Poster Session III

STUDIES IN NHL
ABSTRACTS - Fourth International Conference on Malignant Lymphoma, Lugano


DSL has features in common with the low grade follicular lymphoma, and with chronic lymphocytic leukemia (CLL). We assessed the clinical features of 156 pts with DSL, including pts with the following subtypes or variants: plasma cell dyscrasia, paraimmunoblastic, accelerated phase, and centrocytic. We included pts with absolute lymphocyte counts (ALC) of 2000 per mm3 (10%). Initial management ranged from observation only without therapy (Rx), for 49 pts, to combined chemotherapy and radiation. Median age was 57 years (range 25-90). There were 108 males and 58 females. Distribution by Ann Arbor Stage was: I, 7; II, 10; III, 3; IV, 8. III, 1; IV, 15. For pts with stage I-I1 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 rate was 85% at 5 yr and 21% at 10 yr. The median failure-free survival for those who received initial Rx was 3 years. For patients selected for observation, the median time to institution of Rx was 21 mo. for 31 pts who had required Rx; another 18 pts remain untreated for a median of 27 mo. (range 0-106). The survival of this subset of pts was 60% at 5 yr. Most deaths (76%) were directly or indirectly attributed to DSL; a large number of deaths unrelated directly attributed to DSL; a large number of 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-II disease; 2) common involvement of the BM, with or without PB involvement; 3) frequent association with chronic liver disease; 4) an indolent yet ultimately fatal course.


Stage IV LGL is usually associated with a continuous relapse pattern following therapy regardless of type and thus is considered treatable with currently available Rx.

With a variety of chemotherapy approaches ranging from single agents to multi-drug combinations, 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 (CRR). Results were compared with 96 control pts treated from 1974-81 with CHOP-Bleo alone. Forty-two pts received the initial 8 wk phase of IFN (X2) (24 CRR, 22 CR). Partial remission (PR), and 37% minor response (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.

FFS CRs:

<table>
<thead>
<tr>
<th>CHN</th>
<th>FBS</th>
<th>SURVIVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>72</td>
<td>24</td>
<td>67</td>
</tr>
<tr>
<td>50</td>
<td>20</td>
<td>50</td>
</tr>
</tbody>
</table>

P 2  CHLORAMBUCIL/PREDNISOLONE (CVP) VERSUS CHOP IN SYMPTOMATIC LOW GRADE LYMPHOMAS. E. Einblut & H. Teitelbaum. Southwestern Oncology Group, Central Sweden (LOCG) Dept of Radiation Division of Hematology, Danderyd Hospital and Dept of Oncology, Karolinska Institute Hospital 6-104 01 Stockholm, Sweden.

Low grade non-Hodgkin's lymphomas (NHL) are heterogenous diseases with a highly variable clinical progem. The therapy for NHL has changed significantly over the last decade. From a randomized study comparing CVP (Carmustine 200 mg/m2 d1, prednisolone 60 mg/m2 d1-5) and CHOP (Cyclophosphamide 500 mg/m2 d1 and Prednisolone 50 mg/m2 d1-5) (CVAE 1982,1985) there was no difference in response, duration of response, or time to relapse. In a randomized study comparing CVP (Carmustine 40 mg/m2 d1 and prednisolone 75 mg/m2 d1) and CHOP (Cyclophosphamide 500 mg/m2 d1 and Prednisolone 50 mg/m2 d1-5) in 400 patients with low-grade NHL stage III and IV with symptomatic disease (CVAE 1985,1989) there was a difference in the patients who relapsed. The CHOP combination was used for histological upstaging. Half of the patients (53%) were leptomeningeal disease (CVAE 1985) with the highest frequency (62%) in the CVP group. The CHOP group was the lowest. The time from diagnosis to relapse (time with symptomatic disease)/disease longer than 10yr in the patients with NHL stage III and IV relapsing with 8 months in patients with NHL stage III and IV treated with CVP.

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

Table:

<table>
<thead>
<tr>
<th>Therapy</th>
<th>CLN</th>
<th>IC</th>
<th>(BS)</th>
<th>0 (HB)</th>
<th>H</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVP</td>
<td>42</td>
<td>24</td>
<td>10</td>
<td>25</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>CHOP</td>
<td>43</td>
<td>21</td>
<td>6</td>
<td>20</td>
<td>15</td>
<td>15</td>
</tr>
</tbody>
</table>

The therapeutic strategy was to achieve an asymptomatic state in the CVP 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 between the two groups was found. Within the CLI group, early significant survival advantage could be seen with CHOP. In the other histological subgroups there were insufficient numbers of patients to make any meaningful conclusions. Leptomeningeal and non-leptomeningeal patients did not differ regarding response rate or total survival.

Conclusion: Our results at present do not support the use of aggressive chemotherapy as first line therapy in symptomatic CLN and other low grade NHL.


P 4  Non-Hodgkin lymphoma stage I, with 10 year of follow up Report of the HDCTC trial 20751.

J. M. V. Burger, M. van de Velde, Ch. de Wolf-Peeters.

The Netherlands Cancer Institute, Amsterdam.

During the period 1975-1980 the HDCTC cooperative lymphoma group executed trial 20751 for all stages of Non-Hodgkin lymphoma. The aim was to treat patients under 65 years of age with NHL (patients (pts) registered, 117 pts were in stage I. Staging was according to clinical examination, histological and liver function tests, chest x ray, laparoscopy, bone marrow biopsy. Laparotomy was advised for pts < 60 yrs. Histological material was centrally reviewed according to the same criteria for 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 (Cyclophosphadine (CP), 300 mg/m²/day) (1.2, 2, 3, 4, 5, 6, 7, 8 weeks) or CHOP (Cyclophosphadine (CP) 40 mg/m² x 2, 4, 6, 8, 10 weeks) (1.2, 3, 4, 5, 6, 7, 8 weeks) (1.2, 3, 4, 5, 6, 7, 8 weeks).

