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T 153

BONE MARROW TRANSPLANTATION FOR LYMPHOPROLIFERATIVE DISORDERS.
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Recent developments have clearly shown that bone marrow transplantation (BMT) has a place in the treatment of lymphoproliferative disease. We report our experience in the last year. 3 patients were treated, 1 with autologous, 2 with allogeneic BMT. They have been conditioned with VP-16, 30 mg/kg over 4 hours, cyclophosphamide 120 mg/kg and fractionated TBI (6x2 Gy). Prophylaxis against graft-versus-host disease consisted of cyclosporine A and T-cell depletion by elutriation of the bone marrow. The first patient, a 20 year old woman, with stage IV A lymphoblastic T-cell lymphoma with mediastinal bulk underwent autologous BMT after an ALL-regimen containing DNR, VCR, MTX, ASP and 2 courses of high dose cytosine-arabinoside and VP-16. She is 6 months after BMT in complete remission with persisting pancytopenia, free of infections but depending on occasional blood transfusions. The second patient, a 29 year old man, had a refractory Hodgkin's disease type mixed cellularity stage IV B. Before transplantation a biopsy of the lung showed extensive infiltrations by Hodgkin's disease. After BMT he engrafted without initial problems but died 45 days after transplantation from graft-versus-host disease and interstitial pneumonia. At that time there was no evidence of the Hodgkin's disease neither in the bone marrow nor in his chest X-ray. Autopsy was refused. The third patient, a 35 year old man, had chronic lymphatic leukemia (CLL) diagnosed 2 years before transplantation. Before BMT the marrow was still heaviliy infiltrated by lymphoid cells. 45 days post BMT he is clinically well and shows a good take without evidence of CLL in the bone marrow aspiration. In conclusion, allogeneic and autologous BMT might be a true alternative for refractory or high risk lymphoproliferative disorders. It seems, that a conditioning regimen with VP-16, cyclophosphamide and TBI can eradicate the refractory disease not responding to conservative therapy. The exact place and time of transplantation and the optimal conditioning regimen needs yet to be defined.

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AUTOLOGOUS BONE MARROW TRANSPLANTATION IN HODGKIN'S DISEASE: RESULTS AND INDICATIONS.
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34 patients with advanced Hodgkin's disease have been treated by high dose chemotherapy and autologous bone marrow transplantation (ABMT) in our centre. There were 26 males and 8 females. The medi age was 29 years (range 14-55 years). All patients were in relapse of disease at the time of ABMT. 3 patients had primary resistant disease with relapse through alternating first line chemotherapy (LOPP/EVAP). The remaining 31 patients had relapsed following at least 2 courses of salvage chemotherapy with localised radiotherapy given in addition to 17 patients. 3 patients received total body irradiation as conditioning. The remaining 31 patients received multiple chemotherapy regimens alone. 4 patients (12%) died of sepsis during the aplastic phase. All surviving patients were assessed by computed axial tomography (CAT) at three months post AB to assess response to the procedure. 15 patients entered complete remission (CR). The median follow-up of this group is 17 months. 4 patients have subsequently relapsed. One patient died of cardia failure at 8 months post ABMT. The remaining 10 patients remain disease-free. 14 patients had only partial response of their disea 3 patients have died of progressive disease. 3 patients have received localised radiotherapy to sites of residual disease and have subsequently entered CR. 2 patients defined as PR at 3 months were in CR at 6 months post ABMT with no further therapy given. Only one patient had no response of her disease to high dose chemotherapy. Those who entered CR had a significant survival advantage over those who did not ($p > 0.001$). We believe these results are encouraging but most of our patients were grafted with disease status too advanced to achieve good results from ABMT. We have therefore attempted to identify patients in 'poor risk' groups who may benefit from ABMT at an earlier stage of their disease. The fate of treatment failures of the 340 patients entered into the BNLI MOPP/LOPP study between 1979-1984 was examined. Three 'poor risk' groups were identified. Those who had no response to first line therapy had the wrost prognosis. Patients with poor prognostic features of Grade III/IV, B symptoms and raised ESR at diagnosis who relapse after first line therapy have a 5 year survival less than 25%. Similarly, those who failed any two sequential modalities of therapy have a 5 year survival less than 25%. The fate of those patients who fail alternating front line therapy is unclear but may represent a fourth group of patients in whom ABMT is indicated at an early stage in their disease.

