T 73 MACOP-B CHEMOTHERAPY FOR PATIENTS WITH DIFFUSE HISTIOCYTIC LYMPHOMA

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Thirty-nine patients (32 male and 7 female) with histologically proven diffuse histiocytic lymphoma were treated with the MACOP-B regimen (Klimo and Connors, 1985). Sixteen patients had stage IV, 5 stage III, 13 stage II, and 5 less than stage II disease. Constitutional (B) symptoms were reported by 15 patients. Results of the treatment could be evaluated in 36 patients. Nineteen patients (52.7 %) achieved complete remission (CR), 15 (41.6%) partial remission (PR), 1 patient (2.7%) showed no change (NC), and 1 patient (2.7%) had progressive disease (PD). Of all patients who achieved CR and PR (n=34) 70.5 % are currently alive (CR: 17/19 and PR 7/15; median follow up: 16 months). WHO grade IV toxicities were observed for leukopenia in 7 patients, anemia in 1 patient, and thrombocytopenia in 1 patient. One patient died due to septicemia during myelosuppression. Two patients died from interstitial pneumonitis resulting in acute respiratory distress syndrome. The pretherapeutic serum lactic dehydrogenase level proved to be a highly significant prognostic marker for achieving CR. The 52.7 % CR rate observed in diffuse histiocytic lymphoma does not appear to be superior to that induced by a variety of other treatment regimens for this lymphoma. The long-term remission and survival rates, however, compare favorably to the ones reported for the original protocol. Thus, MACOP-B is an efficacious treatment for the diffuse histiocytic lymphomas. We caution, however, against the use of this considerably toxic regimen without intensive and constant toxicity surveillance.

T 74 INTENSIVE TREATMENT OF STAGE III-IV AGGRESSIVE MALIGNANT LYMPHOMAS (PROTOCOL TPL-84).

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In the past decade, major progress have been obtained in the treatment of aggressive non Hodgkin's lymphomas (NHL) thanks to higher doses of chemotherapy, alternating regimens and autologous bone marrow transplantation (ABMT).

From January 1984 to December 1987, 86 patients (51 men, 35 women, age range 19-79) with stage III-IV intermediate and high grade NHL have been treated in a multicenter protocol (TPL protocol) according to their age. Histologies included diffuse centrocyto-centroblastic (n=20), centroblastic (n=34), immunoblastic (n=32) types. Patients younger than 60 years (group I = 38 patients) received 3 monthly cycles of a CHEP-BLEO schedule (doxorubicin 75 mg/m² d1, cyclophosphamide 1,2 g/m² d1, vindesine 3mg/m²/d d 1 and 8, bleomycin 10 mg/m²/d d1 and 8, prednisolone 50 mg/m² d1 to 10), then 3 monthly courses of VAMA schedule (teniposide 80 mg/m² d1, cytosine arabinoside 200 mg/m²/d d2 to 5, L-asparaginase 1000 U/kg/d d6 to 11, methotrexate 1,2g/m² with leucoverin rescue d21) and finally, 3 courses of CHEP-BLEO regimen. Patients between 60 and 75 years (group II = 48 patients) received 10 monthly cycles of CAVP-BLEO regimen (doxorubicin 50 mg/m² d1, cyclophosphamide 500 mg/m² d1, vindesine 3mg/m²/d d 1 and 8, bleomycin 10 mg/m²/d d1 and 8, prednisolone 50 mg/m² d1 to 10). An excess of immunoblastic type (20/48) and of stage IV (35/48) was noticed in group II. In both group, toxicity was tolerable. In group I, complete remission (CR) rate was 71%. 1 patient died of toxicity in CR. 26% of patients relapsed. 22 patients (58%) remain in CR with a median follow up of 33 months (19 first CR, 1 first CR after allogenic marrow transplantation, 2 in second CR after ABMT). Median survival time is 48 months, and the probability of disease free survival (DFS) reaches a plateau at 48,5% after 24 months. In group II, CR rate was 54%. 4 patients died of toxicity, 5 relapsed and 19 (39%) are well and alive. Median survival time is 24 months, and the probability of DFS of 45,8%. There is no significant difference between the 2 groups in term of DFS. Though group I schedule appears capable to induce a higher rate of CR in stage III-IV agressive NHLs, there is a high rate of relapse within the first 2 years, possibly salvaged by ABMT as second line therapy.

T 75 ADRIABLASTINE-TENIPOSIDE-CYCLOPHOSPHAMIDE (T-CAM) VERSUS EPIRUBICINE-TENIPOSIDE-CYCLOPHOSPHAMIDE (T-CEM) FOR INTERMEDIATE GRADE NON-HODGKIN LYMPHOMA

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119 patients with intermediate grade NH lymphoma(Working formulation)clinical stage II-IV entered the study. 62 received T-CAM (Adriablastine 4o mg/m2 day 1, Teniposide 14o mg/m2 day 2, Cyclophosphamide 3oo mg/m2/24 h. days 3-5, Methylprednisolone 5o mg/m2/24 h. days 3-6). 57 received T-CEM with Epirubicine substituting Adriablastine on day 1, and were further randomised to 3 Epirubicine dosages:T-CEM I (2o patients, Epirubicine 4o mg/m2),T-CEM II (2o patients, Epirubicine 6o mg/m2) and T-CEM III (17 patients, Epirubicine 12o mg/m2). Allgroups were matched regarding age and sex. The complete response rates (CRR) and overall response rates (RR=CR+PR) were:

T-CAM: CRR 35/62, RR 56/62
T-CEM as a whole: CRR 14/57, RR 35/57
T-CEM I: CRR 6/2o, RR 15/2o
T-CEM II: CRR 4/2o, RR 12/2o .
T-CEM III : CRR 4/17, RR 8/17

Testing of differences between CRR and RR in different groups according to treatment schedule was performed with the X2 or the Fisher exact probability tests.

There was no significant difference either in CRR or RR between T-CEM I, T-CEM II and T-CEM III groups. T-CAM proved to be superior to T-CEM as a whole both in CRR (36/62 vs 14/57, X2= 12,34, p< o.oo5) and in RR (56/62 vs 35/57, X2=12,24, p< o.oo5).

As patients receiving T-CEM I might have been anthracyclin-underdosed, differences were tested between T-CAM and T-CEM II + T-CEM III groups, and results proved again to be in favour of T-CAM both for CRR (36/62 vs8/37,X2= 11,o3, p<o.oo5)and RR(56/62 vs 2o/37, X2=15,12, p< o.oo5).

To assess the effects of Epirubicine dose escalation to 12o mg/m2, differences were tested between T-CAM and T-CEM III groups.The results were in favour of T-CAM both for CRR (36/62 vs 4/17, X2=5,o6, p < o.o25) and RR (56/62 vs 8/17, X2=13,5, p< o.oo5).

T-CEM treatment regimens seem active for NH lymphoma histological types included in the study.However, Adriablastine seems to superior to Epirubicine at least within the treatment schedule used in this study and to NH lymphoma types included in it. The lower cardiotoxicity of Epirubicine might have its advantages in selected cases.

T 76 MACOP-B TREATMENT IN NON-HODGKIN LYMPHOMA (NHL) PATIENTS (pts) OF INTERMEDIATE AND HIGH GRADE AND OF THE Ki1-SUBTYPE.

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Preliminary results of a prospective study of pts with NHL of intermediate and high grade (acc. to the Working Formulation, 1982) treated by a slightly modified MACOP-B regimen are presented. Compared to the version initially published by Klimo and Connors (Ann. Int. Med. 102: 596, 1985) the dose escalation of doxorubicin and cyclophosphamide as well as the antibiotic prophylaxis against bacterial and Pneumocystis carinii infections were omitted. Histologies of the individual lymphomas were: generalized peripheral T-cell (N=1), centroblastic-centrocytic (N=1), centroblastic (N=6), immunoblastic (N=2), high grade unclassified (N=1) and Ki1 (N=8). 19 pts (14 males, 5 females) with a median age of 44 years (range 24-72) presented with the following stages (acc. to the Ann Arbor Conference Criteria): IIA (N=1), IIB (N=5), IIIA (N=1), IIIB (N=3), IVA (N=2) and IVB (N=7). An objective clinical response rate of 90% was achieved; 10 pts (53%) presented clinical complete (cCR) and additional 7 pts (37%) partial remissions (PR). Duration of cCR ranges between 1+ and 41+ months. Of the 8 pts with Ki1 lymphoma 4 achieved cCR, 2 PR and 2 died of progressive disease under therapy. Maximal observed toxicities (acc. to WHO) were: mucositis grade 3 (N=6), leucopenia grade 3 (N=4), nausea and vomiting grade 2 (N=2), paraesthesia grade 2 (N=2), in addition one infection with pneumococci and in 3 pts thromboembolic complications including one fatal pulmonary embolism were registered. MACOP-B seems to be an effective, fairly well tolerable and feasible therapy for the out-patient treatment of pts with NHL with special emphasis on the Ki1-type.

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T 77 "L-VECAMP" REGIMEN FOR INTERMEDIATE AND HIGH GRADE NON HODGKIN ADULT LYMPHOMA.

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The actual 3rd generation regimens for the treatment of high grade NHL see a phase of swift intensification by cycle-specific drugs, followed, during myelodepression, by a sequential supply of non-myelotoxic agents: in this way it was registered the highest percentage of complete response, (over the 65%), with more than 2/3 of patients in complete remission (CR), disease free at 4-5 years; anyway the toxicity of these schemes tends to be high, expecially for patients (pts) with bulky disease, elderly and imperfect hepato-renal functionality. To reduce the toxicity of a tried scheme as F-MACHOP, we have modified the sequence in this way: VCR 0,5 mg/mq d 1, h 0 - h 12; CTX 750 mg/mq, ARA-C 1 g/mq, ADR 60 mg/mq d 2, h 0-6, without Fluorouracil. MTX 500 mg/mq h 0-6 and folinic rescue 30 mg bid were subsequently supplied on day 12 and 13, 14. 30 pts were treated, 26 male and 4 female, (range 26-77 yrs) W.F.: F-J stage II E - IV B. 17 pts shawed the following presentation: gastrointestinal: 4, skin: 3, bone marrow: 6; Bulky disease: mediastinum: 2, abdomen: 2. 18 pts achieved CR (60%), 7 PR (partial response) (23,3%) and 5 experienced progressive disease. In 7/30 pts fever of unknown origin; exceptionally pulmonary and urosectic events. No case of toxic death, no evaluable hemorragic syndrome resulted, as well as nausea, vomiting, hepato-cellular damage or mucositis. Grade II-III alopecia was constant but reversible. 93% of pts showed granulocytic and platelet nadir between 10 to 15 d, and 8 to 13 respectively. This regimen was mostly performed in out patient setting. The median overall survival and the event free survival havent't been reached yet 32 months after the start of the therapy, and 53% of pts are alive and disease free at 27 months after CR. In conclusion we registered a less percentage of CR most aggressive regimens (60% vs > 65%) but the complete response tends to be lasting. The treatment seems to be effective and moderately toxic: it can be tolerated by elderly pts too and could represent, in our opinion, a good therapeutic alternative for pts untreatable by the actual intensification regimens.

T 78 A Phase II study with CEOP (C = Cyclophosphamide, E = Epirubicin, O = Vincristine, P = Prednisolone) in stage III-IV Non-Hodgkin's lymphoma.

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Thirty-one patients with stage III (n = 6) and stage IV (n = 25) Non-Hodgkin's lymphoma were enrolled in a first line phase II clinical trial testing a combination chemotherapy with C 750 mg/m2 I.V. d1, E 60 mg/m2 I.V. d1, O 1,4 mg/m2 I.V. d1 (max 2 mg) and P 100 mg/m2 p.o. d1 to d5. The median follow-up of the study is 33 months. The mean age of the patients was 56 ± 11 years (range 28 - 74 years). Of these patients, 18 were male and 13 female. At entry, 19 patients presented with a performance status (PS) (WHO) 1 and 12 a PS 2. No CNS prevention was performed. Response (WHO) to treatment was as follows : CR : 15, PR : 10 and NC : 6 (Response Rate : 81%). In stage III, 5 CR's out of 6 were observed while in stage IV 10 CR's out of 25 were recorded. Median time to the best response was 71 days (range 21 - 279 days). The median duration of response is not yet reached. The median time to progression is 21 months (stage III : not yet reached, stage IV : 14.7 months). The median survival time is not yet reached for all the patients while for stage IV it is 29 months. The median of the number of administered cycles was 14 (range 4 - 17). The median cumulative dose of E was 695 mg/m2 (range 182 - 990 mg/m2) ; 12 patients received more than 800 mg/m^2 E. Treatment delays and dose reductions were applied in 70, 81 cycles respectively, on a total of 381 cycles of chemotherapy. Toxicities per patient (WHO grade 2 or more) were as follows : anemia grade 2 : 1 ; thrombocytopenia grade 2 : 1 ; leucopenia grade 2 : 7, grade 4 : 1 ; nausea and vomiting grade 2 : 16, grade 3 : 3 ; mucositis grade 2 : 2 ; infection grade 2 : 1 ; alopecia grade 2 : 16, grade 3 : 8 ; neurotoxicity grade 2 : 11, grade 3 : 1. One patient died from untreatable cardiac failure and generalisation of lymphoma (cum. dose of E 440 mg/m2), while one patient developed a drop in LVEF of more than 20% relative (cum. dose of E 695 mg/m2).
In conclusion, the results achieved with this treatment are comparable with more aggresive regimens, with very acceptable toxicity.

T 79 P-COMM-B AS INDUCTION CHEMOTHERAPY IN INTERMEDIATE AND HIGH GRADE NON-HODGKINS LYMPHOMA (NHL).

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Between December 1986 and September 1989, 38 patients with intermediate and high grade NHL were treated with oral prednisolone 75mg daily for 12 weeks; cyclophosphamide 350mg/m² iv and mitozantrone 10mg/m² on days 1,15,29,43,57 and 71; vincristine 1.4mg/m² on days 8,22,36,50,64 and 78; methotrexate 400mg/m² iv on days 8,36 and 64; bleomycin 10mg/mg² iv on days 22,50 and 78. None had received previous chemotherapy. One had received previous radiotherapy.

Age range was 14-66years (median 53). 19 were male. At diagnosis 4 patients had stage II, 9 patients stage III, and 25 patients had stage IV disease. Histological classification according to the International Working Formulation placed 1 patient in category D, 1 in E, 7 in F, 17 in G, 8 in H, 1 in I, 3 in J. Performance status ranged from 0-4.

22 patients achieved CR (58%) including 3 patients who received local radiotherapy and one who had a partial gastrectomy after P-COMM-B. 6 patients achieved PR (16%) 6 showed progressive disease (16%), and 4 were inevaluable for response (10%). Product limit estimates of overall survival and relapse-free survival at 2 years are 45% and 64% respectively. The most severe toxicity has been neutropenia (WHO grade III-IV in 23%). Proximal myopathy confined 4 patients to a wheelchair/bed temporarily. Mucositis, peripheral neuropathy and nausea were frequent but rarely severe. There were no chemotherapy-related deaths.

P-COMM-B offers effective first-line chemotherapy in advanced aggressive NHL with acceptable toxicity.

T 80 CAVBP/DEP ALTERNATING CHEMOTHERAPY FOR THE TREATMENT OF INTERMEDIATE AND HIGH GRADE NON HODGKIN'S LYMPHOMA.

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From May 1984 to June 1986 40 patients (pts) with intermediate or high grade non Hodgkin's lymphoma were treated with CAVBP (cyclophosphamide, doxorubicin, vincristine, bleomycin, and prednisone) alternating with DEP (cisplatin, etoposide, and prednisone), an innovative program emphasizing short cycle interval, (3 weeks) and alternating early use of multiple drugs, with putatively different mechanism of action, in order to overcome drug resistance. Particularly, DEP chemotherapy included two drugs, such as cisplatin and etoposide, with recently discovered activity against lymphomas and which have shown synergism in human lymphoma cell lines. Median age of the group was 50 (19-71), median follow-up now exceeding 40 months. There were 5 stage I, 11 stage II, 5 stage III and 19 stage IV pts. Bulky disease (> 10 cm) was present in 9 pts, "B" symptoms in 13.
21 pts (52.5%) achieved a complete response, 11 pts (27.5%) had a partial response. Eight of the complete responders (38%) relapsed 5 to 24 months after completion of treatment. Factors negatively associated with response included "B" symptoms (p=0.05), stage (p=0.02), bulky adenopathy (p=0.0045), ECOG performance status (p=0.03), number of extranodal sites of disease (p=0.01). Toxicity was moderate, with no treatment-related deaths, only 6 cases of severe leukopenia (< 1000/mmc), and four cases of a disventilatory restrictive syndrome, which required discontinuation of bleomycin. Given the cellular Kinetics of aggressive lymphomas, and the general transalation of disease free survival > 2 years into long term cure, we can conclude that 32.5% of treated pts and 62% of complete responders have been cured by this combination chemotherapy program.
The above results do not seem to be sufficiently promising to justify comparison of CAVBP/DEP with more efficacious third generation regimens in prospective randomized trials.

T 81 RESULTS OF SEQUENTIAL COMBINATION CHEMOTHERAPY (CABOPP/VIM) IN HIGH-GRADE MALIGNANT NON-HODGKIN LYMPHOMA.

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A new treatment program was used in 42 patients with high-grade malignant lymphomas in an attempt to improve the results without increasing toxicity. Two effective, relatively well tolerated and non-cross resistant drug combinations were given sequentially according to the response of disease. Therapy was started with a combination consisting of Cyclophosphamide, Adriamycin, Bleomycin, Vincristin, Procarbazine, and Prednisone (CABOPP). In patients who achieved complete remission with CABOPP, this program was continued for a total of 6 cycles. In patients with progressive disease or with only a partial remission after a maximum of 4 cycles of CABOPP, therapy was switched to a combination consisting of Etoposide, Ifosfamide, and Methotrexate (VIM). Complete remission was achieved in 86% of the patients. 69% of the patients obtained complete remission with CABOPP alone and 17% after changing to VIM. The complete remission rate was 100% in patients with stage I or II of disease, 91% in patients with stage III, and 69% in patients with stage IV. The projected survival at 2 years is 66%. 56% of patients with complete remission are predicted to have continued complete remission at 2 years. Thus, CABOPP/VIM appears to be an effective and well tolerated program for the treatment of aggressive lymphomas. How this program compares with other newly developed protocols, can only be established in prospective randomized studies.

T 82 LONG-TERM FOLLOW-UP OF CHOP-TREATED NON-HODGKIN LYMPHOMA OF HIGH-GRADE MALIGNANCY.