In total 115 pts were randomised, 60% were males, 35 pts were < 40 yrs, 40% were 40-60 yrs, 31 were > 60 yrs. 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, 7 a mixed and 43 a diffuse pattern. Follicular cell pts were more frequent between 40 and 60 yrs. Inguinal localisation was more often follicular. Clinical and histological characterstics were evenly divided over the 3 treatment arms, but arm 3 (RT only) contained more pts with diffuse cell pts.

For the whole group the 10 yr survival (81%) was 1 in 4 and disease free survival (DFS) 68%: there are no differences between the 3 treatment arms after adjustment of choice bias. For 5C the CVP arm seemed marginally better than the CVP arm, but DFS was equal. For follicular pts there was no difference between the 3 treatment arms and 3 year survival 63% and DFS 63%. For diffuse pts 63% and DFS 63%. For enormous localisation the 10 yr survival 91% and DFS 91% for neck and Waldeyer’s ring is 88% and 91%, and 60% and 60% for DPS 60% 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 stage I follicular non Hodgkin lymphoma, and of inguinal localisations is excellent after treatment with regional radiotherapy. Patients with diffuse histology 10 year survival was 63% and adjuvant chemotherapy did not improve prognosis.
P 5

BNI TRIAL OF CHOP vs CHLORAMBUCIL IN AGGRESSIVE LOW GRADE STAGE III/IV NON HODGKIN LYMOPHMA: A PRELIMINARY REPORT.

G VAUGHAN-HUDSON  BNI, Sir Jules Thorn Building, Middlesex Hospital, London W1, UK.

Since 1985, 148 patients presenting with stage III / IV low grade non Hodgkin's lymphoma which was either symptomatic, progressing rapidly or causing critical organ impairment were randomized to receive either chlorambucil or CHOP. CHOP 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 maximum 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/m²/day 1 & 8, hydroxydaunorubicin 25 mg/m²/day 1 & 8, vincristine 1.4 mg/m² (max 2mg) day 1 & 8 and prednisolone 50 mg/m²/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 group 11 were due to failure in remission, 2 due to infection with disease still present and 3 to progressive lymphoma. In the CHOP arm only 8 of the 17 deaths were due primarily to progressive disease even though 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 LYMOPHMA. M. Martinsson, B. Gimelius, H. Hogberg, C. Sundström, Dept of Oncology and Pathology, University Hospital, S-751 85 Uppsala, Sweden.

In a consecutive series of 168 cases of low grade NHL stages I-II/IV diagnosed on the basis of Diagnosing Medicine and International Medicine 1979-85, 76 pts (45%) were initially asymptomatic, 19 (11%) had "local" symptoms, and 73 (44%) were symptomatic at presentation. The median 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: thyroglobulin, kappa, lambda, and pancytopenia. For the prediction of symptom-free survival, histopathological subgroup (Ki67 classification), stage of 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<0.001), additional S-17 (increased p-value = 0.007), S-haptoglobin (lnrcr. p<0.034) and histopathological subgroup (lnrcr. p<0.042).

Of the 76 initially asymptomatic patients, 64 had therapy deferred until symptoms occurred. In this group, those becoming symptomatic within 6 months had as poor survival as those who were initially asymptomatic (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<0.002).

Within the "immediate symptomatic" group, i.e. without delay to therapy (median 57 mo.), none of the other variables could predict survival.

Elevated levels of S-17 and S-haptoglobin can also predict progressive disease in patients still asymptomatic, in BCC lymphomas, also transformation to a high grade lymphoma.

P 7

PRIMARY NON-HODGKIN LYMOPHMA OF THE UTERINE CERVIX.


Oncology Center, Department of Murbid Anatomy and Pathology, Division of Medicine, S. Chiara Hospital, 38100 Trento, Italy.

Secondary involvement of the female genital tract by generalized Non Hodgkin lymphoma (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 estimated to represent less than 1% of all extranodal NHL. Only 30 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 same genetic and molecular markers of 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 X-ray, hematological and biochemical tests, total body CT scan; 3 had a lymphangiogram; 3 had bone marrow biopsy. The stage according to FNCLCC was IB, IA, ID, IB. 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 disease after 12, 24 and 36 months respectively. The last patient developed a widespread disease after 7 months; performance status, age and associated unrelated diseases contraindicated further therapies; she died 4 months without evident 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 work-up and have to be defined.

P 8

PRIMARY CHEMOTHERAPY FOR LOCALIZED NON-HODGKIN'S LYMOPHMA OR UNFAVORABLE TYPE ARISING FROM (LPWALDER'S RING. K. Sampi, T. Takagi, M. Hattori, Division of Hematology, Saltama Cancer Center and Chiba Cancer Center.

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 consisted of cyclophosphamide, vincristine, prednisone and Adriamycin (LPW) together with radiotherapy. Forty-six patients were treated with chemotherapy and radiotherapy. The number of patients treated with chemotherapy alone was 42 (91.4%) of the 46 patients. Two of these patients did not attain the complete response. Two of these patients were treated with cyclophosphamide and vincristine with a complete response of 84% in 5 months. 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.
ABSTRACTS - Fourth International Conference on Malignant Lymphoma, Lugano


From 1973, 90 patients (pts) affected by gastrointestinal lymphomas were observed in our Institution. More than 50% of pts were not evaluated for disease diffusion to general lymphomas, bone marrow, liver or spleen, according to the criteria of Dawson et al. (1963). The characteristics of 70 pts with primary gastrointestinal lymphomas were analyzed. There were 35 males and 35 females 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 histologically classified according to the WHO Classification and the International Working Formulation. We had 3 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 = 4 pts. The median follow-up was 25 months. 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 70 pts nearly 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 25% of the pts who underwent only exploratory laparotomy with biopsy, are alive and free of disease 5 years after treatment. 12 pts, mostly stage I and low intermediate grade histology, were treated only with surgery: their 5 years survival is 6%. 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 5 years). The relapse rate after complete resection was 4% in stage I and 20% in stage II E.