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CENTRAL NERVOUS SYSTEM INVOLVEMENT IN PATIENTS RECEIVING AUTOLOGOUS BONE MARROW TRANSPLANTATION (ABMT) FOR NON-HODGKIN'S LYMPHOMA.
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Of 231 patients reported to the EBMT with non-Hodgkin's lymphoma who have been treated by ABMT, 20 (8.6%) had CNS involvement. 18/20 were males and 2/20 were females 10 were aged 0-15 years and 10 were aged 16-60 years (median 43 years). 3 had intermediate grade histology, 7 had lymphoblastic and 10 had Burkitt's lymphoma. 13 patients (5.6%) had CNS involvement at diagnosis, of whom 7 also had CNS disease at ABMT. 7 further patients developed CNS disease at relapse so that 14 patients (6%) had CNS involvement at the time of ABMT. 8/20 (40%) of patients achieved CR. One had CNS relapse at 4 months post ABMT. The remaining patients (one with intermediate grade, 2 with lymphoblastic and 4 with Burkitt's lymphoma) remain disease-free at 7-55 months post ABMT (median 28 months). One patient achieved a partial response to ABMT and died at 8 months post ABMT. The remaining 11 patients died of progressive disease within 2 months post ABMT. Of 14 patients with CNS relapse at ABMT, only 3 (21%) survive at 13, 48 and 55 months post ABMT. The overall survival of the 20 patients is not statistically different from the NHL group as a whole ($p = 0.67$) although those patients with CNS involvement at ABMT have poor survival.

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INTENSIVE CYTOTOXIC THERAPY FOLLOWED BIJ AUTOLOGOUS BONE MARROW TRANSPLANTATION FOR ADVANCED NON-HODGKIN'S LYMPHOMAS OF HIGH GRADE MALIGNANCY.
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Twenty patients with advanced non-Hodgkin's lymphomas (NHL) of high grade malignancy received cyclophosphamide (120mg/kg) and total body irradiation (8 Gy) followed by autologous bone marrow transplantation (ABMT). All patients were treated before with combination chemotherapy. Seventeen out of twenty patients had bulky disease (>10cm) at presentation. At the time of ABMT five patients had drug-resistant (DR) disease, five patients were in partial remission (PR) and ten patients were in complete remission (CR; seven in 1 st CR).
Three out of five DR patients achieved CR but relapsed within 6 months. All five PR patients achieved CR; one died from septicaemia, two relapsed within 6 months and two remained in CR at 30 + and 58 + months after ABMT. Seven out of ten CR patients are in CR 6+, 7+, 11+, 16+, 43+, 44+, 61+ months after ABMT. Toxicity of this approach was mild, two therapy-related deaths were observed in patients in poor clinical condition (and DR disease).

ABMT can improve the outcome of patients with advanced non-Hodgkin's lymphoma's of high grade malignancy, especially for patients in CR or PR.

T 157 AUTOLOGOUS BONE MARROW TRANSPLANTATION IN MALIGNANT LYMPHOMA: High dose combination chemotherapy versus total body irradia--tion.

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Twenty-one patients with non-Hodgkin's lymphoma who failed on standard chemotherapy were treated with either regimen A or B followed by an autologous bone marrow transplantation. Regimen A consisted of BCNU 200 mg/M^2 IV on day 1, Cytosine arabinoside 100 mg/M^2 IV every 12 hour on day 2-5, Cyclophosphamide 1.5 gm/M^2/d IV on day 2-5 and 6-Thioguan--ine 100 mg/M^2 PO every 12 hour on day 2-5. Regimen B consisted of Cyclophosphamide 60 mg/kg/d IV on day -7,-6; rest on day -5,-4 follow--ed by total body irradiation 200 rads twice a day on day -3,-2,-1. Autologous bone marrow infusion was given 48 hours after completion of chemotherapy in regimen A and 24 hours after total body irradiation in regimen B.

Ten patients (5 DUL, 4 DHL, 1 Lennert's lymphoma) were treated with regimen A. Seven patients (70%) achieved complete remission, three of these patients are still alive free of disease at 2, 2 and 6 years after therapy. Three patients with partial remission showed disease progression within short period of time. Three patients relapsed at 1, 3 and 9 months. One patient died in remission 6 weeks after. Eleven patients were treated with regimen B (2 DUL, 6 DHL, 1 DML, 1 T cell). There were six complete remission (54.5%), 2 partial remission, 3 no response and 1 early death. Two patients are alive in remission at 12 and 14 months after transplantation. Four patients relapsed at 3, 6, 8 and 9 months.

Even though the number of patients are small, our study suggests that high dose combination chemotherapy BACT is as effective as Cyclophosphamide and total body irradiation in the treatment of refractory lymphoma. Patients with small tumor burden at the time of transplantation have longer duration of remission.

T 158 MONOTYPIC PLASMA CELL POPULATIONS AFTER ALLOGE-NEIC BONE-MARROW TRANSPLANTATION.