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The longterm outcome of 116 high grade malignancy NHL patients (38 CB, 33 IB, 24 LB, 11 high grade unclassified, 9 PTCL, one Ki-1 lymphoma according to the modified Kiell classification) treated with age adjusted CHOP between 1980 - 1985 was evaluated. The median age was 64 years. Of these patients 28% had significant comorbidity. 35% of all patients are alive after a median followup of 5 years. CB patients had the best outcome; median survival has not been reached after 110 months, however the differences between all histologic entities are not significant (p=0.08). Risk factors were balanced between the histologic entities. 56% of the patients had localized disease after clinical staging. CR rate was 47%. 9 out of 12 relapses occurred within 2 years. Median time to relapse was 9 months. Salvage therapy was usually not successful, none of IB and LB patients achieved CR, five CB had remissions with secondline therapy, four of these patients had PR after induction treatment, one patient had relapse after 30 months. 15% of CR patients developed second (or third) neoplasms. Only one acute myeloblastic leukemia was seen. According to our results age adjusted CHOP is a well tolerated and effective treatment for elderly patients and patients with localized disease, but new therapeutic approaches are necessary for advanced disease and patients with accumulation of risk factors. The future value of ABMT in selected patients will be discussed.

T 83 RESULTS OF THE COP-BLAM I REGIMEN IN 30 PATIENTS WITH INTERMEDIATE AND HIGH GRADE NON HODGKIN'S LYMPHOMAS.

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Between January 1986 and May 1989, 30 patients with intermediate and high grade non Hodgkin's Lymphomas were treated. The average age was 57 years (28-75), the relation males/females was 10/20. The histologic distribution was the following DHL 19 (63%), DM 3 (10%), DLPD 3 (10%), Inmunoblastic 3 (10%), Clinical stages were as follows stage II: 11 (36%), III: 8 (26%), IV: 11 (36%); all stages III and IV were B. 15 cases (50%) had bulky disease. A correlation study showed that 52% of patients with B symptoms had high LDH and all asymptomatic patients had normal values (P=0.015). The group we studied had 4 high risk factors: advanced stage, B symptoms, bulky disease, high LDH values. The lymph node areas involved in stages II and III were axillae 10 (53%), retroperitoneal area 11 (58%), cervical area 7 (37%). In stage IV patients, the affected organs were: lungs 6 (54%), bone marrow 3 (27%) and soft tissues 2 (18%).
Patients were treated with de COP-BLAM I regimen, after 6 cycles remission was evaluated. In 21 patients (70%) complete remission (CR) was obtained with an average duration of 28 months. In 9 patients (30%) partial remission was reached. The total survival at 12 months was 83% and disease free survival was 79% at 18 months, total survival 64%, disease free survival 61%, both values were maintained up to 38 months. The average observation was 16 months. We recommend the COP-BLAM I regimen as a National protocol in Venezuela and in other undeveloped countries, its high effectivity (70% of CR with a 2 year total survival of 61%), and low toxicity.

T 84 ETOPOSIDE, CYCLOPHOSPHAMIDE, MITOXANTRONE AND PREDNISONE (VEMP) IN THE TREATMENT OF NON HODGKIN'S LYMPHOMAS: PRELIMINARY RESULTS OF A PHASE III STUDY.

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Considering both satisfactory therapeutic results achieved and low toxicity registered by using four-drug combination regimen of Etoposide, Cyclophosphamide, Mitoxantrone and Prednisone (VEMP) as salvage treatment for advanced aggressive NHL refractory or relapsed to optimal first-line therapy we utilized the some schedule in previously untreated pts with NHL. A pilot study has been performed in our Department to evaluate these polichemotherapeutic regimen as first-line therapy for pts presenting one or more of following criteria: P.S. 2-3, aggressive histology at stage I-IIE, low grade histology B-symptoms stage III-IV, age over 65. Up to today 38 pts entered this study. Median age is 64 years (range 34-72); most of pts (69%) were in stage III-IV; B-symptoms were present in 10 pts (26%) and extranodal disease in 24 (63%). Pts at stage I-IIE received 3 cycles plus involved field radiotherapy while pts at stage III-IV received a minimum of 6 cycles (when responding). At present 26 pts are evaluable for response: CR was obtained in 20/26 (77%), PR in 2/26 (8%), PD in 4/26 (15%). Five pts relapsed within one year after the CR. Hematologic, cardiac or hepatic toxicity was low and the therapy was generally well tolerated. These data suggest that VEMP is safe and effective as more aggressive regimens and is also indicated for pts not eligible for anthracycline-including protocols.

T 85 TOXICITY AND PRELIMINARY RESULTS WITH A NEW 9-DRUG REGIMEN (CEOP-IMVP-DEXA) IN THE TREATMENT OF AGGRESSIVE LYMPHOMAS.

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Achieving a rapid and complete remission is the most important goal in the treatment of aggressive lymphomas. In order to overcome early resistance and regrowth of lymphoma in treatment free intervals we chose a 9-drug regimen with weekly therapy. We combined two non-cross-resistant regimens, CEOP (Cyclophosphamide 750mg/m^2 d 1, Epidoxorubicin 70mg/m^2 d 1, Onkovin 1,4mg/m^2 d1+8 and Prednisolon 100mg d1-5) and IMVP-Dexa (Ifosfamide 2g/m^2 with Uromitexan uroprotection d15-17, VP-16 100mg/m^2 d15-17, Dexamethasone 40mg d15-19 and Methotrexate 800mg/m^2 with Ca-folinat rescue d22) and gave them every 4 weeks, 3 to 6 times according to response. Dose reductions were not applied as long as granulocyte counts were over 0.5x10^9/L. Therapy was withheld if counts dropped below 0.2x10^9/L. Patients with untreated histologic proven high and intermediate grade Non-Hodgkin lymphoma and measurable disease were treated, if they gave an informed consent.

To date 8 Austrian centers entered 37 patients in this multicenter trial. Data are available from 33 pts. 3 were excluded, two because of pretreatment, one because of wrong histology. Male/female ration was 1, age between 25 and 72 years, median 56.5 years. Histology was centroblastic in 16, immunoblastic in 3, lymphoblastic in 3, Ki-1 in 3, undifferentiated in 3, plasmablastic in 1 and diffuse centrocytic-centroblastic in 1. 5 patients were stage I, 11 stage II, 3 stage III and 11 stage IV, 13 patients had B-symptoms. Karnovsky status at presentation was between 100 and 60, median 85. Observation time was 0.4-23.8 months, median 8.8 months.

Toxicity was primarily hematologic with 53.3% of patients having granulocyte nadirs below 0.5x10^9/L and 3.3% under 0.1x10^9/L. Although 60% of patients had infections, there was only one life threatening infection in an AIDS patient. Other important toxicities were nausea/vomiting, stomatisis and hair loss. 8 patients died, 4 of lymphoma after 4, 22, 35 and 65 weeks respectively, 2 of AIDS after 22 and 33 weeks and two were early deaths within 10 days after registration.

25 patients are evaluable for response, 21 had a complete and 3 a partial remission, two of them entered a complete remission after radiotherapy to residual disease, resulting in a complete remission rate of 92%. Only one patient progressed during therapy. Until now 3 patients were progressive after achieving a remission. Median time to treatment failure, to relapse and median survival are not reached.

CEOP-IMVP-Dexa can be given safely even in smaller hematologic centers and is able to achieve a high rate of complete responses in patients with high and intermediate grade malignant Non-Hodgkin lymphomas.

T 86 IFOSFAMIDE AND MITOXANTRONE IN RELAPSED AND REFRACTORY NON-HODGKIN's LYMPHOMA AND HODGKIN'S DISEASE

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There is a need to identify alternative chemotherapy for patients with active high grade non-Hodgkin's lymphoma (NHL) and Hodgkin's disease (HD) who have previously received most of the principal effective agents. Fifty-five patients, initially treated for advanced high grade NHL or HD, refractory to first-line treatment or in relapse, were given an ifosfamide-mitoxantrone combination (I-M). Ifosfamide 6mg/m^2 was infused over 48 hours. Mesna, as prophylaxis against haemorrhagic cystitis, was given as a 1g IV bolus at 0 hours with additions of 2g to the infusion at 12 hourly intervals. Mitoxantrone 12mg/m^2 was given over 30 minutes, following completion of the ifosfamide infusion. The regimen was repeated at three weekly intervals, the total duration of treatment being determined by response. Patient details were: 35 NHL, ages 15-76 (median 52), M:F 22:13, primarily refractory 9, relapsed 24, relapsed and refractory 2; 20 HD, ages 21-45 (median 31), M:F 14:6, primarily refractory 7, relapsed 11, relapsed and refractory 2.

Overall, 207 complete courses have been given to date, 8 being the maximum received by any patient. Delays in treatment or dosage modification were mainly due to myelosuppression. Neutropenia NCI grade 3/4 occurred following 70% of courses, whereas thrombocytopenia grade 3/4 occurred in only 15% of courses. There were 11 instances where post-chemotherpy neutropenia required hospitalisation and IV antibiotics. Ten patients showed evidence of CNS toxicity and decreased levels of consciousness necessitated withdrawal of trial therapy in 4 of those patients. There was only one treatment-related death, due to septicaemia.

Of 32 patients with NHL evaluable for response; 10 (31%) achieved CR and 5 PR (overall response rate 47%); in 9, disease was static and in 8 progressive. Two patients achieving CR went on to subsequent BMT (one allogeneic, one autologous). Of 17 patients with HD evaluable for response, 6(35%) achieved CR and 6 PR (overall response rate 70%); in 2 disease was static and in 3 progressive. Two patients (one CR and one PR) went on to subsequent ABMT. Responses in both NHL and HD were predominantly in patients with relapsed as opposed to primarily refractory disease.

In conclusion, the I-M regimen shows useful activity in both high grade NHL and HD, with acceptable toxicity given the outlook of the patient categories. This combination is clearly of value in relapsed patients, especially where therapeutic options are limited because of previous multidrug treatment.

T 87 ACTIVITY OF MITOXANTRONE, CYTOSINE ARABINOSIDE, AND PREDNISOLONE IN PRETREATED PATIENTS WITH HIGH GRADE MALIGNANT NON-HODGKIN'S LYMPHOMAS.

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Between 1986 and 1988, 10 patients with heavily pretreated high grade malignant NHL were treated with Mitoxantrone 8 mg/m^2 iv days 1+2, Cytosine Arabinoside 100 mg/m^2 sc days 1-5 and Prednisolone 80 mg/m^2 po days 1-5 (MAP). Treatment cycles were repeated beginning on day 29. According to the Kiel-classification, 5 patients had a centroblastic, 2 an immunoblastic and 3 a high grade malignant lymphoma, which could not be further classified. All patients were pretreated with CHOP and VIM-Bleo, a modification of the IMVP-16 protocol. 4 patients had had additional radiotherapy. With this pretreatment, 6 patients had achieved a complete remission for 1 - 10, median 6 months. 3 patients had achieved only a partial remission and 1 patient stable disease. All but one patient with a partial remission had a relapse and progressive disease at the time of start of the MAP-protocol. 2 patients had stage II disease with massive mediastinal involvement, 3 stage III and 5 stage IV disease. Treatment resulted in a complete remission (CR) in 3 patients, 1 patient had a partial remission, 3 a minor response and 3 progressive disease. CR is still stable in 2 patients at 24 and 2 months so far, the third patient with CR relapsed 15 months after start of MAP therapy. Main toxicity was hematotoxicity with leukopenia < 1000 /mm^3 in 7 patients. 1 patient develloped thrompbopenia < 20000/mm^3. Leukopenia resulted in infections in 4 patients (WHO grade 2: 3 patients, WHO grade 3: 1 patient). Other toxicity was mild. We conclude that MAP is an active regimen in heavily pretreated NHL which has considerable hematotoxicity but can produce stable CR in some patients.

T 88 METHYL-GAG, IFOSFAMIDE, METHOTREXATE AND ETOPOSIDE (MIME) AS SALVAGE THERAPY FOR MALIGNANT LYMPHOMAS.

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Patients with Hodgkin's disease (HD) or high grade malignant non-Hodgkin's lymphoma (NHL) who fail to respond to or who relapse after first-line chemotherapy have a poor prognosis. A combination designated MIME was recommended as salvage therapy in Sweden for HD after initially positive reports from the group at MD Anderson Hospital, Houston, USA, and it became increasingly used for NHL. A retrospective study was initiated in order to evaluate the therapeutic effect and toxicity when given on a routine basis in a great number of hospitals.

Retrospective study: One hundred and three patients with HD and NHL treated with MIME at 26 hospitals in Sweden between October 1984 and July 1988 were evaluated. All patients were heavily pretreated. Thirty-seven of the 44 patients with HD, 34/47 with high-grade malignant and 9/12 with low-grade malignant NHL were evaluable for response. Sixteen (43%) patients with HD achieved complete remission (CR) and 4 partial remission (PR), giving a total response rate of 54%. Five patients with high-grade NHL achieved CR and 8 PR, giving a response rate of 38%. Of 9 evaluable patients with low-grade NHL, 2 achieved CR. The main toxicity was leukopenia, trombocytopenia and infections. Twenty-six percent of the patients developed septicemia, which was fatal in 6 cases. In conclusion, MIME could induce remissions in heavily pretreated lymphoma patients, particularly in HD, and it was relatively well tolerated.

Prospective study: The promising results of the retrospective study led to the initiation of a nation-wide prospective study of MIME as second-line therapy for malignant lymphomas. Patient inclusion started in July 1988. Until Dec 1989, 68 patients have been included, 45 high-grade and 12 low-grade (all after failure on adriamycin-containing regimen) NHL and 11 HD. Preliminary results from this study will be presented.

T 89 PRELIMINARY RESULTS OF A RANDOMIZED STUDY OF "HIGH RISK" AGRESSIVE NON-HODGKIN'S LYMPHOMA: COMPARISON BETWEEN DOXORUBIN AND MITOXANTRONE IN THE INDUCTION PHASE.

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Between October 1987 and December 1989, 498 adult patients with agressive non-Hodgkin's lymphoma were entered Group 2 of a multicentric randomized study (protocol LNH87). In this protocol, patients were stratified on the basis of prognostic factors which are considered to be associated with poor complete response rate and high relapse rate: low performance status, high number of extranodal localizations, large tumoral mass, bone marrow involvement and high grade histologic subtype (Burkitt and lymphoblastic). The presence of at least one of these factors defined "high risk" patients who were further subdivided according to age; thus group 2 included "high risk" adult patients under 55 y. Patients were randomized for induction treatment between two anthracyclin-containing regimens: ACVBP (doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone) and NCVBP (mitoxantrone, cyclophosphamide, vindesine, bleomycin, prednisone). Response to treatment was assessed after 4 courses given every two weeks. Complete remission (C.R) patients were further randomized for consolidation between sequential chemotherapy and autologous bone marrow transplantation with chemotherapeutic conditioning regimen.
The main characteristics of these 498 patients were as follows: the sex ratio was 1.6; there was a predominance of the large-cell subtype (52%) and of stage IV disease (60%); LDH level was elevated in 53% of patients. At the time of analysis (December 89), the response to induction treatment could be evaluated in 311 patients. 65% achieved CR and 29% did not; 6 % died during the induction phase. CR rate did not differ between the two induction regimens nor did toxicity, as assessed on the basis of either the degree of myelosuppression or the occurence of infectious complications and the time spent in hospital as a result. No cardiac, hepatic and renal toxicity was observed to date. Among the 18 (6%) deaths observed during the induction phase, 3 resulted from disease progression alone, whereas 15 were possibly treatment-related, 3 being associated with neurologic toxicity and 12 with infection.

T 90 VP-16, IFOSFAMIDE AND METHOTREXATE COMBINATION CHEMOTHERAPY FOR AGGRESSIVE NON-HODGKIN'S LYMPHOMAS AFTER FAILURE OF THE LNH 84 REGIMEN.

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LNH 84 is an intensive chemotherapy regimen for the treatment of intermediate and high-grade non-Hodgkin's lymphomas. Induction therapy is composed of adriamycin 75 mg/m2 D1, cyclophosphamide 1200 mg/m2 D2, vindesine 2 mg/m2 D1 and 5, bleomycine 10 mg D1 and 5, and methylprednisolone 60 mg/m2 D1 to 5. It has produced a 75 % complete response rate and 3-year survival rate of 58 %. Usually patients who failed after an intensive induction chemotherapy have a poor prognosis. We studied the efficacy of VIM regimen as salvage therapy in patients who failed the LNH 84 regimen. VIM is composed of VP-16 : 100 mg/m2 D1, 3 and 5 ; ifosfamide : 1 g/m2 D1 to 5 ; and methotrexate : 30 mg/m2 D1 and 5. Courses were repeated every 21 days for a maximum of 6 cycles.
Twenty four patients were treated with VIM therapy. Eighteen of them failed the LNH 84 regimen after 3 or 4 induction cycles. The six remaining patients relapsed either during LNH 84 consolidation (2 cases) or after completing the whole treatment programme (4 cases). Mean age of the patients was 48 years (range 21-71). Histological subtypes (WF) were diffuse small cleaved cell : 2 ; diffuse mixed cell : 8 ; diffuse large cell : 4 ; large cell, immunoblastic : 3 ; lymphoblastic : 5 ; small noncleaved cell : 1 ; histiocytic : 1. Seventeen (71 %) patients had a stage IV extension ; 7 of them had a bone marrow involvement. Thirteen (54 %) patients had a poor performance status ($\geq$ 2, WHO criteria).
Twenty three patients were evaluable for response. One patient died of infection after the first cycle of VIM and could only be evaluated for toxicity. A total of 10 patients (43 %) achieved CR and 4 (17 %) attained PR. Treatment failed in 9 cases (39%). Of the 10 complete responders to VIM, 5 relapsed after 4, 6, 14, 37 and 42 months respectively and 5 are still alive with no evidence of disease after 23, 26, 53, 54 and 56 months.
Myelotoxicity was the most common side effect. A total of 101 courses of VIM were given ; eight infectious episodes, one of which was fatal, were recorded in five patients. No renal or liver dysfunction was observed and no hemorrhagic cystitis occured.
In conclusion, VIM regimen can provide a high CR rate in patients who failed an intensive, high-dose adriamycin containing induction chemotherapy ; VIM is well-tolerated and long term survival can be obtained in these patients.

T 91 SALVAGE CHEMOTHERAPY WITH MITOXANTRONE, ETOPOSIDE, VINDESINE AND PREDNISOLONE (MEVP THERAPY) FOR REFRACTORY OR RELAPSED MALIGNANT LYMPHOMA.

