T 141 MULTICENTER COMBINED CHEMOTHERAPY PROTOCOL FOR YOUNG PATIENTS TREATMENT OF LOW GRADE NON HODGKIN'S LYMPHOMA.

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PURPOSE : a prospective trial with a new combination of cyclophosphamide, doxorubicin, vindesine, prednisolone and bleomycine (CHEP-BLEO) devised for patients with low grade non-Hodgkin's lymphoma (NHL) in the Kiel classification, was undertaken.

PATIENTS AND METHODS : between 1984 and 1991, from 5 hematological french centers, 34 consecutive unselective patients (median age : 48 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 diagnosis were as follow : lymphocytic lymphoma (1 case), centrocytic follicular small all cleaved (9 cases), centrocyto-centroblastic follicular (15 cases) and centrocytic diffus (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, vindesine 3 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 lymphoïd irradiation (1 case) were performed.

RESULTS : among the 32 assessable patients, the objective response rate was 90% ; 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 thrombopenia (rares 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 paralysis (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 onset, % were free from relapse. The 7 partial response patients and the 3 stable disease patients e treated either by chemotherapy alone (4 cases) either by interferon α alone (1 case) or by both treatment (4 cases). Three autologous (1 death, 1 relapse and 1 CR) and one allogeneic (alive 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 PREDNIMUSTINE

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39 patients with low grade non-Hodgkin's lymphoma refractory to chlorambucil and prednisolone were treated with prednimustine, 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 prednisolone 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 prednisolone. Of the 39 patients treated with prednimustine, 18 were female and 21 were male. Median age was 63 years (range 38-85 years), and the histology was CLL in 20 patients, immunocytoma 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%, 95% confidence interval 27%-59%) had an objective remission (5 CR, 10 PR). Median time to progression was16 weeks for all 35, and 32 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 the 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 prednimustine in low grade NHL goes beyond that of chlorambucil and prednisolone at a manageable level of toxicity.

T 143 TOTAL BODY IRRADIATION (TBI) AND PREDNIMUSTINE (PDM) IN ADVANCED LOW GRADE NON-HODGKIN LYMPHOMAS (NHL).

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Little data are available on TBI followed by chemotherapy in low grade NHL. From January '84 to September '92 41 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) nger than 65 years (yrs) median age was 55 yrs (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 ≤ 70 in 5 pts, 80 in 13 pts and 90 in 23 pts.

Treatment: TBI (6 MV linear accelerator 150 cGy/10 fr/ 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 (PRO) in 2 (5%). Toxicity was acceptable; high grade (3-4 WHO) thrombocytopenia in 19%, anaemia in 2% and leukopenia 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 (≥65 vs <65), stage (III vs IV), PS (≤70 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.

T 144 PENTOSTATIN (2' DEOXICOFORMYCIN, dCF) IN PATIENTS (pts) WITH MALIGNANT LYMPHOMAS: A PHASE II STUDY OF THE EORTC EARLY CLINICAL TRIALS GROUP.

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From February 1988 to June 1992, 45 pts with non-Hodgkin's lymphomas (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 dCF. The pts were selected for pretreatment with no more than 2 chemotherapeutic 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 dCF 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: 5 partial responses were observed (2/13 low grade NHL, 3/16 high grade NHL). The median (range) duration of responses was (weeks) 36 + (13-115). The only evaluable 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 platelets 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) 1-2, 2 g 3; 2 constipation g 1-2; 4 reversible pneumonia g 1-2; 6 conjunctivitis g 1-2, 2 g 3; 3 skin toxicity g 1-2, 1 g 3; 2 lethargy g 1-2; 3 renal g 1-2, 2 g 3; 2 infection g 1-2, 1 drug fever g 1-2, 2 tachycardia g 1-2. In conclusion, low dose dCF 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 ocular 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.

T 145 INTERFERON-ALPHA2b TREATMENT FOR EARLY PHASE CHRONIC LYMPHOCYTIC LEUKEMIA - FIRST RESULTS OF A RANDOMIZED MULTICENTER AIO-STUDY WITH RISK ADAPTED STRATIFICATION.

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B-cell chronic lymphocytic leukemia (B-CLL) is known to have a very variable clinical course. About one third of patients in the early phase (stage Binet A) expects a disease progression within two years after diagnosis. The aim of our study was to identify stage A patients at risk for an early progression and to treat this group in a randomized multicenter study with interferon-alpha2b (IFN-a2b). The endpoints of this IFN-treatment study were freedom from progression and/or chemotherapy, and overall survival. The following prognostic factors were evaluated: 1) Diffuse bone marrow infiltration (DBMI), 2) serum thymidine kinase (TK) levels > 5 U/l, and/or 3) a leukocyte doubling time (LDT) < 12 months. Patients with DBMI and a TK > 5 U/l, and/or LDT < 12 months were randomized into either a treatment group (arm A) which received IFN-a2b at a dose of 3 x 5 Mill. I.E./week, or a "watch and wait" 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. Additional studies were performed to quantify the expression of various surface antigens on lymphocyte subpopulations under the influence of IFN-a2b treatment. Up to now 110 patients in seven centers have been recruited in this study (arms A, B, C). In the vast majority of patients randomized into arm A the treatment with IFN-a2b was well tolerated. In arm C (no risk factors) the median time to progression was > 17 months, in arm A and B 12.5 and 13.3 months respectively (p = 0.03; arm C vs. arms A/B). Patients with more than one risk factor exhibited a significantly higher risk of progression as compared to those patients showing only one of these factors. Our results seem to prove the validity of the risk parameters chosen to identify a "high risk" subgroup within stage A patients. Furthermore both the serum thymidine kinase and the leukocyte doubling time seem to represent independent factors not linked to each other. It is still too early to evaluate the possible benefit of IFN-a2b treatment for the "high risk" stage A patient group with regard to time to progression and longterm survival.

T 146 IMPACT OF INTERFERON INTEGRATING CHEMOTHERAPY AND AS MAINTENANCE ON MULTIPLE MYELOMA. PRELIMINARY RESULTS ON A MULTICENTER STUDY OF ITALIAN NHLCSG.

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In 1990 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. Accordingly, 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 response rate was 60%. Sixty-two percent of 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 on relapse rate, both in good and poor prognosis patients. Neverthless 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 the maintenance regimen.
In conclusion, IFN integrating MP did not improve the response rate to MP alone, but even these data are preliminary, this combination seems to have some impact on relapse rate.

T 147 LONGTERM REMISSION OF AILD AFTER TREATMENT WITH INTERFERON-α

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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-α (IFN-α) in a case of AILD, who relapsed after first remission induced by polychemotherapy. IFN-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. A direct causative role of IFN-α seemed highly unlikely. Immunophenotyping of PB MNC revealed a normal distribution of B- and T-lymphocytes. However, CD8+ 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-γ was approximately fourty times and neopterin (reflecting IFN-γ production) fifteen times above normal. Also, soluble IL-2 receptor (sIL-2R) was substantially increased while TNF-α levels were normal. IL-6 and GM-CSF were below detection limits. It is remarkable that similar findings were reported for severe aplastic anemias (SAA). We speculate that in our patient the CD4/CD8 cell ratio was impaired by an unknown mechanism (viral?), thereby leading to an increased production of IFN-γ and sIL-2R. Wheter these cytokines were causally involved in hematopoietic stem cell suppression is difficult to determine.
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T 148 AGRESSIVE B-CELL LYMPHOMA IN HAIRY-CELL LEUKEMIA AFTER TREATMENT WITH ALPHA-INTERFERON (IFN).

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Hairy cell leukemia (HCL) is a chronic leukemia of predominantly B-cell origin. Contrarily to other terminal B-cell malignancies, both nodal involvment and agressive lymphomas are rare complications. In an other hand, association with various malignancies have been reported with HCL. Immunodeficiency rather than histological transformation (*eg* Richter's syndrome) is generally evoked but never prooved. Recent observations regarding a relationship of HCL to the Epstein-Barr virus (EBV) are conflicting. We report here a patient where HCL was diagnosed in april 1989. He received IFN-alpha2b : 2 MU/m2 x 3/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 Membran Protein). In situ hybridization studies (ISH) to EBV RNA were performed using a previously reported ISH technique with biotinylated 30-base oligonucleotide which is complementary to EBER1, a region of the EBV genome which is actively transcripted in latently infected cells. Evaluation was performed with BAM H1 W and EBERs probes. There were no evidence of EBV DNA and RNA in the diffuse large cell lymphoma both into the spleen or in adenopathies. These ISH studies were confirmed by viral genome detection using Southern Blot, after DNA extraction, who was also negative. Further studies are in process to elucidate the problem of clonal origin of both hairy cells and large cells, suggested by Merciea *et al* (BJH 1992 ; 82 : 547-54). However, immunologic modifications secondary to IFN therapy may lead to an increase risk of lymphoma unlinked with EBV, as noted by Habermann *et al* (ASH - 1992 - Abst 1861).

T 149 α 2b INTERFERON (INTRON-A) AND CEOP REGIMEN IN LOW GRADE NON HODGKIN'S LYMPHOMAS.

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Background. Previous clinical experiences have indicated that α interferon (IFN) alone : 1) is an useful agent in the treatment of low grade non Hodgkin's lymphomas (LG-NHL) for inducing a response; 2) may increase the quality of response to conventional chemotherapy and 3) is particularly useful in the phase of "minimal residual disease" to maintain a response. As not all the investigators agree with these statements, objectives of our study are to verify these statements.

Methods. From 1/91 to 12/92, 52 previously untreated patients with LG-NHL (class A,B,C according to Working Formulation) were randomized to receive (n=26) or not (=26) a 3 months pretreatment period with Intron-A at the dose of 3 MU/sqm 3 times a week. Thereafter, non progressive patients have received 6 courses of CEOP (Cyclophosphamide 800 mg/sqm day 1, Epirubicin 60 mg/sqm day 1, Vincristine 1.4 mg/sqm day 1 and Prednisone 50 mg/sqm days 1,2,3,4,5) repeated every 21 days. Progressive patients were treated with the CEOP regimen at the time of progression. After 6 CEOP courses, responding patients stratified according to previous treatments were randomized to receive or not maintenance with Intron-A.

Results. As of 12/92, a total of 35/52 patients have completed the 3 months period preceeding the CEOP phase. Of these, 16 were randomized to receive Intron-A and 19 to the control group. Before the initiation of the CEOP regimen a response was observed in 8/16 (50%) Intron-A pretreated patients and in 1/19 (5%) patients in the control group (P<0.01). Among the 20 patients who have completed the 6 courses of CEOP, no difference in the quality of response were so far observed between the 2 groups. As for the maintenance phase it is too early to have some results.

Conclusions. Our preliminary results confirm that IFN alone is capable of inducing a response in newly diagnosed LG-NHL.However, as for quality and duration of these responses we need a greater number of patients to be randomized and a longer follow-up.

T 150 CYCLOPHOSPHAMIDE, EPIDOXORUBICIN, VINCRISTINE AND PREDNISONE THERAPY, WITH OR WITHOUTH IFN-α2a IN LOW-GRADE MALIGNANCY NON-HODGKIN'S LYMPHOMA.

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Clin.Med.I Perugia[o], Ematol.Napoli[♥], Ist.Tumori Napoli[♦],Oncol. Trieste[♦], Ematol.Ancona[♦], Oncol.Bari[■], Clin.Med.II Modena[∞], DIMO Bari[J]. ITALIA.

The aims of our study on low-grade malignancy non-Hodgkin's lymphoma patients (groups B,C of the Working Formulation) were to evaluate: 1) the percentage of objective responses to CEOP (cyclophosphamide (CTX), epidoxorubicin (EPI), vincristine (VCR) and prednisone (PDN)] chemotherapy; 2) the capacity of IFN-α2a to transform a partial response (PR) into a complete response (CR); 3) the effect of IFN-α2a on response duration. CEOP chemotherapy (750 mg/m² CTX iv day 1, 70 mg/m² EPI iv day 1, 1.4 mg/m² VCR iv day 1 max value 2 mg, 100 mg PDN x os days 1-5) was administered every 21 days for 6 cycles. At termination of chemotherapy, patients in PR or CR were randomized so that some received IFN-α2a ($6x10^6$ IU/day for the first 14 patients, $6x10^6$ IU alternate days for those enrolled later), for the next 12 months. 76 patients (43 f, 33 m, median age 58 ys (23-70) have been entered in the study, 55 at diagnosis (GI) and 21 at 1st or subsequent relapse (GII). The median follow-up from patient entry into study to date is 12 months (range 2-36). So far 60 patients have completed chemotherapy. 26 achieved CR (43%) and 26 PR (43%) for an overall objective response of 86% (52/60). The median response duration for the entire group is 8+ months (1-30). So far 19 patients have relapsed (5 who had obtained a CR and 14 PR). Previously untreated patients (GI) responded better to CEOP than previously treated patients (GII). 23/43 GI patients obtained a CR (53.5 %) and 16 a PR (37.2%), while 3/17 GII patients achieved a CR (17.6%) and 10/17 a PR (58.8%). The median duration of response for GI patients is 9.5+ months (1-30) with 27/39 patients still on remission and 1/39 died in remission while for GII patients is 6.5 months (1-18) with 8/13 patients already relapsed. Chemotherapy was well tolerated. More than 85% patients received 100% of the CTX, ≥ 84% 100% of the EPI and ≥89% 100% of the scheduled VCR and PDN doses in all 6 cycles. 26 patients were randomized to receive IFN-α2a maintenance therapy and 26 to be followed only. The first 14 received $6x10^6$ IU day. However, only 5 tolerated this dose, while it had to be reduced in the other 9 owing to toxicity. For this reason the dose was given on alternate days to the next 12 patients. None of the PR cases randomized to receive IFN-α2a achieved CR during maintenance therapy. The median response duration of patients randomized to receive IFN-α2a is 7+ months (1-30). 14 patients are still in remission, 1 died in remission and 11 have relapsed.In the control group the median response duration is 9+ months (1-24) with 17 patients still in remission, 1 died in remission and 8 relapsed. 10 of the 19 relapsed patients have presented disease at new sites, 4 a leukemia picture and 3 histological evolution. Although these preliminary results show that the proposed treatment is feasible, it will not be possible to provide an answer to the 3rd point until 80 patients have been enrolled in each of the randomized arms.

