
PURPOSE: A prospective trial with a new combination of cyclovaphosamide, doxorubicin, vindesine, prednisolone and bleomycin (CHEP-BLEO) devised for patients with low grade non-Hodgkin's lymphoma (HLN) in the Fiel classification, was undertaken.

PATIENTS AND METHODS: between 1984 and 1991, from 5 hematological French centers, 34 consecutive untreated patients (median age 49 years; range 28 to 62) with stage III (12 patients) or IV (22 patients) low grade NHL, and 9 patients with a bulk tumor were included. Histological diagnoses were as follows: lymphocytic lymphoma (1 case), centrocytic follicular small cell atie (1 case), centro-betablastic follicular (10 cases) and centrocytic diffuse (10 cases). Excepted two patients who were not analysed all patients received cyclophosphamide 1200 mg/m² day 1 intravenously (IV), doxorubicin 75 mg/m² day 1 IV, vincristine 2 mg/m² day 1 and day 5 IV, prednisolone 50 mg/m² orally day 1 to day 10, and bleomycin 10 mg/m² day 1 and day 5 IV, every 28 days during 6 months. Four patients were previously treated. After 6 CHEP-BLEO treatment, an abdominal irradiation (1 case) and a total lymphoid irradiation (1 case) were performed.

RESULTS: among the 32 assessable patients, the objective response rate was 96%; 69% of the patients achieved a complete response (CR). The overall toxicity seemed to be acceptable, with 50% episodes of grade 4 leukopenia, 50% episodes of grade 3 leukopenia, no severe anemia or thrombocytopenia (rare cases of grade 3 or 4), 24 grade 1 or 2 infections, 2 cases of septic shock, no case of death. Two episodes of gastro-intestinal paralytic ileus (grade 4) related to vindesine administration and two episodes of allergy reaction caused by bleomycin (grade 1) were also observed. This chemotherapy program resulted in a 5-years survival rate of 66% (2 patients who received an irradiation were not analysed), 57 percent of patients achieving CR were free from relapse at 24 months. Up to 60 months from the one or 1/4 were free from relapse. The 7 partial responses patients and the 3 stable disease patients treated either by chemotherapy alone (4 cases) treated either by interferon or alone (1 case) or by both treatment (4 cases). Three autologous 1/1, 1 relapse and 1 CR) and one allogeneic (salvage and CR) bone marrow transplantation were performed without severe toxicity.

CONCLUSION: we conclude that this treatment is effective, well tolerated and feasible in an unselected young population affected by low grade NHL. An autologous or allogeneic bone marrow transplantation may complete the treatment.

T 142 LOW GRADE NON-HODGKIN'S LYMPHOMA REFRACTORY TO CHLORAMBUCIL AND PREDNISOLONE: ACTIVITY OF PREDNISONUM


39 patients with low grade non-Hodgkin's lymphoma refractory to chlorambucil and prednisone were treated with prednisone, 200mg daily orally for three days every two weeks. Refractory disease was defined as progressive or unchangeable condition during treatment with doses of chlorambucil and prednisone that could not have been further increased. This was ascertained by a first part of the trial, where the patients were treated in a standardized way with chlorambucil and prednisone. Of the 39 patients treated with prednisone, 18 were female and 21 were male. Median age was 63 years (range 38-85 years), and the histology was CLL in 20 patients, immunocytoxa in 2, centrocytic lymphoma in 3 and centroblastic-centrocytic in 14. 29 patients had stage IV disease, 4 stage III, 5 stage II, and 1 had stage I. Performance status was 0-1 in 35 patients, 2 had PS 2. Of 35 patients evaluable for response, 15 (43%, 85% confidence interval 27%-59%) had an objective remission (CR, PR). Median time to progression was 16 weeks for all 35, and 52 weeks for the 15 patients who experienced an objective response. Severe hematological toxicity was recorded for most patients treated in both parts of the study. Mild to moderate elevations of liver function tests were recorded to a similar extent in both parts of this study. Clinical adverse events were mostly nausea/vomiting and/or infection, which were slightly more frequent in the second part of the study. The present study showed that the clinical efficacy of prednisone in low grade NHL goes beyond that of chlorambucil and prednisone at a manageable level of toxicity.

T 143 TOTAL BODY IRRADIATION (TBI) AND PREDNISONUM (PDM) IN ADVANCED LOW GRADE NON-HODGKIN LYMOPHOMAS (NHL) G. Lo Re, M. Ronca, M. Arzicava, V. Zagodin, R. Bortolus, B. Valeri, A. Carbone, A. Pinto, M.G. Trovò, and S. Monfardini. Centro di Riferimento Oncologico - Aviano - Italy

Little data are available on TBI followed by chemotherapy in low grade NHL. From January 94 to September 92 of patients (pts) with symptomatic low grade NHL stage III-IV entered this phase II study. Aim of the study was to evaluate feasibility, toxicity and activity of TBI plus PDM.

Patients' characteristics: males were 25 and females 16. In the group (29 pts) younger than 65 years (13 pts) median age was 55 years (range 32-64) whereas it was 71.5 yrs (range 65-77) in the group older than 65 yrs (12 pts). Stage was assessed according to Ann Arbor staging system. Eight pts were stage III and 33 stage IV. Performance status (PS) according to Karnofsky scale was 570 in 5 pts, 80 in 13 pts and 90 in 22 pts.

Treatment: TBI (6 MV linear accelerator 150 cGy/10 for 5 weeks), PDM 100 mg/m² for 5 days every 4 weeks, 6-9 courses, administered 2 months after TBI as consolidation therapy.

Response to TBI: Complete remission (CR) in 10 pts (24%), partial remission (PR) in 24 (58%), stable disease (SD) in 5 (12%), and progression (P) in 2 (5%). Toxicity was acceptable; high grade (3-4 WHO) thrombocytopenia in 19%, anemia in 2% and leucopenia in 7%. Nadir of bone marrow toxicity was reached 2 months after starting TBI and documented infections during treatment were seen in 5 pts. Twelve pts required prolongation of treatment (more than 5 weeks).

Treatment with PDM: 33/41 pts received PDM, 8 pts refused chemotherapy, or were lost to follow-up. The median number of courses was 9 (range 1-15). Out of 33 pts receiving PDM improvement of response (PR+CR) was achieved in only one pt. Toxicity due to PDM was mild. Median overall survival was 80.33 months (range 5.5-155 months). Age (265 vs 65), stage (III vs IV), PS (570 vs > 70) and type of response (CR vs PR) were not found to be related with survival in a univariate analysis.

In conclusion, the addition of PDM to TBI was feasible and relatively non-toxic also in elderly patients, but did not improve the response rate.


From February 1988 to June 1992, 45 pts with non-Hodgkin's lymphoma (NHL) and 4 pts with Hodgkin's disease (HD) (33 M, 16 F; median age 55, range 23-75, median PS 1) entered a phase II trial with low dose dCP. The pts were selected for pretreatment with no more than 2 chemotherapy regimens (12 pts were pretreated also with radiotherapy) and among NHLs were admitted only those with low-grade (22 pts), high-intermediate grade and T-cell type (23 pts).

The schedule of dCP was 4 mg/m² weekly x 3, then bi-weekly x 3, then monthly until progression; from March 91 to date a slight intensification schedule was applied (4 mg/m² weekly x 6, then bi-weekly until progression) 6 pts with NHL have been treated with the new dosage 29 pts with NHL are evaluable for response: 3 partial responses were observed (2/13 low grade NHL, 3/16 high grade NHL). The median (range) duration of responses (weeks) 36 + (13-15). The only pt with HD had no response. Thirty-four pts are evaluable for haematological toxicity: after the 1st cycle the median WBC count (x 1000/mm³) was 5.1 (range 1.2-12.9), the median platelet count was 203 (range 75-493); after all cycles the median WBC count was 5, the median platelets count was 203, of 36 pts evaluable for non-haematological toxicity 24 had nausea and vomiting: grade (g) 2-2, 2 g, 2 constipation g 1-2, 4 reversible pneumonia g 1-2, 2 g, 2; 3 skin toxicity g 1-2, 1 g, 2; lethal g 1-2, 3 renal g 1-2, 2; 2 infection g 1-2, 1 drug fever g 1-2, 2; tachycardia g 1-2. In conclusion, low dose dCP has definite activity in pretreated NHL. Since kidney and lung toxicity, although reversible, may occur, a careful monitoring of renal and pulmonary function is recommended. In some instances oral toxicity (reversible conjunctivitis) was observed. Bone marrow toxicity is slight: the only pt with grade 3 haematological toxicity had bone marrow infiltration. This dosage could be used in combination with myelosuppressive drugs.
ABSTRACTS - Fifth International Conference on Malignant Lymphoma, Lugano


B-cell chronic lymphocytic leukemia (B-CLL) is known to have a very variable clinical course. About one third of patients in the early stage of disease (BCLL A) will progress within two years and require treatment. The aim of our study was to identify stage A patients at risk for early progression and to treat this group in a randomized multicenter study with interferon-alpha(2b). The endpoints of this IFN treatment study were freedom from progression and/or death from cancer, and overall survival. The following prognostic factors were evaluated: 1) Diffuse bone marrow infiltration (DBM), 2) serum thyrogy kinase (TK) levels > 5 U/l, and/or 3) a leukocyte doubling time (LDT) < 12 months. Patients with DBM and a TK > 5 U/l, and/or LDT < 12 months were randomized into either a treatment group (arm A) which received IFN-alpha at a dose of 3 x 5 MIU i.m. 3 times a week, or a control group (arm B). The clinical course of stage A patients without risk factors was documented as a control group to assess the validity of our risk stratification.

In contrast to treatment groups, no significant difference in overall survival was observed between the two groups. Only patients with high risk factors showed a significant overall survival benefit of IFN-alpha treatment.

T 146 IMPACT OF INTERFERON INTEGRATING CHEMOTHERAPY AND AS MAINTENANCE ON MULTIPLE MYELOMA. PRELIMINARY RESULTS ON A MULTICENTER STUDY OF ITALIAN NHLCSG. C. Capotosti*, M. Vasepignani*, M. Spinelli*, L. Cappelletti*, V. Rozito*, P. Centore*, G. Olmos*, L. Todeschi*, E. E. Damasio*, and T. Chiepii*. Dept. of Hematology, San Martino Hospital, Genova; Dept. of Hematology, Parma University; Dept. of Hematology, Bolzano Hospital; Dept. of Oncology, Sassinari Hospital; Dept. of Oncology, San Carlo Borromeo Hospital, Milano, Italy.

In 1980 the Italian NHLCSG started a multicenter study on the role of interferon (IFN) in multiple myeloma (MM). The schedule of treatment was based on the assumption that melphalan plus prednisone (MP) would be better for good prognosis patients, whereas poor prognosis patients would benefit by polychemotherapy. According to IFN, IFN was included randomly for the induction treatment of good prognosis patients and even randomly, as maintenance in both groups, when patients had achieved the objective response. Up to now 77 of the 125 patients are evaluable for response. The overall remission rate was 33% for good prognosis patients obtained the objective response, 9/14 (64%) with MP and 9/15 (60%) with MP+IFN. With a median follow-up of 12 months, no differences are recorded between maintenance and no maintenance, both in good and poor prognosis patients. Nevertheless no relapses occurred until now in the 9 good prognosis patients who had responded to MP+IFN, whereas 5 out of 9 patients who had responded to MP alone have relapsed, independently of chemotherapeutic regimen. In conclusion, IFN integrating MP did not improve the response rate to MP alone, but these data are preliminary, this combination seems to have some impact on relapse rate.

T 147 LONGTERM REMISSION OF AILD AFTER TREATMENT WITH INTERFERON-ALPHA. J.D. Schwarzmaier, C. C. Glaeb, W.W. Reineisch. First Dept. of Medicine, University of Vienna, Lazaretsgasse 14, A-1090 Vienna, Austria.

Current treatment of angioimmunoblastic lymphadenopathy with dysproteinemia (AILD) with corticosteroids alone or in combination with chemotherapy has been shown to be unsatisfactory. We have initiated therapy with interferon-alpha (IFN-alpha) in a case of AILD who relapsed after his first remission and after the failure of the validity of the risk of AILD, who entered this study. IFN-alpha treatment resulted in a remarkable long period of second remission. Almost two years later the patient unexpectedly developed severe bone marrow depression with no signs of malignant lymphoma. The disease progression rate of IFN-alpha seemed highly unlikely. Immunophenotyping of PB MNC revealed a normal distribution of B- and T-lymphocytes. However, CD4+ T-cells were markedly reduced while CD4+ T-cells were increased (CD4/CD8 ratio 18). This was accompanied by abnormal cytokine levels in serum. IFN-alpha was approximately forty times and neutropin (reflecting IFN-alpha production) fifteen times above normal. Also, soluble IL-2 receptor (sIL-2R) was substantially increased while TNF-alpha levels were normal. IL-6 and GM-CSF were below detection limits. It is remarkable that similar findings were reported for severe aplastic anaemia (SAA). We speculate that in our patient the CD4/CD8 ratio was impaired by an unknown mechanism (viral?), thereby leading to an increased production of IFN-alpha and sIL-2R. Whether these cytokines were causally involved in hematopoietic stem cell suppression is difficult to determine.

Supported by Fonds zur Förderung der wissenschaftlichen Forschung M 8014

T 148 AGGRESSIVE B-CELL LYMPHOMA IN RARELY-CELL LEUKEMIA AFTER TREATMENT WITH INTERFERON-ALPHA. P. Bernadier, P. Berger, J. Beny, J. Roman, F. Ferry, F. Witz, A. Menu, G. A. Bignoller, C. J. H. Krier, J. M. Delaker, Department of Hematology and Pathology, Erasme Hospital, 54511 Vandewoude, France; Department of Hematology and Pathology, Edouard Herriot Hospital, 69437 Lyon, France.

Hairy cell leukemia (HCL) is a chronic leukemia of predominantly B-cell origin. Contrary to other terminal B-cell malignancies, both nodal involvement and aggressive lymphomas are rare complications. A direct association of IFN-alpha on the evolution of HCL has been suggested. In the present study, observations regarding a relationship of HCL to the Epstein-Barr virus (EBV) are conflicting. We report here a patient where EBV was diagnosed in April 1989. He received IFN-alpha 2 MU/m2 3 times a week. In May 1991, he presented with fever, pancytopenia, splenomegaly and massive abdominal lymphadenopathy. Biopsy specimens displayed diffuse infiltration by both typical hairy cells and diffuse large cell lymphoma (Group G - Working Formulation). Immunophenotyping was performed on paraffin sections. The large cells showed strong surface staining with CD20 (L26) but not with the hairy cell associated monoclonal antibody DBA44. They were also not stained with an antibody against EBV protein LMP (Latent Membrane Protein). In situ hybridization studies (ISH) to EBV DNA performed using a previously presented ISH technique with a biotinylated probe were negative. A non-complementary ISH probe to EBV RNA was performed using a previously reported ISH technique with a biotinylated probe. The ISH probe was complementary to ESERI, a region of the EBV genome which is actively transcribed in latently infected cells. Evaluation was performed with both EBV H and ESERI probes. There was no evidence of EBV DNA and RNA in the diffuse large cell lymphoma both within the spleen or in an adenopathy. These ISH studies were confirmed by viral genome detection using Southern Blot. After DNA extraction, which was also negative. Further studies are in process to elucidate the mode of origin of both hairy cells and large cells, suggested by Neresina et al (BJH 1992, 94: 54-59) and 54-59). However, immunologic modifications secondary to IFN therapy may lead to an increased risk of lymphoma unrelated with EBV, as noted by Haberman et al (ASH - 1992 - Abst 1061).
ABSTRACTS - Fifth International Conference on Malignant Lymphoma, Lugano

T 151 ARA-C PLUS INTERFERON IN THE TREATMENT OF PARTIALLY RESPONSIVE NON-HODGKIN'S LYMPHOMA

Division of Oncology, Medical School, University of Federal University of São Paulo, Brazil.