It will be discussed the importance of an homogeneous therapeutic approach to this potentially curable disease, based on 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.


The efficacy of multimodal treatment of gastric lymphoma (GL) was examined in a retrospective study (1969-1989) of 46 patients. Only patients meeting the criteria of Dawson et al. (Br J Surg 49: 80-89, 1961) for primary GL were included. 22 of our patients were included in a staging according to Ann. Intern Med 197: 218-221 (1977) for staging according to Ann. Intern Med 197: 218-221 (1977). The staging according to Ann. Intern Med 197: 218-221 (1977) was used. Patients with lymphoblastic lymphomas were excluded.

The principal treatment plan: the majority of the pts 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 NH:

A) no residual disease - low grade NHL (LGNH) - no more treatment

B) microscopic residual disease at the resection line and/or SI11 or SI22 LGNH - RT LGNH - CHT + RT and/or surgical resection

LGNH patients without resection - RT. LGNH with inoperable GL with bulk disease were treated by CH/RT. In most patients RT field was the upper part of the abdomen; RT dose 20-30 Gy. CHT was mostly CHOP given at 45 days intervals - 6 cycles.

Results: The medium follow up of 46 patients with LG was 3 years (range 6 months-10 years). 6-year disease-free survival was 100% for 2/46 pts who survived 6 years after diagnosis. 7 out of 49 pts died because of lymphomas: the first one with primary inoperable bulky disease had local progress, whereas the second patient had disseminated disease 12 years after diagnosis. 15 of 49 LG patients treated only by resection (4/46) or resection + RT (6/46) was 100%; in the group of LGNH patients treated by resection + CHT it was 100%, whereas those treated by resection + CH + RT had 97% DFS.

Conclusion: The results suggest that we are on the right way with our treatment plan. Although patients had no treatment-related toxic effects, our future plan is a less toxic therapy, i.e. lower RT dose and smaller RT field. CHT.


The prognosis of non-African Burkitt's lymphoma (high-grade malignant lymphoma 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 NHL regimen, a protocol originally developed for lymphoma in children (Müller-Wehrich et al. Klin. Pädiat. 1968; 135:142). Seven patients received the COMP regimen (Moxley et al. Cancer Res. 27, 1258-63, 1967) and three patients were treated with 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% (4/7) and a long term CR-rate 43% (3/7). Of these patients were treated with other protocols one achieved a short term CR (4 months) and one a late relapse. Long-term remission rates were strongly chemotherapy-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. Other side effects were nausea, vomiting and anorexia. 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 chemotherapy.


Eighty patients (pts) (34 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, Vinocristine (V) 1 (0) 15 mg/m² and Prednisone (P) 60 mg/m², followed by one year maintenance with CHOP and 2) LNH84 protocol (30 pts) with 4 cycles of reinforced CHOP with increased doses of C 1200 mg/m² and V 75 mg/m² over 3 months, followed by consolidation therapy during 6 months; 3) some lymphoblastic leukemia protocol (29 pts) with Doxorubicin (D) 50 mg/m² d1-3, O 1.5 mg/m² d18,12,22, C 600 mg/m² d14, 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 allogeneic bone marrow transplantation (BMT) in 1st complete remission (CR). Median age was 30 years (15-75 yrs). 3 pts were stage I, 18 stage II, 2 stage III, 35 stage IV (37 bone marrow, 5 CNS involvement, 36 pts had leukaemic LBL, 18 pts had blastic cells > 25 % or presence of circulating blasts without pancytopenia). 34 pts had B lymphomas, 50 pts mediastinal mass, 26 pts abdominal adenosmas. 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 = 0.001), absence of BM symptoms (p = 0.07) of abdominal adenosmas (p=0.05), normal LDH level (p=0.002). Median CR duration was 10 months. One relapse occurred in 1st CR patients with BMT. BMT in overall survival duration was 30 months, survival was maintained to 40% at 60 months. Factors associated with shorter overall survival were: increase I.D.H. (p=0.0001), weight loss (p=0.004), CNS involvement (p=0.01), B symptoms (p=0.07). 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 allogeneic bone marrow transplantation needs to be confirmed.
ABSTRACTS - Fourth International Conference on Malignant Lymphoma, Lugano


From 1/87 to 6/89, 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 60 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). 67% of patients were homosexual. 12% FVDA. 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 (2/46) than in IL (15/20) 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 (stage IV), bone marrow involvement was more frequent in BL (20/31) than in IL (6/14) and LCL (6/19) (p=0.01). 88% of BL patients had no previous manifestations of AIDS, whereas 40% of IL and LCL occurred in patients with full blown AIDS (p=0.01). CD4 cell count was higher in BL (286) than in LCL (224) and IL (117) cell/ml. 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. 51% of stage I/II and 24% of stages III/IV achieved complete remission (CR). Overall median survival was 5 months (0-32). There was no difference in CR and actual survival 2-year survival rate according to histological subtypes. The two-year survival was 19% and 10% for stages I/II and III/IV, and 25% and 0% for asymptomatic/PGL and ARC/AIDS groups respectively (p=0.01). The cause of death was mostly tumor progression. The prognosis of these tumors is still very bad. Main prognostic factors are the underlining status of HIV infection and the extent of NHL (Supported by AREMAS and Ligue Nationale Contre le Cancer).


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 lesions) 8 patients; stage III 13 and stage IV 18 patients.

Twentyone received MACOP-B according to the timing and doses as originally reported by the investigators. 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 (50%), partial remission in 8 and resistant disease was ascertained in 5. Four deaths were due to septic 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 leukemias, 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 undoubtedly benefit from this treatment and the results appear comparable to those obtained in the younger population.