T 151 ARA-C PLUS INTERFERON IN THE TREATMENT OF PARTIALLY RESPONSIVE LIMPHOMAS.

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ARA-C at low doses and interferon (IFN) determine growth inhibition in myelodisplastic syndromes and acute leukemias in vivo. Moreover they induce differentiation of human myeloid leukemia cells and of human neuroblastoma cell lines, without cell killing or affecting cell viability. ARA-C and IFN are effective agents in lymphomas. We postulated that the administration of the two agents at low doses could be of use in killing the malignant cells which survived aggressive chemotherapy. On these grounds, in 1990 we began a study to evaluate the effectiveness of ARA-C at low doses plus interferon in the treatment of Non Hodgkin 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 B 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 all continued interferon as maintenance therapy. Five complete responses (CR) and 1 PR was observed. Median duration of CR has been 24^+ months (range 19^+-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 these pts the possibility to achieve CR of long duration.

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

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Interferon (IFN) alfa has been found to be effective as an antitumor agent in patients with low-grade non-Hodgkin's lymphoma (NHL). Greater interest has focused on maintenance interferon after cytotoxic drugs have induced a remission. Therefore in July 1991 we began a prospective, randomised phase III study to investigate whether prolonged interferon administration in the phase of the "minimal residual disease" will increase relapse-free survival or pospone progression of disease. Previously untreated patients older than 15 years with advanced NHL (Working Formulation class B, C) are elegible. Stages I and II are elegible if they have either serum LDH > 450 IU/L or serum beta-2 microglobulin > 3.5 mg/L or at least one lymph node more than 5 cm in diameter. All patients receive 8 courses of CNOP combination chemotherapy (cyclophosphamide 750 mg/m² i.v. on day 1; mitoxantrone 10 mg/m² i.v. on day 1; vincristine 1,4 mg/m² i.v. on day 1, for a maximal dose of 2.0 mg; prednisone 50 mg/m² per os on days 1 through 5). Courses are given every three weeks. After CNOP all patients are being evaluated and submitted to iceberg radiotherapy. Thereafter, responding patients are randomized to either recombinant alpha-2a interferon (Roferon-A) 3 x 10^6 IU s.c. three times per week for a period of 12 months or to "no further treatment". As of December 1992, 36 patients have been enrolled of wich 28 are now evaluable for response to CNOP with an overall response rate of 93%, i.e. 14/28 (50%) complete remission (CR), and 12/28 (43%) partial remission (PR). CNOP regimen was well tolerated, i.e. grade 3 (WHO) toxicity was observed only in the 2.8% of the 148 courses which could be evaluated. The average dose of mitoxantrone and cyclophosphamide administered per cycle was 96% and 99% of the ideal dose for each drug. So far, 26 patients have been randomized: 14 to maintenance with IFN, 12 to "no further treatment". Nearly 100% of the prescribed dose of IFN was administered. Only in 1 patient IFN treatment was stopped because of grade 3 (WHO) hepatic toxicity. Over a median period of observation after randomisation of 7 mos. (range, 1-19 mos.), 2 patients in the maintenance arm have relapsed requiring further treatment.

T 153

TREATMENT OF ADVANCED LOW-GRADE NON HODGKIN'S LYMPHOMA: COP vs. PmM FOR INDUCTION AND α-INTEFERON (α-IFN) vs. NO TREATMENT FOR MAINTENANCE. R. Herrmann, A. Neubauer, M. Unterhalt, D. Huhn, W. Hiddemann. Departments of Medicine, University Hospitals CH-4031 Basel, D-W 1000 Berlin 19, DW-3400 Göttingen

Between 4/89 and 12/92 92 institutions in Germany, Austria, Sweden and Switzerland have 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 B-symptoms, bulky disease, progressive lymphoma or 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 (cyclophosphamid 400 mg/m2/d i.v. x 5d, vincristine 2 mg day 1, prednisone 100 mg/m2/d p.o. x 5 d) or PmM (prednimustine 100 mg/m2/d p.o. x 5 d, mitoxantrone 9 mg/m2/d i.v. x 2 d). Treatment was repeated every 3 weeks (COP) or every 4 weeks (PmM) for 8 cycles or CR plus 2 cycles. Responding patients (CR or PR) were then randomized to receive α-IFN 2b maintenance 5 x 10^6 U s.c. 3 times per week until relapse/progression or no further treatment. At the present time no significant differences are revealed between response rates after COP or PmM. Overall remission (CR + PR) was achieved in 83 %. Side effects were different, however, in that PmM caused significantly less peripheral neurotoxicity and alopecia. Myelotoxicity, N + V, infection and cardiotoxicity were not significantly different. Median eventfree survival of all evaluable patients is 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 α-IFN on remission duration or survival. However, actual follow-up data will be presented.

T 154

TREATMENT OF LOW GRADE NON-HODGKIN'S LYMPHOMAS (LGNHL) WITH CHLORAMBUCIL AND α2b-INTERFERON (α2b-IFN). GA Pangalis, Ch Tsekouras, VA Boussiotis, Ch Poziopoulos, M Angelopoulou, DA Gribabis, Ch Kittas. Lymphoma Clinic, University of Athens School of Medicine, Laikon General Hospital, Athens, Greece.

Alpha-interferon has shown to be effective in the treatment of LGNHL. In the present analysis 53 patients were studied, in order to further investigate the contribution of α2b-IFN in the treatment of LGNHL. Patients' entry criteria to this trial were as following: histologic type of LGNHL, performance status 0,1, or 2 and clinical stage II, III or IV. Our 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 α2b-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, 3MU/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 (53%), partial remission in 11 (32%) and stability or progression 5 (15%). 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 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 12.2+ mo respectively for arm A and 8 and 12+ mo for arm B. The duration of CR was slightly longer for patients treated with the arm B protocol (20+ mo vs 16+). Between patients in whom maximum response was achieved (CR or PR) 12 received maintenance therapy with Intron A and 17 did not. Among the maintenance group, 5 patients (41%) relapsed and among the non-maintenance 7 (41%), with a median time of relapse 14 and 15.6 mo respectively. We concluded from our study that addition of Intron-A to Leukeran as induction treatment of LGNHL has an advantage over Leukeran alone, however, it is not possible to estimate if this non-maintenance has an effect on the duration of CR. Besides we observed that the addition of Intron-A as maintenance treatment did not improve relapse rate.

T 155

a2b INTERFERON VS a2b INTERFERON PLUS CHEMOTHERAPY IN PATIENTS WITH NON-HODGKINS' LYMPHOMA (NHL) ACHIEVING SIGNIFICANT PARTIAL REMISSION AFTER m-BACOD. V. Pavone, A. Guarini, A. Mileti, A. Ostuni, G. Colucci, M. Carotenuto, A. Riezzo, E. Durini, G. Serravezza, M. Monaco, G. Lucarelli, G. Pisapia, A. Fragasso, V. Liso. Ematologia - Bari Cooperative Group - Policlinico, Universita' degli Studi - Bari, Italy

Clinical studies carried out in recent years have emphasized a same effectiveness of Interferon (IFN) in association with chemotherapy (CHOP-like protocols or Chl) in inducing responses (CR/PR) or as maintenance therapy in low-intermediate grade lymphoma patients (pz). The aim of our study is to evaluate IFN alone vs IFN in association with m-BACOD in a randomized study in pz with low and intermediate NHL in significant partial remission (sPR=partial remission >70%) after 4 cycles of m-BACOD.

PATIENT CHARACTERISTICS: 136 non pretreated pz with NHL histology A-F (WF), were included in a multicenter study from july '90 until january '93; 74 pz (54%) with low grade (WF A-C) and 62 pz (46%) with intermediate grade (D-F). The median age was 55.8 years. 41 pz in stage I+II (30%) and 95 pz in stage III+IV (70%) were enrolled into the study (still open).

TREATMENT: All the pz were treated with 4 cycles of m-BACOD. The pz achieving Complete Remission (CR), after 2 other cycles of the same chemotherapy, were randomized to stop therapy (random 3) or to receive a2b IFN (3x10 IU sc 2t/wk) for 12 months (random 4). The pz in sPR were randomized to receive IFN (10x10 IU sc 3t/wk) for 12 months (random R1) or IFN (10x10 IU sc 3t/wk) in association with m-BACOD (2 other cycles) for 12 months (random R2).

RESULTS: After 4 cycles of m-BACOD, 110 pz were evaluable for response. 24 are "too early" and 2 died because of the progressive disease. 44 (40%) CR and 46 (41.8%) sPR, (CR+sPR=81.8%) were observed.

Pz	CR	sPR	PR+F
110	44(40%)	46(41.8%)	20(18.2%)

Random	**R3** 23 (Stop therapy)	**R1** 23 (IFN)	--
	R4 19 (IFN)	**R2** 20 (IFN + m-BACOD)	

There were no differences in response between the low and intermediate grade NHL pz. 4 relapses in R3 (7-9-11 and 12 mos) and 2 in R4 (18-19 mos) occurred. 7 progressive disease in R1 and 5 in R2 groups were observed. Median follow up was of 13.21mos.

COMMENT: In agreement with data reported in literature, m-BACOD provided reproducible results (CR + sPR=81.8%) in our study also. Concerning IFN evaluation in randomized pz no tentative analysis ca be draw because of the short follow up of the pz.

T 156

THERAPY OF RESISTANT LOW-GRADE NON-HODGKIN'S LYMPHOMA WITH ANTHRACENODIONES AND INTERFERON. PRELIMINARY RESULTS

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Purpose.- To evaluate the efficacy of the anthracenodiones 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 chemotherapies, and they have received no therapy at ' for the two previous months. As induction therapy was employed mitoxant. 4 mg/m^2, days 1-2 and prednimustine 100 mg/day, days 1-5 repeated each 28 days for 6-9 months. The patients who achieved remission (partial or complete) were treated with alpha-2-b interferon (IFN) 9 mU/week and dexametasone (DMT) 15 mg/m^2 days 1-4, repeated 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 NHL, MALT type. The mean age was 63.8 years, and M/F ratio 1.9. Twenty one cases showed bone marrow imvolvement. The previous therapy was chlorambucil alone or with prednisone in 10 cases, alkylant agents + CHOP, CVPP or PROMACE in 5, chemotherapy in 5 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 DMT. The induction and maintenance therapy was well tolerated, with mild myelotoxicity in 5 patients and severe in 1 patient.

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 LYMPHOMA

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Chronic cutaneous T-cell lymphoma (CTCL) are a group of rare disorders comprising primarily of mycosis fungoides and Sezary'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 indicative of 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 TIW SQ which was gradually increased to a maximum of 20 MU TIW over a period of 3-6 months amongst the responders. Three of 6 pts demonstrated a response: two achieved a complete remission (CR) at 4 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). Toxicity attributed to IFN was common: mainly flu-like symptoms and was totally reversible. Our limited experience, to date, is supportive of the notion that IFNs 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.

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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 6 HCL patients. The results demonstrate 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 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.

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T 159 HIGH EFFICIENCY OF 2-CHLORODEOXYADENOSINE (2-CdA) ON BULKY LYMPHADENOPATHY IN HAIRY CELL LEUKEMIA (HCL).

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Development of massive lymphadenopathy is very unusual in HCL. Some of these patients may respond to 2'-deoxycoformycin (DCF) treatment (*Mercieca et al, Br J Haematol, 1992*). 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 alpha-IFN in 1986, then with DCF in 1990 with a partial response (PR) to these treatments. In March 1992, he presented with a bulky abdominal mass (largest diameter = 30 cm). A Tru-cut biopsy confirmed the HCL localization. A first course of 2-CdA (0.1 mg/kg/d 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 retroperitoneal 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 (CDA) FOR SYMPTOMATIC HAIRY CELL LEUKEMIA (HCL).

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2-chloro-2'-deoxyadenosine (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 bioavailability studies (JCO 1992;10:1514) we could recently document a similar efficacy when CdA was given in subcutaneous injections daily for seven days (Blood 1992; 80(suppl): 359a).