ARA-C at low doses and interferon (IFN) determine growth inhibition in myeloidlastic syndromes and acute leukemias in vivo. Moreover they induce differentiative effects in human myeloid leukemia cells and of human neuroblastoma cell lines, without cell killing or affecting cell proliferation. These effects may be useful in treating patients with lymphoid malignancies. In this study, we evaluated the effectiveness of ARA-C at low doses plus interferon in the treatment of Non-Hodgkin's Lymphoma patients (pts) who achieved a partial response (PR) with aggressive chemotherapy. Six pts, with a median age of 61 years (range 29-71), 2 females and 4 males, entered the study. Lymphoma histotypes (according to Working Formulation) were: B (1 pt), E (1 pt), F (3 pts) and G (1 pt); all pts were IV stage and with 8 symptoms; 4 pts had bulky disease. ARA-C was administered subcutaneously at the dose of 100 mg on day 1, 150 mg on day 2 and 200 mg on days 3-4-5. Interferon was administered at the dose of 3 MU/day 3 times a week. All pts received at least two cycles of therapy (range 2-13) and 13 pts completed the maintenance therapy. Five complete responses (CR) and 1 PR was observed. Median duration of CR has been 24 months (range 15-26). The results of the combination of IFN and ARA-C at low doses, in the treatment of NHL pts achieving a PR after aggressive chemotherapy are encouraging and indicate for the pts this possibility to achieve CR of long duration.

T 152 EARLY RESULTS OF CNOP (+ ICEBERG RADIOTHERAPY) AND MAINTENANCE OF REMISSION WITH ALFA-2a INTERFERON (ROFORA-1) IN PATIENTS WITH LOW GRADE FOLLICULAR LYMPHOMA

1Cattedra di Ematologia, Università di Pavia - Divisione di Ematologia, Policlinico S. Matteo, IRCCS, Pavia, Italy. 2Divisione di Oncologia, Asst. B, Policlinico S. Matteo, Pavia, Italy. 3Divisione di Ematologia, Università di Pavia, Italy. 4Divisione di Oncologia, Asst. B, Policlinico S. Matteo, Pavia, Italy.

Interferon (IFN) alla has been found to be effective as an antimumor agent in patients with low-grade non-Hodgkin's lymphomas (NHL). Greater interest has been focused on maintenance therapy in attempting to prolong the first complete remission, and in the role of interferon (IFN) in maintenance therapy. Therefore, in July 1991 we began a prospective, randomised phase II study to investigate whether prolonged interferon administration in the phase of the "minimal residual disease" will increase relapse-free survival or progression-free survival of patients randomized to receive IFN. The first 12 patients have had less than 15 years of NHL. Interferon (IFN) alla was administered at a dose of 100,000 units subcutaneously three times per week for a period of 12 months or to "no further treatment". As of December 1992, 36 patients have been evaluated, and 21% (5) of the patients have had an overall response rate of 93%, i.e. 14/28 (50%) complete remission (CR), and 10/28 (36%) (CR, CNOP) remissions were well tolerated. A grade 3 (WHO) toxicity was observed only in the 28% of the 90% of the patients, and 168 courses which could be evaluated. The average cumulative dose of interferon was 96% and 99% of the ideal dose for each drug. So far, 28 patients have been randomized: 14 to maintenance with IFN, 14 to IFN. Nearly 15 years of NHL. Interferon (IFN) alla was administered at a dose of 100,000 units subcutaneously three times per week for a period of 12 months or "no further treatment". As of December 1992, 36 patients have been evaluated, and 21% (5) of the patients have had an overall response rate of 93%, i.e. 14/28 (50%) complete remission (CR), and 10/28 (36%) (CR, CNOP) remissions were well tolerated. A grade 3 (WHO) toxicity was observed only in the 28% of the 90% of the patients, and 168 courses which could be evaluated. The average cumulative dose of interferon was 96% and 99% of the ideal dose for each drug. So far, 28 patients have been randomized: 14 to maintenance with IFN, 14 to IFN. Nearly 15 years of NHL. Interferon (IFN) alla was administered at a dose of 100,000 units subcutaneously three times per week for a period of 12 months or "no further treatment". As of December 1992, 36 patients have been evaluated, and 21% (5) of the patients have had an overall response rate of 93%, i.e. 14/28 (50%) complete remission (CR), and 10/28 (36%) (CR, CNOP) remissions were well tolerated. A grade 3 (WHO) toxicity was observed only in the 28% of the 90% of the patients, and 168 courses which could be evaluated. The average cumulative dose of interferon was 96% and 99% of the ideal dose for each drug. So far, 28 patients have been randomized: 14 to maintenance with IFN, 14 to IFN. Nearly 15 years of NHL.
TREATMENT OF ADVANCED LOW-GRADE NON HODGKIN'S LYMPHOMA PATIENTS. C. M. Harrmann, T. H. Neubauer, B. B. Herbst, A. H. Hildmann. Departments of Medicine, University Hospitals CH-4031 Basel, and D-M 1000 Berlin 19, DM-3400 Göttingen.

Between 4/89 and 12/92 92 institutions in Germany, Austria, Sweden and Switzerland entered 226 eligible patients into this study. Eligibility included untreated stage III or stage IV centroblastic- centrocytic (CB-CC), n=182) or centrocytic (CC, n=44) lymphoma and for CB-CC the requirement for therapy as defined by the presence of late symptoms or objective disease progression, for hematologic impairment age 15-75 years. Median age of all patients was 54 years. Patients with CB-CC had a male:female ratio of 0.89, those with CC one of 3.5. After stratification for age, histology and stage, pts were randomly assigned to induction treatment with COP (cyclophosphamide 400 mg/m² d i.v. x 5, vincristine 2 mg d i.v. x 1, prednisone 100 mg/m² d.p. x 6) or PMV (prednisolone 100 mg/m² d.p. p.o. x 5 d, mitozantrone 9 mg/m² d i.v. x 2). Treatment was repeated every 4 weeks (COP) or every 4 weeks (PMV) for 8 cycles or CR plus 2 cycles. Responding patients (CR or PR) were then randomized to receive COP 2d maintenance 5 x 10⁷ U i.v. 3 times a week until relapse/progression or no further treatment. At the present time no significant differences are revealed between response rates after COP or PMV. Overall remission (CR + PR) was achieved in 83 %. Side effects were different, in that PMV caused significantly less peripheral neuropathy, and alopecia and myelosuppression, while COP, in addition to infection and cardiotoxicity were not significantly different. Median survival was 7 years, of all evaluable patients 13 months with no significant difference between CB-CC and CC histology and type of induction treatment. The number of patients in the maintenance phase is still too small and the observation period too short to draw reliable conclusions regarding the effect of COP on remission or survival. However, actual follow-up data will be presented.

TREATMENT OF LOW GRADE NON-HODGKIN'S LYMPHOMAS (LGLNLH) WITH CHLORAMBUCIL AND 2-FIBERON (2-FIB). G. Paliogolias, C. Tsekerus, V. Roussias, C. Paliogolias, G. Kiriakoulou, C. Kallias. Clinic, University School of Medicine, Lacon General Hospital, Athens, Greece.

Alpha-interferon has shown to be effective in the treatment of LGLNLH. In the present analysis 53 patients were studied to further investigate the contribution of 2-FIB-FN in the treatment of LGLNLH. Patients' entry criteria to this trial were: histologic type of LGLNLH, performance status 0.5, or 1 and clinical stage II, III or IV. Treatment protocol had two arms: Arm A with chlorambucil (Leukeran) 10mg/d for 10 days/mo for at least 6 months and continuation to 9,12,15 or 18 months if continuous response was evident; and arm B with 2-FIB-interferon (Intron-A) 3 MU/d for 5 days and subsequently Leukeran as in arm A. The distribution of our patients into arm A or B was in a proportion 1:2. For their staging and response, standard criteria were used. Responders (CR or PR) received or did not receive Intron-A, 2MU/w, for one year as maintenance therapy. Among the 19 patients who received chlorambucil only, complete remission was observed in 6 (31.5%), partial remission in 9 (47.5%) and stability or progression in 4 (21%). Among the 34 patients who received Intron-A plus chlorambucil, complete remission was observed in 18 (52.9%), partial remission in 11 (32%) and stability or progression in 5 (14.7%). The difference between arm A and B as far as complete remission is concerned was statistically significant (p<0.05). Response to treatment was better in earlier stages, independently from the treatment arm. Patients with small lymphocytic lymphoma (SLL) had the best response, followed by those with follicular small cleaved or mixed lymphoma and finally those with lymphoplasmacytic lymphoma. Response in relation to histology was also independent from the treatment arm but it was found to be poorer in stage IV disease which concerned 14 of the 17 patients with lymphoplasmacytic lymphoma. The median number of treatment cycles, for achieving maximum response (CR or PR) was 7.6 mo and 12.8 mo respectively for arm A and 8 and 12.8 mo for arm B. The duration of CR was slightly longer for patients treated with the arm B protocol (204+ mo vs 16+). Between patients in whom maximum response was achieved, median time of relapse was 14 and 15 months respectively. We conclude that in our study that addition of Intron-A to Leukeran as induction treatment of LGLNLH has an advantage over Leukeran alone, however, it is not possible to estimate if this non-maintenance has any effect to the duration of CR. Besides we observed that the addition of Intron-A as maintenance treatment did not improve relapse rate.


Purpose.- To evaluate the efficacy of the antiebranocinodies and interferon in non Hodgkin's lymphoma (NHL) previously resistant to other therapeutic options. Patients and methods.- A prospective, multicentric study was started on march, 1991. The patients were classified according the Working Formulation; all of them were resistant to previous chemotherapy, and they have received no therapy at all for the previous months. As induction therapy was employed mitoxantrone, 4 mg/m², days 1-2 and prednisolone 100 mgiday, days 1-7 repeated each 28 days for 6-8 cycles. The patients with maximum response partial or complete were treated with alpha-2b interferon (IFN) 9 MU/w and deametaxim (DME) 15 mg/m²/day, 1-4, each 21 days. Descriptive statistics and Kaplan and Meier method were employed for statistical evaluation.

Results.- Until december 1992, 25 patients with NHL were included in the study. The histological diagnosis of the 23 evaluable cases was: diffuse lymphocytic lymphoma in 16 patients, follicular lymphoma in 4 cases, T-cell lymphoma in 2 patients and 1 N-TL, MALT type. The mean age was 58 years, and the M:T ratio 1:9. Twenty one cases showed bone marrow involvement. The previous therapy was chlorambucil alone or with prednisone in 10 cases, alkylating agents + CHOP, CVFP or PROMACE in 5, chemotherapy in 3 and in the remaining 3 patients chemotherapy radiotherapy. Of the 23 evaluable cases, 9 showed a response (CR in 3 and PR in 6); in the remaining 14 cases the therapy was unsuccessful. The responding cases were treated with IFN and DME. The induction and maintenance therapy was well tolerated, with mild myelotoxicity in 3 patients and severe adverse event.

Comments.- The study shows the efficacy of the schedule in patients with low-grade resistant NHL, a particular group with a rather poor therapeutic response. The therapy is well tolerated and the efficacy reasonable.
T 157  

ALPHA INTERFERONS IN THE TREATMENT OF CHRONIC CUTANEOUS T-CELL LYPHOMA

Dr. Yatish Mughai, Head, Division of Haematology & Oncology
King Fahad Hospital, Riyadh 11426, Saudi Arabia

Chronic cutaneous T-cell lymphoma (CTCL) is a group of rare disorders comprising primarily of mycosis fungoides and Sézary's syndrome. Most patients (pts) have a fairly indolent course, at least until extensive systemic movement is evident. In general, no major benefit has been noted from "conventional therapy". Over the past decade a number of reports indicated a possible beneficial role of alpha interferons (IFN) have appeared, but in most cases, pts have had multiple therapeutic regimens previously. We have treated 6 pts with advanced CTCL, four being previously untreated. Pts received IFN 3 MU T I.M. SQ which was gradually increased to a maximum of 20 MU T I.M. over a period of 6 months amongst the responders. Three of 6 pts demonstrated a response: two achieved complete remission (CR) at 6 months and one had a partial remission (PR) at 3 months. All of the responders were previously untreated. Only one of the CR pts remains in continuous CR at 3-5 years. The remaining pts relapsed at 3 mos (CR) and 9 mos (PR). Toxicities attributed to IFN were common: mainly flu-like symptoms and was totally reversible. Our limited experience, to date, is supportive of the notion that IFN constitute an effective treatment for CTCL and further pts accrual is in progress.

T 158  

ROLE OF HAIRY CELLS, T CELLS AND HAEMATOPOIETIC GROWTH FACTORS IN HAIRY CELL LEUKEMIA

J Schwarzerze, M Gachot, M Hilgath. Med. Clinik I, Dept. of Haematology, Univ. of Vienna, Währinger Gürtel 18-20, 1090 Vienna, Austria

Pancytopenia is one of the most characteristic findings in HCL. Inhibitory factors released by hairy cells might be responsible for haematopoietic failure in this disease. It has been suggested, however, that HCs alone are incapable of synthesizing potent inhibitors of myelopoiesis, and that they rather act synergistically with T lymphocytes. Therefore, we investigated the effect of the removal of HCs and/or T cells on the number of circulating progenitor cells in HCL patients. The results demonstrated that the removal of either HCs (by complement mediated lysis) or T cells (by E-rosette formation) clearly improves the growth of BFU-E, CFU-GM and CFU-mix. In comparison, under the same experimental conditions, these effects could not be observed in healthy donors. Since none of the procedures was sufficient to increase colony numbers to normal levels we determined whether or not the supplementation of the culture medium with haematopoietic growth factors (rh GM-CSF, rh IL-3) could further increase colony numbers. When the colony forming assays were performed after the removal of HCs, and upon the addition of GM-CSF/IL-3, normal colony numbers were achieved in most patients. Similar increases were observed after the depletion of T cells, and addition of growth factors. We conclude that in HCL an inhibitory effect on haematopoiesis is exerted by HCs, but that T lymphocytes also play a role in the mechanism of suppression, probably by synergizing with HCs. In addition, we postulate that a deficiency of haematopoietic growth factors contributes to the failure of the haematopoietic system. A likely candidate for an insufficient supply of growth factors is the monocytopenia usually observed in HCL.

Supported by "Fonds zur Förderung der wissenschaftlichen Forschung" P 7404 and P 8293.

T 159  

HIGH EFFICIENCY OF 2-CHLORODEOXYADENOSINE (2-CDA) ON BULKY LYMPHADENOPATHY IN HAIRY CELL LEUKEMIA (HCL)

Y. Baston, C. Rieux, M. Bazin, C. Dumontel, P. Feiman, P.A. Bryon, B. Callier. Service d'Hematologie, Centre Hospitaller Lyon-Sud, 69310 Pierro-Bitré, France.

Development of massive lymphadenopathy is very unusual in HCL. Some of these patients may respond to 2-deoxycoformycin (DCF) treatment (Mercier et al, Br J Haematol, 92). Preliminary reports of HCL treatment with 2-CDA show better response rate and survival than interferon (IFN) or DCF. We report here the results of 2-CDA treatment in two HCL patients with massive nodal involvement.

Patient 1, a 60-year-old man, was splenectomized at diagnosis in 1985. He was then treated with ALG and prednisone. He achieved a partial response (PR) to these treatments. In March 1992, he presented with a bulky abdominal mass (largest diameter = 30 cm). A Trucut biopsy confirmed the HCL localization. A first course of 2-CDA (0.1 mg/kg/day for 7 days by continuous infusion) led to a dramatic decrease of the tumoral mass with a minimal residual bone marrow infiltration. A second course was administered in July 1992 with a subsequent tumoral regression. He is now in good PR.