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Lymphoplasmacellular hyperplasia is a regular finding in lymphoid organs from patients after allogeneic bone-marrow transplantation (ABMT). We studied autopsy tissue from 8 patients who received ABMT as treatment for leukemia. Seven of these patients died one-four months after transplantation from complications of graft-versus-host disease or infections. Plasmacellular hyperplasia was found in lymph nodes and spleen from three patients. In immunohistochemis-try, the plasma cell populations comprised mainly monotypic cells with cytoplasmic λ light chain and either α, γ, or ε heavy chain expression. These monotypic plasma cell populations did not exhibit features of plasmacytoma or myeloma. In one other patient plasmacel-lular hyperplasia comprised a polytypic population, and three other patients had no plasmacellular hyperplasia in lymphoid tissue. There was no relation between the presence of plasmacellular hyperplasia and a preceding graft-versus-host disease or cytomegalovirus infec-tion. The 8th patient developed a non-Hodgkin's lymphoma along the gastro-intestinal tract, which could be related to an Epstein-Barr virus infection. The lymphoma comprised fields with IgM-κ positive cells, fields with IgM-λ cells and areas with mixed populations. Southern-blotting analysis using J_H-gene segment specific probes did not indicate the presence of clonally-restricted B-lymphocytes. We conclude that lymphoplasmacellular hyperplasia after ABMT is the result of expansion of a restricted number of B-lymphocyte clones.

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T 145 MITOXANTRONE AND HIGH-DOSE CYTARABINE (NOAC) FOR THE TREATMENT OF REFRACTORY MALIGNANT LYMPHOMA.

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Both mitoxantrone (Novantrone) and high-dose cytarabine (Ara-C) have been shown in monotherapy trials to be effective in pretreated non-Hodgkin-lymphomas (NHL). This study is undertaken to assess the efficacy and toxicity of the combination in refractory malignant lymphomas. Refractoriness is defined as follows: in patients with low grade NHL, resistance or relapse after at least 3 different chemotherapy regimens (e.g. Chlorambucil + Prednisone, COP, IMVP-16) and in patients with high-grade NHL, resistance or relapse after at least 2 different chemotherapy regimens (e.g. CHOP or COP-BLAM, IMVP-16 or ProMACE/MOPP). The regimen consists of high-dose Ara-C 3g/M²/12h as a 3-hour infusion, (X2 on day 1 for the first cohorts of 14 patients, and escalated to X4 on days 1 and 2 if no serious toxicity was observed). This is followed by mitoxantrone 10mg/M²/d IV bolus injection on days 2 and 3. Treatment courses are repeated every 4 to 6 weeks until maximal response but at most for 5 courses. Of the 14 patients presently evaluable for response, 2 complete remissions and 5 major, stable partial remissions are observed. Median duration of response was at the time of report 19.5+ weeks. The median age of the patients was 47.5 years (range 25-66). Major toxicities included nausea in 10 patients (mainly grade 2-3), diarrhea in 6 (mainly grade 2), stomatitis in 6 (mainly grade 2), and infections or fever of unidentified origin in 11 (mainly grade 3). The median number of days with severe neutropenia (< 0.5/nl) after therapy was 7 days and that with severe thrombocytopenia (< 20/nl) 5 days. Thus the combination of mitoxantrone and high-dose Ara-C seems to be an effective regimen for refractory NHL without undue toxicity. Further study is required to confirm this encouraging results and the long term duration of response.

T 146 MITOXANTRONE IN THE TREATMENT OF PATIENTS WITH NON-HODGKIN'S LYMPHOMA.

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Mitoxantrone, a synthetic anthracendione derivate, was administered at a dose of 14 mg/m^2 i.v. every 3 weeks to 35 patients with malignant non-Hodgkin's lymphoma. According to the Working Formulation, 18, 15 and 2 were of low, intermediate and high grade malignancy, respectively. 34 patients were evaluable for response, and all had relapse from or failure to previous chemotherapy.

3 patients achieved a complete response, 12 a partial response, 8 stable disease and 11 progressive disease. The objective overall response was 43% for all patients. The responses were clustered in patients with low grade malignancy.

Myelosuppression was the dose-limiting factor. The granulocyte and platelet counts were suppressed to WHO-grade 3 in 48% and 14% respectively, of all 155 cycles given. Nausea/transient vomiting was seen in 13% and 9% respectively and mild alopecia in 9%.

The data indicate that Mitoxantrone is a safe and effective treatment for non-Hodgkin's lymphoma.

T 147 MITOXANTRONE, VINDESINE AND DEXAMETHASON IN ADVANCED NON-HODGKIN'S LYMPHOMA. A PILOT STUDY.

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15 patients (pts) with advanced non-Hodgkins's lymphoma (NHL) were treated with mitoxantrone 12 mg/m² day 1 as short-time infusion, vindesine 1.2 mg/m² day 1 - 5 as i.v.-injection and dexamethason 30 mg/m² day 1 - 5 as short-time infusion. Therapy was recycled on day 28.