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Twenty-two patients with refractory or relapsed malignant lymphoma were treated with a combination chemotherapy with mitoxantrone, etoposide, vindesine and prednisolone (MEVP therapy). All of the patients have previously been treated with doxorubicin-based combination chemotherapy; 18 with CHOP, 2 with VEP-THP, or 2 with VEPA regimen. Nine patients had the refractory lymphoma and 13 had relapsed one to previous CHOP, VEP-THP or VEPA regimen. MEVP therapy consisted of 10 mg/m^2 of mitoxantrone (DIV on day 1), 2 mg/m^2 of vindesine (IV on day 1), 200 mg/m^2 of etoposide (PO on days 1-3) and 40 mg/m^2 of predonisolone (PO on days 1-5). Of the 20 evaluable patients, 6 (30.0%) attained to CR and 7 (35.0) to PR according to WHO criteria. CRs were obtained only in those who had attained to CR with previous CHOP or VEP-THP regimen. No CRs were seen in the patients with refractory lymphoma to previous treatment. Histological types in the five patients obtaining CR were B cell lymphoma of low, intermediate or high grade malignancy and included was one patient with AILD (IBL-T cell lymphoma). CR duration ranged from 6+ to 70+ (median 59+) weeks.
A severe leucopenia (<1,000) and granulocytopenia (<500) were seen in 12 (54.5%) and 17 (77.3%) patients, respectively. Moderate to severe anemia (<8.0 g Hb/dl) was seen in 13 (59.1%) patients. Thrombocytopenia was mild. One patient died due to MRSA enterocolitis followed by severe hepatic dysfunction. Nausea/vomiting was mild and alopecia was moderate. Neither ECG abnormalities nor clinical signs of cardiotoxicity related to MEVP therapy were seen in this study.
MEVP therapy is effective for relapsed B cell lymphomas of histologically low, intermediate or high grade malignancy and T cell lymphoma of low grade malignancy. Severe leucopenia with granulocytopenia could be a dose-limiting factor for MEVP therapy. Dose modification will be required for those patients who have been heavily treated previously. Further investigations are needed for searching a new effective chemotherapy for CHOP-refractory malignant lymphoma, particularly for T cell lymphoma of high grade malignancy (ATL and clear cell T lymphoma).

T 92 PHASE II-TRIAL OF IFOSFAMIDE AND MESNA IN PREVIOUSLY TREATED PATIENTS WITH NON-HODGKIN'S LYMPHOMA: CANCER AND LEUKEMIA GROUP B STUDY 8552.

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Ifosfamide (IFF), an analog of cyclophosphamide, has demonstrated promising activity in early studies of lymphoma and other malignancies. Hemorrhagic cystitis has been a significant complicating factor limiting its utility. A CALGB phase II trial was initiated to evaluate the efficacy of IFF in lymphoma and to study the possible prevention of the urotoxicity of IFF by mesna, a sulfhydryl compound which has demonstrated genitourinary detoxification of the oxyzaphosphorine derivatives. IFF at an initial dose of 1.25g/m^2 was given i.v. over 4 hours/day x5 days every three weeks (over 5 minutes) 15 minutes prior to each dose of IFF and q4h x5 doses after each dose of IFF therapy. One liter of i.v. hydration was given daily. Urinary output was maintained with diuretics if necessary. Therapy was given for a minimum of 2 cycles unless rapid progression. In responding patients (pts) therapy was continued 3 cycles beyond maximum response.

Forty-six previously treated patients with non-Hodgkin's lymphoma have been treated on this protocol. Median age was 61 years (range 18-93), performance status 1 (0-2), and number of prior regimens 3 (1-4). Responses were observed in 29% with a median duration of remission of 2.5 months (range 1-12 months). Responses were seen in favorable and unfavorable histologies. Myelosuppression was the dose-limiting toxicity: median nadir WBC 2400/mm^3 (range 200-33,500) and platelets 145,000/mm^3 (15,000-498,000). Nausea/vomiting was observed in 65% of patients and was usually mild/moderate. Alopecia was observed in 38%. One case each of neurotoxicity (confusion and disorientation) and anaphylaxis were observed. Hematuria was observed in 3 patients. In 2 patients gross hematuria was observed and therapy was discontinued; one patient with microscopic hematuria tolerated a reduced dose of ifosfamide without further hematuria. Ifosfamide is active as a single agent in non-Hodgkin's lymphoma.

T 93 MITOXANTRONE-CONTAINING REGIMENS IN REFRACTORY OR RELAPSED NON HODGKIN'S LYMPHOMAS: RESULTS OF A PHASE II STUDY.

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In the aim of finding out a more effective salvage drug-combination for patients (pts) with intermediate/high grade NHL refractory or relapsed to front-line treatment of second or third generation a study is being performed by our Department using Mitoxantrone in association with conventional agents to assess both the efficacy in inducing a response and clinical and hematological toxicities. According to different combinations (VEMP, CEMP), the treatment schedule was as follows: A) Mitoxantrone (12mg/m2 i.v. on day 1) + Etoposide (150mg/m2 i.v. on day 1) + Cyclophosphamide (650 mg/m2 i.v. on day 1) + Prednisone (60mg/m2 i.v. or i.m. on days 1--5); B) Mitoxantrone (8mg/m2 i.v. on day 1) + Etoposide (150mg/m2 i.v. on day 1) + Cisplatin (20mg/m2 i.v. on days 1--5) + Prednisone (40mg/m2 i.v. or i.m. on days 1--5). Therapy was repeated every 21 days for a minimum of 4 cycles in responding pts. Preliminary data on the therapeutic results with these regimens are summarized in the table:

	N° of evaluable patients	RESPONSE CR	PR	None	% CR+PR	None
A	25	5	8	12	52	48
B	13	4	4	5	62	38

An acceptable toxicity either hematologic and cardiac or hepatic was registered. Nausea and vomiting were common but generally well tolerated and less important than using Anthracycline, with the exception of the combination including Cisplatin. The results of our Phase II study indicate that Mitoxantrone-containing regimens can play a role in the treatment of refractory or relapsed NHL. Moreover the low toxicity, with particular care for cardiac adverse effects suggests that these regimens might be recommended also in the old pts.

T 94 MITOXANTRONE, ETOPOSIDE, CISPLATIN AND DEXAMETHASONE (MEPD) AS SALVAGE CHEMOTHERAPY IN RESISTANT NON-HODGKIN'S LYMPHOMA (NHL).

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Various salvage regimens have been proposed for resistant NHL; results are heterogeneous and optimal treatment has not yet been defined. Cisplatin (P), Etoposide (E) have been found active both as single agents and in combination in NHL. Phase I-II studies have established Mitoxantrone (M) as active in refractory NHL as single agent, a lack of cross-resistance between Doxorubicin and M has been demonstrated in human lung cancer cell line. Based on these observations we initiated a study to assess the efficacy of MEPD combination as salvage chemotherapy (CT)in pts with resistant NHL (not responders to primary CT or relapsing after first line CT). From June 1988 through September 1989, 20 pts received MEPD with the following schedule: M 10 mg/sqm i.v. on day 1, E 70 mg/sqm days 1-3, P 60 mg/sqm on day 1 and D 8 mg/sqm days 1-5. Treatment was repeated every 3-4 weeks. Intense hydration with saline and mannitol was given on day 1 during P administration. There were 9 males and 11 females, median age was 54 yrs (range 27-68). 10 pts had intermediate grade NHL and 10 diffuse large cell lymphoma (DLCL). 17 pts were in advanced stage (10 IV, 7 III) and 3 in stage II bulky. All pts were previously treated with doxorubicine:11 received MACOPB and 9 CHOP or its variants. 8 pts were not responders to primary CT and 12 were in early relapse after first line CT. The majority of pts had high LDH level. 5 pts (25%) achieved a CR, 5 (25%) a PR, 2 a minor response, 7 (35%) were treatment failures and one patient with DLCL died after one course due to acute tumor lysis syndrome. The overall response to MEPD was therefore 50% Pts with relapsing lymphoma responded better than those with primary refractory NHL as follows:

	Pts No	CR	PR
relapsing	12	4	3
refractory	8	1	2

The main serious toxicity was myelosuppression but only 3 pts had fever due to neutropenia. Nausea and/or vomiting were present in most of the pts. However 13 pts were given MEPD on an outpatient basis. MEPD was reasonably well tolerated and proved to be effective as salvage CT in resistant NHL.

T 95 MITOXANTRONE AS SINGLE AGENT OR IN COMBINATION: SECOND LINE CHEMOTHERAPY IN REFRACTORY OR RELAPSED NON-HODGKIN'S LYMPHOMAS. REPORT OF THE NON-HODGKIN'S LYMPHOMA CO-OPERATIVE STUDY GROUP (NHLCSG).

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The failure to cure first line chemotherapy resistant leukaemias and lymphomas, must incite to experiment with new and more active agents. In 1986 the NHLCSG began a phase II study in wich patients, come out not or partially responders to a 2nd or 3rd generation regimen, were treated by Mitoxantrone. In the first phase Mitoxantrone was administered as a bolus iniection (30 minutes) at 14mg/mq i.v., repeated every 21 days for 6 courses as maximum (range 2-6). Fifteen patients with non-Hodgkin's lymphomas in advanced stage (W.F. Groups F,G,H,K) and with a median age of 57 years (range 41-72) entered this study: of these, 9 were relapsed and 6 were refractory to the first line chemotherapy (CHOP, MACOP-B, etc.). Four patients obtained a CR (27%), 4 a PR (27%) and 7 were not responders or showed a progression of the disease (CR+PR=54%). Of the 4 patients in CR, 3 relapsed at 4,5,13 months respectively, while the fourth one is still alive and well 22 months after the treatment. In the second phase Mitoxantrone was employed in association with VP 16-213 and Prednisone (VMP) with the following schedule,repeated every 28 days for 6 cycles as maximum (range 2-6): MITOXANTRONE 6mg/mq/i.v. days 1,2,3; VP 16-213 100mg/mq/i.v. days 1,2,3; PREDNISONE 60mg/mq days 1-5.Twenty patients with the same characteristics of the first group (Histology, median age, stage), entered the second phase and presently eleven are evaluable for response and toxicity. A complete remission (CR) was obtained in 5 out of 11 patients (45%), while 6 did not respond to the treatment. The five patients in whom a CR occurred, are still now alive and well after 6+,7+,10+,10+,14+ months. Leucopenia and trombocytopenia were the most frequent hematological toxicities (grade 2-4), while nausea, vomiting, mucositis, hair-loss and fever were mild. Cardiological toxicity of grade 2 was observed only in one case. In conclusion Mitoxantrone appears an active and a safe-utilization drug. These first results suggest that a further employment of this drug in more organized regimens, could have an important role in the therapy of non-Hodgkin's lymphomas.

T 96 PTT-119 PROTER IN PATIENTS WITH NON HODGKIN LYMPHOMAS (NHL) LOW AND INTERMEDIATE GRADE: TRIAL OF AN ACTIVE NEW AGENT.

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PTT-119 Proter, isomeric meta of L-phenil-alanyl mustard, is a new tripeptic agent non cross-resistant with other alkylating drugs: cancer cells avidity for L-aminoacids contained in the peptide sequence is the basis for sensitivity to this cytotoxic compound. Pretreated high grade NHL demonstrated an overall response (70%) more consistent than low (43%) or intermediate ones. (Tura S., Haematologica, vol.73, No.6, 504-8). In a phase II program 13 patients (pts) with stage II-IV, WF A-F, were studied. 5 pts were given no prior chemio-radiotherapy, 8 pts were pretrated with alkylating drugs. All pts showed adeguate hepatic, renal and cardiac functions and measurable disease. Pts characteristics: median age 61 yrs (range 55-68), median PS (ECOG-WHO)=2 (range 1-3), men=4, women=9. 10 pts were adeguate for evaluation. PTT-119 Proter was administered i.v. at the dose level of 3 mg/kg, for 6 cycles, with dosage adjustment according to tolerance for the drug. Overall response (CR+PR) was 70%. 2 pts died for progressive disease, 1 patient showed stable disease (SD); CR was observed in 2 pts, previously untreated: duration 12+ 15+ months. Grade I-II mucositis and nausea occurred in 25% pts; Leukopenia and Thombocytopenia (gr.II-III) in 25%, while alopecia (gr.II) was registered in 44% and chemical phlebitis was recorded in 35% pts. No cardiac, hepato-renal or pulmonary impairement occurred. We conclude that PTT-119 Proter is an active and relatively not much toxic agent for low and intermediate grade NHL. Further trials studying this drug as a single agent or in combination therapy are indicated.

ABSTRACTS - Fourth International Conference on Malignant Lymphoma, Lugano

T 97 CARBOPLATIN PHASE II STUDY IN RESISTANT MALIGNANT LYMPHOMA

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Thirteen patients (pts) with malignant lymphoma were entered in a phase II trial of Carboplatin between January 89 and December 89.
Carboplatin was administered in the day hospital at 400 mg/sqm in 500 ml of 5% dextrose over one hour by intravenous infusion at 28 day intervals.
Median age was 42 years (24-63).
Histological diagnosis was 6 Hodgkin's disease (HD) and 7 Non-Hodgkin Lymphoma (NHL) of intermediate type (3 F, 4 G).
All pts had progressive disease (2 relapsed and 11 refractory) and had previously received anthracycline combined chemotherapy.
Median number of drugs administered before Carboplatin was 12 (4-14).
Eight pts received previously ≥ 3 different regimens and 7 pts were irradiated.
The Interval between diagnosis and Carboplatin treatment ranged from 10 to 60 months (median = 12 m).
WHO performance status was ≤ 3. All pts had mesurable disease.
Toxicity and response were evaluated according WHO criteria.
A total number of 21 Carboplatin cycles was administered.
Hematological toxicity is shown in table :

WHO GRADE	0	I	II	III	IV
WBC	7	6	7	0	1
PN	9	4	7	0	1
Platelets	5	4	5	4	3

Nausea and vomiting (≥ 2) were noted during 10 cycles.
No significant nephrotoxicity or neurotoxicity was encountered.
There were 2 partial responses (1 HD, 1 NHL).
The first patient died 4 months later of hemorrhage after high dose therapy followed by autologous bone marrow transplantation and the second patient is alive in complete remission 10 months later after consolidation by radiotherapy.
These preliminary results merit further investigation and patient accrual should be continued.

T 98 CIS-BMP CHEMOTHERAPY FOR LYMPHOMAS WITH BONE MARROW FAILURE.

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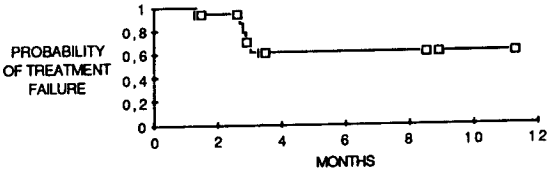
Despite progress in curative treatment of lymphomas, there is a category for whom only palliative therapy can be offered for the relief of pain or B symptoms, or psychological support. However the most effective drugs have already been used and bone marrow is often involved or irradiated. From 1/89 to 9/89, 16 patients (pts) were treated with a combination of drugs which have only a mild aplastic effect : CISPLATINUM 100 mg/m2 day (d)1, BLEOMYCINE 15 mg Total Dose (TD) d1 d 2 and d 15, METHYL-GAG 500 mg/m2 d 2 and d 15, METHYL-PREDNISOLONE 120 mg TD d 1 and d 2, 240 mg TD d 15. Full dose was given regardless of the blood counts. Second cycle at d 28 if blood counts was comparable. **Patients Characteristics** were as follows : 12 males, median age 57 years, (range (r) = 34 -76), PS (WHO) ≥ 2 (8 pts). **Disease** : histology (Non Hodgkin Lymphomas = 15, Hodgkin = 1). Tumoral status : Pts were at advanced stage : median number of perceptible phase : 2 (r = 1-4) ; Refractory 11; B Symptoms 10 ; hypoplastic blood counts 8 ; Marrow involvement 9. **Previous therapy** : Pts were heavely pretreated : radiotherapy 9 (extensive: 3), median number of different chemotherapy regimens received : 3 (r = 1-5). **Results** : 53 cycles were administered. Treatment failure (TF) was defined as follows : 1° STAB or PROGR after ≥ 2 cycles - 2° Reapparence of B Symptoms - 3° Alteration of quality of life due to therapy - 4° Toxicity ≥grade 2 or infection ≥ grade 3. Treatment was continued until TF or maximum of 6 - 8 cycles according to respiratory function ; **Toxicity** : 1° Hematology : 50 % of the cycles were given at d 28, 90 % before d 35 ; 2° Infections grade 1 (3) grade 2 (3) - 3° Others : one hemorrhage related death due to autoimmune thrombopenia. Hair generally regrew under treatment. Otoxicity grade 2 (1). Neuropathy grade 2 (1). **Response** : 2 CR and 6 PR out of 11 mesurable disease. Surprisingly 2 pts were able to be autografted. **Treatment failure** is described as follows :



Conclusion : CIS-BMP gives thus promising results in this context.

T 99 AUTOLOGOUS BONE MARROW TRANSPLANTATION IN RELAPSED B CELL NON-HODGKINS LYMPHOMA: VERY LOW TREATMENT RELATED MORTALITY IN 130 UNIFORMLY TREATED PATIENTS.

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High dose ablative therapy and ABMT has been shown to be the only potentially curative modality for patients (pts) with relapsed NHL. More widespread use of this treatment has been limited by significant fatal toxicity and infiltration of the bone marrow (BM) by lymphoma cells. One hundred thirty pts with B cell NHL in sensitive relapse or incomplete first remission (13 pts) were uniformly treated with high dose chemoradiotherapy and anti-B cell monoclonal antibody treated ABMT. All of these pts demonstrated good performance status with Karnofsky score of ≥80%. However, the majority of these pts had one or more adverse prognostic features including a failure to achieve a complete remission with conventional combination chemotherapy (52 pts), BM infiltration (90 pts), a history of extranodal disease other than BM infiltration (56 pts), and histologic conversion from a low to intermediate grade NHL (18 pts). At the time of ABMT, only 64 pts were in CR; however, all pts had achieved a minimal disease state (≤ 2 cm lymph node masses and BM involvement of ≤ 20%).following conventional intensive therapy. At harvest, 50 pts had histologic evidence of BM infiltration. Following high dose ablative therapy (cyclophosphamide 60 mg/kg x 2 and 200 cGy x 6), two acute in-hospital toxic deaths occured (1 CNS bleed, 1 VOD). Four late non-infectious deaths were observed, not due to recurrent NHL. All patients achieved hematologic engraftment with a median of 26 days for granulocytes (>500 PMN/mm^3) and 27 days for platelets (>40,000/mm^3). The late complications have been limited with 16 pts with pneumonia (3-P. carinii, 1-CMV, and 12-culture negative), and 27 pts with H. zoster (25-dermatomal, 2 disseminated). Of the remaining 124 pts, 79 are in unmaintained CR with a median follow-up of 17.9 months. Of the 13 pts undergoing ABMT in incomplete first remission, only 2 have relapsed. The majority of relapses were in sites of previous disease (32 old sites, 7 old and new sites) while 7 occurred in only new sites. Sixteen pts relapsed in the BM, 12 of whom had a prior history of BM infiltration, and 9 of whom had BM involvement at harvest. BM involvement with NHL either historically or at harvest did not adversely influence overall DFS. Moreover, remission status at ABMT as well as a history of extramedullary extranodal disease did not affect DFS. Kaplan-Meier actuarial analysis predicts 50% probability of DFS at 42 months. This study demonstrates that high dose chemoradiotherapy and ABMT can be employed with very low treatment related mortality and in pts with persistent BM infiltration at harvest. This low mortality has now permitted us to employ high dose chemoradiotherapy and monoclonal antibody purged ABMT as consolidative therapy for patients with both low and intermediate/high grade lymphoma who are not considered cureable with conventional therapy.