Patient 2, a 62-year-old woman, was splenectomized at diagnosis in 1982 and then treated with IFN in 1988 and in 1990 with a good PR. In April 1992, she presented with breast nodules and superficial and retropertioneal lymphadenopathy extending from coeliac region to aortic bifurcation. HCL localization was confirmed by breast biopsy. She received a first course of 2-CDA in July 1992 with complete regression of lymphadenopathy and minimal residual bone marrow infiltration (< 5%). She received a second course of 2-CDA and is now in good PR.

In both patient, 2-CDA was well tolerated without any severe infectious complication. We conclude that 2-CDA may be highly effective on nodal localizations of HCL, even in patients with bulky tumors and those already treated with IFN or DCF.

T 160  

PRETREATMENT ANEMIA BUT NOT NEUTROPENIA PREDICTS NEUTROPENIC FEVER FOLLOWING TREATMENT WITH 2-CHLORO-2'-DEOXYADENOSINE (2-CDA) FOR SYMPTOMATIC HAIRY CELL LEUKEMIA (HCL)

Gunmar Juliuussen, Jan Liliebrak. Division of Clinical Oncology and Hematology, Dept. of Medicine, Huddinge Hospital, S-141 86 Huddinge,

2-chloro-2'-deoxyadenosine (2-CDA) is a purine analogue with a great efficacy in the treatment of symptomatic hairy cell leukemia (HCL). The complete remission rate is about 80%, following just one week of therapy. Most of the remaining patients achieve an asymptomatic disease with normal blood counts but residual leukemia cells in the marrow. The established administration route is a continuous intravenous infusion, but, as predicted from our pharmacokinetic and biavailability studies (JCO 1992;10;1514) we could recently document a similar efficacy when 2-CDA was given in subcutaneous injections daily for seven days (Blood 1992;80(suppl):359a).

The main toxicity of 2-CDA in HCL is neutropenic fever, which develops in about one third of the patients, always within the first three weeks following treatment. We have been able to document opportunistic infections, such as candidass, aspergillosis and CMV viremia on several occasions. In our initial trial with 2-CDA in continuous infusions (Blood 1992;79:880) we found that neutropenic fever only developed in patients with pancytopenia at start of treatment.

Since January 1992, we treat hairy cell leukemia patients with 2-CDA as subcutaneous injections, 3.4 mg/kg daily for seven days. Of 57 evaluated patients, neutropenic fever developed in 15. In seven cases no origin to fever was found. Two patients had culture negative pneumonia, one had septicemia with staphylococci, one had a skin infection, one had febrile CMV infection documented through serology, and one had febrile candida infection documented by serum antigens. Two patients had systemic mycobacteriosis developing prior to therapy, and again fever posttreatment.

Pretreatment anemia was a strong predictor of subsequent neutropenic fever, in contrast to leukocyte counts with differentials (see Table below). Neutropenia is a very common finding in symptomatic HCL, whereas anemia indicates a more severely depressed hematopoiesis.

**Blood Counts at Start of 2CDA Treatment**

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD</th>
<th>Neutrophil Count Given Intravenous Antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>15</td>
<td>22</td>
</tr>
<tr>
<td>Hemoglobin (g/l)</td>
<td>95 ± 22</td>
<td>124 ± 17 (&lt;0.0005)</td>
</tr>
<tr>
<td>Lymphocyte count (x10^9/l)</td>
<td>4.5 ± 5.4</td>
<td>4.1 ± 5.7</td>
</tr>
<tr>
<td>Neutrophil count (x10^9/l)</td>
<td>0.83 ± 0.9</td>
<td>0.98 ± 0.6 (n.s.)</td>
</tr>
<tr>
<td>Monocyte count (x10^9/l)</td>
<td>0.06 ± 0.1</td>
<td>0.07 ± 0.1 (n.s.)</td>
</tr>
<tr>
<td>Platelet count (x10^9/l)</td>
<td>81 ± 79</td>
<td>118 ± 62 (p &lt; 0.01)</td>
</tr>
</tbody>
</table>

150
T 161 EFFECTIVITY AND TOXICITY OF FLUDARABINE PHOSPHATE IN PRETREATED ADVANCED CHRONIC LYMPHOCYTIC LEUKEMIA-RESULTS OF A PHASE II TRIAL. K. Fischer, K.C. Enzer, K. Liebmann, P. Mitrou, T. D. D. V. Dierck, H. D. Hoezler. 1st Div. of Haematology, Medical University, Innsbruck/M., FRG. FDep. of Internal Medicine, University Clinics, Cologne, FRG

Fludarabine phosphate (FAMP) has been shown to be effective in pretreated chronic lymphocytic leukemia (CLL) and to induce even complete remissions (CR). Here we report treatment results in 31 patients (pts.) with advanced and resistant CLL, 29 with B-CLL, 2 with T-CLL. FAMP was administered at a dosage of 25 mg/m² as a bolus infusion daily for 5 days and repeated every four weeks. Dosage and time course were adapted according to toxicity. After 3 and 6 cycles reevaluation was performed. 141 cycles of FAMP were administered. 1 of 28 (3%) evaluable pts. achieved complete remission, 17 of 28 pts. (61%) achieved partial remission, 5 of 28 (18%) had stable disease, and 5 of 28 (18%) showed progressive disease (PD). In most cases, PR was achieved within 2 cycles of FAMP. The duration of partial remission was in median 6 months, with a range of 3-12+ months. 2 of the 3 patients in PR relapsed after 2 and 7 months, 8 patients in PR died due to infection. Major toxic effects included infections in 14 patients of WHO-grade 3 and 4 and nausea in 6 patients of WHO-grade 1. Among the severe infections, germs like pneumocystis carinii and aspergillus fumigatus could be observed. In one case a tumor lysis syndrome was observed. The development of pulmonary, even opportunistic infections can possibly be explained by FAMP-induced reduction of CD4+ positive cells down to minimal counts of 17 cells/µl, namely in patients achieving PR or CR. In conclusion, fludarabine is highly effective in patients with advanced CLL, but severe opportunistic infections due to CD4 reduction requires antibiotic prophylaxis.

T 162 FLUDARABINE PHOSPHATE IN THE TREATMENT OF RELAPSED OR REFRACTORY LOW GRADE NON-HODGKIN LYMPHOMAS.


Fludarabine phosphate is a fluorinated adenine nucleoside which has major activity in patients (pts) with de novo or refractory B-cell chronic lymphocytic leukemia. In order to investigate this agent in other lymphoid malignancies, we have treated 24 pts with advanced stages of low grade non-Hodgkin lymphoma (NHL). Sixteen pts were male, and 8 were female, ranging in age from 38 yr to 80 yr (median 56 yr). The histologic classification was as follows: immunocytoplasia (a), n=4, centroblastic-centrocytic (b), n=9, centrocytic (c), n=10, MALTOM, n=1. Two pts had stage III, and the remaining 22 pts had stage IV disease. Five pts had one, 8 pts had two, and the other 11 pts had more than two prior chemotherapeutic regimens. LDH levels were <240 U/l in 7, and >240 U/l in 17 pts. Fludarabine phosphate was administered at a dosage of 25 mg/m² at a 4 week interval up to a maximum of 12 cycles. Two pts had intercurrent therapy with prednisone and cyclosporin A because of hemolytic anemia. Twenty-three pts are so far evaluable for response and toxicity. Responses were seen in 11/23 (30%), including one CR (NHL ec) and 6 PR (NHL cbc=33, NHL cc=m, MALTOM, n=1). Durations of response are 1m+, 3m, 7m, 9m, 11m+, 14m+ for the pts achieving PR, and 7m for the pts with CR. There was one early death (NHL ec) most likely due to a tumor lysis syndrome. The major hematologic toxicity was thrombocytopenia in 11/23 (48%) pts and leukopenia in 11/23 (48%) pts. Major non-hematologic toxicity was infection in 15/23 (65%) pts. In conclusion, fludarabine phosphate used as a single agent is active in approximately 30% of patients with advanced-stage low grade malignant lymphomas. Fludarabine deserves further investigation in pts with less prior treatment, and as part of combination chemotherapy regimens in pts with advanced stages of these diseases.

T 163 PULMONARY TOXICITY INDUCED BY FLUDARABINE MONOPHOSPHATE IN A PATIENT WITH ADVANCED STAGE B-CELL CHRONIC LYMPHOCYTIC LEUKEMIA.

K. Fischer, Ch. Degenhart, P. Möller, B. Witt, H. Döhner, W. Hunstein, Medizinische Klinik und Poliklinik, V. Pathologisches Institut, University of Heidelberg, 69120 Heidelberg, Germany

Fludarabine monophosphate is a fluorinated adenine nucleoside which has major activity in patients (pts) with de novo or advanced stage B-cell chronic lymphocytic leukemia (CLL). Because of its high activity in CLL the drug is increasingly being used in other low grade non-Hodgkin lymphomas (NHL). In an early phase I studies myelosuppression and neurotoxicity proved to be dose-limiting toxicities. In the widely used schedule of 25mg/m² every 4 weeks, side effects other than myelosuppression are rarely seen. Among 75 pts. with various lymphoproliferative diseases (CLL=48; low grade NHL=22, hairy cell leukemia=2, others=3) treated with fludarabine at our institution, we encountered one pt. who developed the clinical, radiologic and histopatologic signs of acute interstitial pneumonitis. CLL stage Rai II was diagnosed in a 59 year old man in 1994; he had a 30 year history of smoking (20 cigarettes per day) and three episodes of pneumonias during the last three years. From April 1987 to May 1991 the pt. received intermitent treatment with prednisone and chlorambucil (150mg total dose); because of progressive disease (leukocytosis and lymphadenopathy) the pt. was given one cycle of COP combination chemotherapy in October 1991; there was no objective response. Therapy with fludarabine (225 mg/m² every four weeks) was started in November 1991. Partial remission was achieved after four cycles. After eight courses the pt. was hospitalized because of fatigue, dyspnea, nonproductive cough, and fever (38.6°C). The chest x-ray demonstrated a diffuse reticulonodular infiltrate involving primarily the lower lobes. Capillary blood findings revealed pO2 61mmHg and PCO2 32mmHg. A transbronchial lung biopsy showed an interstitial pneumonitis with slight fibrous thickening of the alveolar septa as well as lymphocytic and plasmacellular infiltrates; all special stains and cultures were negative for infectious agents; there was no histological evidence of lung infiltration by CLL. Therapy with prednisone (100mg q.i.d) was started: symptomatic improvement was noted within 48 hours and the reticulonodular infiltrates resolved within approximately ten days. Acute phase proteins and capillary blood findings normalized. Prednisone was tapered over two months. The pts disease is now in a 9 months continuous partial remission; there were no more signs of respiratory distress. In conclusion, fludarabine associated pulmonary toxicity is a rare but important side effect. Lung biopsy should be performed to exclude an infectious etiology or lung infiltration by the underlying disease. Previous therapy with high cumulative doses of alkylating agents such as chlorambucil may represent one predisposing factor.

T 164 PHASE II STUDY OF THE COMBINATION OF FLUDARABINE, MITOXANTRONE, AND DEXAMETHASONE (FND) FOR PATIENTS WITH RECURRENT LOW-GRADE LYMPHOMA (LGL), P. Maclaganhan, F. H. J. R. Romaguera, A. Younes, M. Keating, F. Cabanillas. Dept. of Hematology, University of Texas M.D. Anderson Cancer Center, Houston, TX 77030 USA

Our Phase I study of FND (Proc AACR 1992; 33:228) defined a maximum tolerated dose of: fludarabine 25mg/m²/day 1; mitoxantrone 10mg/m²/day 1; and dexamethasone 20mg qd, days 1-5. Starting 1/9, 20 pts were treated 22 patients (pts) with FND on an ongoing Phase II trial. In addition to LCL pts, there were also 3 with follicular large cell and 3 with centrocytic lymphomas treated. The median age was 60 (range 37-75). The median number of prior treatment regimens was 2 (range 1-6); 7 pts had never previously achieved complete remission (CR). To date, there have been 9 CR (41%) and 12 (55%) partial remissions (PR). Five PR's remain on therapy, so the CR rate may increase. The only non-responder had centrocytic lymphoma. While follow-up is short, only 2 CR's have relapsed, at 4 and 10 mo, and only 2 PR's have progressed, at 6 and 7 mo. Toxicities are mainly myelosuppression, including apparent cumulative myelosuppression with delayed hematologic recovery, especially platelets, in 4 pts. Infections occurred in 7 pts; 1 suspected pneumocystis pneumonia, and 5 episodes of H. zoster. We conclude that FND is an active combination for pts with recurrent LCL. It is important to consider the use of prophylactic antibiotics or withholding steroids if high-risk pts can be identified.
T 165 STAGE II HHV-8-NEGATIVE LYMPHOMA (HLN)
F. Burgle, J.M.V. Burger, W. Rykenbroek, A.H. Hart
Netherlands Cancer Institute, Amsterdam,
Daniel den Hoed Cancer Centre, Rotterdam.

Stage II HLN was studied, as its behavior is distinct from stage I, in two centres, with special attention to pattern of relapse in relation to pathology, presentation and applied radiotherapy. Formal staging procedures included lymphangiography and bone marrow biopsy. Pathology slides were reviewed according to the Working Formulation into low, intermediate and high grade (gr.) of malignancy (table).

Data from 170 patients (pc) were collected, 65 from Amsterdam and 105 from Rotterdam. The mean age of the total group was 60 years (22-93 years). Presentation was supradiaphragmatic in 104 pc (70.6% Ring of Maldeyer), of whom 16 pc were low gr., and intradiaphragmatic in 66 pc of whom 36 pc were low gr. For nodal size and gr. see table.

Treatment regimes varied between regional radiotherapy 40 Gy (RT): 58 pc, same radiotherapy followed by CVP (RCT): 59 pc, starting chemotherapy including Adriamycin followed by limited radiotherapy (CRCT): 46 pc, or chemotherapy alone (CT): 17 pc, while 2 pc had other treatment. Survival at 5 years (S5) was 56% for the whole group. Most low gr. pc received RT or RCT with S5 70%. While for intermediate gr. the boot S5 was 71% after CRCT. S5 was significantly related to nodal size with 3 cm: 78%, 4-5 cm: 59%, > 6 cm: 41%, but not to number of afflicted regions and total number of nodes (missing data 10 pt). Relapse (or progression) occurred in 79 patients (62%) of whom two thirds had isolated nodal relapses, 22/28 pt in low gr. and 42/37 in intermediate gr., while 18/22 and 18/24 of those relapses were in irradiated areas only (see table).

Conclusion. However after correction for age and nodal size, no significant difference remains in S5 between treatment RT, RCT or CRCT, for low and intermediate grade, but for patients 1 gr. alone is worse. The pattern of relapse suggested that additional RT might improve results. 100 pc all 56% 67% 78% 24

S5 low gr. 56% 67% 78% 24
S5 RT 41% 70% 78% 0%
S5 RCT 56% 70% 59% 58%
S5 CRCT 67% 40% 77% 0%

n 170
size < 3 cm 51 29 13 4
5-4 cm 36 7 24 5
> 4 cm 36 3 12 4
replase all (%) 79 (66%) 28 (54%) 37 (44%) 14 (20%)
isol. nodal 53 22 24 7
isol. nodal no RT 32 10 18

T 166 SERUM LEVELS OF TUMOR NECROSIS FACTOR-α IN PATIENTS WITH B-CELL CHRONIC LYMPHOCYTIC LEUKEMIA. F. Adami, A. Guarini, M. Pini, F. Siviero, R. Sancetta, M. Massaia, L. Trentin, R. For, G. Semenzato - Department of Clinical Medicine, University of Padua; Department of Biomedical Sciences and Human Oncology, University of Turin.

Tumor Necrosis Factor-α (TNF-α) is a cytokine with a wide spectrum of biological activities, including a definite effect on the proliferation of neoplastic lymphocytes of B-chronic lymphocytic leukemia (B-CLL) and hairy-cell leukemia (HCL) in vitro. Neoplastic lymphocytes from both B-CLL and HCL have also been shown to release TNF-α spontaneously in vitro: furthermore, increased serum levels of TNF-α in B-CLL and HCL have been detected in vivo. To clarify the clinical relevance of the increased serum TNF-α levels in B-CLL and to ascertain if a relationship can be established with the extent of the disease and/or some of the events naturally occurring in this disorder, we evaluated the serum TNF-α levels in a large series of B-CLL patients. The data obtained were correlated with currently used hematological and immunological parameters.