Pts characteristics: 11/15 relapsed after initial chemotherapy; 3/15 with low grade NHL, 3/15 with intermediate grade NHL and 9/15 with high grade NHL. Stage II: 1/15, III: 2/15, IV: 12/15. Karnofsky-Index: Between 60 - 100 %. Median age was 56 years.

Results: Overall response: CR 7/15, PR 6/15, NC 2/15, CR+PR: 13/15. Pts with relapsed NHL: CR 6/11, PR 4/11, NC 1/11, CR+PR: 10/11. Pts with relapsed high grade NHL: CR 3/8, PR 4/8, NC 1/8. All responding pts are still in remission.

Toxicity: Leukopenia: WHO grade II: 6/15, grade III: 2/15, grade IV: 2/15, thrombocytopenia: WHO grade II: 2/15, grade III: 1/15. Nausea and vomiting was not observed.

Conclusions: Chemotherapy of relapsed NHL with mitoxantrone, vindesine and dexamethason is effective with acceptable toxicity. The study will accrual additional pts to confirm these preliminary results.

T 148 NEW ANTHRACYCLINE, (2'R)-4-TETRAHYDROPYRANYL ADRIAMYCIN (THP-ADM) IN MALIGNANT LYMPHOMAS.

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THP-ADM is a new antitumor agent developed in an attempt to improve the clinical effectiveness of currently used anthracyclines. In preclinical studies, THP-ADM had been shown to produce less cardiotoxicity and alopecia, with comparable antitumor effects to ADM. The phase I clinical study has been revealed mild upper GI toxicity and bone marrow depression. The DLF was leukopania which rebound quickly. The MTD was considered to be 70mg/m2. The phase II clinical studies were conducted with administration schedules 50mg/m2 every 3 weeks I.V. bolus or 50mg/m2 divided in 3-5 days I.V. bolus every 3 weeks. The objective responses were seen in malignant lymphoma, acute leukemia, ovarian carcinoma, cervix carcinoma and breast carcinoma.

The multiinstitutional study for malignant lymphoma with two above mentioned shcedules were carried out. Sixty-eight NHL and 8 HD were studied with response rate of 16.2, 50.0% CR and 48.5, 75.0% PR & CR respectively. There was no statistical difference between two schedules. Another study for virgin cases, 3 CR and 1 PR in 4 NHD cases, and 1 CR out of one HD were obtained. These results indicated similar responses compared with those obtained ADM with comparable dose and schedule.

The cardiac toxicity was monitored by physical, X-ray, EKG and left ventricular function studies. Ten cases had received between 900 and 1,000mg/m2 as a cumulative dose and had revealed no signs or symptoms of cardiac failure. Above these doses, two cases had received 1,920mg/body(1,390mg/m2) and 1,860mg/body(1,410mg/m2) as the highest total dose of these trials. The former patient had not revealed any signs or symptoms of cardiac toxicity, however, the later patient has developed signs and symptoms of irreversible cardiac failure, including dyspnea, palpitation, cardiomegaly, inverted ST, T waves and decreased left ventricular function. Above findings suggest strongly that THP-ADM is not producing cardiotoxicity up to cumulative dose of 900mg/m2 in these administration schedule. And the total dose bewteen 900mg and 1,400mg/m2 is the turning point of THP-ADM cardiotoxicity. Further, the cardiotoxicity incidence increases dramatically above a total dose of 1,400mg/m2. Nevertheless, this fact indicated usefullness of THP-ADM at least more than twice of ADM in the treatment of malignant lymphomas.

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T 149

HIGH DOSE INTENSITY CHEMOTHERAPY FOR POOR RISK B CELL MALIGNANCY IN CHILDREN

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A short duration, high dose intensity, 4 drug regimen was devised for the treatment of high risk B cell NHL (multiorgan Stage 3, Stage 4) and B ALL. Fractionated cyclophosphamide (1.2g/m2),adriamycin (60mg/m2),was alternated with cytosine arabinoside (12g/m2).High dose methotrexate (2.5g/m2) was given between each course at the nadir of blood count to minimise the period of non exposure to chemotherapy. Standard folinic acid rescue was used. CNS directed treatment was with regular triple intrathecal therapy(AraC,MTX,hydrocortisone), no irradiation was given.
16 patients have been treated. 3 received high dose consolidation with AraC,cyclophosphamide,TBI and bone marrow transplant but all others recieved 3 cycles of chemotherapy ie 6-7 months treatment.
3 had relapsed after standard therapy and of these 1 (CNS relapse off treatment) remains in remission.
6/7 Stage 4 cases with marrow disease are disease free 6-29 months off treatment. 1/3 with advanced Stage 3 disease is alive. None of the Satge 4 cases with initial CNS disease is alive but 2 of these were induction deaths. Although the number of patients is relatively small and the follow up short these results are clearly superior to our previous experience in this very high risk group.