The main toxicity of 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 candidosis, aspergillosis and CMV viremia on several occasions. In our initial trial with CdA in continuous infusions (Blood 1992;79:888) 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 CdA as subcutaneous injections, 3.4 mg/sqm daily for seven days. Of 37 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 leucocyte counts with differentials (see Table below). Neutropenia is a very common finding in symptomatic HCL, whereas anemia indicates a more severly depressed hematopoiesis.

Blood Counts at Start of CdA Treatment

Mean ± SD.	Neutropenic Fever given Intravenous Antibiotics		
	Yes	No	p-value
Number of patients	15	22	
Hemoglobin (g/liter)	95 ±23	124 ±17	<0.0005
Lymphocyte count (x10(9)/l)	4.5 ±5.4	4.1 ±5.7	n.s.
Neutrophil count (x10(9)/l)	0.83 ±0.9	0.98 ±0.6	n.s.
Monocyte count (x10(9)/l)	0.06 ±0.1	0.07 ±0.1	n.s.
Platelet count (x10(9)/l)	81 ±79	118 ±62	<0.1

T 161 EFFECTIVITY AND TOXICITY OF FLUDARABINE PHOSPHATE IN PRETREATED ADVANCED CHRONIC LYMPHOCYTIC LEUKEMIA-RESULTS OF A PHASE II TRIAL.

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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/m^2 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 2-12+ months. 2 of the 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 CD 4+ positive cells down to minimal counts of 17 cells/yl, 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

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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: immunocytoma (ic), n=4; centroblastic-centrocytic (cbcc), n=9; centrocytic (cc), 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/m^2 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 7/23 (30%), including one CR (NHL ic) and 6 PR (NHL cbcc, n=3; NHL cc, n=2; MALTOM, n=1). Durations of response are 1m+, 3m, 7m, 9m+, 11m+, 14m+ for the pts achieving PR, and 7m for the pt with CR. There was one early death (NHL cc) 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 nonhematologic 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-CLL.

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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 early phase I studies myelosuppression and neurotoxicity proved to be the dose-limiting toxicities. In the widely used schedule of 25mg/m^2 every four 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 histopathologic signs of acute interstitial pneumonitis. CLL stage Rai II was diagnosed in a 58 year old man in 1984; he had a 30 year history of smoking (20 cigarettes per day) and three episodes of pneumonia during the last three years. From April 1987 to May 1991 the pt. received intermittent treatment with prednisone and chlorambucil (1500mg 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 (25 mg/m^2 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 pO_2 61mmHg and PCO_2 32 mmHg. A transbronchial lung biopsy showed an interstitial pneumonitis with slight fibrous thickening of the alveolar septae 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 (100 mg/d i.v.) 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).

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Our Phase I study of FND (Proc AACR 1992; 33:228) defined a maximum tolerated dose of: fludarabine 25mg/m^2/d, days 1-3; mitoxantrone 10mg/m^2 day 1; and dexamethasone 20mg qd, days 1-5. Starting in 1/92, we have treated 22 patients (pts) with FND on an ongoing Phase II trial. In addition to LGL pts, there were also 3 with follicular large cell and 3 with centrocytic lymphoma treated. The median age was 60 (range 37 - 79). 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 myelosuppressive, including apparent cumulative myelosuppression with delayed hematologic recovery, especially platelets, in 4 pts. Infections have included 1 proven and 1 suspected pneumocystis pneumonia, and 5 episodes of H. zoster. We conclude that FND is an active combination for pts with recurrent LGL. Because of the risk of opportunistic infections, consideration should be given to the use of prophylactic antibiotics or withholding steroids if high-risk pts can be identified.

T 165

STAGE II NON-HODGKIN LYMPHOMA (NHL)

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Stage II NHL was studied, as its behaviour is distinct from stage I, in two centres, with special attention to pattern of relapse in relation to pathology, presentation and applied radiotherapy. Normal staging procedures included lymphangiogram 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 (pt) were collected, 65 from Amsterdam and 105 from Rotterdam. The mean age of the total group was 60 years (22-93 years). Presentation was supradiafragmatic in 104 pt (70 pt Ring of Waldeyer), of whom 16 pt were low gr., and infradiafragmatic in 66 pt of whom 36 pt were low gr. For nodal size and gr. see table.
Treatment regimes varied between regional radiotherapy 40 Gy (RT): 58 pt, same radiotherapy followed by CVP (RTCT) 50 pt, starting chemotherapy including Adriamycine followed by limited radiotherapy (CTRT): 46 pt, or chemotherapy alone (CT): 14 pt, while 2 pt had other treatment. Survival at 5 years (S_5) was 56% for the whole group. Most low gr. pt received RT or RTCT with S_5 70%, while for intermediate grade, the best S_5 was 77% after CTRT. S_5 was significantly related to nodal size; < 3 cm: 79%, 4-5 cm: 55%, > 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 (46%) of whom two thirds had isolated nodal relapses, 22/28 pt in low gr. and 24/37 pt in intermediate gr., while 18/22 and 18/24 of these relapses were in unirradiated areas only (see table).
Conclusion: However after correction for age and nodal size, no significant difference remains in S_5, between treatment RT, RTCT or CTRT, for low and intermediate gr. but for high gr. RT alone is worse. The pattern of relapse suggested that additional RT might improve results.

	all	low gr.	interm. gr.	high gr.
n	170	52	84	34
S_5 all	56%	67%	52%	43%
S_5 RT	41%	70%	29%	0%
S_5 RTCT	56%	70%	50%	54%
S_5 CTRT	67%	40%	77%	67%
size < 3 cm	51	29	18	4
4 - 5 cm	36	7	24	5
6 - 9 cm	36	2	25	9
> 10 cm	37	11	12	14
relapse all (%)	79 (46%)	28 (54%)	37 (44%)	14 (40%)
isol. nodal	53	22	24	7
isol. nodal no RT	39	18	18	3

T 166

SERUM LEVELS OF TUMOR NECROSIS FACTOR-α IN PATIENTS WITH B-CELL CHRONIC LYMPHOCYTIC LEUKEMIA.

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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 CD5+ B-CLL patients (31 men and 60 women; mean age 65±9). There were 35 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 (39±7 pg/ml) and group 3 (87±13 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 ($P<0.002$) 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, CD5+ B-lymphocytes, CD57+ lymphocytes, platelet count and serum levels of IgG, IgA or IgM.

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 LYMPHOMAS.

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Phenalol - n/di(2-chlorethyl)-amino/phenylacethyl-L-phenylalanin 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 20 Hodgkin's lymphoma patients who progressed during the COPP polychemotherapy and to 10 non-Hodgkin's lymphoma patients who progressed during CVP polychemotherapy. Partial regressions were achieved in 12 of 20 (60%) 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-Hodgin's lymphoma patients. The duration of regressions was 5 to 6 weeks. Phenalol is less toxic compared to other chlorethylamines. Dyspeptic signs were observed in less than 60% of cases, and mild myelosupression was observed in less than 40% of cases. There were no cases of agranulocytosis. Subsequently phenalol was included in COPP and CVP regimens instead of cyclophosphamide and FOPP and FVP regimens were obtained. During the treatment of Hodgkin's lymphoma patients with FOPP polychemotherapy partial regressions were achieved in 7 of 10 (70%) of cases. The duration of regressions was 8 to 10 weeks After repeated courses the duration of regressions was 12 weeks and more. During the treatment of non-Hodgkin's lymphoma patients with FVP 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 has a perspective in the treatment of malignant lymphomas refractory to standard chemotherapy. We suggest that it may be useful to include the preparation into combination chemotherapy regimens.

T 168

RADIONUCLIDE THERAPY WITH HIGH DOSE 67-GALLIUM INTRAVENOUSLY IN NON-HODGKIN'S LYMPHOMA.

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67-Gallium (67GA) accumulates rather selective in malignant lymphoid tissues. In vitro we found a cytotoxic effect of 67GA in human cell lines U 937 and HL60 compared with 90 Ytrium[1] and low dose rate external irradiation. In a pilot study, 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 progresssive disease. No acute side effects were noted with doses of 20-60 mCi. Bone marrow suppression was seen in all patients and persistent pancytopenic requiering platelet transfusions occured in the first patient who had received three weekly doses of 20, 40 and 60 ml respectively. The other two patients receives 2 doses of 40 m Ci 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-scanning. The response was short lived (5-12 weeks) and most remarkebly, different in magnitude from site to site.
We conclude that high dose 67Ga can savely be administered intravenously without any site effect apart from myelosuppression and has cytostatic effects in large cell Non Hodgkin's lymphoma, deserves further exploration.

[1] Brit J Cancer 1993;67.

T 169 DIPYRIDAMOLE AND LOW - DOSE METHOTREXATE FOR MYCOSIS FUNGOIDES.

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Methotrexate (MTX) is widely used for treatment of cutaneous T-cell lymphomas(CTCL). The drug is cytotoxic because it interfere with de novo biosynthesis of physiologic nucleosides.Dipyridamole(DP) is well-known inhibitor of facilitated diffusion of nucleosides that permits transport downwards in a concentration gradient. Hence, 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 1991 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 Sézary cells in peripheral blood,were normal or negative. A diagnosis of CTCL (stage III, $T_4N_{-}B_0M_0$, low-grade peripheral) was made. The patient was treated with MTX-DP regimen, using the following treatment schedule: MTX was administred 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 both orally and i.m. Intramuscular administration of DP was done at the same days(in 18 hrs),as MTX, at a dose of 100 mg x 6 for 6 weeks, followed by 100 mg x 3. By oral route DP was given at a dose of 50 mg x 6/24 h for 4 weeks, followed by 50 mg x 3/24 h for 7 weeks,and then 25 mg x 4/24 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 11 - 4(achievement of complete remission). A relapse occurred at week 42 - TBI 14 and disease slowly progressed despite of the continuous therapy: weeks 46 and 50 - TBI 44, weeks 52 and 60 - 120, and treatment was discontinued at week 64, TBI 135. No side-effects were observed. Our patient showed a good responce to very low doses of MTX in this regimen(a total dose of 490 mg) and we believe that the combination of DP with MTX in CTCL is worth further evaluation.

T 170 CHEMOTHERAPY FOR PERIPHERAL T-CELL LYMPHOMAS (PTCL).

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Peripheral T-cell lymphomas are a subset of lymphomas more often identified by special phenotype. They are morphologically heteregenous and include diffuse mixed and diffuse 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 agressive protocols.

We have retrospectively reviewed 37 cases of unequivocal PTCL 29 of which were seen at the onset of their disease and are considered for the present analysis. In three patients PTCL 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 CD1 negative) 3 expressed only CD8 antigens and 20 only CD4 antigens, two of them CD30+ (K1). The three remaining patients were classified on the basis of positivity with a Pan-T Antigen.

18 patients were male and 11 females. Median age was 39 (range 19-68). The first clinical presentation was variable but with exception of two patients who had smouldering disease all had clinically agressive, most often widespread disease, and one patient was in leukemic phase with meningeal involvement. According to W.F. 8/29 (27%) patients were diffuse large cells immunoblastic, 19/29 (65%) diffuse large or mixed cells not Immunoblastic, two Lennert's LNH and one angio-immunoblastic lympho-adenopathy like.

Patients were treated with two protocols, 17 had CHOP or CHOP like regimen and 12 had an intensive protocol consisting of seven drugs given every three weeks with weekly injections of antimetabolites (ESMO, Lugano, 1988 Abstract 21). 6/17 patients (35%) achieved CR with CHOP (or similar schedule) median survival is 18 months. Five of them (29% ± 22) are long survivors, median 38 months ranging from 12 to 69 months (one after salvage therapy). With an agressive treatment designed for Burkitt and PTCL 10/12 patients (83%) obtained CR. The duration of response ranges from 2 to 61 months, median 25 months. Two patients received complementary radiotherapy after treatment. Median survival is not reached with a median follow up of 39 months, 8/12 patients (66% ± 27) are alive free of disease up to now. Although, the difference is not statistical significant ($p = 0.1$) due to small number of patients, we believe that peripheral T-cell lymphoma may benefit from agressive chemotherapy and that immune phenotyping of diffuse lymphoma is mandatory prior to therapeutic decision. The present data suggest that a more agressive treatment may be warranted in PTCL.

T 171 LONG-TERM RESULTS OF CHEMOTHERAPY WITH OR WITHOUT RADIOTHERAPY IN STAGE I AND II HIGH GRADE MALIGNANT NON-HODGKIN'S LYMPHOMAS (NHL)

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The optimal treatment approach in patients (pts) with localized aggressive NHL is still controversial. It is particularly uncertain whether the addition of radiotherapy 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 CABOPP/VIM* as primary chemotherapy. In 21 pts additional irradiation (30-50 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 chemotherapy plus radiotherapy (88% vs 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.

* Nowrousian 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 03 TRIAL.