Blood samples were collected from 91 CDS+ B-CLL patients (31 aged <60 years; mean age 65±9). There were 39 patients in group 1 (Rai stage 0), 38 patients in group 2 (stages I and II) and 18 patients in group 3 (stages III and IV). Serum levels of TNF-α were measured using an immunoradiometric assay (Medgenix).

While control sera showed undetectable values of TNF-α, in B-CLL the mean levels are different in the three groups. Increasing values were observed from group 1 (7±2 pg/ml) to group 2 (9±6 pg/ml) and group 3 (3±7±3 pg/ml). A statistically significant difference was found to separate the three groups (P<0.05). Significant correlations were established with the absolute number of circulating monocytes (r=0.002) and with the level of hemoglobin (P<0.001).

No significant correlation was observed between serum levels of TNF-α and the absolute number of peripheral blood (PB) white blood cells, lymphocytes, CD8+ lymphocytes, CD57+ lymphocytes, platelet count and serum levels of sIgG, sIgA or sIgM.

This study confirms that in B-CLL patients serum levels of TNF-α are significantly increased with respect to controls and demonstrates that the values increase with disease progression. A correlation between TNF-α serum levels and the number of PB monocytes and the level of hemoglobin has also been established. The neoplastic lymphocytes are likely to represent the major source of the serum TNF-α in B-CLL, but a role for cells belonging to the monocyte/macrophage lineage cannot be ruled out. The inverse relationship between serum levels of TNF-α and the level of hemoglobin further points out the active role of this cytokine on hematopoiesis.

T 167 PHENALOL IN THE TREATMENT OF MALIGNANT LYMOPHOMA. P. Brelis, Department of Hematology, Lithuanian Cancer Centre, 2600 Vilnius, Lithuania.

Phenalol - n/di(2-chlorethyl)-amino/phenacetyle-phenazinamide is a new anticancer drug developed in Lithuanian Cancer Centre. The drug is effective in the treatment of malignant lymphomas refractory to standard chemotherapy. Phenalol was administered to 50 Hodgkin’s lymphoma patients and 20 non-Hodgkin’s lymphoma patients who progressed during and after chemotherapy. Partial remissions were achieved in 15 of 20 (75%) of Hodgkin’s lymphoma patients. The duration of regressions was 6 to 8 weeks. Partial regressions were achieved in 4 of 10 (40%) of non-Hodgkin’s lymphoma patients. The duration of regressions was 5 to 6 weeks. Phenalol is less toxic compared to other chemotherapy drugs. Dyspeptic signs were observed in less than 15% of cases, and mild alopecia was observed in less than 2% of cases. There were no cases of agranulocytosis. Subsequently phenalol was included in other protocols and regimens instead of cyclophosphamide and POMP and VP regimens. However, during the treatment of Hodgkin’s lymphoma patients with PFP polychemotherapy partial regressions were achieved in 7 of 10 (70%) of cases. The duration of regressions was 6 to 8 weeks. After repeated courses the duration of regressions was 12 weeks. However, during the treatment of non-Hodgkin’s lymphoma patients with PFP polychemotherapy partial regressions were achieved in 4 of 10 (40%) of cases. The duration of regressions was 6 to 8 weeks. It can be concluded that phenalol is effective in the treatment of malignant lymphomas refractory to standard chemotherapy. We suggest that it may be useful to include it into combination chemotherapy regimens.

T 168 RADIATION THERAPY WITH HIGH DOSE 67-GALLIUM INTRAVENOUSLY IN NON-HODGKIN’S LYMPHOMA. A. Jorkhoff, P.C. Huygen, O.H. Hoekstra, G.J. Ossenkamp, G.J.J. Teule. Free University Hospital, Department of Haematology and *Department of Nuclear Medicine, Amsterdam, The Netherlands.

67-Gallium (67Ga) accumulates rather selective in malignant lymphoid tissues. In vitro we found a cytoxic effect of 67Ga in human cell lines U 937 and HL60 compared with 80 Yttrium and low dose irradiation. Intravenously high dose 67Ga was administered intravenously to three patients with end stage large cell non Hodgkin’s lymphoma who had failed autologous bone marrow transplantation and had progressive disease. No acute side effects were noted with doses of 20-60 mCi. Bone marrow suppression was seen in all patients and persistent pancytopenia requiring platelet transfusions occurred in the first patient who had received three weekly doses of 20, 40 and 60 mCi respectively. The other two patients receives 2 doses of 40 mCi 67Ga with a 4 weeks interval.

In all patients some tumour reduction of 25-75% was noted, as judged by physical examination, CT scanning and 67Ga imaging. The response was short lived (5-12 weeks) and most remarkably, different in magnitude from site to site. We conclude that high dose 67Ga can safely be administered intravenously without any site effect apart from myelosuppression and has cytostatic effects in large cell Non Hodgkin’s lymphoma, deserves further exploration.

# Brit J Cancer 1992;67.
ABSTRACTS - Fifth International Conference on Malignant Lymphoma, Lugano

T 169

DIPHOTAMOLE AND LOW DOSE RETROVIRUS FOR MYCOSIS FUNGOIDES. I. Hristov, E. Obradovskova, A. Lalova, Department of Dermatology, Medical Faculty, Sofia, Bulgaria

Retrovirus (RTV) is widely used for treatment of cutaneous T cell lymphoma (CTCL). However, it is toxic because it interferes with various humoral and cellular immune processes and activates a variety of viral particles that prevent transport downwards in the concentration gradient. In this study, the combination of MTX and DP could be more effective. We report a case of CTCL effectively controlled with DP and low doses of MTX. A 72-year-old male presented in 1993 with a generalized exfoliative erythroderma, intense itching, and axillary and inguinal adenopathy. A skin biopsy specimen showed the characteristic findings of mycosis fungoides; the patient refused lymph node biopsy. Results of laboratory evaluation, including normal cells in peripheral blood, were normal or negative. A diagnosis of CTCL (stage III, T R B C, low-grade peripheral) was made. The patient was treated with MTX-DP regimen, using the following treatment schedule: MTX was administered i.m. at a dose of 25 mg weekly for 6 weeks, followed by 15 mg weekly for 5 weeks, then 10 mg biweekly continuously. DP was given orally and i.m. Intravenous administration of DP was done at the same time (in 15 h), MTX, at a dose of 100 mg x 6 for 6 weeks, followed by 100 mg x 2. By oral route, DP was given at a dose of 50 mg x 2/4 h for 4 weeks, followed by 50 mg x 3/24 h for 7 weeks, and then 25 mg x 5/24 h continuously. In order to estimate the clinical course, the tumour burden index (TBI) was used: before treatment - TBI 200, at week 4 = 150, at week 12 = 100 (a complete remission). A relapse occurred at week 52 - TBI 184 and disease slowly progressed despite the continuous therapy: week 96 weeks 52 and 60 = 120, and treatment was discontinued at week 66, TBI 155. No side effects. Our patient showed a good response to low doses of MTX in this regimen (a total dose of 600 mg) and we believe that the combination of DP with MTX in CTCL is worth further evaluation.

T 170


Peripheral T-cell lymphomas are a subset of lymphomas more often identified by special pathologists. They are morphologically heterogeneous and include diffuse mixed and large cell lymphomas of the Working Formulation. Therefore, although they have been described both in Japan and in western countries as associated with a poor outcome, in the absence of immune phenotype they are classified together with intermediate grade lymphomas and can be treated with insufficiently aggressive protocols.

We have retrospectively reviewed 37 cases of unclassified P TCL of whom were seen at the onset of their disease and are considered for the present analysis. In three patients P TCL was secondary to other hematologic malignancies (CLL, HCL and HD) and in one case AIDS related. Three of them expressed both CD4 and CD8 antigens (but were CD4 negative) 3 expressed only CD8 antigens and 20 only CD4 antigens, two of them CD20+ (1). Three of them were classified as stage IB, II and III respectively.

We have treated patients with 10 mg/m²/cycle with a range of 0.65 - 2.10. In all cases, we administered a standard dose of the following agents: Cytarabine (200 mg/m²/cycle), vincristine (1.4 mg/m²/week), etoposide (100 mg/m²/cycle), prednisone (40 mg/m²/day), and bleomycin (15 mg/m²/cycle).

The results of these treatments were highly variable, with some patients achieving complete remission, while others did not respond or relapsed. Overall, the median duration of response was 20 months, with a range of 6-48 months. The median survival for all patients was 36 months, with a range of 6-72 months.

T 171

LONG-TERM RESULTS OF CHEMOTHERAPY WITH OR WITHOUT RADIOThERAPY IN STAGE I AND II HIGH GRADE MALIGNANT NON-HODGKIN'S LYMPHOMAS (NHL).

Nowroussian M.R., Kath R., Becks E., Nephath K., Seeger B., Department of Internal Medicine (Cancer Research), West German Tumor Centre, University of Essen, F.R.G.

The optimal treatment approach in patients (pts) with localized aggressive NHL is still controversial. It is particularly uncertain whether the addition of radiation therapy to chemotherapy improves the results. This report deals with the long-term results of primary chemotherapy with or without radiotherapy in 51 pts (33 males, 18 females) with early stage aggressive NHL who were treated in our institution between 6/1983 and 6/1990. The median age was 48 yrs (range 16-79). 13 pts had clinical stage (CS) I and 38 CS II disease. Histologic subtypes of the tumors (Kiel classification) were: centroblastic 34, immunoblastic 12, and undifferentiated large cell 5. B-Symptoms were present in 13 pts, bulky disease (> 5 cm) in 25 pts, and extranodal involvement in 29 pts. 6 pts were treated with CHOP, 20 pts with MACOP-B and 25 pts with CA-BOPP/VIM® as primary chemotherapy. In 21 pts additional irradiation (30-45 Gy) was given to the involved field after completion of chemotherapy. An overall complete remission (CR) rate of 94% was achieved. The CR rate was 100% in pts with stage I and 92% in those with stage II disease. With a median follow-up of 62 months, 87% of pts with CR are predicted to be disease-free at 105 months. The probability of disease-free survival (DFS) is 92% in pts with stage I and 84% in those with stage II disease. There is no significant difference in the probability of DFS between pts who were treated with chemotherapy alone and those who were treated with combined chemotherapy and radiation therapy (p < 0.84%). The probability of survival is 81% for the whole group of pts, 92% for pts with stage I and 76% for pts with stage II disease.

Nowroussian et al., Acta Oncologica 28, 495-500, 1989

T 172

LOCALIZED AGGRESSIVE NON-HODGKIN’S LYMPHOMAS (NHL). 6-YEAR RESULTS ON 81 PATIENTS TREATED WITH THE POF 83 TRIAL. B. DESABLENS (Amiens), A. LE MEBEL (Nantes), Ph. COLOMBAT (Tours), Ch. GANDOUR (Rennes), N. SZA/-PO/R (Angers), Ch. BERTHOU (Brest), B. MAHE (Nantes), A. SADOUN (Poitiers), J. C. GRULLOUS (Rennes), Ph. CAZASSUS (Bobigny) - PARIS-OUEST-FRANCE Group.

From July 1985 to March 1992, we treated 81 localized (skin and gastrointestinal involvement excluded) aggressive NHL with 3 courses of CHP (cyclophosphamide 750 mg/m² d1, doxorubicin 50 mg/m² d1, vindesine 3 mg/m² d1 and procarbazine 60 mg/m² d1 to d5) followed by a focal or regional radiotherapy (40 Gy) and combined with a CNS prophylaxis for high risk patients (pts). Pts were aged from 65 to 75 years (median 68) and their sex-ratio was 1:08 (42 M/39 F). 39 pts had an extranodal disease (Waldeyer's or sinus; 22; thyroid; 6; bone; 3; soft tissues and miscellaneous 5) and 42 pts had a nodal presentation of whom 7 had an extranodal involvement (peripheral nodes 34, abdominal nodes 6 and non lymphoblastic mediastinal NHL 3). A bulky presentation was seen in 34 pts and according to Ann Arbor classification there were 45 CS A, 22 B1, 30 B2 and 4 MB. Mean values of séric LDH and séric microglobulin levels were respectively 985 µg x 10⁶ x 11 and 2.60 x 10⁶ mg/l. 13 pts were in obvious complete remission (CR) after initial biopsy and the 3 CHP induced a CR in 75/86 pts (83.8%). After the whole treatment, we noted 1 toxic death (1.2%), 1 failure (1.2%) and 79 CR (97.5%). On January 1st 1993, the median follow-up was 40 months and we observed 18 relapses (occurred within 36 months except for 1 pt) and 17 deaths (toxic death 1, failure 3, relapse 14 and non-related death 1).

The 6.5-year survival rate (SR) was 69% for all the pts and 70.7% for the 79 pts in CR after the protocol. We found prognostic factors for CR and survival: Age > 60 years (p < 0.05), bulky disease (p < 0.005), high serum LDH levels (p < 0.005) and high séric microglobulin levels (p < 0.005). The only factor which was an independent risk factor after a multivariate analysis was bulky disease (p < 0.005). The POF 03 regimen appears to be more effective and in better aged patients with localized aggressive NHL.

153
ABSTRACTS - Fifth International Conference on Malignant Lymphoma, Lugano

T 173
LOCALIZED AGGRESSIVE NON-HODGKIN’S LYMPHOMAS (NHL): 7-YEAR RISKS OF 199 PATIENTS TREATED WITH THE POD PROTOCOL. A. LE MEVIEL (Nantes), B. DESABLENS (Amiens), Th. LAMY (Reims), J-F. ABRILLARD (Brest), J-M. TOURANI (Paris-Laumont), Ch. GANAZOUR (Dijon), Ph. COLOMBAT (Tours), Ch. POUSSAULT (Angers), Ph. MOREE (Nantes), A. SADOUN (Nantes), Ph. CASASSUS (Bobigny) - PARIS-OUEST-FRANCE Group.

From January 1985 to August 1992, we treated 209 localized (skin and gastrointestinal involvement excluded) aggressive NHL, with a short intensive chemotherapy (3 courses of VACOP, vincristine 3mg/m² d1 & d5, prednisone 100mg/m² d2, cyclophosphamide 1500mg/m² d1 & d4, and prednisone 80mg/m² d1) followed by a focal or regional radiotherapy (40Gy) and combined with a CNS prophylaxis for high risk patients (pts). Our pts were less than 65 years (median: 51) and their sex-ratio was 1.34 (120/109). We included 94 pts had an extra-nodal disease (Waldeyer's ring or sinus in 49; primary cerebral NHL in 11; bone 9; paraplegia 7; thyroid and miscellaneous 11) and 112 pts had a nodal presentation of which 44 had an extra-nodal involvement (peripheral nodes 65; non lymphomatous mediastinal NHL 39; abdominal nodes 8 and spleen 2). A bulky presentation was seen in 101 pts and according to Ann Arbor classification there were 106 CS IA, 8 II B, 73 III A and 19 III B. Mean values of serum LDH and β2-microglobulin levels were respectively 170U/L (range: 44-831) and 10.1mg/dl (range: 0.7-70). 40 pts were in obvious complete remission (CR) after initial biopsy and the 3 VACP induced a CR in 13/169 pts (78%). After the whole treatment, we noted 7 toxic deaths (3.9%); 11 failures (5.5%) and 191 CR (94%). On January 1st 1993, the median follow-up was 50 months and we observed 28 relapses (occurred within 36 months except for 2 paz) and 44 deaths (toxic death 7; failure 10; relapse 18; ANL 1; solid tumor 2 and non-related death 6).
The 7-year survival rate (SR) is 37.9% for all the pts, 76.7% for the CR pts after the protocol and 80.9% after excluding the non-related deaths. We found a prognostic value for 4 parameters:

- SR (p) No 84.9% (108) Yes 65.6% (101) < 10-5
- LDH < 1.25xN 79.1% (108) > 1.25xN 56.8% (32) < 10-4
- PS < 2 73.4% (161) ≥ 2 52.1% (39) < 10-5
- Nodal Sympt. Yes 89.0% (127) No 50.2% (27) < 10-3

Analysis by initial sites and prognostic multivariate analysis will be presented.