T 150

HIGH-DOSE CHEMO-RADIOTHERAPY FOLLOWED BY AUTOLOGOUS BONE MARROW RESCUE IN MALIGNANT HISTIOCYTIC TUMORS.

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Patients with neoplasms arising from true histiocytes treated with conventional chemotherapy represent a poor prognosis group. In order to prolong the DFS we employed Autologous Bone Marrow Transplantation (ABMT) in 5 patients in CR or PR as consolidation program. Four patients were children (median age 14 yrs) and 1 adult (26 yrs). All patients, four stage III and one stage IV were symptomatic. No evidence of bone marrow or CNS involvement was observed at diagnosis. Marrow stem cell collection and cryopreservation were performed before beginning induction chemotherapy consisting of 3-4 courses of m-BACOD chemotherapy (Cy, ADM, VCR, BLEO, PDN, MTX). One patient showing persistance of disease after 3 m-BACOD courses received an additional course of F-MACHOP chemotherapy: (VCR, Cy, 5-FU, ARA-C, ADM, MTX, PDN) obtaining clinical CR. Of the other 4 patients 3 achieved CR and 1 underwent ABMT in PR. Conditioning pretransplant regimen consisted of Cytoxan 120 mg/kg and 10.20 Gy TBI fractionated in 6 doses over two days. Mean number of reinfused nucleated marrow cells was 2.1 x 10^8/kg body weight. Pretransplant therapy was well tolerated with no major problems. In all cases hematological recovery was prompt reaching PMN > 500/ul in a median of 13 days (range 11 to 16) and PLTs > 50.000/ul in a median of 21 days (range 14 to 25). The patient who received additional F-MACHOP chemotherapy before ABMT relapsed in the bone marrow after complete hematological recovery and died on day +31 from bone marrow infusion. The 3 patients transplanted in CR remain alive and well in unmantained CCR after 26+, 21+, 12+ months respectively from ABMT. The patient transplanted in PR obtained CR after ABMT, but showed recurrence of disease in the thyroid after 12 months. The shortness of the total treatment and the low risk of complications make ABMT a promising approach in this poor prognosis group of patients. Bone marrow collection performed at diagnosis allows a prompt engraftment after CY+TBI reducing the risks of prolonged aplasia. A larger number of patients and a longer follow-up are required to determine the real efficacy of this treatment in this poor prognosis disease.

Supported by AIRC and by a grant CNR, PFO, Contract no. 86.00466.44 and M.P.I. 40%.

T 151

PURGING OF A PERIPHERAL BLOOD DERIVED STEM CELL AUTOGRAFT.

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The autologous bone marrow transplantation (ABMT) proves to be a useful treatment for patients with non-Hodgkin's lymphomas. A crucial step in the ABMT is the purging of the autograft from residual tumor cells. The use of monoclonal antibodies (MoAbs) plus complement has been shown to be a specific and efficient technique. Recently, Körbling et al. reported a successful engraftment of peripheral blood-derived stem cells in a patient with Hodgkin's disease in complete remission. We applied this new therapeutical strategy in a patient suffering from a non-Hodgkin's lymphoma (centrocytic-anaplastic in according to the Kiel classification) in whom no complete remission could be achieved by the conventional polychemotherapies (6 cycles of Pro-Mace-MOPP and 3 cycles of IMVP-16). Before the transplantation the bone marrow involvement as assessed morphologically by bone marrow biopsy, aspiration and indirect immunofluorescence was around 35%. During the collection phase there were 5-10% B cells in the peripheral blood. The purging procedure consisted of 3 cycles of treatment with 2 x 10^7 cells/ml . The cocktail of MoAbs consisted of HD237 (CD19), HD60 (CD20) and HD28 (CD37). The MoAbs were used at a concentration of 10 ug/ml with a baby rabbit complement (Pel-Freeze) at the optimal lytic concentration. After this treatment about 1% of B cells were left. Pretransplant conditioning therapy consisted of superfractionated total body irradiation with 1460 rad and a chemotherapy with 200 mg/kg of cyclophosphamide. A total of 3.8 x 10^8 cells/kg or 2.1 x 10^8 mononuclear cells/kg, were transplanted. The total number of CFU-GM was 1.5 x 10^4/kg. 14 days post transplantation an engraftment could be demonstrated by bone marrow aspiration. On day 35 no B-cells could be detected by immunoenzymatic technique (APAAP). Now, on day 48 the peripheral white blood cell count was 1,000 with 200 granulocytes. At this time platelets and erythrocytes still need to be substituted. No further information is available about the long-term reconstitution of the lymphohemopoietic system.
In conclusion the use of peripheral derived blood stem cells after purging with an appropriate cocktail of monoclonal antibodies could be used in patients with non-Hodgkin's lymphoma with severe bone marrow infiltration and where the contamination of the peripheral blood with tumor cells is less especially when a purging procedure is added.