In a national Swedish study, 100 patients with high-grade malignant NHL were treated with MACOP-B. Inclusion in the study started in September 1980 and was completed in June 1988. The mean age was 47 years (range 17-78). The patients were divided into the following stages: I 7 (all bulky), II 26 (11 bulky), III/IV 63, A 47 patients, B 5 patients, the "Larger Tumour" (Kiel) Classification (B 45, I 18, LB 7, Anaplastic 2, MUD 26). During the first year of the study, no antibiotic prophylaxis was administered and prednisone was given intermittently. Therefore 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 carinii) during the period when antibiotic prophylaxis was not administered. Three patients died of sepsis, 1 of gastrointestinal bleeding and 1 of tumor necrosis.

Conclusion: MACOP-B is a highly toxic regimen and an antibiotic prophylaxis 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 47 years (range 16-77) compared with 67 years in this study. A randomized study between MACOP-B and CHOP has therefore been started.


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 Connor 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 190 infectious episodes, the majority of which were clinically or microbiologically documented. The infections were: Candida mucositis (36), pneumonia (24), meningitis (not due to Candida) (16), viral infections (16), Varicella-Zoster (10/15), upper respiratory tract infections (11), soft tissue infections (8); urinary tract infections (6) bactereemia 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 9/92 (9%). 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 29% and 0%; during the second month 40% and 0%, during the third month 24% 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 60 yrs (19-68). It was 56 yrs (39-67) in the 9 pts who died because of infection. Because of the infection, CT was delayed in 36 (17%) and definitively interrupted in 9/203 (4%) of pts. The mean length of delay was 19 days (7-120). We observed only one episode of interstitial pneumonitis 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 during the third month of CT were few but severe; 5) the cotrimoxazole prophylaxis of Pneumocystis carinii pneumonitis seemed to be adequate.
ABSTRACTS - Fourth International Conference on Malignant Lymphoma, Lugano

P 17 INTENSIVE WEEKLY CHEMOTHERAPY FOR THE INITIAL TREATMENT OF ADVANCED INTERMEDIATE AND HIGH GRADE NON-HODGKIN'S LYMPHOMA (NHL). J.M. Sweetman, and J.M.A. Whitelaw. CRC Westmead Medical Oncology Unit, Southport General Hospital, Tremosa Road, Southport 5090, AUS., U.K.

High response and overall survival rates have been reported for MACOP-B chemotherapy for the initial treatment of advanced intermediate and high grade NHL. We have developed a similar regimen, with lower dose methotrexate and 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 the trial. The trial is still open. Results will be presented at the conference.

P 18 ALTERNATING NON-CROSS-RESISTANT MULTI-DRUG CHEMOTHERAPY (CAMEBO-VIP) FOR NON-HODGKIN'S LYMPHOMA OF INTERMEDIATE AND HIGH GRADE MALIGNANCY: A PILOT STUDY. M. Kirano, M. Okamoto, O. Iwamoto, K. Kishi, Department of Hematology, Fujita Health University, Toyoake 470-11, Japan

Early exposure to multiple dose-intensively administered non-cross-resistant drugs has been associated with an improvement of chemosensitivity in non-Hodgkin's lymphoma of aggressive histology. We have tested the alternating non-cross-resistant drug chemotherapy consisting of gemcitabine therapy combined in phase I and II with leucovorin, etoposide and vincristine. Results: Among chemotherapy in 10 patients, the median complete remission rate was 80% (9/11), and the median time to progression was 17 months. The overall response rate was 91% (10/11), and the median survival time was 17 months. The most frequent side effects were myelosuppression, nausea and vomiting.

P 19 Randomized comparison of weekly chemotherapy with standard cyclical chemotherapy for high grade lymphoma. Stuart Nsa1, Blajko CR1, Chandler CJ1, Bussel EM1, Cullen MH1, Grieve RP2, Simmons AV1, Fletcher S1, Sykes VI, Queen Elizabeth Hospital, Birmingham, Greater London, UK., Leeds City Hospital, Oxford, UK.

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. We present here a randomized comparison of high response rates with weekly chemotherapy. In cooperation with the Cancer Research Campaign, we have undertaken a randomized study. Patients entered to this study have 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 in a curative intent.

The weekly regimen (CAPOMEL regimen A) comprises: Day 1: Cyclophosphamide (CYC) 500mg/m², doxorubicin (DOX) 50mg/m² both i.v., vincristine (VCR) 2mg/m² (i.v. Day 1), prednisolone (PDN) 60mg daily, methotrexate (MTX) 2.5mg/m² on day 15, vincristine (VCR) 2mg/m² on day 15, and methotrexate (MTX) 2.5mg/m² on day 15. The second regimen (CAPOMEL regimen B) comprises: Day 1: CYC 750mg/m² i.v., Doxorubicin (DOX) 50mg/m² both i.v., methotrexate (MTX) 2.5mg/m² both i.v. on day 2, vincristine (VCR) 2mg/m² on day 2, and methotrexate (MTX) 2.5mg/m² on day 2. Both regimens are repeated every 3 weeks for 8 cycles. Patients who have achieved complete remission (CR) after 4 cycles are randomized to continue with 4 cycles of the original regimen (5 max, 8 cycles).

At the time of analysis 339 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, 8; stage II, 17; stage III, 15; stage IV, 14; and for group B, stage I, 10; stage II, 14; stage III, 15; stage IV, 12. The median age of patients with CR was 58 years (range 19-80). The main toxic effects included: myelosuppression, mucositis, nausea and vomiting, and nausea and vomiting. In general, the toxic effects were comparable between the two regimens.