T 174
A PILOT STUDY OF ProMHC/CytaBOM IN AGGRESSIVE NON-HODGKIN’S LYMPHOMA. J-P. Dargent et al, Erasmus University Hospital Brussels, Belgian Lymphoma Group, Cyamand Benelux S.A./N.V.

Mitoxantrone is a relatively new drug in the management of non-Hodgkin’s lymphomas, which yields fewer troublesome toxicities and cardiotoxicity than doxorubicin. We have conceived to investigate mitoxantrone (5mg/2g) instead of doxorubicin (25mg/2g) in one of the most efficacious third generation regimen i.e. ProMHC. This work is aimed to verify the activity, the safety and the feasibility in a group setting. We report here the preliminary results obtained in the first 20 registered cases.

Demographic data were: Female 11, male 9; mean age 53.7-years-old; extra-nodal involvement 15/20; International Working Formulation D=2, F=3, D=11, E=1, Other=2; Coiffier Index I=4, II=7, III=6.

Response rate after 6 cycles was: CR8%, PR=5% (2 of them became CR after additional radiotherapy) PD=2, early deaths =2.

The maximal toxicity (mean of the highest WHO grade/patient) studied through 101,5 cycles was moderate: Hb:1.4; PMN:2.5; Platelets:0.3; Neutropenia/Vomiting:1.2; Alopecia:1.1; Infection 0.9; Peripheral Neuropathy 0.4; Cardiotoxicity 0.3.

The administered dose intensity (101.5 cycles) was excellent with the following percentage of the ideal dose: Cyclophosphamide 88.5%; Mitoxantrone 88.5%; Etoposide 91.3%; Cycarbin 78.8%; BLM/doxorubicin 89.2%; Vinristine 82.8%; Methotrexate 87.3%.

Conclusion: ProMHC/CytaBOM is an effective regimen in aggressive non-Hodgkin’s lymphoma. The toxicity is low enough to permit possibly with the use of either or G-CSF, to dose increment increases the anthracyclic component, which is one of the most powerful prognostic factor (L. Micak et al.,1990) in aggressive non-Hodgkin’s lymphoma.

T 176
A PROTOCOL INCLUDING IADBIRICIN AND ETOPOSIDE AS FIRST LINE TREATMENT IN INTERMEDIATE NHL. A. De Beno, A. Semprato, L. Santoro, E. Attingi, A. D’Acroc’, B. Rotoli. Division of Hematology, University of Naples Federico II Medical School, Division of Medicine, Fava del Tirreni Hospital, Italy.

It is still debated which is the most appropriate treatment for eradicating advanced stage intermediate NHL. Intensive schedules are potentially curative, but are harmful and difficult to be administered on patient basis. In a pilot study we have tried a five drug regimen which is a reinforcement of the classical CHOEP: vincristine 2mg/day, cyclophosphamide 600mg/m² idadubicin 10mg/m²/day 1 to 3, etoposide 100mg/m²/day 1 to 3, dexametess 90mg/m² for 5 days. Six courses with a three week interval were schedule for any of stage III to IV intermediate NHL.

Up to the time of the abstract, 14 patients entered the study (4 N and 10 F, median age 55, range 36-75). Complete remission was obtained in all evaluable patients but one, who achieved partial remission. No organ toxicity was observed, except transient alopecia that occurred in all patient. Hematological suppression was moderate (grade II-IIII), with a nadir at day 14. Dose reduction and longer interval between courses were needed in only one patient, who was the oldest in the series (75 y old man). 4 patients required RBC transfusion; plates transfusion was never necessary. Stage IV patients with liver (1 cases) and pleural (3 cases) involvement went into CR after 1-2 courses; pleural effusion needed not be drawn in 2 patients and did not recur after a single drawing in the third. Thus, a five drug regimen including idarubicin and etoposide as main cytotoxic drugs and dexametess as substitution for prednisone seems effective and well tolerated in intermediate NHL. A larger follow up and a randomized trial with a conventional four drug regimen are needed to assess a possible superiority of such a protocol.
Intermediate grade non-Hodgkin's lymphomas are very heterogeneous and a standard chemotherapy regimen remains controversial. We evaluated 30 consecutive patients (13 males and 17 females) with intermediate grade histology (4 D, 11 E, 15 F, according to WF) treated with MACOP-B between June 1986 and May 1992. Median age was 55 years (range 28-71). Five patients had stage I, 8 stage II, 9 stage III disease; 7 out of 8 patients with stage IV disease had bone marrow (BM) involvement. All patients with limited stage disease received also regional RT. The program was completed in 26 patients; one patient died for septic shock, at the 7th week of treatment; two patients discontinued the program after 6 and 10 weeks respectively, because of hepatic toxicity and GI bleeding due to reactivation of a preexisting parasitosis; a fourth patient refused further treatment after 4 weeks. There was one more treatment-related death, due to acute hepatic failure, occurring a few weeks after MACOP-B.

Other toxicities (gr. III-IV) did not affect program completion and consisted of neutropenia (7 patients) and oral mucositis (9 patients). Overall, 12 patients (40%) reached CR. Only 1 out of 7 patients with BM involvement reached CR. Median disease-free survival (DFS) was 55 mos., with a projected DFS of 40% at 92 mos. As of December 1992, 19 patients (63%) are alive (median follow up = 49 mos.), and 12 are in continuous CR. Limited stage disease showed a trend for better DFS and overall survival compared to advanced stage; however, bone marrow involvement had the most adverse impact on both CR achievement and prolonged survival. In conclusion, our data suggest that an intensive program such as MACOP-B may be an effective treatment also in patients with intermediate grade histology, with the exception of patients with BM involvement, who still require alternative approaches.

**T 179**

A NEW HYBRID REGIMEN (CEOP-IMVP-DEXA) IN THE TREATMENT OF HIGH-GRADE NON-HODGKIN'S LYMPHOMAS (NHL). AN AUSTRIAN MULTICENTRAL TRIAL.


Purpose of the study was to evaluate the efficacy, toxicity and feasibility of a new chemotherapy regimen for high-grade NHL in a multicentric setting. We combined two non-cross-resistant regimens, CEOP (Cyclophosphamide 750mg/m² iv d1, Etoposide 70mg/m² iv d1, Oncovin 1.4mg/m² iv d1 and Prednisolone 150mg p.o. d1-5) and IMVP-DEXA (Ifosfamide 2g/m² iv with Uromitexan uroprotection iv d1-7, VP-16 100mg/m² iv d1, Cisplatin 100mg/m² iv d1, 5-fluorouracil 500mg/m² iv, with Ca-folinic rescue p.o. d2) and repeated it in 4 week intervals, 3 to 6 times according to response. We made no dose reductions as long as granulocyte counts exceeded 0.5x10⁹/L. We withheld therapy for one week if counts dropped below 0.2x10⁹/L. Patients with untreated histologic proven high malignant NHL according to the Kiel Classification and measurable disease were included. Ten Austrian centers entered 81 patients; 68 were evaluable. Median age was 55.5 years. Forty-seven percent were in stage I or II and 53% in stage III or IV. CR-rate was 53.8% (81/154), after a median observation time of 23.9 months, overall survival and time to relapse after 3 years was 68% and 64%, respectively. Age >60 and stage III or IV was the only independent finding for a high relapse rate. We found 4 risk groups: age <60 years and stage I or II, age <60 years and stage III or IV, age >60 years and stage I or II, age >60 years and stage III or IV. In these 4 risk groups 81%, 69%, 45%, and 0% were free of relapse after 24 months respectively.

Toxicity was primarily hematological with a median granulocyte nadir of 0.5x10⁹/L. Seventy-one percent of patients had infections, but only 26% of them required hospitalization. Toxic death rate was 4.4%.

CEOP/IMVP-DEXA is a highly effective regimen for high grade NHL and is safe even a multicenter setting.

**T 180**


Since October 1988, we have treated 62 consecutive patients (pts) with intermediate (I/I) and high grade (HG) NHL with CEOP-B (CTX 750 mg/m² d1, Etoposide 60-90 mg/m² d1, D4 a 1.4 mg/m² d1, VP-16 80 mg/m² d1) and VIMD (Ifosfamide 6g/m² d1, VP-16 80 mg/m² d1, Bleomycin 10 mg/m² d1) every 3 weeks. The program was repeated iv IV until a CR, PR, SD, or PD was obtained. In 55 of the 62 pts were temporarily symptomatic, 25/39 pts (79%) achieved CR, 7/39 achieved PR, the remaining pts were minimally responded. The CCR at the end of all cycles, was 79.3% and the overall survival 70%.

Conclusion: VIMD seems to be a tolerable and highly effective schedule for treatment of high-grade NHL.

**T 178**


The prognosis of high-grade non-Hodgkin lymphomas (NHLs) depends on various prognostic factors (e.g. stage, stage, age, sex, mass) and seems to be determined by induction of early complete remissions (CR). Several trials therefore focus on dose intensification of cytostatics by addition of haematopoetic growth factors for reduction of hematotoxicities.

Study design: We conducted a phase-II trial in patients with high-grade NHLs with an intensive chemotherapy in short-term intervals. Patients with histologically proved high-grade lymphomas according to the Kiel classification (exclusion criteria: positive bone marrow) were treated with VACPE (ifosfamide 6g/m² d1, etoposide 100 mg/m² d1, cyclophosphamide 800 mg/m² d1, prednisone 60 mg/m² d1-7 p.o. and etoposide 120 mg/m² d1-3 i.v. (VACP)). For patients >60 years, adriamycin was administered only every two days and etoposide was reduced to 100 mg/m² d1-3. Most patients received GM-CSF beginning on day 4 of each cycle or have been included in a randomized trial (L GM-CSF). The cycles were repeated every three weeks. Patients with stage IV received six cycles of VACP, all other patients received five cycles VACP. After end of chemotherapy, pts received radiation therapy. The pts were reevaluated after two and four cycles, after finishing chemotherapy and after radiotherapy.

Results: Up to now, 23 of the 24 high-grade NHLs have been included into the study. 9 pts are too early for evaluation, 3 pts had an early death (1x stroke, 2x treatment-related). SD occurred in 5 pts (1x d1-10). The patients were reevaluated after two and four cycles, after finishing chemotherapy and after radiotherapy.

Results: Up to now, 23 of the 24 high-grade NHLs have been included into the study. 9 pts are too early for evaluation, 3 pts had an early death (1x stroke, 2x treatment-related). SD occurred in 5 pts (1x d1-10). The patients were reevaluated after two and four cycles, after finishing chemotherapy and after radiotherapy.

The overall survival 70%.

Conclusion: VACPE seems to be a tolerable and highly effective schedule for treatment of high-grade NHLs.

**T 177**


Intermediate grade non-Hodgkin's lymphomas are very heterogeneous, and a standard chemotherapy regimen remains controversial. We evaluated 30 consecutive patients (13 males and 17 females) with intermediate grade histology (4 D, 11 E, 15 F, according to WF) treated with MACOP-B between June 1986 and May 1992. Median age was 55 years (range 28-71). Five patients had stage I, 8 stage II, 9 stage III disease; 7 out of 8 patients with stage IV disease had bone marrow (BM) involvement. All patients with limited stage disease received also regional RT. The program was completed in 26 patients; one patient died for septic shock, at the 7th week of treatment; two patients discontinued the program after 6 and 10 weeks respectively, because of hepatic toxicity and GI bleeding due to reactivation of a preexisting parasitosis; a fourth patient refused further treatment after 4 weeks. There was one more treatment-related death, due to acute hepatic failure, occurring a few weeks after MACOP-B.

Other toxicities (gr. III-IV) did not affect program completion and consisted of neutropenia (7 patients) and oral mucositis (9 patients). Overall, 12 patients (40%) reached CR. Only 1 out of 7 patients with BM involvement reached CR. Median disease-free survival (DFS) was 55 mos., with a projected DFS of 40% at 92 mos. As of December 1992, 19 patients (63%) are alive (median follow up = 49 mos.), and 12 are in continuous CR. Limited stage disease showed a trend for better DFS and overall survival compared to advanced stage; however, bone marrow involvement had the most adverse impact on both CR achievement and prolonged survival. In conclusion, our data suggest that an intensive program such as MACOP-B may be an effective treatment also in patients with intermediate grade histology, with the exception of patients with BM involvement, who still require alternative approaches.
ABSTRACTS - Fifth International Conference on Malignant Lymphoma, Lugano


From February 1986 to June 1989, 96 previously untreated, poor prognosis NHL patients (pts) were entered in a prospective randomized trial comparing CHOP-B and ECHOP-B. Epidoxorubicin (E) was initially administered at a dosage of 60 mg/m2 and subsequently at 60-70 mg/m2. Both groups were similar for presence of adverse prognostic factors and also for age, histology, LDH value and extranodal disease. Cumulative remission (CR) rate was comparable: 63% with CHOP-B and 66% with CHOP-B. The increase in 4-Epi dosage provided neither a better response rate nor an increase in bone marrow toxicity. Both regimens were well tolerated; toxicity was slightly higher in CHOP-B arm. No case of congestive heart failure was observed, even though echocardiography evaluation of ejection fraction of left ventricle did show a significant decrease but within the normal range in CHOP-B treated pts; moreover, in the same group, a degree of atrioventricular block and a transient episode of cardiac ischemia were observed. Actuarial 8 year disease free survival (DFS) and overall survival (OS) did not differ in the two treatment arms. In addition, the relative dose intensity (RDI: delivered dose intensity/planned dose intensity) for CR and relapsed pts in ECHOP-B arm was comparable; median RDI for CR pts was 65% and 64% for relapsed pts. We conclude that clinical response duration is not influenced by RDI for 4-Epidoxorubicin in CHOP-B regimen.


Division of Oncology, Ospedale S. Carlo Borromeo, 20137 Milano, ITALY.

In our Institution, in last decade, we treated with CHOP regimen a group of patients (pts) affected by intermediate and high grade histology non-Hodgkin’s lymphoma. The records of eighty pts were reviewed to evaluate the rate of complete response (CR); overall survival (OS) and disease free survival (DFS); now prognostic factors predicting outcome were analysed.

53 pts were male and 27 were female with a median age of 55 years (range 20-76); ECOG 0-4: 16; I: 8; II: 23; III: E: 4. The histology according to the Working Formulation was D: 16; E: 5; F: 24; G: 26; H: 18; I: 5.

20% of pts had bulky disease and the same percentage had mediastinal or bone marrow involvement. 38 pts were in stage I-II and 48 in stage III-IV. Only 20/80 pts had diastolic systonic.

The CR rate was 64% with a CS/PA rate=88%. The 3 years DFS and OS were respectively 83% and 68%. We performed an univariate analysis on our data: ECOG, number of disease sites, mediastinal and bone marrow involvement, stage and LDH level, appeared significant prognostic factors for response and ECOG, LDH level, bone marrow involvement and extranodal disease for survival. The analysis of the outcome of the pts with 0 vs 1 or > 1 adverse prognostic factors for survival confirmed a decrease both in CR and OS rate as shown in the table below:

<table>
<thead>
<tr>
<th>H. prognostic factors</th>
<th>NCR</th>
<th>OS (3 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>92</td>
<td>91</td>
</tr>
<tr>
<td>1</td>
<td>80</td>
<td>77</td>
</tr>
<tr>
<td>2</td>
<td>70</td>
<td>61</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>*</td>
</tr>
</tbody>
</table>

No > pt had 4 adverse prognostic factors.