T 100 Autologous bone marrow transplantation (ABMT) in the treatment of lymphoma with emphasis on cardiac complications.

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High dose chemotherapy (HDCT) followed by ABMT offers one way to circumvent treatment resistance of patients (pts) with lymphoma. From December 81 to December 89, 32 patients (19 males, 13 females), median age of 31 (range 16 - 57) years underwent ABMT. 16 pts had non Hodgkin's lymphoma and 16 pts had Hodgkin's disease. HDCT was BEAC (BCNU 300 mg/m2 d1, cyclophosphamide (CPA) 60 mg/kg d2-3, VP16 500 mg/m^2 d2-3, ARA-C 400 mg/m^2 d2-5) for 22 pts, CPA 60 mg/kg d1-2 and total body irradiation in 5 pts, AVE (ADR 135 mg/m^2 d1, CPA 3 g/m^2 d1, VP16 250 mg/m^2 d1-3) in 4 pts and BAM (BCNU 550 mg/m^2 d1, AMSA 150 mg/m^2 d2-5) in 1 pt. 20 pts were in sensitive relapse, 11 pts were in resistant relapse (RR) or progressive disease (PD) and 1 pt with poor prognostic lymphoblastic lymphoma was in complete remission (CR). None of the pts with RR or PD are alive and the median survival was 2 (0-80) months. Among the 20 pts grafted in sensitive relapse, 9 (45%) are alive and 6 (30%) are disease-free with a median follow-up of 20 (3-96) months. The pt grafted in CR is alive, in continous CR. All pts had a normal cardiac function before ABMT (isotopic ejection fraction and/or routine bidimentional echocardiography), none were symptomatic. We observed 3 non-fatal pericarditis and 4 fatal myocarditis. Myocarditis-related manifestations included daily weight gain, decrease of the QRS complexes, altered left ventricular function and presence of pericardial effusion. These 4 pts had all previous mediastinal radiotherapy (≥ 30 grays) within 2 years of the graft, previous treatment with adriamycine and a conditioning regimen including high dose CPA. We suggest therefore that high dose CPA should be avoided in pts with prior mediastinal irradiation and anthracycline therapy.

T 101 PARMA INTERNATIONAL PROTOCOL : EARLY NON RANDOMIZED PILOT STUDY OF DHAP FOLLOWED BY INVOLVED FIELD RADIOTHERAPY AND BEAC WITH ABMT : REVIEW OF A GROUP OF 50 PATIENTS WITH A MINIMUM FOLLOW UP OF 3 YEARS.

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Fifty patients with intermediate or high grade non-hodgkin's lymphoma who had relapsed following a complete remission induced by an Adriamycin containing chemotherapy regimen participated in this pilot study. The patients ranged in age from 16-60 years (median 40 years). All patients received Dexamethasone, high dose Cytarabine, and Cisplatin (DHAP) for two courses at 3-4 weeks intervals. Patients achieving a partial or complete response received involved field radiotherapy and high dose Carmustine, Etoposide, Cytarabine, and Cyclophosphamide (BEAC), followed by autologous bone marrow transplantation (ABMT). The response to DHAP in 48 evaluable patients (i.e. one was lost to follow up and one had no measurable disease) was complete response (CR) 7 patients, partial response (PR) 21 patients and non response progressive disease 20 patients. Two patients died for treatment related toxicity and five others declined autologous bone marrow transplantation. The patient with non mesurable disease did not progress on DHAP and was submitted to ABMT. Twenty-two patients underwent autologous bone marrow transplantation. Two patients received Cyclophosphamide plus total body irradiation and 20 received the BEAC protocol. Out of theses 20 patients, 11 are alive (7 patients are disease-free) and two (9%) died from toxicity ; event free survival is 45% at 24 months. This prospective multicentre trial documents the ability of DHAP followed by autologous bone marrow transplantation to produce durable complete remission in a significant proportion of patients with relapsed aggressive non Hodgkin's lymphoma unselected at time of relapse from a conventional protocol.

T 102 HIGH DOSE SEQUENTIAL CHEMOTHERAPY WITH AUTOLOGOUS BONE MARROW TRANSPLANTATION IN RELAPSED OR PROGRESSIVE NON-HODGKIN'S LYMPHOMA.

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Eleven patients with relapsed or progressive non-Hodgkin's lymphomas were treated with an innovative scheme, recently developed at Istituto Nazionale Tumori of Milan, including the sequential administration (2-3 weeks interval) of cyclophosphamide (7 g/mq), methotrexate (8 g/mq) + Vincristine (1.5 g/mq) + folinic rescue, Etoposide (2 g/mq), melphalan (120-160 mg/mq) + TBI (11.0-13.2 Gy) followed by autograft of bone marrow + peripheral blood stem cells. In 5 patients presenting with bone marrow involvement the scheme was partially modified by adding prednisolone (100 mg/mq/die) for 5 consecutive days following cyclophosphamide, and one course of DHAP regimen between methotrexate and etoposide. Two patients had a progressive low grade lymphoma, one had a relapsed Burkitt's lymphoma, while 8 had intermediate-high grade lymphoma previously treated with MACOP-B. Three patients died during the treatment (one for cyclophosphamide toxicity; the second for disease progression; the third for severe hepatotoxicity followed by disease progression). The remaining 8 patients completed the treatment without major complications. Graft procedures were unusually well tolerated due to the high number of hemopoietic progenitors reinfused, by harvesting both bone marrow and peripheral blood stem cells after either cyclophosphamide or etoposide. Indeed, a high number of circulating CFU-GM was observed during the period of harvest. Seven out of 11 patients (63.6%) obtained a complete remission. One had a partial remission. All patients with extensive bone marrow involvement attained a pre-transplant complete remission proved by bone marrow biopsy and molecular analysis (one patient). As of december 31, 1989, 7 patients are still alive, 5 (45.4%) are in unmaintained complete remission at 6-18 months from autograft. The results demonstrate the tolerability and the therapeutic effiacacy of the high-dose sequential chemotherapy scheme in high-risk heavily pretreated lymphoma patients.

T 103 RESULTS OF COLLECTION OF PERIPHERAL BLOOD STEM CELLS IN VIEW OF AUTOGRAFTING IN RELAPSE LYMPHOMA.

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Peripheral blood stem cells (PBSC) were collected from 10 patients (pts) with high grade, stage IV non hodgking lymphoma (NHL) in second or third relapse. The conditioning regimen prior PBSC collection included AMSACRINE = 200 mg/m2/d x 3 days and CYTOSINE-ARABINOSIDE (ARAC) = 500 mg/m2 twice a day x 4 days (n=5) or ARAC 1g/m2 twice a day x 5 days (n=4) ; one pt received AMSACRINE 200 mg/m2/d x 3 days and ARAC 3 g/m2/12 h x 6 days. Median aplastic phase duration was 18 d (range = 9 - 26). PBSC collection began after leucocytes count reached 1500/mm3 at day 21 (range = 18 - 29) 3 to 5 apheresis were performed in all cases. A median number of 5 x 10^8/kg (range = 1,5 - 10) nucleated cells were collected per pts corresponding to 12.10^4/kg CFU-GM cells (range = 0 - 68.8). In 3 cases, we didn't obtain sufficient number of CFU-GM ; in one pt a second phase of ARAC induced aplasia allowed us to collect enough CFU-GM. No toxic related death was reported during the aplastic phase. After high dose chemotherapy and radiotherapy, 5 patients have already been transplanted with leukaphereses products. The engrafment was observed in every case.

Our results suggest that
. chemotherapy with AMSA and/or ARAC is a potential and safe conditionning regimen in order to collect PBSC in heavy treated lymphoma.
. PBSC collected can induce hemopoietic reconstitution after myeloablative chemotherapy.

Currently the follow up after PBSC autograft remains too short to evaluate the usefulness of such therapeutic approach in malignant lymphoma.

T 104 TREATMENT OF ADULT ACUTE LYMPHOCYTIC (ALL) AND UNDIFFERENTIATED LEUKEMIA (AUL) IN RELAPSE.

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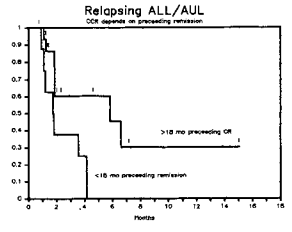
38 patients (28 male, 10 female, mean age 28 yrs.; [17 - 62 yrs.]) with a preceeding first CR of more than 6 months have been treated for relapsed ALL and AUL. A first induction phase contained vindesine, DNR, Pred, asparaginase and a second Hd (Id) AraC and VP16. Patients in CR are assigned for two consolidation regimen, one with Hd ifosfamide and vindesine, the other with Id MTX, AraC, VM26, and dexamethasone. 24/38 patients achieved a CR (63%), 16 of them after induction phase I, 8 after phase II. The median disease-free survival was 3.5 mo, the median survival 6.6 mo. Patients with a preceeding CR of less than 18 months had 47% CR. Those with a preceeding CR more than 18 months had a CR rate of 76%, however (p = 0.06). Patients with a short preceeding CR had a shorter disease-free survival (not significant). Side effects of induction phase I consisted predominantly in hematotoxicity with subsequent infections and gastrointestinal toxicity. The median duration of critical granulopenia <500 /µl was 13 days In phase II some patients experienced additional cutaneous, ocular and hepatic toxicity. Granulopenia lasted for a median of 15 days and thrombopenia <20,000 /µl for 11 days. Four patients died during induction. Nine patients had allogeneic and seven autologous BMT. Six of the patients with allogeneic BMT, and one with autologous BMT remain disease-free. The treatment regimen is effective in remission induction, but the remissions are short. The duration of the preceeding remission is the main prognostic factor.



ABSTRACTS - Fourth International Conference on Malignant Lymphoma, Lugano

T 105

Research on Non-Hodgkin's Lymphoma Arising from the Lymph Nodes. Y. R. Huang, Y. Sun, S.Z. Sung. Cancer Institute, Chinese Academy of Medical Sciences, Beijing, China.

From June 1983 to June 1986, 108 patients with non-Hodgkin's lymphoma arising from the lymph nodes were treated. The clinical data as below: male 82 and female 26; ages ranged from 9-63 years; according to the Working Formulation there were 9 low grade, 34 intermediate, 61 high grade and 4 unclassified; using Ann Arbor Staging there were 21 stage I, 23 stage II, 33 stage III and 31 stage IV; twenty-seven patients had the B-symptom. For stage I and II patients radiotherapy by local extented fields were given first and followed by adjuvant chemotherapy in some of the patients. The tumor dose in the primary focus should not be less than 50GY, while proplylactic dose not less than 45GY. For stage III and IV patients, the treatment is chiefly by chemtherapy on regimens of CHOP, BACOP etc. And some of them was followed by local radiotherapy. In 105 patients who received full dose treatment, 42 patients achieved CR, 38 PR and 25 stable or progressive disease. The five year survival rate for stage I and II was 69.6% and 45.8 for the whole group. The recurrence rate for the CR patients was 40.3% and 55% for the PR patients. It is shown that the recurrence was mainly related to the histoltgical type. Other-wise the importance of subdiaphramatic involment as an important prognostic factor was analysed. Among the failures 58% with subdiaphramatic involment, while among the whole group the figure was 39.8%. The results indicated NHL arising from the lymph nodes as well as that arising from the Waldeyer's ring, it is often shown the subdiaphramatic involment. The authors suggest that chemtherapy or abdominal irradiation is indicated after radiotherapy especially for the high grade type.

T 106

NASAL LYMPHOMA - A CLINICO-PATHOLOGIC STUDY. R. Liang[1], D. Todd[1], D. Choy[3], T.K. Chan[1], E. Chiu[1], F. Ho[2]. University Departments of Medicine[1] and Pathology[2] and the Institute of Radiotherapy and Oncology[3], Queen Mary Hospital, Hong Kong

Between 1975 and 1988, sixty adult Hong Kong Chinese patients were diagnosed to have nasal lymphomas which comprised 6.5% of all cases of lymphomas. Only cases involving the nasal cavity and nasal sinuses were included. There were 42 males and 18 females. The median age was 49 years. 31 patients had stage I disease, 10 stage II, 3 stage III and 16 stage IV disease. According to the Working Formulation, there were 1 case of SL, 1 FSC, 2 FM, 1 DSC, 5 DM, 14 DLC, 5 DIB, 1 DLB, 1 DSNC, 16 unclassifiable and 13 polymorphic reticulosis. Immunophenotype was known in 18 cases. There were 12 T-cell, 4 B-cell and 2 were inconclusive. Twenty seven patients with stage I/II disease received radiotherapy alone and the remaining 33 patients had chemotherapy (m-BACOD 10, BACOP 2, CHOP 12, COPP 5, CVP 4). 11 patients had additional radiotherapy following chemotherapy. Ann Arbor Staging was the only significant prognostic factor. Patients with stage I/II disease had a 5-year survival of 55% and chemotherapy did not appear to be more effective than radiotherapy alone in treating these patients. Stage III/IV patients had significantly ($p = 0.0005$) poorer prognosis with a 5 year survival of only 17%.

T 107

EXTRANODAL LYMPHOMAS; REPORT OF 9 CASES OF PRIMARY BREAST LYMPHOMA. M.Antonopoulos,S.Vasilaros,J.Papadiamantis,A.Tsikkinis, J.Sakellaris,S.Tsiliakos,E.Kouri,H.Karaiosifides,D.Anagnostou-Keramida.Medical,Ist Surgical and Path.Depts of "H.Venizelos Hosp." and Haematopath.Dept of "Evangelismos" Hosp.Athens,Greece.

A considerable number of lymphomas arise from extranodal sites . Primary Hodgkin and non-Hodgkin lymphomas of the breast are a rare occurence. Their incidence is 0,05-0,53% of all breast neoplasms . Our aim was to evaluate the primary lymphomas of breast we had had in our clinics, where a large population of breast cancer patients has been studied. The incidence of HD and non-HD was found of the order of 0,03%. Nine patients presented with localised disease to the breast (stage IE) or the breast and ipsilateral axillary lymph nodes (stage IIE). In this series is included a case presented with brain involvement due to breast lyphoma.The pathological material was classified according to the Working Formulation classification and all patients were evaluated with physical examination,laboratory investigation including CT abdominal and in a few brain scans, chest x- ray , bone scan and bone marrow biopsy . No patient underwent staging laparotomy. Treatment included lumpectomy in a few cases , chemotherapy and radiation therapy.Our results indicated complete remission in 5/9 6 months to 5 years since the diagnosis. Partial remission was obtained in 3/9 and one failure to combined treatment in the case with brain involvement (CHOP plus RT) . Localised RT was given to 2/9 and chemotherapy only with Chop in 3/9 cases. Bulky disease (tumor size > 5 cm and LDH high) was treated with combined chemo/ RT. Prognostic factors like bulky disease and high LDH were the most useful parameters. We cannot draw any firm conclusion at the present time,because of the rarity of the primary breast lymphomas and the optimum management require further evaluation.

T 108

PRIMARY EXTRA-NODAL NON-HODGKIN LYMPHOMAS (PENNHL): REPORT OF A CLINICAL STUDY OF 104 PATIENTS. R. Sabbioni°, A. Ambrosetti*, A. Perini°, G. Todeschini*, F. Pasini°, D. Veneri*, T. Franceschi°, G. Perona*, G.L. Cetto°. Institute of Medical Pathology, Divisions of Hematology (*) and Medical Oncology (°). University of Verona, Italy.

Non-Hodgkin Lymphomas (NHL) which arise out of central lymphoid system (lymph nodes, spleen, thymus), without (stage IE) or with involvement of regional lymph nodes (IIE) are classified as PENNHL.
From 1973 to 1989, 695 patients (pts) with NHL were referred to our Institutions; 104 of these (14.9%) fulfilled the criteria mentioned above: 60 were males and 44 females (ratio 1.3:1), median age was 57 years (range 12-84), seventy-two (69%) were staged as IE and thirty-two (31%) as IIE. The sites involved were:gastro-intestinal tract in 52 pts (50%), head and neck region in 17 pts (16.5%), skin in 10 (9.6%), central nervous system in 8,gonads in 6, breast in 4, lung in 4, bone in 2, and uterus in one.
Histologically, the diffuse pattern (90/104) was more frequently observed, compared to the nodular one (14/104). According to the Working Formulation, a prevalence of the high grade malignancy subtype (56/104) was detected, compared to those of the intermediate (42/104) and the low grade (6/104).
Eigthy pts (77%) underwent surgery; in 51/80 chemotherapy was performed and in 15/51 involved field radiotherapy was associated to the chemotherapy. In the 24/104 pts, who did not undergo surgery, treatment was: chemotherapy in 11 pts, radiotherapy in 4 pts, and chemotherapy plus radiotherapy in 9 pts.
Complete remission (C.R.) was achieved in 100/104 pts (96%); to date, 74/104 are still alive and 68 are in C.R., with a median follow-up of 32 months (range 3-142); 36 pts survived more than 5 years. The overall median survival is 131 months.
Our data, outlined the good results in terms of C.R. and long term survival in PENNHL, suggesting the importance of an integrated therapeutic approach.

T 109 PRIMARY GASTRIC LYMPHOMA: RETROSPECTIVE DATA FROM 39 CASES.

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Involvement of the stomach is the second most common extranodal site after Waldayer's ring, accounting for 9% of all NHLs in our experience. Despite this fact, the disease is relatively uncommon and it is difficolt for large numbers of pts to be accrued into single centre trials. To date, the majority of the reported series about results of treatment of pts with primary gastryc lymphoma have been based on retrospective analyses. Our study refers to 39 cases of primary gastric lymphoma (20 m. and 19 f., mean age 56 yrs, range 27-78 yrs).
At the onset, the most common symptoms were epigastric pain (56%),weight loss (33%) and dyspepsia. Hematemesis was observed in two cases. In the majority of istances the disease was localized at gastric body (41%), followed by antrum (35%) and fundum. In six cases (16%) a multicentric involvement of the stomach was observed. Ulcerating lesions surronded by elevated borders or infiltrating the gastric wall(66%), as well as lesions diffusely infiltrating (16%) were the macroscopic appearance more frequently observed. According to the Working Formulation, intermediate and high grade NHLs were found in 79% of cases (LG 8, IG 17, HG 14). The Musshoff staging system showed 20 pts in stage I, 12 in II (IIE1 8pts, IIE2 4pts), and 7 pts in stage III/IV. Treatment consisted, when possible, in surgery followed by cyclic chemotherapy (CVP for low grade or in pts more than 65 yrs; CHOP/CHOP-Bleo/CEOP for intermediate -high grade).
CR was achieved in 33 pts (84.6%) and PR in 2 pts (6.8%). 4 pts with advanced disease and high grade NHL died within few months from diagnosis (surgery not possible 2 pts, gastrointestinal bleeding or refused therapy in the other 2 cases). Four relapses were observed at +31, +18,+18 and +24 months (2 local and 2 nodal); one of these pts, who relapsed after surgery, achieved 2nd CR by chemotherapy. The remaining 3 pts died with progressive disease.
At present time, 31 pts (79.4) are alive and well with a follow-up from +4 to +110 months (mean 38.4 months).

