the diagnosis, were purged with ASTA-Z at the dosage of 70-100 $\mu g/2x10^7$ cells/ml. The procedure-related deaths were 6.6% (2/30) for patients transplanted in CR, while in other conditions were 33% (5/15). Presently 21 out of 30 patients (70%) transplanted in CR are in continuous complete remission (CCR) with a probability of 4-year DFS of 67%. On the contrary, 9 out of 18 patients transplanted in PR, relapse or progression, obtained CR (50%) but 6 of them relapsed and died in few months for progression of the disease.
In conclusion, our experience showed that first or subsequent CR are the more favourable moments to perform ABMT in poor-prognosis NHL, while in relapse or progression the results are very poor.
We have to establish now wich patients in CR should be scheduled for this procedure.
This problem will be discussed.

P 39 Autologous bone marrow transplantation of non-Hodgkin's lymfomas with marrow purged with immunomagnetic beads.

S. Kvaløy, M. Korbling, S. Funderud, Ø. Fodstad, B. Dørken, E. Jakobsen, K. Beiske, P. Herve, R. Langholm, V. Jetne, E. Smeland, A. Høiby, A. Pihl, A. Foss Abrahamsen, H. Høst and G. Kvalheim. The Norwegian Radium Hospital, Oslo, Norway, University of Heidelberg, W. Germany and BMT Unit Besancon, France.

Previously we have shown in model experiments that lymphoma cells can be rapidly and efficiently removed from human bone marrow by the use of monoclonal antibodies and superparamagnetic polymer particles (1, 2).
Here we report the results obtained in 12 high grade non-Hodgkin's lymphomas autotransplanted with bone marrow purged with immunomagnetic beads. Nine patients had B-cell lymphomas (6 lymfoblastic, 2 centroblastic and 1 centrocytic) and 3 had T-cell lymfoblastic lymphomas. The median age was 29 (range 15-49). Eigth patients were transplanted in first CR, 3 in second CR and one in a chemosensitive PR.

Among the B lymphoma patients the bone marrow was purged with beads and a mixture of the monoclonal antibodies HD 37(CD19), HD6(CD22) and HH1(CD37) (n=6) or AB1(CD19) and AB4(HLA-DR) (n=3) as described earlier (1, 2). The T-cell malignancies had their bone marrow purged with beads the anti T-cell monoclonal antibodies B-H1(CD2), B-B8(CD5) and B-F12(CD7). The recovery of total number of mononuclear bone marrow cells after purging varied from 41-80%. At the time of purging 3 of the B-cell lymphoma patients had from 5-20% tumor cells in the bone marrow. After purging no tumor cells could be detected by immunohistochemical examination.
The pretransplant regimen consisted of hyperfractionated TBI and cyclophosphamide.
Except for one patient that had a late recovery of platelets (8 months) and one patient with a treatment related death, all patients engrafted quickly, reaching $0,5x10^9/l$ granulocytes at day 18-26 and $20x10^9/l$ platelets at day 18-35 posttransplant.
Among the 12 patients transplanted 9 are in continuous complete remission with a observation time of 4-31 months. Two of the patients who had bone marrow involvement before purging are in complete remission 21 and 25 months postransplant.

We conclude that immunomagnetic purging of bone marrow used in ABMT of non-Hodgkin's lymphomas is a rapid, efficient and a safe procedure.

1. Kvalheim G., Fodstad Ø., Pihl A., et al. Cancer Res., 47, 846-851 (1987).
2. Kvalheim G., Sørensen O., Fodstad Ø., et al. Bone Marrow Transplantation, 3, 31-41 (1988).