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 group. The PROCHOME/MOPP regimen versus MACOB-B. From January 1968 up to January 1990 191 pts have been enrolled in this study. Median age of pts in the entire group is 46 years (range 19-65). According to histology all pts were categorized as F-G-II of W.H.; 25 pts were in stage I, 31 in stage II, 36 in stage III and 66 in stage IV with 69/122 (44%) presenting bulky disease above or below diaphragm. The two groups were balanced with respect to age, stage, performance status, B-symptoms, number of extranodal sites, and CR pts treated with a minimum of 6 cycles of alternating therapy. About 60% of CR has been registered with no PR rate obtained in both arms. In 10% of pts we obtained a PR, and 30% of pts didn't respond. As far as the toxicity is concerned we had an increased incidence of general toxicity (alopecia, nausea, vomiting, and mucositis in MACOB-B arm. The hematologic toxicity resulted lower in PROCHOME/MOPP group on the contrary of the relapse rate and toxicity of MACOB-B arm. From these preliminary data we can argue that the "used regimens are not different, but that the complete remission rate is higher in the MACOB-B for patients with previous high risk disease. However, 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 proposal for these categories of pts."
ABSTRACTS - Fourth International Conference on Malignant Lymphoma, Lugano


From 11.80 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 cycle (1 course x 6 in responders) combination chemotherapy program. The "MACHOP" regimen is based on the rationale that exposure of rapidly proliferating tumor cells to as many as possible alkylating agents and doxorubicin administered sequentially throughout the entire duration of the cycle will maximize tumor cell kill and significantly reduce tumor burden, thereby decreasing the possibility that resistant clones will arise (Cancer Invest. 15:195, 1987). The overall CR-rate is 79% and the 5 and 10 year 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 (Semk. Oncol. 12[Suppl]:21:198, 1985). We then continued these observations 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 "MACHOP": 91% for CR and 45% for PR and overall survival rates (OS) were 96% and 83% respectively. In conclusion: PTS achieving a 3rd cycle CR have excellent OS and EFS and should be considered for further treatment.


In a multicenter ongoing study we are evaluating two therapeutic schemes (MACOOP 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 enrolled: 75 patients are now evaluable for response and toxicity with a minimum follow-up of three months from the end of treatment: 42 patients were assigned to MACOOP B and 33 to F-MACHOP. Mean age, sex, clinical and histological characteristics were similar in both groups: the median follow-up was 9.3 months for the group treated by MACOOP B and 3.8 months for that by F-MACHOP. The remission rate was 68% in the group treated by MACOOP B and 70% for the group treated by F-MACHOP. According to the CR rate in both groups allowing a risk of less than 5%, however severe hematological toxicity, was recorded in 21% of patients treated by MACOOP B and 20% patients treated by F-MACHOP. Major side effects were infections and mucositis. In conclusion F-MACHOP seems to be superior in inducing stable remission, however it appears a more toxic regimen than MACOOP B. Final conclusion will be drawn in a short period of time.

P23 "PROMACE/MOPP (P/M) THERAPY IN AGGRESSIVE NON-HODGKIN'S LYMPHOMAS (NHL). T. Chiesi - L. Rautenburm (VI), M.H. Sertoli, J. Roca, C. Cere, V. Rizzioli (PF), A. Porcellini (CR), A. Contu (SS), L. Moretti (PS), G. Santini (GE) for the NHL Cooperative Study Group (NHCSG) (ITALY).

From January '85 to April '87 93 untreated patients (PTS) with diffuse large cell NHL, grade II-IV, median age 49, were enrolled in a cooperative study from the NHCSG in order to verify previously reported results of a similar NCI protocol. PTS were treated with 2 cycles of MOPP and 5 cycles of CHOP (CR), or of PROMACE (Cyclophosphamide 650mg/m² iv + Doxorubicin 25mg/m² iv + Etoposide 120mg/m² iv days 1,8, Methotrexate 400mg/m² iv days 1,4 and Prednisone 60mg/m² os) alternating every 28 days with MOPP (Nitrogen mustard 6mg/m² iv + Vincristine 1,4mg/m² iv days 1,8, Procarbazine 100mg/m² os + Prednisone 40mg/m² os from day 1 to 14). At CR pts received additional 2 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 92 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 hematological toxicity, 2 pts suffered cardiac toxicity grade 4, 2 pts hepatic toxicity grade 3-4, 2 pts infections grade 3-4. For the 54 pts achieving CR, Actuarial Survival in 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 (MACOOP B) was started.


From 1982 to 1988 165 patients with diffuse large cell NHL-Hodgkin's Lymphomas were treated with POPE chemotherapy (MOPP x 3, 2nd cycle MOPP x 2, 3rd cycle MOPP x 2, 4th cycle MOPP x 2, 5th cycle MOPP x 2). There was no acceptable toxicity. The overall median age was 59 years, range 18-85 years. The overall response rate was 89%, 60% CR and 29% PR. Responses by stage, age and histology are shown below.

<table>
<thead>
<tr>
<th>STAGE</th>
<th>HISTOLOGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td>CR</td>
<td>60</td>
</tr>
<tr>
<td>PR</td>
<td>20</td>
</tr>
<tr>
<td>NR</td>
<td>30</td>
</tr>
</tbody>
</table>

Median duration of remission and overall survival for all patients have not been reached (median follow-up 3.9 years). However, centroblastic/centrocytic tumours intermediate grade or G2 have a median survival of 3.9 years as well as patients with more than high-grade tumours (NG). Overall toxicity was low with 5 early deaths (due to sepsisemia) and universal alopecia.

Good remission and disease-free survival rates are obtained with this optimized POPE therapy, favoring the use 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.