T 110 STAGE I-II PRIMARY GASTRIC NON-HODGKIN'S LYMPHOMAS (NHL): A RETROSPECTIVE ANALYSIS OF 108 CASES.

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**108 patients (pts) with stage I-II primary gastric non-Hodgkin's lymphoma (NHL) observed from 1975 to 1987 in seven onco-hematological Units in Northern Italy have been retrospectively analyzed. Mean age was 56 yrs (range 20-81); male-female ratio was 1.7:1. Symptoms were similar to those of gastric carcinoma. The most frequent gastric location was the antrum (21%), followed by lesser curve and greater curve. Stage was IE in 63 pts, IIE in the remaining 45. According to Kiel Classification, 50 pts had a high grade lymphoma, 30 pts an intermediate grade lymphoma, 22 pts a low grade lymphoma. In 6 pts, histology was unclassifiable.
The treatment consisted of radical surgery alone in 31 pts, surgery and chemotherapy (CT) in 39 pts, surgery and radiotherapy (RT) in 15 pts, surgery+CT+RT in 9 pts, CT only in 12 pts, CT and RT in 2 pts. Median follow-up is 49 months. Complete remission (CR) was achieved in 86 pts (80%): 9 pts relapsed, 8 of them locally. In univariate analysis, significant prognostic factors were: histological grading (low or intermediate grade vs. high grade), infiltration of sierosa, and the accomplishment of radical surgery. In multivariate analysis, only radical surgery resection mantained its prognostic significance. Data coming from this series suggest that radical surgical resection is recommended as first-line treatment in all the pts with stage I-II primary gastric NHL, possibly being curative by itself in stage I pts without unfavourable prognostic factors. In stage I pts with unfavourable prognostic factors and stage II pts an adjuvant treatment with RT or CT is advisable.**

T 111 REPORT OF A CLINICAL STUDY OF 52 PATIENTS WITH PRIMARY - GASTRO - INTESTINAL - NON - HODGKIN - LYMPHOMA (PGINHL).

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We have evaluated 695 cases of NHL observed in our Institutions from 1973 to 1989. We considered as PGINHL the Non Hodgkin Lymphomas (NHL) which arise from gastro-intestinal tissue without (stage IE) or with involvement of regional lymph nodes (IIE). Only 52 patients (7.5%) can be defined as PGINHL, (34 males, 18 females, ratio 1.9:1); the median age was 58 years.
The stomach was the most frequent localization (45/52). Thirty patients were staged as IE, 22 as IIE of the disease. Histologically we observed a prevalence of a diffuse pattern (43/52) compared to a nodular one (9/52) and a prevalence of high and intermediate grade malignancy (respectively 23 and 25) versus low grade (4 patients), according to the Working Formulation.
The treatment was not homogenous. Forty-nine patients underwent surgery; and 15 of these had surgery alone. The remaining 34 patients had chemotherapy (28), radiotherapy (1) or both (5) after surgery. Only 3 patients were treated with chemotherapy alone.
Complete remission was achieved in 50/52 patients (96%); in two patients the disease progressed; 9/50 (18%) relapsed; 42/52 are alive to date with a median follow-up of 30 months (range 3-142). Median survival is still not reached (60% of survivors at 93 months).
The encouraging results obtained confirme the better prognosis of PGINHL as compared to other NHL, irrespective of histology, and suggest the opportunity for an integrated approach (surgery plus chemotherapy).

T 112 GASTROINTESTINAL NON-HODGKIN'S LYMPHOMA (NHL): A RETROSPECTIVE STUDY ON SURVIVAL PROSPECTS

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Gastrointestinal (GI) tract is the most common site of primary extranodal lymphomas. Although the lymphomas of this anatomic region are in their majority of diffuse aggressive type, several other prognostic factors affect the evolution of disease.

Our aim was to tretrospectively study the survival of patients with primary GI lymphoma, in relation to possible prognostic factors and type of treatment.

We studied 29 patients (15 male, 14 female), treated between 1/80 and 5/89. The median age was 55 years (range, 16 to 72). The primary site included stomach 22 patients, small bowel 3 and large bowel 4. The depth of tumor invasion was in 3 patients superficial, in 7 transmural and in 19 there was serosal penetration. Involvement of lymph nodes had 20 patients, of those 7 contiguous only, 13 and/or not contiguous. Eight patients presented with stage I_E, 14 stage II_E (5:II_{E1}, 9:II_{E2}), 7 Stage IV. Low grade (LG) histology had 2, intermediate (IG) 4, high grade (HG) 20. Twenty five patients underwent surgical procedures, 11 complete resection of disease, 14 laparatomy and biopsies only. All patients received chemoterapy (6 cycles at least), mainly GHOP (21). At a median follow-up of 41 months (6-106+), 20 of 29 patients remained alive. The projected 5-year survival for the entire group is 71,6%. Patients with lymphoma of the stomach have better 5-year probability of survival (80,5%) compared with those of bowel (42,9%) (P<0.05). For Stages I_E to II_{E1} and II $_{E2}$ to IV the projected 5-year survival is 100% and 52% respectively (p<0.005). Also in the resected over the non-resected group 100% v 60% respectively (p<0.05).

These results suggest that localized in the stomach disease and early stage are favorable prognostic factors. Also complete resection of disease prior to chemotherapy, influences positively the survival.

ABSTRACTS - Fourth International Conference on Malignant Lymphoma, Lugano

T 113 THE PRIMARY GASTRIC NON-HODGKIN LYMPHOMA : A RETROSPECTIVE STUDY.

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A retrospective study was carried out on the survival of 54 patients with primary gastric non-Hodgkin Lymphoma (G-NHL),hospitalized at various departments of San Martino Regional Hospital of Genova from 1976 to 1989. 9 patients(pts) were excluded from the analysis due to incomplete data. The remaining 45 pts,18 females and 27 males,median age 66 years(range 21-84),were staged according to Ann Arbor staging system and graded according to the Intenational Working Formulation for clinical usage (WF).11 pts were clinical stage(st)I; 12 st II; 5 st III; 17 st IV. Among the classified Lymphomas,low grade G-NHLs were encountered in 5 pts,intermediate grade in 21,high grade in 19. Out of 45 pts 22 underwent surgery alone (9 st I;5 st II;8 st IV); 11 surgery+chemotherapy (2 pts st I;4 st II;2 st III;3 st IV); 5 chemotherapy alone (4 pts st IV;1 st I);1 radiotherapy alone (stII); 3 surgery+chemotherapy+radiotherapy (1 pt st II;1 st III;1 st IV). 3 pts were not treated (1 pt st IV and 2 pts st III). The median survival was 86 months in early stages (I - II) and 6 months (range 1-20) in stages III-IV. Statistical analyses showed a significant survival advantage (P value : 0.0034 Mantel-Cox) in pts in stages I-II compared to stages III-IV.No significant difference in survival was found among the different treatment groups (Kaplan-Meier function). Age,sex and histologic grade (low + intermediate grade versus high grade) all were nonsignificant factors.
CONCLUSIONS.The initial clinical stage is an important prognostic covariate. According to literature,the study failed to demonstrate a significant prognostic value for the WF in primary G-NHL.The best treatment for these neoplasms still remains uncertain and it is a matter of active debate. It is then important to designe prospective randomized clinical trials on the basis of the results provided by prognostic classifications. To this aim,optimal managements of patients with primary G-NHL can be investigated by conducting multicentre prospective trials.

T 114 MEDIASTINAL B LARGE CELL LYMPHOMA IN ADULTS. A CLINICAL AND PROGNOSTIC STUDY OF 16 PATIENTS TREATED BY CHEMOTHERAPY ALONE(LNH 84 REGIMEN).

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Between january 1985 and june 1989, we diagnosed mediastinal B large cell lymphoma (non lymphoblastic and revealed by symptoms related to a large mediastinal mass) in 16 adult pts (9 females, 7 males, median age: 36 yrs, range: 16 to 69) representing 5.5% of all our adult aggressive NHL. Presenting symptoms were: dyspnea (8), cough (7), dysphonia (3), hemoptysis (2), chest pain (1). 8 pts had systemic symptoms. Physical findings included: parasternal mass (6 pts), Superior vena cava syndrome (5 pts, not correlated with tumor size), arm swelling (4 pts), pleural effusion (4 pts) and symptoms related to pericardial involvment (2 pts). 4 pts had supraclavicular nodes. The chest Xray showed a large anterior mediastinal mass, whose maximal diameter, mesured by CTscan, was $\geq$ 10 cm in 11 cases. There was contiguous extranodal spread in 12 pts: pleura (7 pts, but only 4 large effusions), lungs (6 pts), heart (3 pts: 2 pericardial effusions and 1 diffuse pericardial and myocardial infiltrate), anterior wall soft tissue (6 pts, correlated with parasternal mass). 2/16 bone marrow biopsies were positive. 3 pts had extrathoracic involvement: liver (2), stomach (2), pancreas (1), paraaortic lymph nodes (1), kidneys (1), bone (1), skin (1). After clinical staging, disease was localized in 12 pts (2 I, 1 II, 9 II_B) and disseminated in 4 pts (all IV_B). All pts were treated with the LNH 84 regimen (4 courses of CHOP Bléo at higher doses of Adri (75 mg/m²) and Cytoxan (1,2 g/m²) for induction, followed by sequential consolidations) scheduled for 6 to 8 mos; this third generation regimen gives a 75% CR rate and a 55 to 60% prolonged DFS in agressive non Hodgkin's lymphomas (NHL) (COIFFIER et al, Blood, 1987, 70, 244). No pt received radiotherapy. After induction therapy, 9/16 pts had a tumor reduction > 75% with a residual mass in 5, and 4/16 a reduction between 50 and 75% but with negative control mediastinoscopy; 2 pts had no tumor regression and rapidly died, and one pt had toxic death. Among the 13 responders, 6 relapsed (3 during consolidation therapy and the 3 others 1,2 and 10 mos after the end of treatment), 7 remained in persistent CR_1 (43,7% of the whole series) after 3, 3, 8, 11, 13, 17 and 24 mos respectively. A second remission was obtained in 5/6 relapses with salvage chemotherapy including VP_{16}, Ifosfamide, HDMTX and HDAraC (± Mitoxantrone) and persistent in 3 of them after 5, 16 and 20 mos following transplantation (2 auto, 1 allo) whereas the 2 other pts rapidly relapsed (after autograft in one case). Median overall survival was 28 mos. Although the number of pts was too small to reach statistical significance, stage IV disease was associated with poorer prognosis (1/4 persistent CR_1 versus 6/12 in localized NHL). All relapses and progressions were disseminated in stage IV pts and localized in the mediastinum in initially localized pts. In the 11 pts with localized NHL evaluable for tumor response, mediastinal tumor size $\geq$ 10 cm seemed to be a risk factor of poor response or intrathoracic relapse (5/8 pts with a mass > 10cm failed vs 0/3 with a size < 10 cm) as well as anterior wall soft tissue invasion (4/4 pts with a parasternal mass failed vs 1/7 with no parasternal mass). Our findings suggest that, even with third generation regimens, chemotherapy yields a relatively low incidence of persistent CR in mediastinal B large cell lymphomas, as compared to other types of aggressive NHL. In localized forms, as relapses occur in the mediastinum after chemotherapy, we suggest that mediastinal radiotherapy should be associated. In disseminated forms, as relapses seem to be disseminated, more aggressive systemic therapy (such as autografting in CR) seems warranted.

T 115 PRIMARY LYMPHOMA OF THE CENTRAL NERVOUS SYSTEM: REPORT ON 14 CASES.

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Fourteen (6 females and 8 males) with primary lymphoma of the central nervous system were treated at the Centre Alexis Vautrin between 1971 and 1988. The median age was 52 years. We observed no disturbance of the immune system and no development outside the CNS.

The mean duration of symptoms prior to presentation was 8 weeks with a range of 0-28 weeks. The most common symptoms were headaches, mental impairement and focal neurological signs. Evidence of raised intracranial pressure was present in 4 cases. Two patients presented diabetes insipidus with a severe hyponatremia and coma in one case. There were also two cases of primary spinal localisation.

Histological diagnosis was performed by surgical biopsy (5 cases) and by stereotactic biopsy (8 cases) with excellent results. In one case no biopsy was made because regression had occurred with corticosteroid treatment. This patient is still alive with 8 months follow-up.

We recorded 3 total regressions with corticosteroid treatment. Chemotherapy with different protocols was administered in 6 patients followed by radiotherapy. Radiotherapy alone was used in 6 other patients and 2 were treated with surgery and corticosteroids only. The dose range was 30-50 Gy on the whole brain plus a boost localised on the tumour site in 4 cases to arrive at a total dose of between 37,5 and 50 Gy in 4-6 weeks.

Median survival was 7 months (range 1-22 months). The median survival of patients treated with chemotherapy plus radiotherapy (6 cases) was 9 months (range +1- +17 months), with radiation alone (6 cases) 7 months (range +1- +22 months). Four patients are still alive (+ 4 - +23 months), 3 in complete regression and 1 with tumor.

T 116 Four cases of Non-Hodgkin's Lymphoma of the soft tissue adjacent to a long-standing Pyothorax.

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It is well known that malignant pleural tumors develope in patients with pyothorax resulting from therapeutic pneumothorax for pulmonary tuberculosis (tbc pneumothorax).

In the past 7 years, we have encountered four cases of Non-Hodgikin's Lymphoma, Diffuse Large-cell type, which developed in the soft tissue adjacent to a long-standing pyothorax. Immunohistological studies revealed B cell nature of lymphoma cells in the two cases (Case 1 and Case 2).

Case 1. A 63-year-old male. At the age of 24, he received tbc pneumothorax on the right side. His initial symptom was the right shoulder pain. The main tumor was in the right lateral hemithorax adjacent to the pyothorax, directly invading the right hepatic lobe. Distant metastasis were in the left lung and in the brain. No lymph node involvement was found (LN negative). Chemo- and radiotherapy were partially effective.

Case 2. A 61-year-old male. At the age of 21, he received tbc pneumothorax on the right side. His initial symptoms were the right shoulder pain and the left lower back pain. The tumors were in the right lateral hemithorax adjacent to the pyothorax and in the left upper abdomen. The latter invaded the pancreas, spleen, stomach and diaphragma directly. LN negative. Chemo- and radiotherapy were partially effective. He died of generalized fungal infection.

Case 3. A 67-year-old male. At the age of 20, he was treated for the left pulmonary tbc. His initial symptoms were weight loss and epigastralgia. He died of gastric bleeding before the definite diagnosis was made. On autopsy, there was a large tumor in the left lower hemithorax adjacent to the pyothorax. The tumor invaded the left lung, pericardium, diaphragma, stomach and left hepatic lobe directory. LN negative.

Case 4. A 73-year-old male. At the age of 36, he received tbc pneumothorax on the left side. His initial symptoms were constipation and lumbago for several months, followed by parapregia of lower extremities. The tumor was in the paraspinal space at he level of Th 9-10, extending to the adjacent soft tissue in the left back. He had pneumothorax on the same side. Multiple deposites were in the brain. LN negative. Chemo- and radiotherapy were of little effect. He died of tumor progression.

These four cases have a common feature with the other 40 cases reported in literature (37 cases are Japanese) and are regarded as a group with a common etiology, a long-standing pyothorax.

T 117

THERAPEUTIC BENEFIT BY RECOMBINANT INTERFERON-ALPHA 2a (ROFERON A) IN CUTANEOUS T-CELL LYMPHOMAS.

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From November 1985 to March 1989, patients with Mycosis Fungoides (MF) or Sézary Syndrome (SS) were treated with recombinant human interferon-alpha 2a (ROFERON A). The protocol design consisted of a dose escalation from 3 MU/day for 3 months. After this, all patients underwent other 9 months of therapy with 18 MU three times weekly. Twenty patients entered the study (18 MF and 2 SS); 15 were previously treated by other conventional therapies including PUVA, chemotherapy or both and 5 were not. There were 12 males and 8 females. The median age was 53 years; range of 28 to 75 years.
Five patients (25%) achieved a complete clinical remission, 10 (50%) obtained more than 50% reduction of detectable skin lesion or circulating Sézary's cells, 4 (20%) reached a minor response, and one patient (5%) resulted resistant. The clinical side effects included fever (20/20), flu-like syndrome (18/20), nausea (12/20), itching (1/20), paresthesia (1/20), somnolence (4/20). Hematological toxicity included thrombocytopenia (1/20) and neutropenia (15/20). No treatment-related deaths occurred. Protocol violations included 3 definitive interruptions, 8 reductions of scheduled dose and 4 temporary interruptions.
The median follow-up is 28 months. The projection of survival shows 80% of patients alive at 48 months; the freedom from progression is 50% at the same interval. In conclusion, the daily administration of interferon-alpha 2a has been shown to be highly effective in patients with advanced or refractory MF and SS; the improvement was well documented after a few weeks and continued during the consolidation therapy. We correlated the most part of side effects to the advanced age of some patients and those pretreated with systemic therapy. Since patients over 60 years did not tolerate more than 9 MU dose, we suggest to give no more than that dose to such patients in the future trials.

T 118

A case of simultaneous cutaneous T-cell lymphoma and acute non lymphoid leukaemia.

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A case of simultaneous low-grade cutaneous T-cell lymphoma (non-Sèzary, non mycosis-fungoides) and myelodysplastic syndrome that evolved to acute non-lymphoid leukaemia 10 months later is described. At diagnosis, the superficial dermis was infiltrated by a lymphoid population made up of small lymphocytes with regular nuclei and occasional larger cells with evident nucleoli. Mitotic figures were rare. There was mild-moderate epidermotropism. The results of the diagnostic procedures were:
Axillary lymph node biopsy, infiltration by the lymphocytes described above.
Immunohistology of cryostate sections, the lymphocytes stained for UCHT1 (CD3) and OKT4 (CD4) MoAbs and a few reacted with the Ki67 MoAb.
Bone-marrow aspirate and biopsy, signs of dyserythropoiesis and increased number of myeloblasts (5%), but no neoplastic cells, in either;
Cytogenetic analysis of bone marrow, 47 chromosomes with an extra chromosome 11 in 70% of the metaphases obtained from unstimulated cell cultures.
Treatment with $6x10^6$ / m^2 /IFN-β for 7 days alternate weeks for a total of 3 cycles and then twice weekly for 24 weeks led to disappearance of the lymph node infiltration and the infiltrated erythematous skin lesions, which involved 70% of the body surface, within 2 weeks . Pruritis was greatly reduced 6 weeks after starting therapy. Despite absence of anaemia and thrombocytopenia, blood smears studied at the 20th week of therapy revealed 2-3% circulating myeloblasts. One week post-therapy there was a clear picture of leukaemia, total infiltration of bone marrow by M2 (FAB classification) myeloblasts. At this time, 100% of bone marrow cells showed a 47,XY,+11 karyotype. The patient died 4 months later.