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HIGH DOSE CHEMOTHERAPY AND AUTOLOGOUS BONE MARROW REINFUSION IN PATIENTS WITH REFRACTORY MALIGNANT LYMPHOMAS.

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These studies were undertaken to determine the toxicity and efficacy of high dose combination chemotherapy in patients with disseminated malignant lymphomas. Five heavily pre-treated patients with non-Hodgkin's lymphomas were treated in phase I/II studies of multi-alkylator therapy. One patient received high dose cyclophosphamide (CPA) and thiotepa (TT) (bialkylator) and four patients received high dose CPA, TT and oral melphalan (MEL) (trialkylator). Three patients received reinfusion of non-purged autologous cryopreserved bone marrow. Two patients expired before reinfusion; one from progressive disease and one from complications during marrow procurement. Two patients obtained complete remissions (CR), one bialkylator, one trialkylator. Remission duration was 14, 32 weeks respectively. Both patients progressed in areas of previous disease. One patient died suddenly on day 7 of probable acute pericarditis/cardiomyopathy. The two responders showed evidence of engraftment but one patient had prolonged thrombocytopenia. Major toxicities were mucositis and infections. Three patients, all failed MOPP/ABVD regimens, with refractory Hodgkin's disease, were treated with high dose CPA, carmustine (BCNU) (B) and etoposide (E). All three received non-purged autologous cryopreserved bone marrow. Two patients responded with 1 CR and 1 partial response (PR). Response duration is 29+ weeks for the CR and 28 weeks for the PR. The patient with a PR has now progressed. All patients showed engraftment with return of normal white counts, however, one patient had prolonged thrombocytopenia. Toxicities include nausea/vomiting and mild stomatitis. There were no documented infections. High dose combination chemotherapy with autologous bone marrow reinfusion is an effective means to "salvage" patients with refractory lymphomas, both Hodgkin's and non-Hodgkin's. Further clinical investigation in this area is warranted.

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T 137 ETOPOSIDE IN COMBINATION CHEMOTHERAPY FOR DIFFUSE LARGE CELL LYMPHOMA.

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Etoposide has previously been shown to have significant activity as a single agent in these tumours and this is enhanced by combination with doxorubicin to result in remission rates that match those reported for the BACOP and C-MOPP programmes. However disease-free survival was superior with the latter combinations and to determine whether this was attributable to the drug programmes or to population differences random comparison was prospectively undertaken to BACOP in a pilot study. 39 patients with clinical stage III and IV diffuse large cell lymphoma received etoposide (60 mg/m^2 on 5 consecutive days) with doxorubicin (40 mg/m^2 on day 1) followed by 9 day rest period (group 1: n=17), the same schedule of etoposide but with carminomycin (20 mg/m^2 on day 1), also followed by 9 days rest period (group 2: n=8) or BACOP (group 3: n=14). In all 3 groups responding patients received 8 cycles of therapy. The complete remission rates were respectively 24%, 25% and 28% with further good partial remissions in 41%, 25% and 14%. The incidence of adverse prognostic factors was comparable in the three groups and the low remission complete rates ascribed to bone marrow invasion in 64% of the patients, to extensive gastro-intestinal tract involvement in about 30% and to high-bulk disease in approximately 30%. Actuarially predicted survival has not been reached for group 1, is 12 months for group 2 and 8 months for group 3: the differences are not statistically significant. These results suggest that the regimens have similar anti-tumour activity. The response rates are inferior to those previously reported and reflect the surprisingly high incidence of poor prognostic factors in our population. The survival of patients receiving etoposide and doxorubicin is superior to the other two groups and may be due to minimal residual disease in the partial responders making conversion to complete remission with salvage therapy easier to achieve. It is concluded that these apparently comparable drug combinations are inappropriate for treating advanced diffuse large cell lymphoma. Since BACOP can easily be up-graded to m-BACOD, which is a currently favoured front-line programme, the latter regimen is currently being prospectively compared to our etoposide and doxorubicin containing programme which has been enhanced by adding methotrexate to match that in m-BACOD. In this way the unique challenge of those populations disproportionately loaded with poor prognostic factors can be used as a model to further explore the role of etoposide in these tumours.

Supported by the University of Cape Town Leukaemia Centre and Staff Research (Cancer) Fund, the Medical Research Council, the National Cancer Association and the Gwendoline Moore Trust.

T 138 TREATMENT OF REFRACTORY OR RECURRENT MALIGNANT LYMPHOMAS WITH A COMBINATION OF ETOPOSIDE (VP-16), IFOSFAMIDE, METHOTREXATE AND BLEOMYCIN (VIMB).