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From July 1985 to March 1992, we treated 81 localized (skin and gastrointestinal involvement excluded) aggressive NHL with 3 curses of CHEP (cyclophosphamide 750 mg/m^2 d1, doxorubicine 50 mg/m^2 d1, vindesine 3 mg/m^2 d1 and prednisone 60 mg/m^2 d1 to d5) followed by a focal or regional radiotherapy (40 Gy) and combined with a CNS prophylaxis for high risk patients (pts). Our pts were aged from 65 to 75 years (median: 68) and their sex-ratio was 1.08 (42 M/39 W). 39 pts had an extra-nodal disease (Waldeyer's or sinus 22; thyroid 6; bone 3; soft tissues 3 and miscellaneous 5) and 42 pts had a nodal presentation of whom 7 had an extra-nodal involvement (peripheral nodes 34; abdominal nodes 6 and non lymphoblastic mediastinal NHL 2). A bulky presentation was seen in 34 pts and according to Ann Arbor classification there were 45 CS IA, 2 IB, 30 IIA and 4 IIB. Mean values of seric LDH and β2microglobulin levels were respectively 0.85±0.47 x N/l and 2.2±0.6 mg/l. 13 pts were in obvious complete remission (CR) after initial biopsy and the 3 CHEP induced a CR in 57/68 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 is 40 months and we observe 18 relapses (occurred within 36 months except for 1 pt) and 17 deaths (toxic death 1; failure 1; relapse 14 and non-related death 1).

The 6.5-year survival rate (SR) is 69.0% for all the pts and 70.7% for the 79 pts in CR after the protocol. We found a prognostic value for 3 parameters:

		SR	(n pts)		SR	(n pts)	p
LDH	< 1.25 x N	69.6%	(49)	≥ 1.25 x N	0.0%	(6)	$< 10^{-6}$
Type	Extra-nodal	94.9%	(39)	Nodal	48.5%	(42)	$< 10^{-2}$
Bulky	No	82.0%	(47)	Yes	50.6%	(34)	< 0.05

whereas all other parameters are without significance, specially B symptoms, performance status and clinical stage. Finally the presence of CR after initial biopsy is a favourable prognostic factor (3.5-year SR 82.1%) whereas a partial remission after CHEP is related with a bad prognostic despite irradiation (2.5-year SR 53.3%). The POF 03 regimen appears to be non toxic and effective in aged patients with localized aggressive NHL.

T 173 LOCALIZED AGGRESSIVE NON HODGKIN'S LYMPHOMAS (NHL): 7-YEAR RESULTS ON 209 PATIENTS TREATED WITH THE POF 02 TRIAL.

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From January 1985 to August 1992, we treated 209 localized (skin and gastrointestinal involvement excluded) aggressive NHL with a short intensive chemotherapy (3 curses of VACP: vindesine 3 mg/m^2 d1 & 5, doxorubicine 80 mg/m^2 d2, cyclophosphamide 1500 mg/m^2 d2 and prednisone 80 mg/m^2 d1 to d5) followed by a focal or regional radiotherapy (40 Gy) 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 M/89 W). 94 pts had an extra-nodal disease (Waldeyer's ring or sinus 49; primary cerebral NHL 11; bone 9; paraplegia 7; thyroid 7 and miscellaneous 11) and 112 pts had a nodal presentation of whom 44 had an extra-nodal involvement (peripheral nodes 63; non lymphoblastic 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 109 CS IA, 8 IB, 73 IIA and 19 IIB. Mean values of seric LDH and β2microglobulin levels were respectively 1.0±0.7 x N/l and 2.0±1.0 mg/l.

40 pts were in obvious complete remission (CR) after initial biopsy and the 3 VACP induced a CR in 133/169 pts (78.7%). After the whole treatment, we noted 7 toxic deaths (3.3%), 11 failures (5.3%) and 191 CR (91.4%). On January 1st 1993, the median follow-up is 50 months and we observe 28 relapses (occurred within 36 months except for 2 pts) and 44 deaths (toxic death 7; failure 10; relapse 18; ANLL 1; solid tumor 2 and non-related death 6).

The 7-year survival rate (SR) is 70.2% for all the pts, 76.7% for the 191 pts in CR after the protocol and 80.5% after excluding the non-related deaths. We found a prognostic value for 4 parameters:

		SR	(n pts)		SR	(n pts)	p
Bulky	No	84.9%	(108)	Yes	45.6%	(101)	$< 10^{-5}$
LDH	< 1.25 x N	79.1%	(108)	≥ 1.25 x N	56.8%	(32)	$< 10^{-4}$
PS	< 2	73.4%	(161)	≥ 2	52.1%	(39)	$< 10^{-3}$
Syst. Sympt.	A	72.0%	(182)	B	50.2%	(27)	$< 10^{-3}$

whereas all other parameters are without significance, specially presentation of NHL, initial site and clinical stage. Finally the presence of CR after initial biopsy is a favourable prognostic factor (SR 92.8%) whereas a partial remission after VACP is related with a bad prognostic despite irradiation (5-year SR 53.6%).

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

T 174 PHASE I/II STUDY OF VACOP-B AND HIGH DOSE ETOPOSIDE/CYCLOPHOSPHAMIDE FOR POOR PROGNOSIS ADVANCED STAGE DIFFUSE LARGE CELL LYMPHOMA.

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Between August 1990 and September 1992, 19 patients (pts) (11 male) less than 60 years of age (median 41, range 20 to 56) with poor prognosis advanced stage diffuse large cell lymphoma were treated with outpatient weekly VACOP-B (Proc. ASCO 1990 9:254) for 8 weeks followed by inpatient escalating high dose etoposide (E) and cyclophosphamide (C) at week 9. Poor prognosis was defined by: 1) serum LDH > 3 x normal, 2) stage IV with two or more sites of extranodal disease and LDH > 2 x normal, or 3) stage II bulky, III or IV small non-cleaved non-Burkitt (SNCNB) histology. By the Working Formulation, 4 pts had SNCNB, 5 immunoblastic, 8 diffuse large cell and 2 diffuse mixed lymphoma. The doses escalated from E-900 mg/m^2/C-1800 mg/m^2 given over 3 days to E- 2700 mg/m^2/C-6600 mg/m^2. G- or GM-CSF starting 1 day after the EC, was administered beginning at the E-2100 mg/m^2/C- 4800 mg/m^2 level. The median time from start of EC to recovery of a granulocyte count > 0.5 x 10^9/L was 16 days (r = 13-20) and to platelet count > 50 x 10^9/L was 15 days (r = 0-31). The median number of days with a granulocyte count < 0.5 x 10^9/L was 10 (r = 7-19) and a platelet count < 50 x 10^9/L was 6 (r = 0-26). The median number of days of hospitalization was 20 (r = 16-51). Mucositis was severe in only 2 pts. There were 2 treatment related deaths (1 pulmonary Aspergillosis in a pt with underlying agammaglobulinemia; 1 fulminant hepatitis in a hepatitis B antigen positive pt) and 6 patients have died with relapsed lymphoma. 11 pts remain alive and disease-free with a median follow up of 13 months (r = 5-30) and the projected overall survival at 30 months is 44%

Conclusion: High dose EC following VACOP-B can be delivered with acceptable toxicity in this setting. Dose escalations with growth factor support continue to define the as yet unreached maximum tolerated dose of EC.

T 175 A PILOT STUDY OF ProMNCECytaBOM IN AGGRESSIVE NON-HODGKIN'S LYMPHOMA.

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Mitoxantrone is a relatively new drug in the management of non-Hodgkin's lymphoma, which yields fewer troublesome toxicities and cardiotoxicity than doxorubicin. We considered interesting to investigate mitoxantrone (5 mg/m2) instead of doxorubicin (25 mg/m2) in one of the most efficacious third generation regimen i.e. ProMACECytaBOM and to verify the activity, the safety and the feasibility in a group setting. We report here the preliminary results observed in the first 20 registered cases.

Demographic data were: female 11, male 9; mean age 53.7-year-old; extra-nodal involvement 15/20; International Working Formulation D=2, F=2, G=11, H=1, J=2, Other=2; Coiffier Index I=6, II=7, III=6.

Response rate after 6 cycles was: CR=8, 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; Nausea/Vomiting 1.2; Alopecia 1.1; Infection 0.9; Peripheral Neurotoxicity 0.7; Mucositis 0.5; 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 %; Cytarabine 70.8 %; Bleomycin 89.2 %; Vincristine 82.8 %; Methotrexate 87.3 %.

Conclusion: ProMNCECytaBOM is an effective regimen in aggressive non-Hodgkin's lymphoma. The toxicity is low enough to permit possibly with the support of G- or GM-CSF, a dose increment of the anthracenedione component, which is one of the most powerful prognostic factor (LW.Kwak et al.,1990) in aggressive non-Hodgkin's lymphoma.

T 176 A PROTOCOL INCLUDING IDARUBICIN AND ETOPOSIDE AS FIRST LINE TREATMENT FOR INTERMEDIATE NHL.

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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 administred on out patient basis. In a pilot study we have tried a five drug regimen which is a reinforcement of the classical CHOP: vincristine 2 mg day 1, cyclophosfamide 600 mg/sqm + idarubicin 10 mg/sqm day 2, etoposide 100 mg/sqm day 1 to 3, deflazacort 90 mg/sqm for 5 days. Six courses with a three week interval were schedule for any type of stage II to IV intermediate NHL.

Up to the time of the abstract, 14 patients entered the study (4 M and 10 F, median age 55, range 34-75). 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-WHO), whith 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; platelets were never decreased below 50x10e9/l; hospitalization was never needed. Stage IV patients with liver (1 case) and pleural (3 cases) involvement went into CR after 1-2 courses; pleural effusion needed not be drown in 2 cases and did not recur after a single drowing in the third. Thus, a five drug regimen including idarubicin and etoposide as main cytotoxic drugs and deflazacort as substitution for prednisone seems effective and well tolerated in intermediate NHL. A longer follow up and a randomized trial with a conventional four drug regimen are needed to asses a possible superiority of such a protocol.

T 177 EFFICACY OF MACOP-B IN THE MANAGEMENT OF INTERMEDIATE GRADE (D-E-F) NON-HODGKIN'S LYMPHOMAS.

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Intermediate grade non-Hodgkin's lymphomas are very heterogeneous, and a standard chemotherapy remains still undefined. Most trials consider high and intermediate grades together. 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 MACOB-B between june 1986 and may 1992. Median age was 55 yrs (range 28-51). 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 178 INTENSIVE CHEMOTHERAPY WITH A COMBINED THERAPY OF VINCRISTIN, HIGH-DOSE ADRIBASTIN, CYCLOPHOSPHAMIDE, PREDNISONE AND ETOPOSIDE (VACPE) IN HIGH-GRADE NON-HODGKIN LYMPHOMAS - RESULTS OF A MULTICENTER PHASE-II STUDY.

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

Study design:
We conducted a phase-II trial in patients with high-grade NHLs with an intensive chemotherapy in short-term intervals. Patients with histological proved high-grade lymphomas acording to the Kiel-classification (except lymphoblastic NHLs) stage $I_{E/bulky}$-IV and age between 18-75 were included. One therapy cycle consisted out of vincristine d1 i.v., adriamycin 25 mg/m² d1-3 i.v., cyclophosphamide 800 mg/m² d1 i.v., prednisone 60 mg/m² d1-7 p.o. and etoposide 120 mg/m² d1-3 i.v. (VACPE). For patients >60 years, adriamycin was administered only 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 into a randomized trial (± GM-CSF). The cycles were repeated every three weeks. Patients with stage IV received six cycles of VACPE, all other patients received five cycles VACPE. After end of chemotherapy, patients received a consolidating radiotherapy. The patients were reevaluated after two and four cycles, after finishing chemotherapy and after radiotherapy.

Results: Up to now, 51 pts. with 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 tumor related). 39/50 pts. are presently evaluable for response (21 centroblastic, 3 immunoblastic, 3 Ki1, 7 pleomorphic T-cell, 2 anaplastic, 3 others). The median age was 52 years (15-77), 3 pts. had stage I_E, 13 stage II, 8 stage III and 14 stage IV. 23/39 patients were symptomatic, 24/39 had elevated serum LDH. 31/39 pts. (79%) achieved CR, 7/39 achievd PR. 4 patients with CR meanwhile relapsed. The CCR after 3 years is 81%, the overall survival 70%.

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

T 179 A NEW HYBRID REGIMEN (CEOP-IMVP-DEXA) IN THE TREATMENT OF HIGH-GRADE NON-HODGKIN'S LYMPHOMAS (NHL). AN AUSTRIAN MULTICENTER TRIAL.

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Purpose of the study was to evaluate the efficiency, toxicity and feasibility of a new hybrid chemotherapy for high-grade NHL in a multicenter setting. We combined two non-cross-resistant regimens, CEOP (Cyclophosphamide 750mg/m² iv. d1, Epidoxorubicin 70mg/m² iv. d1, Onkovin 1,4mg/m² iv. d1+8 and Prednisolon 100mg p.o. d1-5) and IMVP-Dexa (Ifosfamide 2g/m² with Uromitexan uroprotection iv. d15-17, VP-16 100mg/m² iv. d15-17, Dexamethasone 40mg p.o. d15-19 and Methotrexate 800mg/m² iv. with Ca-folinat rescue p.o. d22) 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 $0.5x10^9$/L. We withheld therapy for one week if counts dropped below $0.2x10^9$/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 53/65 (81.5%), after a median observation time of 25.9 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 findings 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 $0.5x10^9$/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 ALTERNATING CEOP-B/VIMB IN THE TREATMENT OF INTERMEDIATE AND HIGH GRADE NON HODGKIN'S LYMPHOMA.