T 119

Ki-1+ LYMPHOMA CELL LINES IN CUTANEOUS T-CELL LYMPHOMA

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A series of 4 Ki-1+ clonal T-cell lines were established from 2 patients with a history of spontaneously regressing skin lesions. Patient 1 had a 17 year history of papulonodular skin lesions beginning in 1971 and mixed cellularity HD in 1975. He developed erythroderma and circulating Sezary-like cells in the blood in 1985. Two years later the skin lesions became larger and more persistent, suggesting that tumor progression had occurred. Tumor cell lines were developed from mononuclear cells in the blood (1985) and each of two skin lesions (1987). Each cell line has a clonal rearrangement of TCR beta chain genes but a germline configuration of TCR gamma chain genes. All cell lines have a stem line chromosome abnormality t(8;9)(p21;p24) with additional marker chromosomes in cell lines from the later stage of disease. All cell lines grow as suspension cultures and consist of a majority of small lymphoid cells and 5-10% RS-like multinucleated cells. All are CD30+; the cell line from the blood expresses CD2 on the surface and CD3 in the cytoplasm. Expression of RNA message for the TCR beta chain can be induced in both blood and skin cell lines with phorbol ester. Each cell line produces IL2 constitutively. The blood cell line expresses IL2R; expression of IL2R is suppressed by phorbol ester or TGF-Beta which down regulates IL2R. The skin cell lines also produce message for the beta chain of PDGF and grow more vigorously than the blood cell line which lacks PDGF message. A fourth cell line was established from patient 2, a 12 year old boy with skin lesions, generalized lymphadenopathy, splenomegaly and peripheral blood lymphocytosis. The blood cells and cell line have remarkably convoluted nuclei resembling Sezary cells. Additionally, the cell line contains about 10% RS-like cells. The cells have the phenotype and genotype of the Ki-1+ anaplastic lymphoma. The phenotype is CD30+, CD25+, CD45+, CD15-. T-cell antigens expressed include CD2, CD7 and the beta chain of the TCR. All cells have the t(2;5)(p23;q35) that has been described recently in some Ki-1 lymphomas. The doubling time in IMDM with 15% FCS is 60 hours. Colony forming efficiency in IMDM with 20% FCS and 0.8% methylcellulose is 5.5%. These results suggest that clonal tumor cell lines can be established from both blood and skin lesions of patients with Ki-1+ CTCL. These cell lines produce and respond to T-cell growth factors. However there is heterogeneity both between and within tumors of individual patients with respect to genotype, phenotype and growth characteristics.

T 120

THE NATURAL HISTORY OF LYMPHOMA IN PRIMARY SJOGREN'S SYNDROME (pSs)

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The purpose of this study was to analyse the incidence, histology, primary site and course of lymphoma in pSs pts. Eight of 120 pts with pSs followed over the past 7 years developed non-Hodgkin's lymphoma (NHL), an incidence of 6.6%. All pts were female with a median age of 55 yrs. Median time from pSs diagnosis to NHL development was 6.5 yrs. NHL were diagnosed according to the Kiel classification. Six pts had immunocytoma, one had diffuse centrocytic- centroblastic (CC-CB) and one nodular and diffuse CC-CB. Most pts had monoclonal k light chains. In 5 of them the malignant lesion was located at the minor salivary glands, two in the cervical lymph nodes and one in the nasopharynx. No immunocytoma pts were treated and they remain well, while the nasopharyngeal lymphoma underwent complete remission following local radiotherapy. It was interesting the fact that in two immunocytoma pts the malignant lesions were regressed spontaneously 6 and 18 months after diagnosis.
CONCLUSIONS: Lymphomas in pSs: 1) represent mainly low grade NHL and especially immunocytomas, 2) can arise primarily at the site of the autoimmune lesion, 3) usually have a benign course, thus conservative approach to treatment is indicated, and 4) spontaneous regression can be seen.

T 121 THE CLINICOPATHOLOGIC SPECTRUM OF VASCULITIS IN PATIENTS WITH NHL AND CLL.

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Vasculitis (VSC) in lymphoma patients (pts) has been very scantly described in the literature.

Between Jan 86-Jan 90,9 cases of skin VSL were diagnosed among 70 NHL and CLL pts,treated and followed in our Department (an incidence of 13 %).Median age was 59 yrs,5 were male and 4 female.Four patients had low and 2 had intermediate grade B-cell NHL,while 3 others had CLL.Skin biopsies revealed lymphocytic VSC (Ly VSC) in 7 leukoclastic VSC (Lc VSC) in 1 and a mixed form in 1.Median time from NHL diagnosis to first episode of VSC was 10 months (1-96).

Palmar erythematous nodules with burning or stinging sensation was the main clinical picture in 2 pts with Ly VSC,while all the rest presented with palpable purpura over the extremities and/or the trunk. Pruritus was present in 3 pts.One patient developed CNS involvement and peripheral neuropathy.The lesions were spontaneously regressed. Recurrence of the lesions was noticed in 4 pts.Neither chemotherapy or steroidsinfluenced the course of VSC.

Full immunologic and autoimmune profile including crycglobulins and anti-cardiolipin antibodies were performed.

CONCLUSIONS: VSC in NHL and CLL pts: 1) is not a rare phenomenon,2) lymphocytic VSC is the most frequent type,3) it affects mainly the skin,4) very rarely can become systemic,5) the lesions can "wax and wane" spontaneously and 6) treatment doesn't seem to alter its course.

T 122 THE PATHOGENETIC MECHANISMS OF LOW SERUM ANION GAP IN MULTIPLE MYELOMA PATIENTS

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It has been reported that in IgG multiple myeloma patients (MM pts), the serum anion gap (SAG) is lower as compared to normal controls. However, the pathogenetic mechanisms of this electrolyte disturbance are still uncertain. In this study, we determined the SAG in 13 IgG MM pts with a median age of 48 years, and we correlated it with the amount of serum monoclonal protein as well as with serum albumin. None of the MM pts had renal failure, hypercalcemia and hypermagnesemia or any other disease affecting acid-base balance and serum electrolytes levels. In none of the patients diuretics were given. Ten normal individuals were used as controls. The SAG in MM pts was 6.0±2.7 (mean ±1SD) mmol/L and it was significantly lower as compared to the controls (11.5±1.2, mean ±1SD),$p<0.01$. There was a significant correlation between the values of SAG and the amount of serum monoclonal protein ($r=0.993$, $p<0.01$). In most of the MM pts the serum sodium was in the lower normal limits (135±3.9 mmol/L,mean ±1SD) and it was correlated significantly with the amount of serum monoclonal protein ($r=0.68$, $p<0.5$). No correlation between SAG and serum albumin as well as between serum monoclonal protein and serum Cl^- or HCO_3^- was found. However, most MM pts had high serum Cl^- (106 ± 4.2 mmol/L, mean ±1SD), whereas serum HCO_3^- was within normal limits (23.5 ±2.6 mmol/L, mean ±1SD). On the other hand, serum albumin was significantly lower in the MM pts (3.8±0.4 g/dl, mean ±1SD) as compared to normal controls (4.5±0.2 g/dl , mean ±1SD), $p<0.05$.

CONCLUSIONS: 1) SAG is low in IgG MM pts, 2) this finding is directly associated with the amount of serum paraprotein, 3) hypoalbuminemia could also be an additional factor in the pathogenesis of this electrolyte disturbance, 4) the study is still in progress.

T 123 HYPERTHYROIDISM FOLLOWING HODGKIN'S DISEASE [8 CASES].

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Association between hyperthyroidism and Hodgkin's disease is unfrequent since less than 30 cases have been reported. We report 8 new cases noted among 407 patients treated by the Hodgkin POF H81/12 and H81/34 trials from October 1981 to September 1988. The incidence is 2.0 % among all our patients, 1.3 % among men and 2.8 % among women (NS):

▲**Case 1:** 25-year-old man - Cervical IA Hodgkin's disease - Complete remission (CR) in December 1985 - Hyperthyroidism in April 1986 without ophtalmopathy or goiter - Diagnosis: iodine-induced hyperthyroidism treated by carbimazole (CBZ) for 5 months -> recovery.
▲**Case 2:** 24-year-old woman - Mediastino-cervical IIB - CR in February 1986 - Hyperthyroidism in May 1986 with goiter but no ophtalmopathy: Graves' disease like hyperthyroidism -> spontaneous hypothyroidism 19 months later.
▲**Case 3:** 46-year-old woman - Cervical IIA - CR in May 1985 - Hyperthyroidism in January 1987 without ophtalmopathy or goiter: Graves' disease treated by 131I -> relapse in November 1987 treated by 131I and CBZ -> remission.
▲**Case 4:** 33-year-old woman - Cervical IA - CR in February 1986 - Hyperthyroidism in June 1987 with goiter but no ophtalmopathy: Graves' disease-like hyperthyroidism treated by CBZ -> remission.
▲**Case 5:** 34-year-old woman - Mediastino-cervical IIA - CR in April 1985 - Hyperthyroidism in October 1987 with ophtalmopathy and goiter: Graves' disease treated by CBZ -> remission.
▲**Case 6:** 18-year-old man - Pulmonary IVA - CR in September 1986 - Hyperthyroidism in January 1988 with goiter but no ophtalmopathy: Graves' disease-like hyperthyroidism treated by CBZ -> remission.
▲**Case 7:** 16-year-old woman - Mediastino-cervical IIA - CR in December 1987 - Hyperthyroidism in January 1988 with ophtalmopathy but no goiter: Graves' disease-like hyperthyroidism -> spontaneous hypothyroidism 4 months later.
▲**Case 8:** 56-year-old man - Splenic IIB - CR in July 1986 - Biological hyperthyroidism in March 1988 with high levels of anti-thyroid antibodies: Hashitoxicosis -> spontaneous hypothyroidism 2 months later.

As reported by other authors, our data suggests that the clinical aspects of hyperthyroidism following Hodgkin's disease are heterogeneous (typical Graves' disease; Graves' disease-like hyperthyroidism; Hashimoto and atypical thyroiditis) and that several etiological factors may be considered (immunological substratum; iodine overload; cervical radiotherapy...). (Work supported by APREMS).

T 124 HODGKIN'S DISEASE IN CHILDREN AND CANCER IN RELATIVES.

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Studies of possible dominant inheritance of leukemia and lymphoma have shown that familial occurence of these diseases is exceptional either in the same generation or in first degree relatives. The authors have investigated cancer in family members of children with Hodgkin's disease, but primarily the occurence of malignancy in first degree relatives. The study involved 50 children treated at the Belgrade University Children's Hospital between 1974-1989. The results showed a high frequency of positive family history regarding the presence of cancer in other family members of children with Hodgkin's disease. In 4 children the presence of cancer was disclosed in their parents; of these, the parents of 2 patients had cancers at the same time as their children. Familial aggregation of hematologic malignancies was also disclosed. It was concluded that further studies are necessary because familial factors are significant in the pathogenesis of malignant lymphoproliferative diseases, particularly of Hodgkin's disease.

T 125 HODGKIN'S DISEASE: A RETROSPECTIVE STUDY OF TREND IN KENYA (1968 - 1987).

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Title page only : type author's name(s) here

In order to show changes (if any) in Hodgkin's disease pattern in Kenya with the onset of AIDS epidemic a retrospective study of the disease was undertaken using Kenya Cancer Registry material covering the period between 1st January, 1968 to 31st May, 1987 (19.5 years). A total of 695 cases (520 males and 175 females) were found; the annual rate ranging from 11 in 1987 to 53 in 1969 with a mean of 34.8. 345 (49.6%) cases were under the age of 20 years with 135 (19.4%) being under 10. Only 84 (12%) were over 40. The age-group with the highest frequency of cases was between 10 and 19 years; representing 30% of all cases. The male: female ratio decreased over the years: 4.8:1 in 1968-72 period to 2.4:1 in 1983 - 87 period. The overall ratio was 2.9:1. Distribution according to districts showed a prediliction for high altitude and tea-growing areas (Kisii, Kericho, Machakos, Meru, Kiambu, Nyeri) as opposed to low-lying, non tea-growing areas. No clusters were seen in areas supposed to have high AIDS transmissions rates. 265 (38.1%) were not histologically subclassified. 201 (28.9%) were of mixed cellularity type, 56 (8.1%) were nodular sclerosing, 57 (8.2%) were lymphocyte predominant type and 116 (16.7%) were lymphocyte depleted type.

With respect to age-groups, sex ratio and histologic types the disease reveals a different pattern from that seen in Western Countries. It seems that the disease prevalance has not changed with onset of AIDS although serology could not be employed in our study. There is an increase in prevalance among females during the study period. There appears to be an association with tea growing areas. These areas may also represent high-income, other cash-crop growing and good nutrition populations. They may also share exposure to a common environmental pollutant. Epidemiological studies in this areas are urgently called for. Since those under 10 years of age are significantly affected a maternal related phenomenon needs to be further investigated. Connection with AIDS cannot be completely ruled out at this time. Since Hodgkin's disease has been associated with

immunodeficiency for a long time additional studies to rule out a connection with AIDS in our areas are necessary.

T 126 A SIMPLE METHOD TO AVOID LENS DAMAGES IN RADIOTHERAPY OF ORBITAL LYMPHOMAS.

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Our method allows to create narrow shield- tunnel encompassing the lens and to move on time by time different portion of the orbit volume. The irradiation is delivered tilting the beam and contemporarily the eye so that the visual axis becomes as much as possible perpendicular to the central axis of the beam (for instance gazing upward with 20 of caudad-cephalad tilting of the gantry). Utilizing four gazes (up, down, medial and lateral) for each photon beam session (6 MeV Linear accelerator), we obtain that impact surface of the lens exposed to the beam is reduced and a minor shield size is requested (we use an elliptical block 0.9 x 1.2 cm at 59.5 cm of source to tray distance). The narrow shield-tunnels and their divergences in the three dimensions guarantes an homogeneous dose distribution in the orbit while sparing the lens. An electron beam session with adequate contact lens shield is delivered to compensate the build up effect of photon session. The most critical procedure is the block placing but the mistake is covered by shield size. No corneal damage was found related to the vacuum contact lens fixer.

T 127 HODGKIN'S DISEASE (HD) PRESENTING WITH SEVERE APLASTIC ANAEMIA (SAA) SUCCESSFULLY TREATED WITH ALLOGENEIC BONE MARROW TRANSPLANTATION (BMT)

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SAA is associated with certain hematopoietic malignancies: about 10% of patients surviving more than two years will develop paroxysmal nocturnal haemoglobinuria and another 10-20% myelodysplasia with or without subsequent acute leukaemia. In HD long term survivors have an increased risk for leukaemia, lymphoma, and solid tumours. We here present a case with simultaneous occurrence of aplastic anaemia and Hodgkin's disease, with as yet a favourable outcome.

A 46-year-old man presented with an upper respiratory infection, fatigue, bruising and a lymph node of 2x1 cm size in his right supraclavicular fossa. His blood counts were: hemoglobin 58 g/l, neutrophils 0.2 x 10^9/l, and platelets 14 x 10^9/l. The bone marrow was patchy, with a mean cellularity of 10%. Thus SAA was diagnosed. Biopsy of the lymph node revealed nodular sclerosing HD. Computerized tomography showed two more non-bulky sites of involvement in the upper thorax, but no abdominal disease. No adequate treatment for Hodgkin's disease could be given because of the bone marrow aplasia. Treatment for SAA with anti-lymphocyte globulin (Lymphoser®) and high dose steroids resulted in a minor and transient improvement of blood counts and bone marrow cellularity. Interestingly, the lymphadenopathy disappeared, as judged from computerized tomography of the chest. Six months from diagnosis allogeneic BMT with an HLA-identical brother as donor was performed. Conditioning consisted of 2.5 Gy fractionated total lymph node irradiation daily for 4 days followed by 4 days of cyclophosphamide 50 mg/kg/day. Eight months after BMT he is in excellent condition with normal blood counts, normal bone marrow and no evidence of HD.

BMT is an attractive mode of therapy in patients with both a lymphoproliferative disease and SAA, and may be the only curative treatment in such cases.

T 128 TREATMENT IN HODGKIN'S DISEASE: A REVIEW OF 1024 CASES

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We reviewed the records of 1024 patients affected by Hodgkin's limphoma and treated at our institution from 1960 to 1987 and followed by us till now. About 64% of patients received, as initial therapy, radiotherapy alone (RT). Apart of the pts. treated with RT before 1970 (who were irradiated on several volumes) the majority received total nodal irradiation (TNI) or subtotal nodal irradiation (as mantle plus lumbar bar or similar). The total tumor dose ranged between 36 and 44 Gy/4-5 weeks. About 21% of patients received, as initial therapy, RT and adjuvant chemotherapy (CT). Apart of few cases treated with RT + CT in the late sixties, the majority, treated after 1970, were submitted to MOPP or ABVD polychemotherapy. In this group the volume treated and the dose delivered with RT was the same as that used in RT group. The remaining 15% of patients received chemotherapy alone (CHT) as initial therapy. 477 pts (after 1971) were submitted to laparosplenectomy: 75% out of those received RT whereas the others received CT + RT.
The disease-free period before relapsing was examined according to the clinical characteristics at the onset of the disease: sex, age, histology, clinical stage, systemic symptoms, mediastinal involvement, "bulky" disease and number of involved areas. The clinical stages II and III was furtherly divided in II2 and II3 and III1, III2 according to the suggestion of Tubiana et al. (Cancer, 54: 885-894, 1984). The time elapsed from the primary treatment and the onset of the first relapse and the patterns of relapses were evaluated. The Kaplan - Meier method for overall and disease free survival and the Cox regression model for the evaluation of independent effects of variables were adopted.
The results show that, apart a little difference in III2 pts., the overall survival is not implemented by the RT + CT association whereas relapses occurr much more in RT group. As far as concern the relapses those occurring within the first year may be related to more "aggressive biology" of the disease; those occurring between the second and the fifth year after treatment may be related to "treatment failure"; and then the relapses, occurring later than seven years could represent a new Hodgkin's disease rather than a relapse of the previous disease.

T 129 PROGNOSTIC VALUE OF ESR IN PATIENTS WITH LOW STAGE HODGKIN'S DISEASE TREATED BY RADIOTHERAPY ALONE.