600 West 10th Avenue, Vancouver, B.C., Canada

From 1985 to 1989, 92 consecutive patients with stage I and II (bulky ≤10 cm) aggressive lymphoma were prospectively treated with 6 weeks of chemotherapy (ACOB) and moderate dose radiotherapy (RT). Histological subtypes (all diffuse) were: mixed 12, large cleaved 27, large non-cleaved 20, Immunoblastic 21, large cell otherwise unclassified 12. Median age was 67 years (21-85) and 37 were over 70 years. Fifty-four were male, 38 female; there were 49 stage I and 43 IA; 66 had extranodal disease or extension. Median follow-up was 26 months (1-40).

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 tapper: cotrimoxazole I DS tablet po 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 6 x 6 after RT.

One patient did not respond, 7 relapsed (of these, 3 remain in remission 29 to 30 months after further treatment). No 2 of 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: 89% and 95%; stage IA: 90% and 93%; age ≥ 70 years: 78% and 84%.

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

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

J A Radford, J Whelan, D Doak, J A Liston, D Crowther, ICRF Dept of Medical Oncology and Radiotherapy, Christie Hospital, Manchester, UK and ICRF Dept of Medical Oncology and 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 III, 10 (9%) were stage IV, 21 (18%) were stage I and 11 (10%) were stage II. 63 of 115 (54%) had either centroblastic or high grade unclassified histology. 41 of 115 (13%) were 7 cell tumours, 11 (10%) were lymphoblastic, 9 (8%) immunoblastic, 6 (5%) CRCC diffuse, 5 (4%) were unclassified and 7 (6%) had either lymphoplasmacytoid, cenocyte or lymphocyctic histology.

After chemotherapy 76 (66%) had achieved CR or CR-equivalent (CR minimal residual abnormality on CXR or CT scan but no palpable disease and BM/biochemistry normal). 41 (34%) PR, 7 (6%) had progressed and 16 (14%) had died. The CR/CR-equivalent CR rate by stage was 92%(II), 86%(III), 90%(III), 93%(IV). Thirty 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; PA from CVA, I from small bowel infarction). OS for the whole group at 12 mths is 60% (95% CI 0.52, 0.69), II 93%, III 79%, IV 50% and RFS for 7 pts (4 CR/CR-equivalent) is 83% (100%, II 95%, III 90%, IV 65%). For stage III/IV pts in CR/CR-equivalent 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%). These findings may allow selection of pts requiring intensive consolidation following remission induction with VAPEC-B.

VAPEC-B is Adr 35mg/m² qd weeks 1,3,5,7,9,11; Cyclo 350mg/m² qd weeks 1,5,9; Enol 100mg/m² qd weeks 1,3,5,7,9,11, Vinc 4mg/m² qd weeks 2,4,6,8,10, Bleo 10mg/m² qd weeks 2,6,10 plus prednisolone 50mg po daily weeks 1-5, 23mgs 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 26 VIM-Bleo/CHOP IN HIGH GRADE MALIGNANT NON-HODGKIN'S LYMPHOMAS: FINAL RESULTS OF A PROSPECTIVE STUDY.

B. Steinke, K. Bros, H.-M. Reindl 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 4 iv days 1-3, Ifosfamide 1.5 g/m² po daily 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. In regions with bulky disease were irradiated after chemotherapy. According to the Kiel-classification, 38 patients (47%) had 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. 8 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 occurred. 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, major 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 28 SEQUENTIAL VS ALTERNATING CHEMOTHERAPY FOR HIGH GRADE NON-HODGKIN'S LYMPHOMAS: A PHASE III MULTI-CENTRE TRIAL.


In a multicentre phase III trial 140 previously untreated patients with high grade non-Hodgkin's lymphomas stages III/IV were randomized to receive either four cycles of CHOP (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, prednisolone 100 mg po d 1-5) (treatment arm A) or four cycles of chemotherapy with CHOP (Cyclophosphamide 1200 mg/m² iv d 1, doxorubicin 40 mg/m² d 1, vincristine 2 mg iv d 1, prednisolone 100 mg po d 1-5) alternating with IVEP (Ifosfamide 1500 mg/m² iv d 1-5, vincristine 3 mg iv d 1, etoposide 120 mg/m² iv d 1-5) (treatment arm B). 24 cycles were planned. 35 Gy was given to all patient 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 CHOP and IVEP. In treatment arm B haematological toxicity was increased after CHOP with an increased morbidity due to neutropenia related infections and two deaths in patients > 70 years. Therefore in CHOP cycles cyclophosphamide and doxorubicin were reduced to 65% in patients > 70 years old. A complete response (CR) was seen in 95% patients (28/140) 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 was projected to be 72% vs 83% for arm A and B respectively. Response rates stage II and III achieved CR rates of 80-100%, patients with stage IV had CR rates of 64% and 59% in arm A and B respectively. Only 63% of patients with immunoblastic or lymphocytic NHL showed complete remission rates of 78% to 93%. So far, no significant difference has been 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 BNL STUDIES IN LARGE CELL AND MIXED SMALL AND LARGE CELL NON HODGKIN'S LYMPHOMA. D.C. Lincoln, G. Vaughan Hudson, MH Bennett, K. MacLennan, B. Vaughan Hudson. BNL, Middsex Hospital, London, UK.