With the limit of a small group of pts and of an univariate analysis, nevertheless, it is important to recognize different prognostic groups of pts, also on the basis the recent advances. Further, it was important to start an uniform staging system to identify the subgroups of pts that need effectively new and more aggressive therapy.

T 182 Long-Term Outcome of Patients with Unfavorable Histology Lymphomas Treated with High-Dose Adriamycin Combination Chemotherapy.

L. Dabich and B. Schmitz, University of Michigan, U.S.A.

Between February 27, 1979 and April 21, 1984, 46 patients with unfavorable histology lymphomas were treated with aggressive intensive chemotherapy consisting of Adriamycin 120 mg/m2 on day one, Vincristine 1.4 mg/m2 on day one and Prednisone 50 mg PO days one to five, repeated at 21 day intervals for three courses followed by three courses of Cyclophosphamide 800 mg/m2 IV day one and Cytosine Arabinoside 1000 mg/m2 IV days one and eight, given at 21 day intervals or when bone marrow recovery was evident. There were four patients with lymphoblastic and three with undifferentiated lymphoma, with two manifesting progression and five short-lived complete remissions (median 8 months). Two of the three Burkitt’s lymphoma patients are free of disease at 122 and 147 months, the other patient, but there was recurrence of disease at 34, 52, and 60 months for three of the four patients with diffuse, poorly differentiated lymphocytic lymphoma; the survivor is free of disease at 150 months. Of the six patients with diffuse mixed lymphoma one demonstrated progression, one relapsed as PDLL, and four remained in complete remission from lymphomas at 109, 121, 127, and 147 months, respectively, but the latter had developed prostatic cancer and carcinomatous lesions of the tongue. The 25 patients with large cell lymphomas included 11 women and 14 men with the median age of 52 years (20-86). The Ann Arbor stages were IIA 6, IIBA 6, IVA 5, and IVB 8. Six were equal to or greater than 60 years of age and LDH was normal (N) in five and more than 2.5 x N in three. There were five patients with more than three extra nodal sites. Two failed to complete a third remission and three died in complete remission during induction, one due to toxicities, two due to acute myeloblastic infarction, and one to hepatitis. There were three other deaths in remission, one of adenocarcinoma, and two due to myelocytic infarction. There were two CNS relapses at 8 and 21 months, the first being treated successfully with intrathecal methotrexate and the second leading to death, as well as six systemic relapses. The others are alive at 111, 115, 119, 123, 128, 141, 142, 154, and 167 months. Of the 46 patients treated, 89% entered complete remission of median 9 years (range 2-14). We have previously reported (Lugano 1990, Abstract T-64) on the efficacy and toxicity of m-BBCOO in NHL. From June 1986 to December 1991, we treated 57 patients (pts) with unfavorable, NHL negative, intermediate and high grade lymphoma, 26 pts age 18-50, 12 pts age 51-65, 13 pts age 66-75, 8 pts age 76 and older. In addition to these, we treated 56 patients with unfavorable NHL and 39% are alive at a median follow-up of 45 months. These are very promising results for the treatment of advanced NHL. We are now using the combination of m-BBCOO and m-BBCOO-N in NHL and have obtained very good results with a median follow-up of 45 months. This combination is being used in the treatment of NHL and NHL-negative lymphoma, with very promising results. We have previously reported (Lugano 1990, Abstract T-64) on the efficacy and toxicity of m-BBCOO in NHL. From June 1986 to December 1991, we treated 57 patients (pts) with unfavorable, NHL negative, intermediate and high grade lymphoma, 26 pts age 18-50, 12 pts age 51-65, 13 pts age 66-75, 8 pts age 76 and older. In addition to these, we treated 56 patients with unfavorable NHL and 39% are alive at a median follow-up of 45 months. These are very promising results for the treatment of advanced NHL. We are now using the combination of m-BBCOO and m-BBCOO-N in NHL and have obtained very good results with a median follow-up of 45 months. This combination is being used in the treatment of NHL and NHL-negative lymphoma, with very promising results.


We have previously reported (Lugano 1990, Abstract T-64) on the efficacy and toxicity of m-BBCOO in NHL. From June 1986 to December 1991, we treated 57 patients (pts) with unfavorable, NHL negative, intermediate and high grade lymphoma, 26 pts age 18-50, 12 pts age 51-65, 13 pts age 66-75, 8 pts age 76 and older. In addition to these, we treated 56 patients with unfavorable NHL and 39% are alive at a median follow-up of 45 months. These are very promising results for the treatment of advanced NHL. We are now using the combination of m-BBCOO and m-BBCOO-N in NHL and have obtained very good results with a median follow-up of 45 months. This combination is being used in the treatment of NHL and NHL-negative lymphoma, with very promising results. We have previously reported (Lugano 1990, Abstract T-64) on the efficacy and toxicity of m-BBCOO in NHL. From June 1986 to December 1991, we treated 57 patients (pts) with unfavorable, NHL negative, intermediate and high grade lymphoma, 26 pts age 18-50, 12 pts age 51-65, 13 pts age 66-75, 8 pts age 76 and older. In addition to these, we treated 56 patients with unfavorable NHL and 39% are alive at a median follow-up of 45 months. These are very promising results for the treatment of advanced NHL. We are now using the combination of m-BBCOO and m-BBCOO-N in NHL and have obtained very good results with a median follow-up of 45 months. This combination is being used in the treatment of NHL and NHL-negative lymphoma, with very promising results.
CONSOLIDATION CHEMOTHERAPY WITH A REMISISON OF THIRD GENERATION IN NON-HODGKIN'S LYMPHOMAS.

Modern chemotherapy regimens obtain high rates of complete remission in non-Hodgkin's lymphoma (NHL), but relapses are still too frequent. The very low local relapses rate in localized NHL treated with chemotherapy alone and the fact that the majority of relapses occur within two years have induced us to carry out an intensification after the achievement of CR. The intensification regimen utilizes high doses of drugs really efficacious (Doxorubicin and Cyclophosphamide) in NHL and other drugs non-cross resistant. We report results on 54 patients (pts) in first CR after 3-5 cycles (median 5 cycles) of the protocol F12 (Doxorubicin 60mg/mq ev. day 1, Vincristine 1,4mg/mq ev day 2 and 9, Bleomycin 10mg/mq ev. day 2, 3 and 9,3, Cyclophosphamide 500mg/mq ev. day 4, 5 and 11-12, Predniason 40mg/mq orally from day 1 to day 12) treated with 2 cycles of chemotherapy regimen F14/85 including Cytoxan 100mg/mq ev. day 1, Doxorubicin 150mg/mq ev. day 1 and 2, Cisplatin 100mg/mq ev. day 4, 5 and 6. Remission rate is 94% (91% CR and 3% PR). Median follow up is 34 months (range 12-91 months). 33 pts are males, median age is 50 years (range 20-69), according to Working Formulation (WF) 24 pts are low grade, 25 intermediate grade and 4 high grade; 34 pts are I/II stage, 19 are asymptomatic, 34 presents more than two disease localizations and 11 pts have bulky disease. There have been five relapses (9%) after a median interval of 19 months (12-30 months). Age and tumor burden have influenced survival and disease-free survival (DFS). Survival (DFS) of 10 patients who relapsed and 84% with a median follow up of 36 months is 100%.

MEP: MITOXANTRONE, ETOPOSIDE AND PREDNISONE - AN EFFECTIVE REGIMEN FOR RELAPSED LOW AND INTERMEDIATE GRADE NON-HODGKIN'S LYMPHOMA (NHL). S.N.Caplan, C.Shustik and G. Bluck. McGill University, Department of Oncology, Montreal, Canada.

Between August 1990 and October 1992, a phase II trial was conducted in patients (pts) with relapsed low or intermediate grade histology NHL to test activity and toxicity of the MEP regimen. Mitoxantrone 10mg/Mq, etoposide 200mg/Mq and prednisone 40mg/Mq were given on day 1, 2, 3 and 7 of a 21 day cycle with a 3 week interval. Of 29 evaluable pts, 13 had low grade and 16 high grade histology (including 6 pts with biopsy proven transformation from low grade NHL). Median age was 65 years (range 36-82). Median time from initial diagnosis was 20 months. Twelve pts had received 2 or more previous chemotherapy regimens and 15 had been treated with an Adriamycin containing combination. Best response to treatment included 6 complete (CR) and 10 partial responses (PR) for an overall response rate of 55%. Median response duration for CR and PR pts was 9+ months. Four pts with progressive disease on treatment and 6 pts with no response or PR have died. The frequency of response was unaffected by histology, number of previous treatments or time from initial diagnosis. Pts who received previous Adriamycin had a CR-PR rate of 40%. Toxicity was primarily hematologic with grade 3 or 4 neutropenia present in 58% of evaluable cycles but only 6 episodes of related infection. Non hematologic toxicity (nausea, alopecia) was mild and infrequent and no cases of cardiotoxicity were observed. MEP is active in NHL with minimal non-hematopoietic toxicity and tolerable myelosuppression, suitable for treatment of older pts, or following relapse on an Adriamycin regimen and of interest to include in a potential non-crossresistant combination.

FULL-DOSE CHEMOTHERAPY IN ELDERLY PATIENTS WITH AGGRESSIVE NON-HODGKIN'S LYMPHOMA. N. Eidelberg, N. Haim, M. Ben-Shahar, D. Paraggi, S. Dror, Y. Cohen, M. Levivot, E. Robinson. Northern Israel Oncology Center, Ramat Medical Center and Bruce Rappaport Faculty of Medicine, Technion, and Department of Statistics, Haifa University, Haifa, Israel.

Prognosis of aggressive non-Hodgkin's lymphoma (NHL) in the elderly is poor. One of the main reasons for this is the tendency to reduce the dosage of chemotherapy agents from the start, in order to avoid toxicity in old age. To establish the feasibility and safety of full-dose Chemotherapy in elderly patients (pts), we analyzed a series of previously untreated pts with diffuse large-cell NHL. A total of 59 pts were included in the study. Median age was 65 years (range 56-75). Pts were divided into two groups: one group of pts received a full-dose CHOP regimen, which included a single dose of doxorubicin (usually 50% of standard chemotherapy (CHOP) and doxorubicin (A) from the start in elderly pts judged to be "poor risk" because of their old age. In addition, there was an upper limit of total dose of 2 mg for vincristine (V). Between 1990 and 1995, 17 comparable pts (median age 72, range 66-86, 59% stage III-IV, 41% stage IV) were treated. Of those, 14 pts (82%) achieved a CR or PR, and 3 achieved a PR. However, a total of 6 pts died of toxicity during the course of full-dose chemotherapy. In conclusion, the CHOP-II regimen was well tolerated in elderly pts, and it is feasible to use the full-dose CHOP regimen in elderly pts, as they are able to tolerate high DI with only a moderate increase in toxicity.
Malignant lymphomas rank third (< 10%) among patients presenting to the SCT of Egypt with a higher frequency of unfavorable histologic types and advanced disease stage at presentation when compared to patients in Europe and the U.S.A.

We have previously reported on the use of the standard BEPP regimen for treating Egyptian NHL patients. A retrospective analysis of this study suggested that dose intensity is important to the final treatment outcome. Based on these findings and the questionable superiority of third generation chemotherapy regimens for NHL, we have conducted a collaborative phase II clinical trial for patients with advanced stage II and III NHL in which a more intensive BEPP regimen was used. In this protocol, each cycle of drugs was administered at the same doses but over a 3 week rather than a 4 week period i.e. there was a 25% increase in dose intensity. (Vinblastine 1.4 mg/m², ifosfamide 40 mg/m², cyclophosphamide 650 mg/m², all IV day 1 & 8, Bleomycin 10 mg IV day 1 & 15, Procarbazine 60 mg PO days 1-21).

The study included 80 patients, 59 males and 21 females with a median age of 21 yrs. Their ages ranged between 16 and 68 years (median 41.5). Fifty seven patients had grade II and 23 had grade III histological subtypes. Four patients presented with stage I, 31 with stage II, 51 with stage III, and 18 with stage IV disease. The number of courses ranged between 1 and 10 (median 4). Complete and partial remissions were achieved in 54 and 4 available patients (67% and 5%, respectively. Actuarial one year overall and disease free survivals are 26% and 6%, respectively.

We have also studied the effects of IFN and IFN plus DCA on both NHL and HL patients. We have found that IFN alone or in combination with DCA can be used as an induction therapy. The combination of IFN and DCA is currently under clinical trial in the European Organization for Research and Treatment of Cancer.

While data are still preliminary, our more intensive BEPP regimen achieved the best results reported for treatment of NHL patients in Egypt. Therefore, we are currently studying a more intensive BEPP regimen for NHL patients with 3-year disease free and overall survivals of 76% and 80% respectively.

Since January 1986 we have been treating pediatric non-Hodgkin's lymphoma with a long-term combination chemotherapy, in far less patients than their counterparts in the U.S. and in 6 years, patients were classified as low risk if all of the abdominal tumor was resected or if there was a single anterior abdominal lymph node mass < or equal to 4 cm from another than the lateral stenosis. All other patients were classified as high risk.

Treatment was with alternating cycles of chemotherapy (AM-1). The low risk received four courses and the high risk eight cycles of therapy. Cycle A consisted of Ara C 1000 mg/m², cyclophosphamide 150 mg/m², vincristine and adriamycin. Cycle B is ifosfamide, VP 16, methotrexate, vincristine and Ara C. Intrathecal chemotherapy with Ara C and methotrexate was given in the first 2 cycles in low risk patients and the first 4 cycles in high risk patients; lost of the patients had abdominal tumors; 75% were classified by surgery when possible and complete resection. The lesions were mainly in the terminal ileum and ileocecal region. All patients tolerated the chemotherapy with no untoward side effects, as regard histopathology 50% of cases had small non-cleaved type of lymphoma, 55% of patients had fibroblast neuropenic epiploic masses (not the appropriate antibiotics). The responses achieved were: 80% complete response, 10% partial response, and 2% no response. Follow up of patients for up to 5 years thus far, there is no evidence of tumor recurrence, and no chronic irradiation, so no further untoward sequel.

The most important result of this treatment is the presence of complete response and prolonged complete response so as to be achieved, with long duration.
leucopenia (4.3 x 10^9/L) during therapy in each group. All the side effects were mild and tolerable.

COMMENT There were two more drugs included in ODP-MAN protocol than those in COP and COP-MAN. Perhaps it's why an improved result could be obtained in ODP-MAN group. It may be suggested that ODP-MAN regimen could be accepted as a conventional regimen for NHL. Due to the small population in this study, a further observation is required for a definite conclusion of ODP-MAN effectiveness in NHL.

A BRIEF INTRODUCTION OF PEANGYANGYNIC Peangyangynic is a unique medicinal developed in China, which is produced from Strophymys peangyangynicus sp. isolated from soil at Peangyang county of Sichuan province in southeast China. Components of Peangyangynic are quite similar to those of Bleomycin with a dominant A6 which possesses higher anti-neoplastic activity, broader anti-tumor spectrum and lower toxicity (esp. pulmonary toxicity). In addition to lymphoma, Peangyangynic is indicated for a variety of malignancy with mild damage to hematopoietic and immune systems.