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Between january 1982 and june 1989, 74 patients (43 males and 31 females) with Hodgkin's disease stage IA (29), IIA (38) or III$_1$A (7), were treated by radiotherapy in the centers participating to the PHDSG: 66 had supradiaphragmatic and 8 infradiaphragmatic disease; no patient with bulky lesions is included in this series. Ages ranged between 15 and 72 years (median 30); staging included laparotomy in all cases except 5 patients with stage I upper neck presentation and 3 patients with stage I inguinal presentation. Patients with supradiaphragmatic lesions received mantle field plus upper paraaortic field except the 5 cases with upper neck disease in whom paraaortic irradiation was omitted, and patients with infradiaphragmatic disease received inverted Y followed by bilateral supraclavicular irradiation; doses were 40 Gy to the involved side of the diaphragm, followed by a boost of 6 Gy to involved areas, and 36 Gy to the uninvolved side. Two patients were lost to follow-up and 4 have not completed radiotherapy yet, thus 68 are evaluable. Complete remissions (CR) were obtained in all cases; 11 patients relapsed: 5 within the radiation field, 2 in non irradiated limphnode areas and 4 with systemic dissemination: all responded to salvage chemotherapy and achieved a CR; 2 patients subsequently progressed and died. Factors influencing the DFS rates were analized: age, sex, type of presentation, stage, type of RT (whether mantle or mantle plus paraaortic), number of involved sites and mediastinal involvement did not significantly affect DFS. Patients with NS histology had a worse DFS (72% vs 88%), showing a trend towards significance (p=0.08). Patients with ESR $<$ 50 had 86% 5 years DFS versus 40% for patients with ESR $>$ 50 ($p < 0.0001$): ESR emerges as the most significant prognostoc indicator in patients with "favourable" Hodgkin's disease: patients with high ESR need more aggressive treatment.

T 130 SEQUENTIAL CYCLIC POLYCHEMOTHERAPY AND RADIATION THERAPY FOR HODGKIN'S DISEASE.

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Since radiation therapy does not guarantee confidence that all pathological sites of Hodgkin's disease (HD) are subjected to the antitumour effect, fifty-eight primary patients have undergone combined chemotherapy and radiotherapy. This has been justified, because the reduction of the volume and total dose of irradiation is being obtained, decreasing the risk of serious postradiation complications by this way. The intensive polychemotherapy was administered with no more than six cycles of CVPP sequentially before and after radiation therapy. It has been stated that such approach to treatment is highly effective: 98.3% of patients achieved remissions and one patient with StageIY HD had a small, less than 50.0% decrease in the tumour size. Moreover, the majority of patients (84.5%) could achieve complete remissions (CR). All patients with localized Stages I-II HD proved to be highly respon - sive to treatment, achieving CR in all the rest si - tuations, except for one patient (2.9%). The thera - peutic effect was rather stable, and by the end of the first year 74.8% of patients remained in remission. The sequential chemo- and radiotherapy is highly active even for generalized Stage IY HD: remissions have been achieved in 85.7% of patients, however, CR - in little more than 28.6%. In this group of patients relapses came faster, and by the end of the first year only 50.0% of patients did not reveal signs of the repeated tumour growth. Due to sequential chemotherapy and radiation, 79.0% of patients survived for 5 years and more, almost 83% of them having localized HD. Taking into account relatively unsatisfactory remote results of generalized HD therapy, tactics of treat - ment for this group of patients should be improved first of all. Evidently, the further intensification of cytostatic therapy is advisable through the addi - tional inclusion of new multiple-agent chemotherapy regimens following the completion of the first stage of chemo- and radiotherapy - the sequential use of several different cycles of polychemotherapy in combination with irradiation.

T 131 Radiotherapy alone of I° and II° clinical stages Hodgkin's disease.

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Staging laparotomy, including splenectomy, liver and abdominal lymph node biopsies, remains the most accurate method for determining involvement of the spleen in clinical stages I and II Hodgkin's disease. However, in some institutions, its routine use is controversial because of its significant morbidity and the long time required for this staging procedure. This study analyses the possibility to spare laparotomy for a selected subgroup of patients with clinical stages I and II. From January 1985 to November 1989, 40 previously untreated patients, with clinical stages IA (14 pts) and IIA (26 pts) non bulky disease, entered into the study. They were 21 males and 19 females, median age of 43 years (range 18-74). Other clinical features of the patients will be discussed. The clinical staging was based on a complete history, phisical examination, routine laboratory studies, chest X ray, total body CT scan, lymphangiography, laparoscopy with random biopsies of liver and spleen and bone marrow biopsies. All patients were treated with radiotherapy alone; mantle field with or without paraaortic-spleen field. Only two patients aged 72 and 74 recieved "involved field" radiotherapy. One patient with IIA lymphocitic depletion histologic subtype, had mediastinal relapse within the radiotherapy field and now is in complete remission after undergoing chemotherapy. All the other patients are relapse free after a median follow-up of 38 months. No significant toxicity was observed. Longer follow-up and further study will be necessary. However, our data suggest that these selected subgroups of patients can avoid laparotomy having a relapse free survival after radiotherapy alone, similar to that obtained with the same treatment administred after surgical staging.

T 132 RISK ADAPTED COMBINED RADIO-CHEMOTHERAPY IN HODGKIN'S DISEASE

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In an open pilot study we tested a program of reduced combined radio- and chemotherapy in Hodgkin's disease in limited stages (I-III) presenting with risk factors and in advanced stages (IIIB+IV). Aim of the study is to reduce the delayed complications of CMT while preserving its effectiveness.
From May 85 to Dec.88 45 previously untreated patients entered into the study. Treatment consisted of alternating CVPP/DBVCy resp. CVPP/DBVCy-hybrid-chemotherapy and low-dose (25 Gy) involved field radiotherapy sandwiched between the 6 cycles of chemotherapy. At present (1.6.89) 40 patients are evaluable for response to treatment. Primary CR reached 32/40 (80 %) pts., PR 5/40 (12.5 %) and NR in 3/40 (7.5 %). Three out of the five PR-patients had a CR after salvage treatment, so total CR-rate amounted 35/40 (87.5 %). After a median observation of 29 months 28/32 (87.5 %) resp.30/35 (85.5 %) patients are in first CR. The survival data after one and two years are as follows:
RFS 1 y 32/32 (100 %), RFS 2 y 25/27 (92 %) overvall survival 1 y 39/40 (97.5 %), overvall surv. 2 y 30/33 (90 %).
So far 4 pts.relapsed after primary CR, three had a nodal relapse (after 14,30,31 ms), one a bone marrow relapse (after 20 ms). In two out of these patients a second CR was achieved by salvage therapy.
Acute toxicity of the treatment program was acceptable, whereas it is too early to report about long-term side effects.
In conclusion we regard our treatment approach useful and the results of the pilot-study encourage us to continuethe study with only few modifications as a multicenter trial

T 133 HODGKIN'S DISEASE (HD) STAGE IA AND IIA. EFFECTIVE THERAPY WITH MOPP COMBINATION AND INVOLVED FIELD RADIATION. DOSE AND TIME RESPONSE ANALYSIS.

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Early stages HD (IA and IIA) treated with radiation, have a relapse rate of approximately 35%. From January 1981 to December 1987 we have treated 48 HD stage IA and IIA patients with MOPP chemotherapy combined with involved field radiation at a dose of 2500 rads. The treatment scedule had as follows: Three cycles of MOPP/involved field radiation/ three cycles of MOPP. All patients were prospectively followed in the same Unit. Twenty eight of them were men and 20 women, with a mean age of 36y (18-77). Their mean follow up time from diagnosis was 43 mo (20-84). Twenty patients had stage IA and 28 stage IIA disease, with the histologic subtypes: lymphocyte predominance 2, nodular sclerosis 29, mixed cellularity 16 and lymphocyte depletion 1. Complete remission (CR) was achieved in 45 patients (94%). The mean time of CR was 38.1 mo (4-82). Ten patients (20%) subsequently relapsed in a mean time of 20 mo (4-54) from the documentation of CR. Factors which could be considered responsible for relapse, such as the clinical stage, the histologic subtype, the presence of mediastinal mass, the mean total nitrogen mustard (NM) and procarbazine (PCZ) dose as well as the mean time deviation from the sceduled drug administration, were analysed in the relapsed and nonrelapsed patients. The only parameter which was found to be significant in this comparison, was the mean total NM dose ($p<0.05$). Thus patients who relapsed, received a mean total NM dose of 80mg as compared to the nonrelapsed who received a mean total NM dose of 93mg. These doses represent the 66.5% and 77.5% of the anticipated 120mg mean total NM protocol dose, respectively. The main reason for dose reduction was myelotoxicity, frequently expressed with neutropenia. We concluded from our analysis that: a reduced NM dose in early stages HD it is still effective, although its significant reduction may result in an increased number of relapses. Whether this dose reduction in the nonrelapsed patients will result to a lower frequency of second neoplasia of our patients remains to be seen.

T 134 LOPP/ABE HYBRID PROGRAM: A COMBINATION CHEMOTHERAPY IN ADVANCED HODGKIN'S DISEASE: PRELIMINARY RESULTS.

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26 patients (pts) with advanced Hodgkin's disease (IIB-IVB) were treated with a new seven-drug regimen (CT). 4 pts with IIA were included because of their risk factors, especially bulky disease. Chlorambucil 6mg/m^2 p.o. d1-7, vincristin 1,2mg/m^2 i.v. d 1, procarbazine 100mg/m^2 p.o. d 1-7 and prednison 75mg/die p.o. d 1-10 were given in a hybrid treatment plan with adriblastin 30mg/m^2 i.v. d 8, bleomycin 5mg/m^2 i.v./i.m. d 8-10 and etoposide 100mg/m^2 i.v. d 8-10 (LOPP/ABE). Cycles were repeated at 28-day intervals. 15 pts received consolidation radiotherapy (RT). Of the 26 evaluable pts 23 (88%) achieved a complete remission (CR). 20pts went into CR with CT alone. From the 5 pts in partial remission (PR) 3 converted in CR with additional RT. 1 pt had a progression of his disease under CT.The 3 non responding pts showed a noticeable frequency of bad prognostic factors (stage, B-symptoms, bulky disease, high sedimentation rate and age). 2 pts relapsed after 2 and 7 months, although no definitive statement can be made about relapse-free survival for the 21 pts still in CR because of the short median follow-up of 20 months (range 8-35 months).

	number of pts	CR	PR	P
after CT alone	26	20	5	1
conversion of PR to CR with RT	5	3	2	0
total	26	23	2	1

The treatment was well tolerated with no cardiotoxicity, neuropathy WHO grade 1 in 5 pts and 2 pts with pneumopathy grade 2. The treatment delivery was excellent as 93% of the treated pts received at least 75% and 60% pts got more than 90% of the calculated dosage. The median nr of cycles was 7,19. These preliminary results indicate that LOPP/ABE for pts with advanced Hodgkin's disease is an effective and well tolerated schema.

T 135 TREATMENT OF ADVANCED HODGKIN'S DISEASE WITH CCNU, ETOPOSIDE AND PREDNIMUSTINE (CEP).

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Patients with Hodgkin's disease (HD) who do not respond to COPP/ ABVD or radiotherapy present serious and still unsolved therapeutic problems. For such cases Santoro and coworkers suggested in 1982 a chemotherapeutic salvage protocol with CCNU, etoposide and prednimustine (CEP).

At our institution this regimen was administered to 26 patients with advanced, chemotherapy resistant HD. In a retrospective study the outcome of CEP therapy was analyzed.

Complete remissions (CR) with a median duration of 16+ months were reached in 42% of the patients. Partial remissions (PR) were seen in 19%. Thus even after failure of a number of previous chemo- and radiotherapies, CEP had the potential of inducing long lasting CR. The protocol showed no cross resistance with COPP/ABVD. Its efficacy did not correlate with the extent of Hodgkin's disease at the beginning of CEP treatment. The median duration of CR lasted mostly longer than that achieved with primary or first relapse therapies. Because of its low toxicity outpatient treatment was possible.

In view of the similarity of CEP to the BMT-conditioning protocol with BCNU/etoposide, CEP seems useful to test sensitivity of HD relapses for possible autologous bone marrow transplantation.

T 136 TREATMENT FOR HODGKIN'S DISEASE RELAPSING AFTER CHEMOTHERAPY; A REPORT OF THE FIRST 18 PTS RECEIVING VAPEC-B,A WEEKLY SCHEDULE COMPRISING 5 CYTOTOXIC DRUGS AND PREDNISOLONE WITH PROPHYLACTIC CO-TRIMOXAZOLE AND KETOCONAZOLE.

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A total of 18 pts (12 male, 6 female; median age 29 yrs) have received VAPEC-B chemotherapy for relapsed HD. Six pts were treated in first relapse, seven pts in second relapse and five pts in third or subsequent relapse. All patients had received at least one previous adriamcyin containing regimen and 17 of 18 pts had also received radiotherapy. Initial stage was I, 1 pt; II, 5 pts; III, 3 pts; IV, 9 pts and histology was nodular sclerosing 10 pts, mixed cellularity 2 pts, lymphocyte predmoninant 3 pts and HD unclassified 3 pts.

A median of 8 weeks of VAPEC-B were administered (range 6-11) and 8/18 pts (44%) achieved CR or equivocal CR (minimal residual abnormality on CXR or CT scan but no palpable disease and BM (biochemistry normal). A further 5 pts achieved PR, 3 had stable disease, 1 pt progressed and 1 pt with extensive lung disease died of sepsis after week 3. The CR/equivocal CR rate was the same for pts treated in 2nd or subsequent relapse as for those in 1st relapse (both 4 of 9, 44%) but overall respone (CR & PR) was greater in this latter group (8 of 9, 88% against 5 of 9, 55%). After VAPEC-B, 12 pts proceeded to high dose cyclo and BCNU followed by ABMR. For reasons of massive disease, advanced age, psychological unsuitability or no auto/allo source of BM, 5 pts did not and of these 2 continue in CR at 12 and 15 mths (1 had nodal disease in 2nd relapse, 1 had nodal disease and heavy BM involvement in 3rd relapse). Apart from 1 septic death after week 3, toxicity has been easily manageable and subjectively the regimen is well tolerated.

We conclude that weekly cytotoxic therapy is effective in relapsed HD and should be considered as a possible alternative to standard three or four weekly treatment in this disease.

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

T 137 ABDIC SALVAGE CHEMOTHERAPY FOR REFRACTORY/RELAPSED HODGKIN'S DISEASE (HD).

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We report the results of salvage treatment with ABDIC in 10 patients (pts) with advanced refractory/relapsed HD. The ABDIC regimen is based on Rodgers et al (Cancer 46:2349-55, 1980), as modified for continuous infusion (CI) by Hagemejster (personal communication), and consists of doxorubicin 25mg/M^2 CI daily x 2, DTIC 200 mg/M^2 CI daily x 5, bleomycin 5 mg/M^2 IV d1 and d5, CCNU 40 mg/M^2 orally day 1 and prednisone 40 mg/M^2 days 1-5, repeated each 28 days. However, 4 pts did not receive bleomycin due to prior pneumonitis(1) or planned bone marrow transplantation (BMT)(3).

At the time of ABDIC treatment, the pts had a mean age of 27 (range 23-52); eight were stage IVB and 2 IIIB. All pts had received previous treatment, with the mean number of prior regimens being 3.4 (range 2-6), and all had failed at least MOPP and ABVD type regimens. The mean time from diagnosis to ABDIC was 6.2 years (range 9 months-14 years). Three pts had never acheived CR, while 2 had CR< 1 year.

Responses included 1 CR (7+ months off therapy), 6 PR (5 ongoing on therapy, 1 having a BMT after 2 cycles), 1 with a brief response but then progression of disease before the third cycle could be given, 1 too early to evaluate, and one with no response. Overall response rate was 7/10 or 70%.

Toxicity was primarily bone marrow suppression and mild nausea. Four pts who had been extremely non-compliant with other regimens tolerated ABDIC well. One patient died of a dilated cardiomyopathy with onset after the fifth ABDIC cycle; she had received prior TNI.

We conclude that ABDIC with doxorubicin and DTIC by CI is an active regimen in our heavily pretreated population. It may have a role in reducing tumor burden of HD in preparation for BMT. It may also be a basis for developing more active combination chemotherapy regimens based on CI as second line therapy for HD.

T 138 LOW DOSE ANTHRACYCLE OR ANTRACENADIONE IN THE TREATMENT OF ADVANCED HODGKIN'S DISEASE. PRELIMINARY RESULTS.

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Thirty patients with advanced Hodgkin's disease (stages III B to IV) were randomly treated with low-dose mitoxantrone (MX) : 5 mg/m2 or 4 epidoxorubicin (4EPI): 25 mg/m2, on days 1 and 14 in combination with bleomycin, dacarbazine and vinblastine at conventional doses by six cycles.
Clinical and histological characteristics were similar in both regimens arms.
Complete response (CR) was observed in 12 of 15 patients treated with 4 EPI (80%). Similar results were observed in the group who received MX: 92 % (14 of 15) achieved CR.
Side effects were minimal and well tolerated. No cardiotoxicity, assessed by the left radionuclide angiography, was observed with doses between 250 to 420 mg for 4 EPI and 55 to 85 mg for MX.
The median survival time is 11 months , and all the patients remains in CR and probably they will have long survival, although, the follow-up is short.
The results observed with use of these new drugs in the treatment of advanced Hodgkin's disease were similar at the achieved with therapeutic approaches, but, the use of low-dose, as herein reported, is accompanied of less side effects and the effectiveness of the chemotherapy remain to be useful.
We felt that new programs with these type of therapy will be performed in patients with advanced Hodgkin's disease.

T 139 Is early death in Hodgkin's disease an indicator of agressive disease?

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In the period 1977-1986 333 patients (pts) with previously untreated Hodgkin's disease were treated in our institute, 30 (9%) died within 2 years of diagnosis. It was found that 10 pts (gr. A) had a progressive course of disease, 8 pts (gr. B) died of complications or concomitant other diseases, in 6 pts (gr. C) relapse after initial remission could not be salvaged and 6 pts (gr. D) never recovered well due to old age and/or concomitant disease.
For these 30 pts division over stage and histology was not different from the total group, however the cellular type of nodular sclerosis occurred in 5 pts of whom 1 in group A, compared to 10 pts in the total group. In the studygroup 30% of pts were < 50 yr, 23% 51-60 yr, 27% 61-70 yr and 20% > 70 yr, compared to 80%, 9%, 7% and 4% for the total group. In the studygroup 21 pts had concomitant diseases, such as hypertension, rheumatic diseases, skin diseases etc. Liver abnormalities were noted in 24/30 pts, 13 had hepato-megaly, 19 had disturbed liver functions, 8 had both; however only in 7 pts this might have been considered st IV on clinical grounds. In 11 pts liverbiopsy was done and 2 only were positive. For comparison all pts > 50 yr of the total group were studied and 12/38 had liver abnormalities, of which 1 only was interpreted as stage IV.
In the 10 pts of gr. A with progressive disease, 6 pts had an ESR > 80 mm, compared to 2/20 of group B, C and D. Only 4 of these pts were > 50 yr. Dubious liverfunctions were present in 9, liver biopsy was done in 7 pts and positive only in 2 pts. Concomitant disease was restricted to skin problems in 4 pts.

Conclusion: early death within 2 yr of diagnosis of Hodgkin's disease occurred in 9% of pts, in 3% due to agressive Hodgkin's disease, in the other due to old age, concomitant disease, or complications.