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Since October 1988, we have treated 62 consecutive patients (pts) with intermediate (IG) and high grade (HG) NHL with CEOP-B (CTX 750 mg/mq d 1, Epirubicin 60-90 mg/mq d 1, VCR 1.4 mg/mq d 1+8, PRD 80 mg/mq d 1 to 5, Bleo 10 mg/mq d 1+8) alternated every three weeks with VIMB (VP16 80 mg/mq d 1 to 3, Ifosfamide 1.5 g/mq d 1 to 3, Mitoxantrone 12 mg/mq d 1, Bleo 10 mg/mq d 15). Treatment for stage I-II pts consisted of 6 alternated cycles (3 CEOP-B/3 VIMB) of chemotherapy (CHT) followed by RT on involved fields, whereas stage III-IV pts were treated with 8 alternated cycles (4 CEOP-B/4 VIMB). Initial staging workup included: complete physical examination, routine blood chemistry, standard chest X-ray, bipedal lymphography, bilateral bone marrow biopsies from iliac crests, abdominal and pelvic CT scans. Laparoscopy with liver and spleen biopsies and barium meal were performed in selected cases. The characteristics of the 62 actually evaluable pts were: median age 57 years (range 28-73, with 61% of pts older than 55 yrs); pathologic stage I-II in 22 pts and III-IV in 40 pts; W.F. histology was low grade in 2 pts (entered the study because of bulky and clinically aggressive disease), IG in 46 and HG in 14 pts. Morover, 18 pts (29%) had constitutional symptoms and 10 (16%) had bulky disease. Results are summarized in table:

Histology	N.	CR(%)	PR(%)	Pro	Stage	N.	CR(%)	PR(%)	Pro
A	2	1(50)	1(50)	--	I	10	10(100)	--	--
D-E-F	16	11(69)	1(6)	4	II	12	10(83)	--	2
G	30	22(73)	2(7)	6	III	13	9(70)	2(15)	2
H-I-J	14	11(78)	1(7)	2	IV	27	16(59)	3(11)	8
Total	62	45(73)	5(8)	12	Total	62	45(73)	5(8)	12

Toxicity was very manageable: 15 pts (24%) had grade III and 11 pts (18%) grade IV leukopenia; grade III or IV thrombocytopenia was observed in 4 (6%) and 1 pts (2%), respectively; grade III anemia occurred in 4 cases (6%). No cardiotoxicity was observed. Alopecia was almost universal. Grade III mucositis was observed in 7 pts (11%) and diarrhea in 3 cases (5%). The 36 months actuarial disease free survival is 74% with an overall survival of 84%. For definitive conclusions from these data, a longer follow-up is needed. Nevertheless, our preliminary results suggest that this alternated regimen is at least as effective as other third generation schedules which are, on the other hand, more toxic and less tolerated.

T 181 A RANDOMIZED TRIAL OF ADRIAMYCIN (M) vs EPIDOXORUBICIN (E) CONTAINING CHOP-B IN NON HODGKIN'S LYMPHOMAS (NHL). UPDATED 6 YEAR RESULTS.

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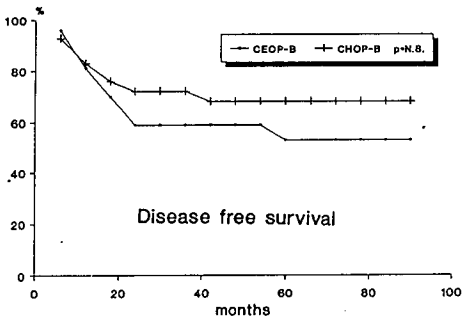
From February 1982 to June 1989, 86 previously untreated, poor prognosis NHL patients (pts) were entered a prospective randomized trial comparing CHOP-B and CEOP-B. Epidoxorubicin (E) was initially administered at a dosage of 50 mg/mq and subsequently at 60-70 mg/mq. Both groups were similar for presence of adverse prognostic factors and also for age, histology, LDH value and extranodal disease. Complete remission (CR) rate was comparable: 63% with CEOP-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 echography 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 I degree 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 CEOP-B arm was compared; 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 CEOP-B regimen.



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

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Between February 27, 1979 and April 21, 1984, 46 patients with unfavorable histology lymphoma were treated with aggressive intensive chemotherapy consisting of Adriamycin 120 mg/m^2 IV on day one, Vincristine 2 mg IV 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/m^2 IV day one and Cytosine Arabinoside 3,000 mg/m^2 IV over two hours on 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 progressing, 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 120 months. Of the six patients with diffuse mixed lymphoma one demonstrated progression, one relapsed as PDLL, and four remained in complete remission from lymphoma at 109, 121, 127, and 143 months, but the latter had developed prostatic cancer and adenocarcinoma of the tongue. The 25 patients with large cell lymphoma included 11 women and 14 men with the median age of 52 years (20-65). The Ann Arbor stages were IIA 6, IIIA 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 enter remission and three died in complete remission during induction, one due to toxicity, one to her second myocardial infarction, and one to hepatitis. There were three other deaths in remission, one of adenocarcinoma, and two due to myocardial infarction. There were two CNS relapses at 8 and 21 months, the first being treated successfully (the patient is alive at 153 months) 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, 84% entered complete remission and 39% are alive at a median of ten years of follow-up, 45% of those with large cell or mixed lymphoma. Cell type, but not stage, seemed to impact on prognosis. New approaches are necessary in order to cure these diseases.

T 183 CHOP TREATMENT IN EIGHTY CASES OF INTERMEDIATE AND HIGH GRADE NON - HODGKIN'S LYMPHOMAS.

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In our Institution, in last decade, we treated with CHOP regimens 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); some 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 O=58, 1=13; 2=5; 3=4. The histology according to the Working Formulation was D=3; E=4; F=24; G=26; H=18; I=5.

20% of pts had bulky disease and the same percentage had mediastinal or bone marrow involvement. 32 pts were in stage I-II and 48 in stage III-IV. Only 20/80 pts had sistemic symptoms.

The CR rate was 64% with a CR+PR rate=89%. The 3 years DFS and OS were respectively 83% and 63%. 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 O vs 1 or > 1 adverse prognostic factors for survival,confirmed a decrease both in CR and OS rate as shown in the table below:

N. prognostic factors	%CR	% OS (3 years)
0	92	91
1	80	77
2	50	61
3	25	25
4	*	*

No pts 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 of the most recent data. Further it seems important to state an uniform staging system to identify the subgroups of pts that need effectively new and more aggressive therapy.

T 184 m-BNCOD CHEMOTHERAPY IN NON-HODGKIN'S LYMPHOMA (NHL)

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We have previously reported (Lugano 1990, Abstract T-64) on the efficacy and toxicity of m-BNCOD in NHL. From June 1986 to December 1991 we treated 57 patients (pts.) with untreated, HIV negative, intermediate and high grade NHL, age over 18. Pts were 41 male, median age 56 (15 pts over 65), PS 0-2 in 40, "B" symptoms in 65%; histology was intermediate grade in 45 (27 Diffuse Large Cell), 12 high grade; Ann Arbour stage was I-II in 19 (15 bulky), IV in 26; extra nodal sites (ENS) were bone marrow (BM) 19, digestive tract 9, lung/pleura 9; 12 pts had 2 or + ENS; LDH was over 400 u/l in 44%.

Pts were treated mostly as outpatients. Main toxicity (55 pts and 377 cycles evaluable) was hematological with leucopenia 2-3 in 23% of the cycles (anemia and thrombopenia were negligible); mucositis 2-3 in 5% of the cycles; neurotoxicity 1-2 in 9% of pts; alopecia 1-2 in 42% of pts (no hair loss in 58%); cardiac rythm disturbances affected 3 pts and 1 patient had congestive heart failure; 26 of 55 pts suffered infection (mostly upper respiratory tract, no admission required); there were 6 treatment related deaths (3 infectious, 1 gastro-intestinal toxicity, 1 congestive heart failure, 1 unknown). The q. 21 day schedule was accomplished in 62% of the cycles, the other having a median delay of 7 days (unrelated to BM status or the number of cycles - delay in cycles 2 to 4 not significantly different from delay in cycles 5 to 7 or 8 to 10). The total dose of Cyclophosphamide and Mitoxantrone was 75% or more of planned in all pts; 1/3 of pts had less than 75% of the planned dose of Methotrexate.

Results are as October 1992 (with 21 pts alive, 27 dead, 9 lost to follow up); 49 pts are evaluable for response. Overall Response Rate is 77% with CR 47% (23/49) and PR 30% (15/49); one patient had CR after localized Radiotherapy and 2 pts had CR after less agressive chemotherapy (making CR 53%). 11 pts relapsed 5-58 months (median 16) after CR; 10/11 pts relapsed in previously involved sites; 7 of 9 who had new biopsy had the same histological subtype (1 relapsed as low grade NHL and 1 as Hodgkin's disease). Overall and CR survival are 40% and 70% respectively at 76 months. Median time to treatment failure is 25 months and median CR duration is 36 months

In spite of unfavourable prognostic factors in this population, our results are comparable to those achieved elsewhere.

T 185 CONSOLIDATION CHEMOTHERAPY WITH A REGIMEN OF THIRD GENERATION IN NON-HODGKIN'S LYMPHOMAS.

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Modern chemotherapy regimens obtein high rates of complete remission (CR) 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 occour 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 efficaciouses (Doxorubicin and Cyclophosphamide) in NHL and other drugs non-cross resistent. We report results on 54 patients (pts) in first CR after 3-6 cycles (median 5 cycles) of the protoco Fi2 (Doxorubicin 40mg/mq ev. day 1, Vincristine 1,4mg/mq ev day 2 and 9, Bleomycins 10mg/mq ev. day 2,3 and 9,10, Cyclophosphamide 300mg/mq ev. day 4.5 and 11.12, Prednisone 40mg/mq orally from day 1 to day 12) treated with 2 cycles of chemotherapy regimen Fi4/85 including BCNU 100mg/mq ev. day 1, Doxorubicin 50mg/mq ev. day 1, Etoposide 60mg/mq ev. day 1,2,3,4, Vincristine 1mg/mq ev. day 2, Cyclophosphamide 600mg/mq ev. day 3 and 4, Ara-C 300mg/mq ev. day 18, Methotrexate 150mg/mq ev. day 19 (with rescue of Citrivorum factor), Prednisone 40mg/mq orally for nineteen days. All pts are evaluable and the median follow-up is 36 months (range 13-91 months). 27 pts are females, 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, 39 are asymptomatic, 34 presents more than two disease localizations and 11 pts have bulky disease. There have been five relapses (9%) after a median period of 19 months (12-30 months). Age and tumor burden have influenced relapses. Three pts have died, two for lymphoma and one for infectious complicance. The overall survival (OS) is 86% with a median follow-up of 36 months and disease free survival (DFS) is 84%. Neither OS nor DFS are influenced by the prognostic factors analysed.

T 186 CVP vs CHOP in Intermediate and High Grade Non-Hodgkin's lymphoma

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Objectives : To compare the outcome,survival rates of intermediate and high grade Non-Hodgkin's lymphoma (NHL) patients treated with CVP or CHOP regimens and to determine factors that influenced the remission.

Design : Randomized, prospective study

Setting : Songklanagarind university hospital

Patients :122 adult patients with stage II-IV NHL during August 1988 - January 1992 were studied.The follow up time ranged 1-45 months.

Intervention :Patients were treated with cyclophosphamide, vincristine and prednisolone (CVP) or cyclophosphamide, adriamycin, vincristine and prednisolone (CHOP). Response was categorized as : complete response (CR), partial response (PR), stable disease (SD) and no response (NR).

Result : male : female was 1.4 : 1. Age ranged 15-83 years (median 51 years). Majority of histologic type (85%) were intermediate grade NHL, most of which were diffuse large cell. Fifty one patients were treated with CVP and 58 with CHOP.Overall response rate (CR&PR) in CHOP group was higher than CVP group (93% vs 76%, p=0.014) and also CR rate (66% vs 43%, p=0.02)

Good performance status, no involvement of paraortic, retroperitoneal and pelvic nodes and normal level of enzyme LDH were favorable prognostic factors for CR. These factors were also important for survival and disease - free survival(DFS) and allowed us to identify three distinct risk groups of patients with good, intermediate and poor prognosis, with 3-year DFS rate of 100%, 60% and 37% and 3-year survival rate of 85%, 35% and 28% in CHOP treated patients. These risk groups also had a correlation with CR rates and with relapse rates.

Conclusion : CHOP gave higher overall response and CR than CVP. A prognostic risk model constructed on the basis of the involvement of paraaortic, retroperitoneal and pelvic nodes and LDH levels indentified 3 distinct risk groups. CHOP were effective in NHL at low or intermediate risk, however we needed further studies to reduce relapse in intermediate risk patients. The poor - risk groups did poorly and they may be benefit from more aggressive therapeutic approaches.