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Patients (pts) with refractory or relapsed malignant lymphomas are known to have a poor prognosis. To improve the treatment results in these pts, we have used a therapeutic regimen consisting of VP-16 (90 mg/m²/day, Days 1,3,5), Ifosfamide (1200 mg/m²/day + Mesna, Days 1-5) and Methotrexate (30 mg/m²/day, Days 1,5). From March 1984 to October 1985, 35 pts (27 males, 8 females), ranging in age from 17 to 66 years (median 37), were treated. Of the 35 pts, 10 pts had relapsed following a complete response to first-line chemotherapy, 22 pts had failed to achieve complete response to front-line therapy and 2 pts had failed to respond to multiple salvage regimens given after the relapses of their diseases. In 1 patient, with Burkitt lymphoma of the stomach, VIMB was given as adjuvant treatment after surgical resection of the tumor. All other pts had received extensive prior chemotherapies, with combinations containing Adriamycin in 24 of 34 pts. Histological types of the tumors (Kiel classification) were: Lymphoblastic 3, immunoblastic 2, immunoblastic-centroblastic 1, centroblastic 6, undifferentiated large cell 4, pleomorphic T-cell 2, centrocytic 2, centrocytic-centroblastic 3, lymphoplasmocytoid 1 and Hodgkin's disease 11.
An overall response rate of 83% was achieved including 34% complete responses, 43% partial responses and 6% minor responses. The median relapse-free interval was 6 months in pts with partial remissions or minor responses and 10 months in those with complete responses. 46% of pts with complete responses were predicted to be without relapse at 24 months. The median survival time in pts with partial remissions or minor responses was 12 months. At a median follow up of 17 months , it had not yet been reached in pts with complete remissions. The probability of survival at 22 months for pts with partial remissions or minor responses was 17% and for those with complete responses 63%. On the basis of these results, VIMB combination appears to be effective in pts with refractory or relapsed lymphomas, particularly in those with high-grade malignant subtypes of non-Hodgkin's lymphomas. Further research appears justified to evaluate the effectiveness of this regimen in relation to the primary treatment of these diseases.

T 139 IFOSFAMIDE, BLEOMYCIN, ETOPOSIDE AND PROCARBAZINE (IBEP); SALVAGE COMBINATION CHEMOTHERAPY IN CHOP-RESISTANT NON-HODGKIN-LYMPHOMAS.

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Since the CHOP regimen has been one of the most frequently used initial remission induction combination chemotherapy in intermediate and high-grade malignant non-Hodgkin-lymphomas (NHL), the management of those NHL with either relapse or fail to attain complete remission (CR) on CHOP chemotherapy remains a therapeutic problem.
In previous studies we could induce partial (PR) or minor remissions (MR) in 7 of 8 chemotherapy refractory NHL by combined chemotherapy with ifosfamide and etoposide. To increase the rate and quality of ifosfamide/etoposide induced remissions we added bleomycin and procarbazine (IBEP regimen) to investigate this 4-drug chemotherapy combination as a potentially non-cross-resistant salvage chemotherapy in NHL which proved to be at least resistant to CHOP.
15 patients (pts) with refractory stage II B - IV B malignant NHL (histology: centroblastic 5 pts, immunoblastic 3 pts, lymphoblastic, centrocytic and centroblastic/centrocytic each 2 pts, immunocytic 1pt) have been treated with the IBEP regimen:
4o mg ifosfamide/kg iv. d 1-5 with mesna prophylaxis,
15 mg bleomycin im. d 1, 8, 15 and 21,
12o mg etoposide/m² d 1, 3 and 5 and
1oo mg procarbazine/m² po. d 1-14,
repeated d 28.
After 1-3 (median 2) IBEP chemotherapy courses in 5 pts a CR and in 7 pts a PR has been achieved with median remission durations of 1o and 3 months respectively; in the remaining 3 pts no change was observed.
Because the IBEP regimen could induce CR and PR in the majority of these CHOP resistant NHL, it proved to be of non-cross-resistance to CHOP. Therefore, the IBEP regimen represents not only an effective salvage chemotherapy of CHOP resistant NHL, but also may contribute a significant improvement of the initial chemotherapy of high-grade NHL by rapidly alternating the CHOP and IBEP regimens as two non-cross-resistant chemotherapy combinations.

T 140 CHOP-VP16 COMBINATION CHEMOTHERAPY AND INVOLVED FIELD IRRADIATION FOR HIGH MALIGNANT NON-HODGKIN-LYMPHOMAS: A PHASE II MULTICENTER STUDY.

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Fourtysix previously untreated patients with high malignant Non-Hodgkin-Lymphomas stage II-IV received cyclophosphamid 750 mg/m² iv day 1, adriamycin 50 mg7m² iv day 1, vincristine 2 mg iv day 1, prednisolone 100 mg po day 1-5 and etoposid 100 mg/m² iv day 3-5 (CHOP-VP16). After 4 courses of this regimen an involved field irradiation with a total dose of 25 Gy was employed and was followed by two additional courses of CHOP-VP16. The overall response rate was 91% with 38 patients (82%) achieving a complete remission (CR). Four patients had a partial response and 4 patients showed no response. During a median follow up period of 34 months 16 out of 38 patients with CR relapsed, four of them achieving a second complete remission with the same drug regimen.