T 140 INFECTIONS IN PATIENTS WITH NON-HODGKIN LYMPHOMA: REPORT OF 110 EPISODES.

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One hundred-ten infectious episodes in 73 pts (females 42, males 31; median age 51, range 18-78) affected by NHL occurred between August 1982 and April 1989 in our Institution. The infection-related deaths were 17/110 (15%);5 more pts(4%) died because of the combined effect of infection and other causes. In 88/110 (80%) cases the infections occurred in pts with lymphoma in progression or in relapse, the remaining 22 episodes occurred at diagnosis or during induction therapy. Before the onset of infection, in 78 episodes the pts received polychemotherapy, in 9 single agent therapy, in 3 surgery, in 1 alpha -IFN, in 1 TBI; in 14 cases the pts had not been previously treated; 4 pts are not evaluable. During the study, the majority of infections were microbiologically or clinically documented, FUO being 9%. There were 77 bacteremias (Gram-positive 39, Gram-negative 28. polymicrobial 10) and 1 Candidemia; 37 out of these 78 episodes were associated with pneumonia. Pneumonias alone were 11. Overall, pneumonia was then observed in 48/110 (44%)episodes. Other infections were: soft tissue infections(4), gastrointestinal tract infections(2), mucositis (2), Herpes Zoster (2), vasculitis (1).
Infectious deaths were observed in presence of Gram-negative bacteremia (9/28 = 32%), Gram-positive bacteremia (6/47 = 12%), polymicrobial bacteremia (4/10 = 40%), pneumonia (1/11 = 9%), FUO (1/10 = 10%).
During bacteremia, the infectious mortality was three times more frequent when pneumonia was associated.
Conclusions.
1) the infections observed were often severe (in the majority of cases bacteremia ± associated pneumonia)
2) the frequency of pneumonia was particularly high, as compared to that commonly observed in other hematologic malignancies
3) the majority of infections occurred when the lymphoma was in relapse or progression, but the disease status was not important for the outcome of the infectious episode
4) pneumonia, persistant neutropenia and age over 50 years seem to be important poor prognostic factor for the outcome of infection.

T 141 SECOND CANCERS AFTER TREATMENT IN PATIENTS WITH HODGKIN'S DISEASE

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In the recent 20 years, the survival of patients with Hodgkin's disease (HD) has increased due to extensive treatment with radiotherapy (RT) and chemotherapy (CT). However, extensive treatment has its price and there is evidence in the literature that modern aggresive treatment may induce severe complications such as second cancers (SC). The aim of this study was to compare the risk of SC in two randomized successive cohorts of patients with HD of Clinical Stages I and II that were followed for 5 to 20 years after the end of their initial treatment.
From 1970 to 1985 were treated 338 patients with Hodgkin's disease all Clinical stages. All patients were treated with chemotherapy and radiotherapy.
Nine secondary tumors have been discovered in this group with varoius localisations in period from 5 to 15 years. Three solid tumors (ST), one non-Hodgkin's lymphoma and 5 acute leukemias were also discovered.
The authors discuss the risk and interval of secondary tumors appearance depending on Clinical Stage,histological finding, applied therapy,age of patient and duration of the remission follow-up.

T 142 TREATMENT INTENTIONS AMONG PRACTISING MEDICAL ONCOLOGISTS AND ONCOLOGICAL SENIOR HOSPITAL STAFF IN SWITZERLAND FOR ELDERLY PATIENTS WITH AGGRESSIVE NON-HODGKIN'S LYMPHOMA.

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The treatment of Elderly Patients with advanced Aggressive NHL (EPANHL) is a controversial issue. Treatment outcome seems related to the thorough application of treatment schedules such as CHOP, and dose reductions or delays are detrimental. Elderly patients (pts) are more susceptible for myelotoxic side effects and often handicapped with numerous concomittant internal diseases. Apart from objective contraindications to aggressive therapy, subjective biases of pts and doctors may prevent the application of potentially curative therapy. In 1989 a questionaire was sent to all practising medical oncologists (PMO, n=34) and to all known senior hospital staff (SHS, n= 36) in the divisions of medical oncology in Switzerland. A detailed therapy schedule for the systemic treatment of EPANHL was asked for, as well as mitigations in dose or dose intensity. 35 forms were returned (50%), 15 (42%) from PMOs and 12 (34%) from SHS, in 8 cases no identification was possible. 12 of the answering doctors choose a CHOP or a CHOP-like regimen for this treatment (34%), 13 a rather more aggressive, second or third generation regime (37%) and only 9 (26%) a clearly less aggressive schedule, such as CVP or COP. One PMO did not treat EPANHL himself. No difference was seen in PMO and SHS as to the aggressivity of the proposed schedules, 22 (63%) intending to give a fully dosed regimen without delays, 3 a delayed (9%) and 7 a reduced (20%) regimen. However, only 21 (60%) suggested irradiation of bulk disease, whereas 9 (26%) rejected any irradiation therapy. The most choosen regime was CHOP. This data indicate, that treatment of EPANHL may be less influenced by personal biases than postulated. To test the real behaviour of doctors and pts a prospective registration of treatment intentions and given treatment in EPANHL is currently under way in Switzerland (SAKK study 39/89).

T 143 IFOSFAMIDE CONTINUOUS INFUSION AND ETOPOSIDE IN THE TREATMENT OF ELDERLY PATIENTS WITH AGGRESSIVE LYMPHOMA. A PHASE II TRIAL.

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Ifosfamide (IFM) is an alkylating agent used in salvage regimen in lymphomas. Pharmacokinetics studies showed that its alkylating activity was increased by divided doses or continuous infusion. Its dose-limiting toxicity is urothelial and could be prevented by the administration of mesna. The better administration scheme is not known for this drug. A potentialisation of its activity in lymphomas has been observed when associated with etoposide. For these reasons we decided to conduct of phase II trial of IFM 1500 mg/m^2/d in continuous infusion for 3 days, mesna 500 mg/m^2 x 3/d for 4 days, and etoposide 100 mg/m^2/d for 3 days in one infusion of 3 hours. This treatment was administered every 4 weeks. 16 patients (pts) aged 70 or more and presenting an aggressive lymphoma were enrolled in this study either after failure of a previous chemotherapy (9 pts) or due to a contraindication to anthracyclins (7 pts).

11 pts were male and 5 female. Median age was 75 y (70 to 81 y). Performance status ranged from 0 to 1. According to the Working Formulation, histologic types were E 1 pts, F 3 pts, G 6 pts, H 5 pts, J 1 pts. At time of treatment, 1 pt had stage III and 15 stage IV.

Toxicity was very mild: 2 pts experience vomiting; out of 65 courses, only 3 episodes of hyperthermia and ≥grade 2 neutropenia; one grade 3 thrombopenia; no cystitis; 16 pts grade 3 alopecia. 1 pt with myocardial infarction history died suddenly during treatment. 2 had to be hospitalized after courses for toxicity.

Among the 7 pts in first line chemotherapy there were 3 CR, 2 good PR, 1 pt died suddenly in PR after 2 courses. Among the 3 pts previously treated but off-therapy there were 2 CR and 1 PR. Among the 6 pts who progressed on-therapy after an anthracyclin regimen there was only 1 PR. Overall response rate is 56%. 3 out of the 4 PR pts progressed 2 to 6 months later and 3 out of the 5 CR pts at 4, 6 and 7 months after treatment.

This regimen is active and well tolerated in aged pts but probably not enough active for younger pts.

T 144 NON HODGKIN'S LYMPHOMAS (NHL) IN ELDERLY. A RETROSPECTIVE STUDY WITH EMPHASIS ON TREATMENT-RELATED TOXICITY.

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This is a retrospective evaluation of select treatment given according to stage,histology and performance status to 53 previously untreated pts with NHL aged 65 years or more (34 M/ 19 F;median age,72 yrs). Distribution of pts into risk categories of Working Formulation (WF) was as follows: low grade,27 cases;intermediate grade,16 cases;high grade,10 cases. As far as first-line treatment is concerned,10 pts recived a single chemotherapic agent (SA) and 43 a combination poly-chemotherapy regimen (Poly-CT) including adriamycine (Poly-CT + ADM) in 14 of them. The three therapeutic groups were alike with regard to age,sex and clinical stage. However,pts of intermediate-high risk categories of WF more frequently were treated with combination Poly-CT ($P < 0.05$). Eleven (20.6%) of 53 evaluable pts obtained CR. No difference emerged among different treatment groups when CR rates were analyzed according to both stage and grade of malignancy. Furthermore, CR was associated with a significant better prognosis ($P < 0.001$).
A higher incidence of significant toxicity was found in pts treated with combination Poly-CT regimens ($P < 0.05$). It should be stressed, however,that the significance of analysis was mainly due to an excess of lethal and severe toxicity observed in pts treated with Poly-CT schemes not including ADM. Twenty-one of 53 pts included in this study were submitted to second-line treatments. Therefore,a total of 15 pts received SA as first or second-line therapy,a total of 30 pts were submitted to Poly-CT without ADM as first or second-line treatment (8 pts received Poly-CT without ADM both as first and second-line therapy) whereas a total of 20 pts were submitted to Poly-CT with ADM as first or second-line treatment (1 pt received Poly-CT + ADM both as first and second-line treatment). In the overall group of 50 pts treated with combination Poly-CT regimens a total of 5 (10%) treatment-related deaths could be detected. The incidence of lethal toxicity not being increased by the addition of ADM.
In conclusion,our data suggest that severe and lethal side effects are associated with standard combination Poly-CT regimens. Devised aggressive treatment for elderly pts should be sought.

T 145 NON-HODGKIN'S LYMPHOMA IN THE ELDERLY PATIENT. A study of 593 consecutive cases aged more than 70.

F.d'Amore for the Danish Lyfo-group.

ABSTRACT

Five hundred and ninety-three cases of non-Hodgkin's lymphoma (NHL) in patients aged 70 or older were studied. They represented 37,9% of all cases (n=1568) of NHL prospectively registered during 6 years in a Danish semi-national lymphoma study. Localized disease (stage I and II) was found in 45%, disseminated disease (stage III and IV) in 50% while clinical staging was incomplete in 5% of the patients. Fifty-two % of cases were nodal and 41% extranodal, 7% of cases were unsufficiently defined as to this parameter. Fifty-nine % of all extranodal cases were localized (stage I_E or II_E). The most frequently involved extranodal site was the stomach (65 cases). Bone marrow infiltration was present in 134 (23%) cases and mostly associated with plasmacytoid histology. One hundred and seventy-six (32%) patients had low-grade, 112 (19%) intermediate and 245 (41%) high-grade histology. Diffuse large cell lymphoma was the most common histological subtype. Overall median survival was 2,0 years. Of the 322 deaths seen 55% were due to lymphoma, 4% to treatment-related toxicity and 26% to other causes. The cause of death was uncertain in 15% of the cases. Statistically significant adverse influence on survival was seen for stage II, III and IV when compared with stage I, for high-grade histology when compared with low- and intermediate grade and for elevated serum lactic dehydrogenase (LDH), hyperuricemia and hypercalcemia. Serum levels of LDH were elevated in 33% and those of uric acid in 17% while hypercalcemia occurred in 4%. Paraproteinemia, mostly of IgM type, was found in 8%.

T 146 P-VABEC CHEMOTHERAPY IN ELDERLY HIGH-GRADE NON HODGKIN'S LYMPHOMA (NHL).

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A new weekly alternating six drugs chemotherapy regimen (P-VABEC) was employed in 30 previously untreated high-grade NHL patients (pts) aged > 60 yrs observed in our Institute from October 1988 to August 1989. This schedule consisted of: Adriamycin 30mg/sqm/i.v. day 1, Etoposide 100mg/sqm/i.v. day 1, Cyclophosphamide 350mg/sqm/i.v. day 1 at week 1-3-5-7; Vincristine 1,2mg/sqm/i.v. day 1, Bleomicine 5mg/sqm/i.v. day 1 were administered at week 2-4-6-8. During entire treatment oral Prednisone 50mg was daily given. Male/females ratio was 15/15, median age was 67 yrs (range 61-79 yrs). All pts had a high-grade NHL according to the Working Formulation. Six pts had a clinical stage I, 4 stage II, 11 stage III and 9 stage IV. The performance status according WHO criteria was ≤ 2 in all pts, a bulky disease was present in 5 (16%) pts, LDH high levels (> 2 times the normal values) were detected in 13 (43%) pts. Complete remission (CR) was obtained in 24/30 (80%) pts, partial remission (PR) in 4/30 (13%), 2 (7%) pts were not responders. After a median follow-up of 7 months (range 3-14), 5 (20%) pts relapsed at 2,2,3,3,6 months respectively. One patient died in CR for cerebral stroke. Hematological toxicity was moderate, in particular polimorfonucleated granulocytes count < 500 ul and/or platelets count < 50 000/ul were never observed. As for the other toxicities two pts had infectious complications (Herpes Zooster and Pneumoniae), polyneurity was observed in 5 pts and reversibile cardiac toxicity in 4 pts. In conclusion the P-VABEC protocol is an active and tolerable first line treatment for elderly NHL. A longer follow-up is needed to evaluate the CR duration.

T 147 HODGKIN'S DISEASE IN THE ELDERLY.

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We analysed the influence of age on the prognosis of Hodgkin's disease(HD) in a retrospective study of 182 patients. Between 1972 and 1983 40 patients(22%) aged 50 year or older were diagnosed and treated in 10, from 1979 cooperating, community hospitals in the Southeastern part of the Netherlands. Staging procedures and treatment at that time were not uniform.

Results(table 1): Overall 5- and 10-year survival rates for the whole group were 73% and 55%, resp.. Survivalcurves showed a significant fall in overall survival after 50 years of age (P<0.001). Relapse-free survival rates of the old and young appear to be identical. Both groups(<50year, ≥50year) were compatible according to sex, systemic(B)-symptoms and histology. Relatively more patients ≥50year had clinical stage(CS) I and IV (P<0.01). 13 patients received incomplete therapy: Chemo(7) because of toxicity and only involved field RTX was given to 6 patients. Survival rates were significantly lower for patients ≥50year, who had incomplete therapy (P<0.03). Failure to achieve CR occurs mainly in patients with advanced CS (table 2) and incomplete therapy. In this study salvage therapy was equally effective in both groups but the group ≥50year included only 5 patients, of those achieved 4 another CR. In the advanced age 15/22 patients(68%) died of HD, 3 treatment related, which is compatible with the group <50year; 28/38 patients(74%), 7 treatment related.

Table 1	n	5-year S	10-year S	CR
<50year	142	77%	60%	93%
≥50year	40	47%	38%	63%
≥50year,CT	25	67%	47%	83%

n:number, S:survival, CR:complete remission, CT:complete therapy

Table 2	CSI-IIIA	CSIIIB-IV
<50year,CR	92%(103/112)	83%(24/29)
≥50year,CR	65%(17/26)	45%(5/11)

Conclusion: 1.Significant decrease in overall survival above 50 years of age 2.Therapy is relatively often incomplete in advanced age 3.With adequate treatment survival and CR were good in the elderly 4.Advanced CS and incomplete therapy were negative correlated with survival 5.Intercurrent disease seems not to be a major contributing factor to the cause of death.

T 148 NON-HODGKIN'S LYMPHOMA (NHL) IN THE ELDERLY : A RETROSPECTIVE STUDY.

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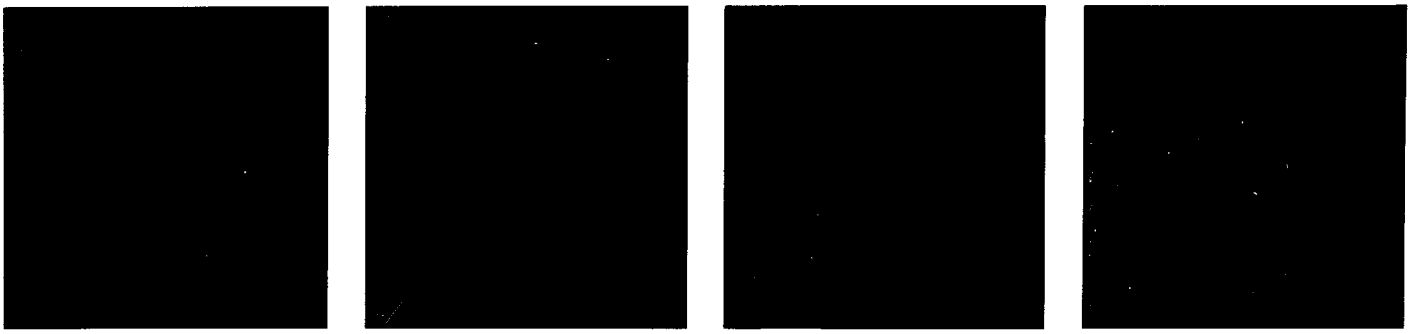
The elderly comprise a group at highest risk for cancer and represent an increasing challenge for oncologists, mainly because of poor tolerance to potentially curable aggressive therapy.

We reviewed our experience in the treatment of NHL in 57 patients ≥ 65 y.old treated from May 1975 to June 1987. Twenty-one patients (37%) presented with low grade NHL but our study focused on the 36 patients (63%) with intermediate and high grade NHL according to IWF. There were 15 males and 21 females with a median age of 75 y.old (65 - 87). Eight patients were more than 80 y.old. Twenty-three had an intermediate grade and 13 a high grade histology. Twenty-four (66%) had a stage I or II and 12 (24%) a stage III or IV disease. Nine patients had an extranodal presentation (Tonsil : 4, bowel : 2, stomach : 1, skin : 2).

A complete clinical and radiological work-up, with bone marrow biopsy was done in 25 patients (69%). Bone marrow biopsy was omitted in 11 cases (31%) among whom 6 were > 80 y.old. Curative treatments were foreseen in 24 patients and palliative ones in 12 patients. Treatment choice was independent of age, performance status or extend of disease. Patients undergoing curative therapy received tailored regimens with anthracyclines (divided doses, less than 6 courses, or anthracyclines analogues), except for one who received a full dose CHOP. Overall, 23/36 patients (64%) had a complete remission, that was obtained in 18/24 (75%) patients treated curatively. The overall actuarial median survival for the whole group was 32 months, with 30% surviving at 5 years. Five patients died in complete remission of unrelated causes.

Leucopenia was seen in 15 patients (mean 1,2 G/l (0,2 - 2.9). Infection developped in 9 patients and gastro-intestinal bleeding in 2 patients without thrombopenia. Heart failure was clearly treatment related in 4 patients. Eleven patients developped WHO grade I peripheral neuropathy , related to Vincristine. Toxic death was diagnosed in 4 patients (11%) (1 lysis syndrome, 2 pneumonia, 1 heart failure).

In conclusion, the treatment of the elderly was heterogenous and based on medical appreciation. Toxicity was severe when aggressive therapy was chosen. Anthracycline regimens were able to produce a complete remission rate similar to that seen in younger patients with a 30% five year survival. In the future, adapted treatment protocols for the elderly should be designed and studied prospectively.



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Fabre 1

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