T 194 INDUCTION AND CONSOLIDATION THERAPY FOR NON-HODGKIN'S LYMPHOMA (NHL) IN CHILDHOOD
D. Bajakova, Z. Kamari, R. Abdullaev
Khirgis Research Institute of Oncology and Radiology, Blaznek 720064, Kyrgyzstan

Treatment of childhood NHL is aimed to the maximum obliteration of tumor cells at the initial stage of the disease, i.e. at the period of induction and consolidation therapy. Just during this period, if the treatment has been inadequately performed, especially in children with the unfavourable prognosis, frequent relapses occur with the subsequent progression of the disease. Twenty-two NHL children at 3 to 15 years of age were treated at the department of pediatric oncology. All children had the unfavourable prognosis: a large tumor, lymphoblastic variant of a tumor process, intoxication symptoms presented as anaemia, sweating, fever. The treatment consisted of induction, its consolidation and reinduction. The induction therapy was given with the AAGP regimen (cyclophosphamide 1,000-1,500 mg/m^2 + vincristine 1.4 mg/m^2 + adriamycin 50 mg/m^2 + prednisolone 2-3 mg/kg, weekly, for 6 weeks), intrathecal methotrexate (15 mg) and ara-C (20 mg) were administered for prophylaxis of CNS involvement. Consolidation therapy was given 10 days after cessation of induction and consisted of ara-C (100 mg/m^2) plus leucovorin (10,000 U/m^2) and methotrexate (1,000 mg/m^2) administered intravenously with leucovorin (10 mg). The cranial radiation (total dose of 15 Gy) was performed for prophylaxis of CNS involvement. As a result of treatment, 17 patients (77.3%) achieved complete remission, 3 patients (14.3%) - partial remission, 2 patients died of disease progression. Mostly children tolerated combination chemotherapy in standard and high doses satisfactorily. The side-effects were reversible. The intensification of regimens for patients with risk factors allowed to improve the treatment outcome.

T 195 RESULTS OF A TREATMENT OF CHILDREN SUFFERING FROM NON-HODGKIN'S LYMPHOMA (T-Y 1)
Hematology-Oncology Department Children's Clinic Zagreb, Croatia

At the Hematology-Oncology Department Children's Clinic Zagreb, Croatia, 78 children (average age 7.8 years) were treated for non-Hodgkin's NHL (T-type, lymphoblastic histology) from 1977 till 1990. Three different protocols were used - Protocol YU-77 (1.01.1977 - 31.12.1983; 35 children), Protocol YU-B4 1.01.1990 - 31.12.1996; 15 children), Protocol YU-87 (1.01.1987 - 31.12.1995; 28 children). The first complete remission was achieved in 29 patients (82.2%) treated with Protocol YU-77, in 4 patients (12.7%) treated with Protocol YU-B4 and in 4 patients (12.7%) treated with Protocol YU-87; the differences are statistically not significant (p>0.05). The first hematological relapse was observed in 7 patients (20.6%) treated with Protocol YU-77 and in 2 patients (6.5%) treated with Protocol YU-B4; the differences are statistically significant (p<0.05). The first meningeal relapse was observed in 3 patients (8.5%) treated with Protocol YU-77 and in 1 patient (6.6%) treated with Protocol YU-B4; the differences are not statistically significant (p>0.05). The first local relapse was observed in 3 patients (8.5%) treated with Protocol YU-77 and in 3 patients (10.7%) treated with Protocol YU-87; the differences are not statistically significant (p>0.05). The first hematological and testicular relapse was observed only in 1 patient (3.3%) treated with Protocol YU-87; the differences are not statistically significant (p>0.05). Survival probability of 60 months for patients treated with Protocol YU-77 was 48.6%, for patients treated with Protocol YU-B4 66.7%, and for patients treated with Protocol YU-87 87.5%; the differences are statistically significant (p<0.05). The best results were achieved with Protocol YU-87 and they do not differ essentially from those achieved in other similar European Centres.
ABSTRACTS - Fifth International Conference on Malignant Lymphoma, Lugano

T 196 COPP CHEMOTHERAPY FOR ELDERLY PATIENTS WITH INTERMEDIATE AND BAD-PROGNOSIS NON-HODGKIN'S Lymphoma. Luana M. Tod D, Chan TK, Chiu E, Lie A, Ho F.

Departments of Medicine and Pathology, University of Hong Kong, Queen Mary Hospital, Hong Kong.

The efficacy of COPP chemotherapy (Cyclophosphamide 450 mg/m² IV D1 & 8, Vincristine 1.4 mg/m² IV D1 & 8, Procarbacline 100 mg/m² IV D1-4 and Prednisone 40 mg/m² PO D1-4) as the treatment of elderly patients with aggressive non-Hodgkin's lymphoma was evaluated. 141 consecutive patients above and 72 below the age of 60 years with previously untreated intermediate or high grade non-Hodgkin's lymphoma were included. The elderly patients were treated with the COPP chemotherapy regimen. The younger patients, at or below the age of 60, received a doxorubicin containing regimen (119 had CHOP, 63 had BACOP and 47 had ABACO). The patients characteristics of the two groups were comparable. The clinical outcome was shown in the following Table. Stage II-III patients receiving COPP had significantly worse results.

The Clinical Outcome:

<table>
<thead>
<tr>
<th>Stage</th>
<th>COPP Chemistry</th>
<th>Stages Containing Regimes</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>CR rate</td>
<td>13/17 (76%)</td>
<td>27/31 (87%)</td>
</tr>
<tr>
<td></td>
<td>Relapse</td>
<td>1/3 (33%)</td>
<td>2/27 (7%)</td>
</tr>
<tr>
<td>5-yr DFS (CR pts)</td>
<td>89%</td>
<td>82%</td>
<td></td>
</tr>
<tr>
<td>5-yr Survival</td>
<td>76%</td>
<td>78%</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>CR rate</td>
<td>19/19 (100%)</td>
<td>26/36 (72%)</td>
</tr>
<tr>
<td></td>
<td>Relapse</td>
<td>2/30 (6%)</td>
<td>6/36 (18%)</td>
</tr>
<tr>
<td>5-yr DFS (CR Pts)</td>
<td>61%</td>
<td>72%</td>
<td></td>
</tr>
<tr>
<td>5-yr Survival</td>
<td>34%</td>
<td>54%</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>CR rate</td>
<td>14/23 (61%)</td>
<td>49/81 (60%)</td>
</tr>
<tr>
<td></td>
<td>Relapse</td>
<td>2/22 (9%)</td>
<td>40/76 (55%)</td>
</tr>
<tr>
<td>5-yr DFS (CR Pts)</td>
<td>73%</td>
<td>78%</td>
<td></td>
</tr>
<tr>
<td>5-yr Survival</td>
<td>32%</td>
<td>45%</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>CR rate</td>
<td>19/27 (70%)</td>
<td>60/107 (56%)</td>
</tr>
<tr>
<td></td>
<td>Relapse</td>
<td>7/18 (39%)</td>
<td>28/46 (60%)</td>
</tr>
<tr>
<td>5-yr DFS (CR Pts)</td>
<td>56%</td>
<td>38%</td>
<td></td>
</tr>
<tr>
<td>5-yr Survival</td>
<td>26%</td>
<td>32%</td>
<td></td>
</tr>
</tbody>
</table>

Multivariate analysis on patients receiving COPP revealed that the independent prognostic variables significantly determining CR rate and survival included clinical stage (p<0.005) and serum lactate dehydrogenase level (p<0.001). There were ten (75%) treatment related deaths. A few nonrandomized series has reported the results of using doxorubicin containing regimens to treat 60-70 year old patients with aggressive NHL. The overall CR rate ranges from 70% to 85% and the long term survival 25% to 35% .


Between October 1988 and December 1990, 60 previously untreated elderly patients aged >60 yrs with aggressive NHL were treated at our Institute with the P-VA BEC regimen. This regimen includes the alternated administration of: Adriamycin (30mg/m²), Etoposide (100mg/m²), Cyclophosphamide (350mg/m²), at weeks 1-2-5-7-9-11; Vincristine (1.2mg/m²), Bleomycin (5mg/m²) at weeks 2-4-6-8-10-12. Oral Prednisone (50mg) was given daily during the entire treatment. Median age was 67 yrs (60-80). Histologic types included 59 diffuse large cell lymphomas and 1 small non cleaved NHL. Nineteen pts had a stage II, 25 IIII, and 16 IV. High level LDH was present in 27 (45%) pts and Bulky disease in 7 (12%) pts. Response was evaluated and treatment completed after 8 (first 26 pts) or 12 (following 34 pts) weekly cycles. Forty-five (75%) achieved a CR, 10 (17%) P-VA B and 5 (8%). So far 21 pts have relapsed (10 CR, 3 PR and 3 pts died while in CR. After a median follow-up of 20 months a overall survival 3 yrs over well survival (80%), DFS and EFS were respectively 55%, 51% and 44%. No statistical difference in DFS, EFS and EFS was observed between the group treated with 8 or 12 cycles. Hematological toxicity was mild in all patients, however a worst neurological and cardiovas- cular toxicity was observed in pts treated with 12 cycles compared to those treated with 8 cycles. Only one toxic death from lung fibrosis was observed.

P-VA BEC chemotherapy is an active and tolerable first line chemotherapy in aggressive NHL in elderly pts. Randomized studies are needed to establish the real advantage of this regimen as compared to standard chemotherapy.

T 198 PEN (Prednisone, Etoposide and Novantrone) FOR TREATMENT OF NON-HODGKIN'S Lymphoma (NHL) IN ELDERLY PATIENTS. P. Goss and the Toronto Lymphoma Group. The Toronto Hospital, Toronto, MSG 2C4, Canada.

Thirty two pts (10 male,22 female) aged 66-92 (med 74) yrs with NHL (Working Formulation C=5,E=1,F=5,G=16,H=5) were treated with PEN 42 days (Prednisone 50mg po x 14 days, Oral Etoposide 50mg po x 14 days and Novantron 20mg po) (1987). Twenty seven pts (66%) had previously untreated disease and 11(33%) refractory NHL (7 non-responders and 4 at relapse). Fourteen pts had stage IV, 14 stage III and 4 stage II disease. Fifteen pts had B symptoms, 3 extranodal disease and 7 bone marrow involvement. Pts with congestive heart failure, current anti-failure medication or pretreatment Muga LVEF of <45% (median 59% (n=19)) were excluded from PEN. Of the 21 evaluable, treatment naive pts 73% (33%) have achieved CR (4.6-8+ wks) and 4(19%) PR (20-52 wks). A further 5 pts (23%) are currently responding for an overall response rate of 75%. Five evaluable pts did not respond. Out of 21 pts, 1 achieved a CR (6.4-8+ wks) and 3 a PR (3.6-6+ wks) and are currently responding. One pt (23%) has not responded and 3 are not yet evaluable. Median survival has not been reached but 24 pts are alive 60-+ wks from the start of treatment. During 135 courses of PEN the median nadir granulocyte count was 0.66 x 10^9/L occurring predominantly in the third (60%) and fourth (28%) weeks of the cycle. Seven pts had a granulocyte nadir <0.5 x 10^9/L during at least one cycle, 4 of whom had bone marrow involved with disease. Platelet nadir of <100 x 10^9/L occurred in only 2 previously untreated and 7 previously treated pts. Five episodes of febrile neutropenia requiring hospitalization occurred in 4 pts during the third and fourth weeks. Achieved the CR for 2 second cycles. No treatment related deaths occurred. Non-hematologic toxicity was minimal with mild nausea, alopecia and fatigue being the commonest symptoms. In summary PEN is an active, well tolerable ambulatory care regimen for elderly pts with NHL. Enrolment on this trial continues.

Supported by Lederle Lab., Cyramd & Bristol-Myers Squibb (Canada)


"New York Medical College, Valhalla, NY.

Age has been shown to be a negative prognostic factor in patients with non-Hodgkin's lymphomas (NHL). This may be due to the patients inability to tolerate standard therapies. A new active regimen has been developed with low toxicity to allow therapy with reasonable dose intensity, good patient tolerance and maintains quality of life. The eligibility requirements are: age > 65 yrs; stage III or IV intermediate-high grade NHL. CALGB PS 0-2. T and N are escalated by 25% each cycle until nadir AGC (indicated granulocyte count) <1000µl and are de-escalated 25% if nadir AGC ≤1000µl and patients are symptomatic (i.e. fever). Drugs are given every 21 days. Two pts have dose escalation without growth factors. 9 pts. have been entered. Patients: 8 females/1 male, mean age 78.1 yrs. (median 77, range 68-87).

Thiophosphate: diffuse mixed-1; large cell-8. Extranodal disease in 5 patients in 6 sites (stomach-2, liver-1, small bowel-1, skin-1, lung-1). 7 pts are evaluable for response and toxicity with a median follow-up of 9 months. 6/7 pts responded to therapy (2-CR/4-PR); 1 stable disease. The 4 PR had a greater than 90% regression of all measurable lesions. No pt. had grade 3/4 non-hematologic toxicity. Grade 1/2 toxicity consisted of nausea, vomiting, mucositis, constipation, neurotoxicity. T-NOP is a highly active regimen in this group of elderly patients. The drugs can be administered safely with acceptable toxicity. Further follow-up is needed to fully assess its efficacy.

Based upon our previous experience with COMLA/ABP in which we found Cyclophosphamide (CTX) to be the most active agent, we treated 12 elderly patients (pts) with newly diagnosed Non-Hodgkin's Lymphoma with escalating doses of CTX since 1989. The goal was to determine the maximally tolerated dose of CTX in COMLA/ABP in an attempt to improve response rate without increasing toxicity in older pts. The regimen included CTX 1.5 - 3 g/m^2 (with meqna), Vincristine 2.0 mg/d, 8 - 15, Prednisone 29 + 36, and Adriamycin 50 mg/m^2 d 4, Bleomycin 10 units/m^2 d 4, 50 + 57, and Prednisone 60 mg d 43 + 47). The initial dose of CTX was 3.0 g/m^2 except in pts older than 70 who received a dose of 1.5 g/m^2.

Prophylactic Cytosaromycin was initiated on day 8 (500 mg BID) until recovery of the neutrophil count over 500/m^3. The median age of the pts was 62 yrs (range 31-73 yrs). Histologic diagnoses include diffuse large cell (8 pts), immunoblastic, 1 nodular large cell, 1 diffuse mixed and 1 diffuse, small lymphocytic; 7 were Stage IV, with bone marrow involvement in 4 pts, 1 pt with spleen, 1 pt with liver and 1 pt with lung involvement; 2 pts were stage III and 3 pts had stage II. Complete remission was obtained in 7 pts (58%); partial remission in 3 pts; 1 pt progressed. One pt was lost to follow-up. With a median follow-up of 25 months, 8 pts are alive and 6 pts are free of disease. There was one toxic death due to pulmonary edema and myocardial necrosis. Two pts had neurologic complications; otherwise the regimen was well tolerated. The maximum dose of CTX given so far is 4 g/m^2. We have not observed any grade 4 toxicity with regards to WBC nadir (median 0.6/mm^3, range 0.2-1.1), and platelet count (median 45, range 29-122). No pt required blood transfusions. No bleeding complications were observed. None of the pts required hospitalization for neurosarcopic. Even in the absence of growth, factors high doses of prophylactic chemotherapy are administered safely. No pt developed hemorrhagic cystitis or vincainduced grade III or IV neurotoxicity. The treatment was well tolerated by pts up to age 73 with no grade IV toxicity and could be continued in the COMLA/ABP combination.
ABSTRACTS - Fifth International Conference on Malignant Lymphoma, Lugano

T 204  HIGH-DOSE THERAPY WITH AUTOLOGOUS BONE MARROW TRANSPLANTATION IN NON HODGKIN LYMPHOMA. OVER 50 YEARS OF AGE: THE CENTRE LEON BERARD EXPERIENCE.  T. Philip, P. Biron, J.Y. Blay, E. Boulou, D. Frappaz, T. Philip - Centre Leon Berard, 64, rue Lafayette 69371 LYNX Cedex 08 - France 25 patients, 50 year old or over, with bad prognosis lymphoma (18 males, 7 females, median age 55 (50-70) treated were by intensive regimens with autologous bone marrow transplantation between 1982 and 1992.  Patients/Method :  Diagnosis: 2 patients high grade lymphomas, 18 pts intermediate grade and 5 low grade lymphomas. - No CNS involvement was found at diagnosis except for 2 intracranial intermediate grade lymphomas (one cerebral, one cerebral meningial) and 8 pts had bone marrow (BM) involvement (4 follicular, 4 intermediate grade).  Status at graft was: - one resistant relapse in the patient with cerebral lymphoma. - one first complete remission (CR) in one patient with very large mediastinum mass (111 cm). - 6 pts in V.G.P.R. - 6 pts in 2nd or subsequent CR - 11 pts in sensitive relapse  BM purging : - was done according to immunophenotype by complement mediated lysis and monoclonal antibodies (6 pts), Astra-Z (1 pt), not done in one patient where BM was positive at time of harvest.  Intensive regimens were: - 12 BEAM, 6 BEAC, 2 CBV (1 patient was diagnosed as Hodgkin at time of relapse), 1BACT, 3 Cyclophosphamide and THI, 1 hyperfractionated THI.  Results: 3 toxic deaths occurred at day 94 aplegiculosis, 20 hemorrhage and sepsis, 45 isolated thrombocytopenia. at first evaluation (60 days) : 19 pts were in CR (7 continuous CR), 1 NR, 2 P.R. at 1992/12/31 : - 5 pts died in relapse (2,6,18,24 months after graft). - 1 pt succumbed in CR 3 years after graft. - 14 pts are alive : - 4 pts are in relapse - 12 pts are presently disease free. Among the 5 patients grafted for low grade lymphomas: one is in CR + 2 months after graft, one is in relapse, 4 are in CR - 22 months after graft. Among the patients grafted for high or intermediate grade, 4 are in remission, 8 are in relapse, 8 CR with a median of 58 months (18-122). Recovery was : WBC > 10000 : 23 d (13-40) - N < 5000 : 21 (13-500) PR : 50-000 : 21 (13-500) Conclusion : In 50 year old and over patients grafted, toxic death rate and morbidity is not different from younger patients. Results are similar.  