T 187 MEP: MITOXANTRONE, ETOPOSIDE AND PREDNISONE - AN EFFECTIVE REGIMEN FOR RELAPSED LOW AND INTERMEDIATE GRADE NON-HODGKIN'S LYMPHOMA (NHL).

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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 the efficacy and toxicity of the MEP regimen. Mitoxantrone 10 mg/M^2, etoposide 200 mg/M^2 day (d) 1 I.V. and prednisone 75 mg d 1-5 were given at 3 week intervals. Of 29 evaluable pts, 13 had low grade and 16 high grade histologies (including 6 pts with biopsy proven transformation from low grade NHL). Median age was 65 years (range 36-85). 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 (stomatis, alopecia) was mild and infrequent and no cases of cardiotoxicity was 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.

T 188 FULL-DOSE CHOP CHEMOTHERAPY IN ELDERLY PATIENTS WITH AGGRESSIVE NON-HODGKIN'S LYMPHOMA.

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Prognosis of aggressive non-Hodgkin's lymphoma (NHL) in the elderly is poor. One of the reasons may be the tendency to reduce the dosage of chemotherapy agents from the start, in order to avoid the expected increased toxicity in old age. To establish the feasibility and safety of full-dose CHOP chemotherapy in elderly patients (pts), we analyzed 2 groups of previously untreated pts with diffuse large-cell NHL ≥ 65 y old. Between 1977 and 1986, 36 pts (median age 71, range 65-79, 58% stage III-IV, 33% "B", 56% bulky) received the CHOP-I regimen, which included a deliberate dose attenuation (usually by 50%) of cyclophosphamide (C) 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 1991, 17 comparable pts (median age 73, range 66-88, 59% stage III-IV, 41% "B", 53% bulky) received the CHOP-II regimen, in which full-dose CHOP was given from the start to pts aged 65-74 y old with only 25% reduction of C and A in pts ≥ 75 y old. The median of the initial average relative dose intensity (ARDI) in all CHOP-II pts was slightly higher than in all CHOP-I pts (0.82 and 0.79, respectively). However, pts aged 65-74 y old received significantly increased initial DI in CHOP-II as compared to CHOP-I: RDI of C (RDIC) 0.91 vs. 0.77, RDIA 0.86 vs. 0.73, RDIV 0.91 vs. 0.79, RDICA 0.89 vs. 0.77, and ARDI 0.90 vs. 0.80, respectively. There was no increase in initial DI in pts ≥ 65 y old in CHOP-II. Pts aged 65-74 also got higher DI along the whole treatment course in the CHOP-II (ARDI 0.90) compared to CHOP-I (0.69). Myelotoxicity of the CHOP-II treatment consisted of 41% grade 3-4 leukopenia in the first cycle and 65% during cycles ≥ 2. In the CHOP-I group the toxicity was 22% and 28%, respectively. Five pts (4 ≥ 75 y old) in the CHOP-II group were hospitalized once for leukopenia and fever. There was no treatment-related death. In conclusion, it is feasible to give initial full-dose CHOP chemotherapy in elderly pts (65-74 y old), as they are able to receive high DI with only a moderate increase in toxicity.

T 189 Impact of dose intensity on response to BECOP in agressive Non-Hodgkin's Lymphoma.

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Malignant lymphomas rank third (≃ 10%) among patients presenting to the NCI of Egypt with a higher frequency of unfavorable histologic types and advanced disease stages at presentation when compared to patients in Europe and the U.S.A.

We have previously reported on the use of the standard BECOP 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 grade II and III NHL in which a more intensive BECOP 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 (Vincrsitine 1.4 mg/m^2, Epirubicin 40 mg/m^2, cyclophosphamide 650 mg/m^2, all IV day 1& 8, Bleomycin 10 u/m^2 IV day 15 + Prednisone 60 mg/m^2 PO days 15-21)

The study included 80 patients , 53 males and 27 females with a M/F ratio of 2 : 1. Their ages ranged between 16 and 68 years (median 45). Fifty seven patients had grade II and 23 had grade III pathologic subtypes. Four patients presented with stage I, 11 with stage II , 53 with stage III , and 12 with stage IV disease . The number of courses ranged between 1 and 9 (median 6). Complete and partial remissions were achieved in 54 and 4 evaluable patients (84% and 6%) respectively. Actuarial one year overall and disease free survivals are 78% and 67%. Toxicities were mostly of grades I and II with 4% mortality of treatment complications.

While data are still preliminary, this more dose intensive BECOP regimen achieved the best results reported for treatment of NHL patients in Egypt. Previous standard BECOP regimen demonstrated CR rate of 67% with 3-year disease free and overall survivals of 36 and 48% respectively .

T 190 FULL DOSES OF VINCRISTINE (1.4 mg/m^2) IN THE TREATMENT OF MALIGNANT LYMPHOMAS.

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The dose of vincristine (VCR) is often limited to no more than 2 mg/dose. Based on some literature data indicating that administration of full doses of VCR (1.4 mg/m^2) is safe and might be an important factor for successful therapy, we have adopted the following policy of VCR administration in our lymphoma protocols: the first dose is 1.4 mg/m^2 (without the arbitrary 2-mg limit). Patients were carefully evaluated for toxicity, and subsequent doses were reduced if necessary. One hundred four consecutive patients (31 with Hodgkin's disease and 73 with non-Hodgkin's lymphomas) were treated with full doses of VCR. Their ages ranged between 18 and 78 (median, 52 years). The average first dose of VCR was 2.44 mg (2.55 mg in males and 2.29 mg in females). The average dose (percent of the planned dose ± SD) during the first, second, and third cycles of VCR was 99.9 ± 2.5, 92.3 ± 16.5, and 90.7 ± 16.1, respectively.

The average cumulative dose of VCR given during the initial 3 cycles of VCR (percent of the cumulative planned dose ± SD) was 96.9 ± 5.8 for 30 patients treated with ProMACE/MOPP, 94.8 ± 9.6 for 29 patients treated with CHOP, and 94.0 ± 9.3 for 29 patients treated with MOPP/ABV. Relatively high doses of VCR were also given to elderly patients; the cumulative dose given to 27 patients aged >65 during the initial 3 courses was 95.4 ± 9.1. Symptoms of neuropathy developed in 96 patients (92%) and included paresthesias in 77%, muscle weakness in 37%, muscle cramps in 45%, muscle/bone pain in 23%, constipation ± abdominal pain in 59%, and jaw pain in 24% of the patients. In most patients, symptoms were mild or moderate and resolved after discontinuation of VCR.

We conclude that the dose intensity of VCR in various lymphoma protocols can be markedly increased by giving full doses. Toxicity with such a policy of VCR administration is acceptable.

T 191 AN INTENSIVE SHORT-TERM IFOSFAMIDE CONTAINING PROTOCOL FOR NON-HODGKIN'S LYMPHOMA: FURTHER STUDIES.

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Since January 1986 we have been treating pediatric non-Hodgkin's lymphoma with a short-term combination chemotherapy. So far 102 patients were treated, their mean age is 8.6 years. Patients were classified as low risk if all of the abdominal tumour was resected or there was a single extra-abdominal site of involvement other than the media stinum. All other patients were classified as high risk. Treatment was with alternating cycles of chemotherapy (A& B). The low risk received four cycles, and the high risk eight cycles of therapy. Cycle A consisted of: Ara C cyclophosphamide, vincristine and adriamycin. Cycle B : 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. Most of the patients had abdominal tumours; 75%. These were dealt with surgically, aiming if possible at 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 60% of cases had small non-cleaved type of lymphoma. 65% of patients had febrile neutropenic episodes managed with the appropriate antibiotics. The responses achieved were: 82% complete response, 10% partial response, and 8% no response. Follow up of patients for a period of 4 months to 6 years, the continuous complete remission is still maintained in 81% while the overall ssurvival is 78%. The study is still ongoing with more cases to be accrued. It has the advantage of being of short duration during induction, hence good comliance. Moreover there is no maitenance therapy, and no cranial irradiation, so no future untoward sequelae. The most important result of this treatment is the 82% complete response and 81% continuous complete response so far achieved, with long duration.

T 192 OBSERVATION ON RESPONSE OF NON-HODGKIN LYMPHOMA TO A NEW PROTOCOL — COP-PYAM REGIMEN.

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Incidence of non-Hodgkon lymphoma (NHL) is much higher than that of Hodgkin's disease (HD) in China. COPP is a conventional regimen for NHL. The response to which is less satisfactory than that in HD. It is considered that the procarbazine in COPP regimen is less effective in NHL than in HD and a replacement with adriamycin to form CHOP regimen was suggested to improve the response. With our previous experience, there was no superiority with CHOP in management of NHL. A new protocol COP-PYAM was developed in my hospital for a therapeutic trial for NHL and a comparison among the responses to COPP, CHOP and COP-PYAM was made.

PATIENTS All 60 NHL cases were diagnosed and staged by pathological and clinical examinations. They aged 13 — 64. 40 males and 20 females. 9 cases in stage I, 20 in II, 18 in III and 13 in IV. 31 cases in stage A and 29 in B. Patients were divided into 3 groups. 21 for COPP, 15 for CHOP and 24 for COP-PYAM. Clinical situation for each group was comparable in age, sex and clinical stage.

PROTOCOL (1) COPP: Cyclophosphamide (CTX) 600 mg/m^2, iv, d 1 and 8, Vincristine (O) 2 mg, iv, d 1 and 8, Procarbazine (M) 50 mg, po, tid, d 1 — 14, Prednisone (PN) 20 mg, po, tid, d 1 — 14. Interval between courses were 14 days. (2) CHOP: O 2mg, iv, d 1, CTX 600 mg, iv, d 2, Adriamycin (A) 40 mg, iv, d 3, PN 20 mg, po, bid, d 1 — 5. Interval between courses were 16 days. (3) COP-PYAM: CTX 400 — 600 mg/m^2 , iv, d 1, O 2 mg, iv d 1, A 40 — 60 mg/m^2, iv, d 1, M 50 mg, po, tid, d 1 — 10, PN 20 mg, po, tid, d 1 — 10, Pingyangmycin (PY) 15 mg, iv, d 10. Interval between courses were 14 days.

RESULTS (1) Complete remission rate (CR) of COP-PYAM was 70.8 % which was higher than those of COPP (38.1 %) and CHOP (40.0 %) ($p < 0.05$). (2) Responsive rate (RR) of COP-PYAM was 91.6 % which was higher than those of COPP (66.7 %) and CHOP (46.7 %) ($p < 0.05$). (3) There were no significant differences of the CR and RR between COPP and CHOP groups ($p > 0.1$). (4) The time at which the tumor mass started to regress in responders in 3 groups was identical (within 1 — 2 courses). (5) The duration to acheive CR after initiation of treatment were 36.2 (10 — 58) days for COP-PYAM, 98 (42 —154) for COPP and 58 (26 — 110) for CHOP. The duration for COP-PYAM was the shortest ($p < 0.05$). (6) Side effects: Nausea and vomiting were the most frequent side effects (64.3 %) in COPP group. In CHOP group, the alopecia (50.0 %). For COP-PYAM group, they were 81.3 % and 43.8 % respectively. There were about 1/3 patients suffered from

(continue)

leucopenia ($<4X10^9$ /L) during therapy in each group. All the side effects were mild and tolerable.

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

A BRIEF INTRODUCTION OF PINGYANGMYCIN Pingyangmycin is a unique medicine developed in China, which is produced from Streptomyces Pingyangensis n. sp. isolated from soil at Pingyang county of Zhejiang province in southeast China. Components of Pingyangmycin are quite similar to those of Bleomycin with a dominant A5 which possesses higher anti-neoplastic activity, broder anti-tumor spectrum and lower toxicity (esp. pulmonary toxicity). In addition to lymphoma, Pingyangmycin is indicated for a variety of malignancy with mild damage to hematopoietic and immune systems.

T 193 EVALUATION OF RESULTS OF CHEMOTHERAPY IN NON_HODGKIN'S LYMPHOMAS AMONG EGYPTIAN CHILDREN(1975-1984).

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Egyptian paediatric non-Hodgkin's lymphoma cases treated at the National Cancer Institute,Cairo University during the period 1975-1984 received either the COP or the St. Jude's regimens.Eighty -five cases were included in this retro-spective study below the age of 16 yrs.The median age was 7 yrs.,with a male to female ratio of 2.9 .Clinically,abdominal presentation was encountered in 43.5% of cases,followed by peripheral lymphadenopathy (42.9%),and mediastinal lymphadenopathy(5.8%).Using Murphy's staging system,63.5% of cases presented with extensive disease (stages III and IV).Pathologically,following the New Working Formulation 45.8% of cases were of the small non-cleaved type,35.3% lymphoblastic, 8.2% mixed, 7% large cell, and 3.5% unclassified type. Fourty-one cases during the period 1975-1980 were treated with the COP regimen,and 44 cases during the period 1980-1984 with the St.Jude's regimen.Complete remission was attained in 48.7% of cases in the first group versus 87% in the second one,and partial remission was 46.3% and 9% respectively.In the COP group, the 10 yrs Survival Rate(SR),and the Disease-Free Survival (DFS) were 28% and 26.5% versus 55.3% and 55% respectively. Among cases with abdominal presentation,the 10 yrs. DFS was 32% in the COP vs.73% in the St.Jude's,both figures being superior to those among the peripheral lymphadenopathy group(25.7% and 40% respectively).Limited disease reported a SR and DFS of 61.8% and 92% in both groups vs. 6% and 35% among the extensive disease cases.