From 1974 to 1984 292 patients with stage III / IV large cell (including immunoblastic) or mixed small and large cell Non Hodgkin's lymphoma were treated initially with CHOP combination chemotherapy (cyclophosphamide 750 mg/m² day 1 and 6, hydroxydaunorubicin 25 mg/m² day 1 and 8, vincristine 1.4 mg/m² [max 2 mg] day 1 and 8 and prednisolone 50 mg/m² 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 40 % 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/m² hydroxydaunorubicin 35 mg/m², etoposide 150 mg/m² every other week alternating with methotrexate 100 mg/m² [plus folinic acid rescue] vincristine 1.4 mg/m² and bleomycin 10 mg/m², prednisolone 50 mg/m²) for 4 weeks and then alternate for 8 weeks and Ct-Trimoxadiazole 1bd weeks 1-14) in a randomized trial. All patients with stage III 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.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Response</th>
<th>CHOP</th>
<th>PACEBOM</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>CR %</td>
<td>85</td>
<td>14</td>
</tr>
<tr>
<td>III/AVA</td>
<td>CR %</td>
<td>65</td>
<td>20</td>
</tr>
<tr>
<td>IIB/VB</td>
<td>CR %</td>
<td>35</td>
<td>25</td>
</tr>
<tr>
<td>Overall</td>
<td>CR %</td>
<td>53</td>
<td>62</td>
</tr>
</tbody>
</table>

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 III AND IV INTERMEDIATE AND HIGH-GRADE LYMPHOMA, COMPARING CHVnP-VCR-bleo VERSUS ProMACE-MOPP, A RANDOMIZED STUDY.
R. Sonner, M. van Glabek, U. Thiel, J. Thomas and P. Carde for the EORTC Lymphoma Cooperative Group, Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX, Amsterdam, The Netherlands.

The results of a non-randomized phase II studies on high dose chemotherapy for confirmation in randomized trials. In an earlier study of the group we demonstrated a higher CR rate for CHVnP-VCR-bleo in comparison to CHVnP.

In the first regimen vincristine-bleo is administered on day 1 between CHVnP courses.

In the EORTC lymphoma cooperative group a randomized phase III study was started in January 1986 for stage III, IV, intermediate and high grade lymphomas comparing the group standard regimen CHVnP-VCR-bleo, consisting of cyclophosphamide 600 mg/m² day 1, VM26 60 mg/m² day 1, Adriamycin 50 mg/m² day 1, prednisolone 40 mg/m² day 1-5, vincristine 2 mg day 15, bleomycin 10 mg day 15, q.210d x 8 days (arm 1) with ProMACE-MOPP consisting of adriamycin 25 mg/m² day 1, cyclophosphamide 600 mg/m² day 1, VPs 160 mg/m² day 1, nitrogen mustard 6 mg/m² day 5, vincristine 1.4 mg/m² day 8, prednisolone 40 mg/m² day 1-15, procarbazine 100 mg/m² day 8-15, methotrexate 500 mg/m² day 15, q.210d x 8 days (arm 2).

In this first interim analysis 159 patients were available for response and 223 for toxicity.

The preliminary results may be summarized as follows:

<table>
<thead>
<tr>
<th>CR at 8 courses</th>
<th>Rem. dur. 30 months</th>
<th>Disfree surv. 30 months</th>
<th>Survival 30 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHVnP-VCR-bleo</td>
<td>67</td>
<td>68</td>
<td>59</td>
</tr>
<tr>
<td>ProMACE-MOPP</td>
<td>65</td>
<td>67</td>
<td>60</td>
</tr>
<tr>
<td>All</td>
<td>65</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

WHO grade III and IV toxicity occurred for WBC in 60%, for platelets in 5%, for G1, G2 and G3 toxicity in 80%, in the CHVnP-VCR-bleo arm figures were: 70% (p=0.03), 17% (p=0.004) and 26% respectively. We found no significant difference in response rate, disease free survival, cliniotal and survival between the two regimens. However, grade IV toxicity in the ProMACE-MOPP arm. The earlier results with CHVnP-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 aggressive non Hodgkin’s lymphoma (NHL) using Epirubicin containing regimen - BECOP".

85% of NHL reporting to NCI, Cairo are of intermediate and high grade types with big tumor burden. Different chemotherapy regimens have been tried, with low CR rate and short relapse free intervals. BECOP regimen aims to improve these results: VENDRISTINE 1.4 mg/sqm, Epirubicin 40 mg/sqm, Cyclophosphamide 650 mg/sqm, all I.V. on day 1,8 while Bleomyacin 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 20% and NR 9.5%, an overall HR 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. Preliminary results with VENDRISTINE and Epirubicin were observed 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 aggressive NHL.


Cisplatin and Cytosine Arabinoside (ARA-C) are effective drugs for the treatment of refractory NHL, but single agent ARA-C in combination with other drugs, DRAP regimen including Cisplatin, high dose ARA-C and Dexamethasone was reported by Velasques et al. to induce a complete remission in 70% of NHL, and 50% of refractory NHL respectively. From January 1987 to March 1989 24 patients, 14 males and 10 females, with a median age of 46 yrs (range 19-75 yrs). According to the WHO classification, 2 pts had low grade malignancy, 4 pts intermediate grade and 18 the histology revealed a high grade NHL. The performance status according to WHO was e 2 in 11 pts. 4 pts had a bulky disease (>7 cm), LHO levels higher than 2 times the normal values were present in 11 pts. Moreover 15/24 pts have been previously treated with a first line Adriamycin containing regimen, response was obtained in 10/14 pts (71%). Of these, 10/14 pts have achieved a partial remission negatively influencing the type of response, presence of bulky disease. Therefore, every patient received the same dose of bleomycin 15 mg/m² and doxorubicin 25 mg/m². All patients received vincristine 1.5 mg/m² weekly for 4 cycles. No patients had side effects attributable to bleomycin and doxorubicin. At the time of the trial, the actual overall survival was 57% at 70 and 24 months respectively. Details of the therapy related deaths were observed. In conclusion, in our experience, DRAP as a second line treatment for non refractory (relapsing and partial responding) NHL.
ABSTRACTS - Fourth International Conference on Malignant Lymphoma, Lugano

P 34 IFOSFAMIDE-ETOPOSIDE COMBINATION CHEMOTHERAPY FOLLOWED BY BEAM AND ASCT AS SALVAGE TREATMENT FOR MALIGNANT LYMPHOMA. P.C. Huiljgens, G.J. Ouseenkoppelle, J. van der Leelte, L.H. Thomas, W.J. Vijnvagardens and C.H. Slaper-Coccione. Free University Hospital, DE BOEWILLI111, 1105 BV Amsterdam, The Netherlands, Academic Medical Center and Central Laboratory of the Netherlands Red Cross Blood Transfusion Services, Amsterdam, The Netherlands.