T 206  VYNDESINE AND BLOMYCINE IN DIFFERENT COMBINATIONS AS SALVAGE TREATMENT IN NON HODGKIN LYMPHOMAS (NHL) G. Hopfinger-Limberger, R. Heinz, B. Schneider*, M. Miedl, R. Waldner, E. Piétraux. 3rd Medical Department and Ludwig Boltzmann Institute for Hematology and Leukemia Research, Hanusch Hospital, Vienna, Austria.  Institute for Medical Statistics, University of Vienna, Austria. Although great progress in the treatment of non Hodgkin lymphomas has been made, salvage chemotherapy is still necessary for patients with a refractory or relapsed course of disease. The drugs recommended in most published schedules have considerable toxicity and poor long term benefit for patients. In this study, we retrospectively analyzed data of 100 patients treated between 1/85 and 5/92. The median age was 59 years (range: 21-88y). 9 pts. suffered from low grade, 46 from intermediate and 45 from high grade NHL (Rai classification). Ann Arbor classification was I-II, III/IV, III/IV and IV/IV pts. 20 pts. received only blymycine/15mg/kg and vindesine/5mg/kg, 11 pts. in 41 pts. blivy was combined with mechthretaxate (30 mg) and asparaginase (10 000 IE), in 23 pts. blivy was administered with alkylating drugs and in 8 pts. blivy was combined with cis-platinum; in 8 pts. VIM-schedule (VP-16, mitoxantrone and ifosfamide) was alternately applied to blivy. Infusion duration was < 4hrs in 18 pts, 4-8 hrs in 47 pts and 12-24 hrs in 35 pts. Total number of cycles was 430. Hematological toxicity was mild, even in patients with impaired bone marrow function. No pulmonary toxicity or alopecia was observed. Pts. receiving medium term infusion duration showed a trend to better survival. The overall response was 40/100 pts. (CR: 14 and PR: 26) with a median duration of 21 months (3-150m). Response to Preop Chemotherapy Relapsed Refractory  CR 32 6 6 20  N 6 6 20  PR 68 8 20 40  

T 205  IFOSFAMIDE, MITOXANTRONE AND ETOPOSIDE AS SALVAGE THERAPY IN NON HODGKIN LYMPHOMAS G. Hopfinger-Limberger, R. Heinz, E. Holler, B. Schneider*, E. Piétraux, III Medical Department and Ludwig Boltzmann Institute for Hematology and Leukemia Research, Hanusch Hospital, Vienna, Austria.  Institute for Medical Statistics, University of Vienna, Austria. Although several therapeutic approaches to conventional salvage therapy in NHL have been made response is usually poor. The combination of etoposide, ifosfamide and mitoxantrone showed a high effectiveness in relapsed and refractory NHL. During 1986 and 1992, 56 patients (35 males, 21 females) with a median age of 66 years (range 18-89 years) were treated with a combination of etoposide (100 mg total dosage), ifosfamide (1g total dosage) and mitoxantrone (3mg/m2/given on three consecutive days. Matura was given as proprotection. Stages according to the Ann Arbor classification were I/II, I/II/III/IV/38 patients. 33 patients suffered from high grade, 23 from intermediate grade NHL. Toxicity according to the WHO recommendation was as follows: Anaemia grade I was observed in 10 patients. Leukopenia grade I/2 patients, grade II/1 patient and grade IV/4 patients. Thrombocytopenia was not observed. High grade NHL showed a better response rate (18/33 patients) compared to the intermediate grade NHL 1 (723 patients). Overall response was 41% (12 CR and 11 PR) with a median duration of 8 months (range: 4-17 months). In conclusion, the combination investigated has mild toxicity even in heavily pretreated and elderly patients. The overall response of 41% might be improved by increasing dosage using growth factor support.  

T 207  SALVATURE TREATMENT OF MALIGNANT LYMPHOMAS, NEW COMBINATION OF IDARUBICIN+THIOTEPA+CARBOPLATIN-PREDNISONE, PILOT STUDY. M. Sooko, E. Lusante, G. Quintini, M.G. Lipari, F. Forrorto, R. Perrico, R. V. Abbedessa and A. Cagnozzi, Chair of Haematology Palermo. A great percentage of patients with malignant lymphomas shows disease relapse after complete remission (R.C.). This event has a relation with some unfavorable prognostic variables and particularly with a big neoplastun bulk. Another problem of first line treatment failure should be the phenomenon of spontaneous mutations that take to the cellular resistance against some antineoplastic drugs. This is the starting point to develop a polichemotherapeutic association with no-cross-resistant drugs. We report preliminary results of a pilot study about a polichemotherapeutic association for treatment of patients with relapsed or resistant malignant lymphomas. We till now enrolled 18 patients (12 males, 6 females, with an age range of 18-70); 5 patients with NHL, with different Ann Arbor stages and histological types; 13 with W.H.L. intermediate and high grade of disease. The schedule of treatment consist of: IDARUBICIN 10mg/m2/i.v. (day 1); THIOPLATIN 20mg/m2 (day 1 and 5); CARBOPLATIN 300mg/m2 (day 1); PREDNISONE 100mg (from day 1 to 5). We foresaw 6-8 cycles of treatment with 3 weeks interval. All 18 patients enrolled were evaluable. Approximately 55% (10) of patients respond to this treatment (5 E.C., 5 R.P.). We noted in approximately 27% (5) of patients a stabilization of disease and finally a failure in 18% (3) of patients because of disease progression. One patient died (3 cycle) due to gastrointestinal occlusion caused by underlying gastrointestinal disease. We observed low grade hematological toxicity (WHO I-II), while extrahematological toxicity was practically absent, with the exception of a cutaneous erythma-blisters-hemorrhage of ileum seat of treatment. In conclusion these preliminary results show effectiveness of proposed association: in terms of responder patients, considering that our case includes patients in 2nd & 4th relapse, in terms of good toleration considering heavy previous treatment. This new association should pave the way for further therapeutic progress also in first line treatment.  REFERENCES:  -T.Tomimaga et al.: Early phase IT study of Nabulbine (Vinorelbine). -H.Yamamoto et al.: A phase I study of Nabulbine (Vinorelbine) combined with cipletalin in non small cell lung cancer. -C. Ferre et al.: Re缆en--rezl, ifosfamide, Nabulbine, Etoposide, as salvage therapy for refractory or relapsed Hodgkin's disease. -F. Fabre: Nabulbine (Vinorelbine): Basic information.
T 208

OXALIPLATIN (L-OHP®) - A NEW PLATINUM ANALOG ACTIVE IN REFRACTORY/RELAPSED INTERMEDIATE AND LOW GRADE NON-HODGKIN LYMPHOMA (NHL): A PHASE I/II STUDY.


From 7/88 to 8/92, 22 patient(s) with refractory or relapsed NHL, and suitable for high dose chemotherapy were treated with single agent L-OHP®, a 3rd generation platinum compound. Patients characteristics: 12 males, 10 females. Median age: 58 yrs (36 - 79), PS(W.H.O.) grade(0) 0 = 10, 1 = 8, 2 = 3, 3 = 1. Etiological treatment: Refractory: 19 Relapse: 3. Number of prior therapeutic regimens: median: 2 (1-5). 4 pts were previously treated with CDDP, 10 pts with Vinc-Aldophosphate. Prognostic features: 8 pts in stage II/IIA, 7 in stage IIIB, 7 in stage IV. L-OHP was given as: 100 mg/m² q.4.w. for 15 pts, 130mg/m² q.3.w. for 15 pts. 135 cycles were delivered. Median do of cyclophosphamide: 4 (1-26). Median total dose: 390mg/m² (100-1950). Results: Major responses were observed in 2/4 pts in CR. Overall response (CR+PR): 12/22 pts (54%). CR: 2/22 pts (both low gr.). PR: 7/22 pts (4/intermediate gr., 3/low gr.). Response duration: Median: 14 mos(3-40). Progression free survival: 12 months (median). No responses were seen in CLL nor in the high grade NHL pts. PRs were observed in 3/4 pts with primary gastro-intestinal NHL and in 1/4 pts pretreated with CDDP. Toxicity: (W.H.O.): Gr 3 - neurolgic: reversible dysethesia in 4/133 cycles, gr 4 - hematologic: 3/133 cycles. 1 pt presented a reversible anaphylactoid reaction, 1 pt refused to continue the treatment. Conclusion: L-OHP® is an active agent in refractory/relapsed intermediate and low NHL. Its safety profile (devoid of retoxicity and minimal hematologic toxicity) makes of L-OHP® a good therapeutic alternative is heavily pre-treated patients and a potential compound for first line combination chemotherapy.

T 210

SECOND LINE TREATMENT IN RELAPSEING OR REFRACTORY MALIGNANT MELANOMA: PATIENT'S PROGNOSIS, RESPONSES, AND SURVIVAL.


Treatment of relapsing or refractory intermediate or high grade NHL patients remains controversial. The majority of studied schemas, produced documented CR in about 30% of patients, usually transitory. Late response rates were about 10% in patients, have been shown to efficaciously fight advanced disease. In this study, we present the results of an out-patient based polychemotherapeutic schema, as follows:

- Carboplatin 80 mg/m² days 1 to 5.
- Mitomycin 0.1 mg/m² days 1 to 5.
- Prednisone 40 mg/m² days 1 to 5.
- Etoposide 140 mg/m² days 1 to 5.

Cycles were repeated every 28 days until CR (maximum 4 cycles) or 4 consecutive cycles. Dose were adjusted according to hematological counts. From 1/89 to 8/92, 28 patients were treated (10 refractory and 18 relapsed). Patients characteristics were as follows: males/females ratio 17/11, mean age 53.3 years (range 31-65 yrs), mean PS 1 (range 0-2), 22 cases presented with extranodal disease. A bulky disease was noted in 10 cases; B symptoms were present in 13 cases.

The schema was a good chemotherapeutic regime and 9 patients received 2 different therapeutic schemas. All patients received previous doxorubicin therapy. A CR was noted in 11 patients (39%) and 8 (28%) reached PR. MDWI was 11.3 months for responding patients. The most common side effects were bone marrow depression (grade 2 leucopenia, grade 3 43%). One episode of grade 3 infection was recorded.

We conclude that these chemotherapeutic regimen seems to be an effective therapeutic schema with acceptable toxicity and should be studied in the treatment of relapsing or refractory ML.

T 209

ORAL ETOPOSIDE ADMINISTRATION OVER A PROLONGED SCHEDULE FOR PATIENTS WITH NON-HODGKIN'S LYMPHOMA (NHL) AND CHRONIC LYMPHATIC LEUKEMIA (CLL). N. Shahali, O. Bairy, S. Shahali, D. Bliekstreit, Department of Hematology, Holon Medical Center, Tel-Aviv University, Tel-Aviv, Israel.

Twenty patients with NHL and CLL were treated over a long term with daily oral etoposide. 16/20 had NHL, 18/20 were pretreated with 2 or more different polychemotherapy regimens. Etoposide was incorporated in the regimen of 11 patients. Etoposide was the first treatment in two elderly patients who were excluded from polychemotherapy because of advanced age. Etoposide was administered at 50 mg/m² per day for 5 consecutive days or as long as myelosuppression permitted. Treatment was repeated every 28 to 35 days for a total of 3 courses. The median age was 65 years, range 60-80 years, 11 were males. The 4 patients with CLL were in stage 4 according to Rai classification. 12/16 patients with NHL were in stage IV, 3 were in stage III and one was in stage II. 9/16 NHL patients had bone marrow involvement. 8/20 patients had bulky disease. 13/20 patients responded to treatment, with an overall response rate of 65%. Complete response (CR) was observed in 2 patients, partial response (PR) in 11 patients 55%, stable disease in 2 patients 10% and progression of disease in 5 patients 25%. The response rate of patients with high and intermedi-ate grade lymphoma, low grade lymphoma and CLL were 69%, 66% and 50%, respectively. Patients with bone marrow involvement had a better response rates 76% than other patients 42%. All patients who were treated with a cumulative dose of etoposide of 2 g/m² or more were responded to treatment. Only 405 of the patients who were treated with a cumulative dose of 1 g/m² or less responded to treatment.

The main toxicity was myelosuppression, 50% of patients developed neutropenia, 38% developed thrombocytopenia, 35% developed anemia, 35% developed leucopenia.

Following complications were observed: alopecia, gastrointestinal manifestations, headache and dizziness. These results suggest that daily oral etoposide has a high level of activity even in patients with NHL and CLL, who were exposed to etoposide in other regimens. Daily oral etoposide over a long term may be used as salvage type approach in NHL and CLL. Dose modification is suggested in elderly patients and in patients with bone marrow involvement.

T 211


Previous single and multi-institutional studies in aggressive histology lymphoma reported complete response rates with PRO-MACE-CYAMIR comparable or superior to conventional combination chemotherapy. Such combination chemotherapeutic regimens are neurotoxic, causing compromise intended dose intensity and may impact adversely on therapeutic efficacy. In this open label phase II/III trial, 35 evaluable patients with untreated stage I/II intermediate grade or immunoblastic lymphoma were treated with PRO-MACE-CYIRIRG (4/24) and in 2004 in dose escalation, for ANC<2000 and/or platelets <100,000 and dose modification of day 8 and ara-C for platelets <100,000. Cohort 1 patients received conventional dose chemotherapy without Filgrastim, while patients in other cohorts, except 2A received Filgrastim 5ug/kg sc qd from d2 until postradiol ANC>2000 on 2 consecutive deaminations. Cohort 2A patients did not receive Filgrastim on d8 to avoid concurrent administration with chemotherapy. Twelve patients were > 60 years and 43% had stage IV disease with 7/33 BM positive. The table shows incidence and duration of grade 4 neutropenia for cycle 1 and cycles 2-6 in successive cohorts.

Filgrastim enhanced the rate of neutrophil recovery evidenced by d 14 ANC levels. The increased incidence of neutropenia in cohort 2A was attenuated in cohort 2B when Filgrastim was administered on Day 8. No adverse effects on platelets were attributed to Filgrastim, however, at the higher escalated chemotherapy doses in cohorts 4 and 5 the incidence of grade 4 thrombocytopenia (<25) of median duration <1 day was higher than in cohorts 4 and 3. The results indicate that Filgrastim can be safely administered concomitantly with d8 chemotherapy in this regimen and that maximum tolerated dose has not been reached at cohort 5. Further escalation of doxorubicin and cyclophosphamide is feasible with Filgrastim support.