T 194 INDUCTION AND CONSOLIDATION THERAPY FOR NON - HODGKIN'S LYMPHOMA (NHL) IN CHILDHOOD.

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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 of children had the unfavourable prognosis : a large tumor, lymphoblastic variant of a tumor process, intoxication symptoms presented as anemia, sweating, fever. The treatment consisted of induction, its consolidation and reinduction. The induction therapy was given with the ACHOP-3 regimen (cyclophosphamide 1,000-1,500 mg/m^2 + oncovin 1.4 mg/m^2 + adriamycin 30 mg/m^2 + prednisolone 2-3 mg/kg, weekly, for 6 weeks). Intrathecal methotrexate (12 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 leunase (10,000 U/m^2), then 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 (77.2%) achieved complete remission, 3 patients (17.4%) - partial remission, 2 patients died of the disease progression. Mostly children tolerated combination chemotherapy in standard and high doses satisfactorily. The side-effects were reversible. The intensification of regimens for pa - tients with risk factors allowed to improve the treatment outcome.

T 195 RESULTS OF A TREATMENT OF CHILDREN SUFFERING FROM NON-HODGKIN'S LYMPHOMA (T-TYPE)

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At the Hematology-Oncology Department Children's Clinic Šalata Medical Faculty Zagreb Croatia, 78 children (average age 7,8 years) were treated for non-Hodgkin's (NHL) lymphoma (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-84 1.01.1984 - 31.12.1986.; 15 children), Protocol YU-87 (1.01.1987 - 31. 12.1990.; 28 children).
The first complete remission was achieved in 29 patients (82.8%) treated with Protocol YU-77, in 13 (86.6%) treated with Protocol YU-84 and in 24 patients (85.7%) treated with Protocol YU-87 ($p > 0.05$). The first relapse was observed in 13 patients (37%) treated with Protocol YU-77, in 3 patients (20%) treated with Protocol YU-84 and in 4 patients (14.2%) treated with Protocol YU-87; the differences are statistically not significant ($p > 0.05$).
The first hematological relapse was observed in 7 patients (20%) treated with Protocol YU-77 and in 2 patients (13.3%) treated with Protocol YU-84; 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-84; 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 (3.5 %) 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-84 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.

T 196 COPP CHEMOTHERAPY FOR ELDERLY PATIENTS WITH INTERMEDIATE AND HIGH GRADE NON-HODGKIN'S LYMPHOMA.

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The efficacy of COPP chemotherapy [Cyclopposphamide 450 mg/m² IV D1 & 8, Vincristine 1.4 mg/m² IV D1 & 8, Procarbazine 100 mg/m² PO D1-14 and Prednisone 40 mg/m² PO D1-14] in the treatment of elderly patients with aggressive non-Hodgkin's lymphoma was evaluated. 141 consecutive patients above and 231 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, 65 had BACOP and 47 had m-BACOD). 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 :

Clinical Stage		COPP Chemotherapy	Doxorubicin Containing Regimens	P-value
I	CR rate	13/17 (76%)	27/31 (87%)	NS
	Relapse	1/13 (8%)	2/27 (7%)	NS
	5-yr DFS (CR pts)	89%	82%	NS
	5-yr Survival	76%	78%	NS
II	CR rate	10/19 (53%)	38/44 (86%)	0.01
	Relapse	3/10 (30%)	6/38 (16%)	NS
	5-yr DFS (CR Pts)	61%	72%	NS
	5-yr Survival	34%	54%	0.05
III	CR rate	12/24 (50%)	40/49 (81%)	0.015
	Relapse	3/12 (25%)	12/40 (30%)	NS
	5-yr DFS (CR Pts)	73%	58%	NS
	5-yr Survival	31%	45%	0.05
IV	CR rate	18/81 (22%)	60/107 (56%)	0.001
	Relapse	7/18 (39%)	236/60 (60%)	NS
	5-yr DFS (CR Pts)	56%	38%	NS
	5-yr Survival	20%	32%	0.05

Multivariate analysis on patients receiving COPP revealed that the independent prognostic variables significantly determining CR rate and survival included clinical stage (p=0.04) and serum lactate dehydrogenase level (p=0.001). There were ten (7%) treatment related deaths. A few nonrandomised series has reported the results of using doxorubicin containing regimens to treat elderly patients with aggressive NHL. The overall CR rate ranges from 30+% to 65% and the long term survival 25% to 36% 36%. These overall results are comparable to that of COPP in our patients. Further clinical trials are essential to determine the optimal therapy for this group of patients.

T 197 P.VABEC REGIMEN FOR AGGRESSIVE NON HODGKIN'S LYMPHOMAS (NHL) IN ELDERLY PATIENTS: 3 YEARS FOLLOW-UP.

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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-VABEC regimen. This regimen includes the alternated somministration of: Adriamycin (30mg/sqm), Etoposide (100mg/sqm), Cyclophosphamide (350mg/sqm), at weeks 1-3-5-7-9-11; Vincristine (1,2mg/sqm), Bleomycin (5mg/sqm) 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 cells and 1 small non cleaved NHL. Nineteen pts had a stage II, 25 III, 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. Fourty-five (75%) achieved a CR, 10 (17%) a PR, no response 5 (8%). So far 21 pts have relapsed (18 CR, 3 PR) and 3 pts died while in CR. After a median follow-up of 25 months actuarial 3 yrs overall survival (OS), DFS and EFS were respectively 55%, 51% and 44%. No statistical difference for OS, DFS, and EFS were observed between the group treated with 8 or 12 cycles. Hematological toxicity was mild in all patients, however a worst neurological and cardiovascular 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-VABEC 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'SLYMPHOMA (NHL) IN ELDERLY PATIENTS.

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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 q28 days (Prednisone 50mg po x 14 days, Oral Etoposide 50mg po x 14 days and Mitoxantrone 8mg/m² iv day 1). Twenty one 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 7(33%) have achieved CR (4-68+ 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. Of the 11 previously treated pts 1 achieved a CR (52+ wks), 3 a PR (3-56+wks) and 3 are currently responding. One pt has not responded and 3 are not yet evaluable. Median survival has not been reached but 24 pts are alive 4-60+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 (46%) 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 wks of either the first or 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 tolerated ambulatory care regimen for elderly pts with NHL. Enrolment on this trial continues.

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T 199 NON-HODGKIN'S LYMPHOMA IN THE ELDERLY. A PILOT TRIAL OF THIOTEPA, NOVANTRONE, ONCOVIN AND PREDNISONE (T-NOP).

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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/IV intermediate-high grade NHL; CALGB PS 0-2; ejection fraction ≥40%; adequate renal and hepatic function; normal CBC. The regimen is: thiotepa (T) 20 mg/m² iv, Novantrone (N) 10 mg/m² iv, vincristine (O) 1 mg/m² (max 2 mg) iv, prednisone 60 mg/m² po d1-5. T and N are escalated by 25% each cycle until nadir AGC (absolute granulocyte count) ≤ 1000/μl and are de-escalated 25% if nadir AGC ≤ 1000/μl and patients are symptomatic (i.e. fever). Drugs are given every 21 days. Two pts had dose escalation without growth factors. 9 pts. have been entered. Patients: 8 female/1 male, mean age 78.1 yrs. (median 77; range 68-87). Pathology: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 four 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, constipation, mucositis, alopecia. 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.

T 200 TREATMENT OF NON-HODGKIN'S LYMPHOMA (NHL) IN ELDERLY: RESULTS OF A NEW CHEMOTHERAPY REGIMEN (MiCEP).

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Elderly patients (pts) (65 years or older) with NHL are usually not treated with chemotherapy regimens commonly used in adults. We want to analyse preliminar results of a chemotherapy regimen specifically devised for elderly pts, MiCEP, which include: Mitoxantrone 7 mg/mq first day, Etoposide 50 mg/mq first, second, ninth and tenth day, Cyclophosphamide 300 mg/mq second, third, tenth and eleventh day all endovenous and Prednisone 40 mg/mq for eleven days orally. From october 1989, 66 consecutive untreated pts aged 65-87 mean 72 years entered this study. 37 were women, 35 were III/IV stage. According to Working Formulation (WF) 25 pts were low grade, 40 intermediate-high grade and 1 was not classified. 22 pts have positive anamnesis for cardiac or metabolic or neoplastic disease. Chemotherapy was well tollerated and only 29/327 (9%) cycles were delaied or omitted for leukopenia. According to WHO criteria leukopenia was grade 3 in 8 pts and 4 in 2 pts. Extrahaematological toxicity was limited to alopecia (20 pts grade 2-3) and vomiting (15 pts grade 2-3). All pts are evaluable for response to therapy; 43 pts (65%) achieved complete remission (CR) and only 4 pts (6%) were considered non responders (NR). Stage and the number of lymphonodal stations involved influenced the achievement of CR (better I/II vs III/IV stage, $p<0,001$ and $<=2$ vs >2 stations, $p<0,001$). The overall survival (OS) with a median follow-up of 16 months (range 3-37) was 60% and the only one prognostic factor significant for survival was response to therapy (CR vs PR/NR $p<0,001$). 19 pts died: 5 for unrelated causes (neither lymphoma nor complicance of chemotherapy). 5 pts relapsed after a median period of 4 months (range 2-6) from CR. 35 pts are actually alive and disease free with a median follow-up of 10 months (range 2-29).

T 201 MACOP-B FOR THE TREATMENT OF HIGH AND INTERMEDIATE GRADE NON-HODGKIN LYMPHOMA IN ELDERLY

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Between Nov. 1990 and Jun. 1992, 26 patients over 65 years old (medium age 72 ± 6) with high (10 cases) or intermediate grade (16 cases) non-Hodgkin Lymphoma (NHL) were treated with MACOP-B as upfront therapy. At the end of the therapy, 14 (54%) achieved a complete remission (CR) and 4 (15%) a partial remission (PR). At medium follow-up of 8 months, 75% of patients continued to be in CR. Treatment-related death occured in 4 (15%) patients because of septic complications after prolonged granulocytopenia (3 cases) and of cardiac infarction (1 case). Mucositis, predominantly with grade III° or IV°(according WHO critera), appeared in over 90% of patients. Neurotoxicity was usually mild, mostly grade I° or II°, though non rapidly reversible. Granulocytopenia was the major side effet and delay of treatment occured in 90% of patients. Severe anemia and thrombocytopenia was a rare event. All patients developed mild cushingoid sumptoms in the second half of the treatment, which were rapidly reversible after the end of the therapy. In this group of old patients, the response rate with a CR of 54% was significantly lower than the reported frequence of CR in young or middle-aged subjects (ranging from 63.3 to 75.0%). Since improved cytoreduction by MACOP-B is likely related to it's early and high-dose intensity (considered to reduce the development of drug resistance), the unavoidable delays (due to granulocytopenia) reduce the efficacy of this therapeutic regimen in elderly. Moreover the frequence of treatment-related death is unacceptably high. In conclusion MACOP-B does not show substantial advantages for the therapy of old patients with NHL, only the extensive use of G-CSF for preventing neutropenia could improve the response rate and reduce the high frequence of fatal toxicities.

T 202 PRELIMINARY REPORT OF A DOSE-INTENSIFIED REGIMEN WITH COMLA/ABP FOR INTERMEDIATE AND HIGH GRADE LYMPHOMAS IN AN ELDERLY PATIENT POPULATION.

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Based upon our previous experience with COMLA/ABP in which we found Cyclophosphamide (CTX) to be the most active agent, we have treated 12 elderly patients (pts) with newly diagnosed Non-Hodgkins 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/m² (with mesna), Vincristine 2.0 mg d 1, 8 + 15, Methotrexate 120 mg/m² d 22, 29 + 36, Leucovorin rescue 10mg/m², Ara C 1g/m² d 22, 29 + 36, Adriamycin 50 mg/m² d 43, Bleomycin 10 units/m² d 43, 50 + 57, Prednisone 60 mg d 43 - 47). The initial dose of CTX was 3.0 g/m² except in pts older than 70 who received a dose of 1.5 g/m². Prophylactic Ciprofloxacin was initiated on day 8 (500 mg BID) until recovery of the neutrophil count over 500/mm³. The median age of the pts was 62 yrs (range 51-73 yrs). Histologic diagnoses include diffuse large cell (8 pts), 1 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 toxicity, one pt had residual mild pulmonary fibrosis; otherwise the regimen was well tolerated. The maximum dose of CTX given so far is 4 g/m². We have not observed any grade 4 toxicity with regards to WBC nadir (median 0.6/mm³, range 0.2-1.2), and platelet count (median 45, range 29-123). No pt required blood transfusions; no bleeding complications were observed. None of the pts required hospitalization for neutropenic fevers. Even in the absence of growth, factors high doses of myelotoxic chemotherapy could be administered safely. No pt developed hemorrhagic cystitis nor vinca-induced grade III or IV neurotoxicity. The treatment was well tolerated by pts up to age 73 and we conclude that high doses of CTX can be given in the COMLA/ABP combination with prophylactic antibiotic support. However, more pts and longer follow-ups are needed to determine the overall safety and efficacy of this regimen in elderly pts.