Twenty-seven patients with high and intermediate grade malignant lymphomas 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 melphalan) and autografted. Of these 27 patients 9 were in relapse, 10 were partial responders and 8 failed CHOP-like therapy. The salvage treatment (BEAM in 24, M-H-E in 3 patients) induced complete and partial remissions in 25 patients; 7 complete remission were achieved following additional chemotherapy. Twenty patients were autografted after BEAM ablative chemotherapy, together with 1 allografted. Nine patients are disease free 7 to 62 months after autografting (median 23 months). Of 8 patients autografted, 1 died 50 months after autografting. There were 3 therapy related deaths: 1 related to M-H-E and 2 to BEAM therapy. Using one of the best salvage therapies combinations followed by high-dose chemotherapy and autografting is feasible. An appreciable number of patients may be cured by this procedure.

P 35 AUTOLOGOUS BONE MARROW TRANSPLANTATION IN MALIGNANT LYMPHOMA. THE EUROPEAN COOPERATIVE BONE MARROW TRANSPLANT GROUP (EBMT). F. Ernst and E. Devul, Departments of Oncology and Biostatistics, King Faisal Specialist Hospital and Research Centre, Riyadh 11211, Saudi Arabia.

EBMT has collected and analysed data on autologous bone marrow transplantation (BMT) in 111 patients with malignant lymphomas (1). This included 54 with lymphomas and 57 with non-Hodgkin's lymphomas between 1979 and 1987. The main results are as follows: 1. CR rates: 2. CR-30%, relapse: 30%. The conditioning regimen was for 101 patients total body irradiation and chemotherapy, while in cases received chemotherapy alone. Results: 90% patients remain in CR or obtained CR after BMT, PK was seen in 2 patients, 6 showed NH with 4 were insensible for response. Acute GVHD was seen in 12/18 (67%). Main causes of death: malignant lymphoma 32 patients, interstitial pneumonitis, 32 patients, chronic GVHD, 12 patients, infections were mainly caused by fungi. 51 patients at time of report alive and well (longest follow-up 5 years), median survival has not yet been reached for lymphomas, but 10 years for NHL. Multivariate Cox analysis reveals that 3 factors are of importance for survival namely: status at time of MTP (1st CR), status of the original NHL (2nd CR), and history of chemotherapy (1st CR). 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 primary involved site was found. Updating of this material will be presented.
ABSTRACTS - Fourth International Conference on Malignant Lymphoma, Lugano

P 37 HIGH-DOSE CHEMOTHERAPY WITH HEMATOPOIETIC RESCUE IN 22 CASES OF LOW GRADE NON-HODGKIN'S LYMPHOMAS. LIMASSI S., COLONNA P., BIKM M., MISETI J.P., FAVRE M., DESBOIS Z., LAMAGNE J.P., PHILIP T.*
Department of hematology, CHU Berne, Switzerland. TOGS.
Department of Bone Marrow Transplantation, Centre Leon Berard, Lyon. 1department of hematology, Hopital 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-HNL), though first results are promising. We report results of intensive chemotherapy with hematopoietic rescue in 22 patients with L-HNL. They were 13 men, 9 women (age range 27-61 (mean = 42.3 years). Histologies included follicular mixed (n=14) and follicular small cleaved 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 anti-CD2 (mil) or with monoclonal antibodies (mab) (n=4). 2 patients received GM-CSF. No death occurred 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. One 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.


G. Santini (Genova)*, P. Conter (Bolzano), V. Rizzioli (Parma), T. Chiari (Vicenza), A. Porcellini (Genova), E. Sertori (Genova), A. Contu (Sassari), L. Salvaggio (Padova), G. Vinante (Milano)*, D. Indriani (Bassano), M. Cioni, D. Pierluigi, F. Rosati, K. Davanzo (Genova). * Dept. of Hematology, Ospedale S. Martino, Genova, Italy.

Up to December 88, 48 patients with diffuse intermediate and high-grade malignant NHL, 33 males and 15 females with a median age of 30 yrs. (range 13-53) 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 CR, 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 2 months. The majority of patients, 37 out of 48, underwent procedure after a conditioning regimen consisting of Total Body Irradiation (10 Gy in a single dose) and Cyclophosphamide (120mg/kg), while the others were treated with different combinations. The number of patients involved in the treatment were purged with anti-CD2 at the dosage of 70-100 µg/ml0. 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 which patients in CR should be scheduled for this procedure. This problem will be discussed.

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


Previously we have shown in model experiments that lymphoma cells can be rapidly and efficiently removed from 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 lymphoblastic, 2 centroblastic and 1 centrocytic) and 3 had T-cell lymphoblastic lymphomas. The median age was 29 (range 15-49). Eight patients were transplanted in first CR, 3 in second CR and one in a chemosensitive PR.

Among the 8 lymphoma patients the bone marrow was purged with beads and a mixture of the monoclonal antibodies HD 37 (CD2), HD6 (CD22) and HEL (CD77) (n=6) or AB1 (CD19) and AB4 (HLA-DR) (n=1) as described earlier (1, 2). The T-cell malignancies had their bone marrow purged with beads the anti-T cell monoclonal antibodies B-01(CD3), B-84(CD4) and B-12(CD8). The recovery of total number of mononuclear bone marrow cells after purging varied from 41-449, at the time of purging 3 of the T-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 pretreatment 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 ungranted quickly, reaching 0.5x10^10 granulocytes at day 18-26 and 2.0x10^10 platelets at day 18-39 posttransplant.

Among the 12 patients transplanted 9 are in continuous complete remission with an 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 posttransplant.

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