T 203 TREATMENT OF POOR PROGNOSIS NON-HODGKIN'S LYMPHOMA (NHL) IN THE ELDERLY WITH NSO (MITOXANTRONE, PREDNIMUSTINE AND VINCRISTINE)

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Elderly patients with poor prognosis NHL treated with combination chemotherapy have a lower response rate and poorer survival than their younger counterparts. This lower response and survival rate can in part be attributed to the toxicity of treatment and the subsequent reduction in dose intensity of chemotherapy. We report on preliminary results with NSO chemotherapy in elderly pts. (≥60 years) with poor prognosis NHL. Patients are treated with Mitoxantrone 10-12mg/m² IV on day 1, Prednimustine 100 mg/m² orally day 1-4, and Vincristine 1.4mg/m² IV day 1. The regimen is repeated every 21-28 days. Eighteen patients have been entered on study. Fourteen are evaluable for response. Median age was 72 (range 61 - 77) with 7 males and 7 females; 5 - Stage II, 6 - III and 3 - IV disease. After four cycles 5 patients were in complete remission, 6 had partial remission, two had stable disease and one had progressive disease. The overall response rate is 79%. The major toxicity was hematological with one patient dying of complications of neutropenic sepsis. Eight patients developed > grade 3 WHO hematologic toxicities. Three patients developed > grade 2 WHO toxicities (nausea, vomiting, peripheral neuropathy). At last follow-up three patients have died from disease progression. NSO appears to be a tolerable regimen in this elderly group of patients with poor prognosis NHL. This study continues to accrue patients and an update of the data will be presented (supported by a grant from Cyanamid Lederle Canada Inc. and Pharmacia Canada Inc.)

T 204 HIGH-DOSE THERAPY WITH AUTOLOGOUS BONE MARROW TRANSPLANTATION IN NON HODGKIN LYMPHOMA OVER 50 YEARS OF AGE: THE CENTRE LEON BERARD EXPERIENCE.

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25 patients, 50 year old or over, with bad prognosis lymphoma (18 males, 7 females, median age 55 (50-70) were treated 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 intracanial intermediate grade lymphomas (one cerebral, one cerebral meningeal) 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 mediastinal mass at diagnosis.
- 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), Asta-Z (1 pt), not done in 1 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 TBI, 1 hyperfractionnated TBI.

Results :

3 toxic deaths occured at day 9 aspergillosis, 20 hemorrhage and sepsis, 45 isolated thrombocytopenia.

at first evaluation (60 days) : 19 pts were in C.R. (7 continuous C.R.), 1 N.R., 2 P.R.

at 1992/12/31 : - 5 pts died in relapse (2,6,6,18,24 months after graft).
- 1 pt suicided in CR 3 years after graft.

16 pts are alive :
- 4 pts are alive in relapse
- 12 pts are presently disease free.

Among the 5 patients grafted for low grade lymphomas : one is in CR + 22 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 relapse, 8 are in CR with a median of 58 months (18-122).

Recovery was : WBC > 1000 : 23 d (13-60) - PN > 500 : 21 (13-500)
Plt > 50.000 : 21 (13-150)

Conclusion : In 50 year old and over patients grafted, toxic death rate and morbidity is not different from younger patients. Results are similar.

T 205 IFOSFAMIDE, MITOXANTRONE AND ETOPOSIDE AS SALVAGE THERAPY IN NON HODGKIN LYMHOMAS

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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. Mesna was given as uroprotector.

Stages according to the Ann Arbor classification were I/6, II/4, III/8 and IV/38 patients. 33 patients suffered from high grade,23 from intermediate grade NHL.

Toxicity according to the WHO recommendation was as follows: Anemia 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 s (7/23 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 206 VINDESINE AND BLEOMYCINE IN DIFFERENT COMBINATIONS AS SALVAGE TREATMENT IN NON HODGKIN LYMPHOMAS (NHL)

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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 analysed data of 100 patients(pts.) 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 (Kiel classification), Ann-Arbor classification was : I/5, II/7, III/18 and IV/70 pts. 20 pts. received only bleomycine/15mg(bl) and vindesine/5mg(vi), in 41 pts. bl/vi was combined with methotrexate (30 mg) and asparaginase (10.000 IE), in 23 pts.bl/vi was administered with alkylating drugs and in 8 pts. bl/vi was combined with cis-platinum; in 8 pts. VIM-schedule (VP-16, mitoxanthrone and ifosfamide) was alternately applied to bl/vi. 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 (3-156m).

Response to Prior Chemotherapy	n	Response to Vi/Bl CR	PR	NR
Relapsed	32	6	6	20
Refractory	68	8	20	40

We conclude that bleomycine and vindesine is an effective combination in the treatment of refractory and relapsed NHL and is well tolerated in elderly patients.

T 207 SALVATAGE TREATMENT OF MALIGNANT LYMPHOMAS,NEW COMBINATION OF IDARUBICIN-VINORELBINE-CARBOPLATIN-PREDNISON.PILOT STUDY.

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A great percentage of patients with malignant lymphomas shows disease relapses after complete remission (R.C.).This event has a relation with some unfavorable prognosis variables and particularly with a big neoplastic bulk.Another explanation of first line treatment failure should be the phenomenon of spontaneous mutations that take to the cellular resistance against some antiproliferative drugs.This is the starting point to develope polichemotherapeutic combinations 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 enlisted 18 patients (12 males,6 females,with an age range of 18-70):5 patients with H.L.,with different Ann Arbor stages and istological types; 13 with N.H.L. intermediate and high grade of disease.The schedule of treatment consist of:IDARUBICIN 10mg/m^{2}i.v.(day 1);VINORELBINE 20mg/m^2 (day 1 and 5);CARBOPLATIN 300mg/m^2(day 1);PREDNISON 100mg(from day 1 to 5).We foresaw 6-8 cycles of treatment with 3 weeks interval.All patients enlisted were valuable.Approximately 55% (10) of patients respond to this treatment (5 R.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(2° cycle) because gastrointestinal occlusion caused by underlying gastrointestinal disease.We observed low grade of haematological toxicity (WHO 1-2),while extrahaematological toxicity was pratically absent, with the exception of a cutaneous erythema-blistered-oedema of limb seat of treatment.In conclusion these preliminary results show effectiveness of proposed association:in terms of responder patients,considering that our cases includes patients in 3°and 4°relapse, and in terms of good tolerance considering heavy previous treatment.

This new association should pave the way for further therapeutic progress also in first line treatment.

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-C.Ferné et Al:Methyl-gag,Ifosfamide,Navelbine,Etoposide,as salvatage therapy for refractory or relapsed Hodgkin's disease.
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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.

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From 7/88 to 8/92, 22 patients(pts) with refractory or relapsed NHL, non 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(gr.) 0 = 10 ; gr.1 = 8 ; gr.2 = 3 ; gr.3 = 1. Previous treatment : Refractory : 19 Relapse : 3. Number of prior therapeutic regimens : median : 2 (1-5). 4 pts were previously treated with CDDP, 19pts with Vinca-Alcaloids. Prognostic factors : B symptoms in 7/22 pts, LDH >or= 1,5 X N in 4/22 pts, bone marrow infiltration in 14/22 pts Histologic grade : 1/22 pts high gr., 6/22 pts intermediate gr., 15/22 pts low gr. (CLL:3). Treatment : starting dose was 65 mg/s.q.m. then up to 130mg/s.q.m every 3 weeks, (intrapatient dose escalation when toxicity was lower than gr.2). 65-99 mg/s.q.m.: 2 pts., 100-129 mg /s.q.m.: 5 pts,130mg/s.q.m.: 15 pts. 133 cycles were delivered. Median no. of cycles/pt : 4 (1-26). Median total dose : 390mg/s.q.m (100-3290). Results: Major responses were observed at all dose levels. Overall response (CR+PR) : 9/22 pts (41%). 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 pt. 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 : neurologic : reversible dysesthesia in 4/133 cycles, gr. 3-4 : hematologic : Leucopenia, thrombocytopenia in 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 relapsed/refractory intermediate and low gr. NHL. Its safety profile (devoid of renal toxicity and minimal hematologic toxicity) makes of L-OHP® a good therapeutic alternative in heavily pretreated patients and a potential compound for first line combination chemotherapy.

T 209 ORAL ETOPOSIDE ADMINISTRATION OVER A PROLONGED SCHEDULE FOR PATIENTS WITH NON-HODGKIN'S LYMPHOMA (NHL) AND CHRONIC LYMPHATIC LEUKEMIA (CLL).

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Twenty patients with NHL and CLL were treated over a long term with daily oral etoposide. 16/20 had NHL, 18/20 were previously treated with 2 or more different polychemotherapy regimens. Etoposide was incorporated in the regimens 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/m^2 per day for 21 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 40-80 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 10%, 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 intermediate grade lymphoma, low grade lymphoma and CLL were 69%, 66% and 50%, respectively. Patients with bone marrow involvement had a better response rate 76% than other patients 42%. All patients who were treated with a cumulative dose of etoposide of 2 gm/m^2 or more responded to treatment. Only 40% of patients who were treated with a cumulative dose of 1 gm/m^2 or less responded to treatment. The main toxicity was myelosupression, 50% of patients developed pancytopenia, 45% during the first course of treatment. 50% had one or more episodes of infection during treatment and were hospitalized. One drug related death occurred. Non hematologic toxicity were alopecia, gastrointestinal manifestations, headache and dizziness. These results suggest that daily oral etoposide has a high level of activity even in previously treated patients with NHL and CLL, who were exposed to etoposide in other regimens. Daily oral otoposide over a long term may be used as a salvage type approach in NHL and CLL. Dose modification is suggested in elderly patients and in patients with bone marrow involvement.

T 210 SECOND LINE TREATMENT IN RELAPISING OR REFRACTORY MALIGNANT LYMPHOMA (ML) INTERMEDIATE/HIGH GRADE.

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Treatment of relapsing or refractory intermediate or high grade ML patients remains controversial. The majority of studied schemas, produced documented CR in about 30% of patients, ussually transitory. Last years several new agents have been show efficacy in some patients. Here we present the results of an out-patient based ply-chemotherapeutic schema, as follows:

- Carboplatin 80 mgs/m2 days 1 to 5.
- Mitoxantrone 8 mgs/m2 day 1.
- Prednisone 40 mgs/m2 days 1 to 5.
- Etoposide 140 mgs/m2 days 1 to 3.

Cycles were repeated every 28 days until CR (maximun 4 cycles) + 4 consolidation cycles. Doses 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: male/female ratio 17/11, mean age 53.3 y (range 31-65 y), mean PS 1 (range 0-2). 22 cases presented with extranodal disease. A bulky disease was noted in 10 cases; B symptons were presented in 13 cases. 19 patients had 1 chemotherapeutic regime and 9 patients received 2 differents therapeutic schemas. All patients received previous doxorubicin therapy. A CR was noted in 11 patients (39%) and 8 (28%) reached PR. MDFI was 11.3 months for responding patients. The most common side effects was bone marrow depression (grade 2 leukopenia 57%, grade 3 43%). One epidode of grade 3 infection was recorded.
We conclude that theese chemotherapeutic regimen seems to be an effective therapeutic schema with acceptable toxicity and should be studied in the tratment of relapsing or refractory ML.

T 211 ADJUNCT FILGRASTIM (rG-CSF) IN DOSE ESCALATED ProMACE-CytaBOM IN INTERMEDIATE AND IMMUOBLASTIC NON-HODGKIN'S LYMPHOMA.

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Previous single and multi-institutional studies in aggressive histology lymphoma reported complete response rates with Pro-MACE-CytaBOM comparable or superior to other combination regimens. Dose reduction and delay due to neutropenia compromise intended dose intensity and may impact adversely on therapeutic efficacy. In this open label phase I/II trial, 35 evaluable patients with untreated stage II-IV intermediate grade or immunoblastic lymphoma were treated with ProMACE-CytaBOM at escalated doses of cyclophosphamide and doxorubicin in successive cohorts with Filgrastim (rG-CSF) support. Treatment consisted of 6 cycles of conventional or escalated dose ProMACE-CytaBOM q 21 d with delay of day 1 treatment for ANC<2000 and/or platelets < 100,000, and dose modification of day 8 MTX 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 postnadir ANC >2000 on two consecutive determinations. 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 7/35 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 (<25,000) of median duration <1 day was higher than in cohorts 1-3. 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.

Cohort	# Pts	CTX (mg/m^2)	ADR (mg/m^2)	ANC < 500 INCIDENCE cycles/total cycles C1	C2-6	Day 14 ANC (MEDIAN) C1	C2-6
1	5	650	25	1/5	3/23	2976	2419
2A	10	650	25	4/10	9/45	11903	11231
2B	7	650	25	2/8	1/39	7303	10040
3	3	1000	25	2/5	0/11	14043	14229
4	4	1000	50	4/6	1/13	2282	1088
5	6	1350	50	5/6	4/8	1166	2079