A maintained complete remission up to 52 months was seen in 51% of all patients initially achieving CR with a plateau at 36 months. The overall survival curve shows a plateau at 60% at 30 months. Mean side effects of this drug regimen were alopecia (89%), nausea (vomiting 76%) and leukopenia (61%). No therapy related deaths were seen. The results of this study demonstrate that this combined modality treatment produces high complete remission rates and that the majority of these patients achieves long term disease free survival.

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T 141 NEW SALVAGE THERAPY WITH METHYL-GAG, H.D. Ara-C, M-AMSA AND IFOSFAMIDE (MAMI) FOR POOR PROGNOSIS MALIGNANT LYMPHOMA

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Relapsed or refractory malignant lymphomas have poor prognosis. This group of patients had already received the best conventional treatment including anthracyclines, etoposide and radiotherapy. New salvage therapy schedules are needed to reduce tumoral mass and select patients for myeloablative treatment with high dose chemotherapy and radiotherapy followed by bone marrow transplantation. Methyl-gag, Ara-C, M-Amsa and Ifosfamide have shown antitumoral activity as single drugs in malignant lymphomas with no cross resistance to drugs used in conventional treatment. MAMI protocol was administered as follows : Methyl-gag 400 mg/m^2 on days 1 and 4 ; Ara-C 2 gr/m^2 every 12 hs. days 1, 2 ; M-Amsa 80 mg/m^2/d. days 1, 2 ; Ifosfamide 3 g/m^2 day 1. On day 28 a second cycle is administered.

Twelve patients were included in this pilot study. Median age was 31 y (13-58) ; 8 male, 4 female. Diagnosis were : Hodgkin disease (HD) 3 ; non-Hodgkin lymphoma (NHL), diffuse large cell, 6 ; lymphoblastic lymphoma (LL) 3. Stage at diagnosis was : 2 bulky stage II, 3 stage III and 7 stage IV.

Patients were heavily treated previously with 9 differents drugs as a median (4-12) and 3 patients received radiotherapy. Median time between diagnosis and MAMI was 13 months (4-84) and clinical status at the moment of MAMI protocol was : 8 refractory disease, 2 first relapse, 2 second relapse.

Hematological toxicity was universal with 11 days (7->14) median granulocytopenia (<0.5 x 10^9/l) and 5.5 days (2-35) median thrombocytopenia (<20 x 10^9/l). Infectious complications were characterized by fever of unknown origin in 8 patients, 2 pneumonia and 1 candida septicemia.

Non-hematological toxicity was mainly nausea and vomiting (11), mucositis (9), abnormal liver biochemistry (3), hemorragic cystistis (1) and transitory Ifosfamide related encephalopathy (2). Two patients died of toxicity (pneumonia).

11 patients were evaluable for anti-lymphoma action with 5 complete remissions, 2 partial remissions, 1 minor response and 3 failures. Duration of response was short with 5 months (4-7) median time of relapse.

Conclusions : MAMI is a pilot study showing an acceptable tolerance in this group of heavily pretreated patients. High anti-tumor response has been observed in relapsed or refractory patients with malignant lymphoma. MAMI protocol should be introduced early for this type of poor prognosis patients.

T 142 Salvage treatment of Malignant Lymphomas (ML) with Mitoxantrone (MXT) based-protocols.

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22 patients (pts) with ML have been treated with 2 protocols. Protocol 1. 6 pts: MXT 14 mg/m2, vindesine 1.8 mg/m2, etoposide 300 mg/m2 all day 1. Protocol 2. 16 pts: MXT 12 mg/m2 d1 , teniposide 150 mg/m2 d1 & 2, methylglyoxal 200 mg/m2 d3, vincristine 1 mg/m2 d3, prednisolone 40 mg/m2 d1 to d3, methotrexate 200 mg d8, acid folinic d9. 1 pt was in 1st perceptible phase, 7 pts in 2nd phase, 10 pts in 3rd phase. 2 pts in 4th phase, and 2 pts in 5th phase. Histologic types are presented in the table. Performance status was good with only 11 pts with PS >=2. 11 pts had a bone marrow localization. 11 pts more than 3 extranodal sites, and 3 a large tumoral mass. 2 pts had a diffuse bone localization.

W.F. type	n	CR	PR	SD	PD	not evaluable
A	2			2		
B	1		1			
E	2		1		1	
F	3	1	1		1	
G	6	1	2	1	1	1
H	2	1				1
J	3				3	
M	3	3				
total	22	6	5	3	6	2

11 pts responded (55%. CR 30%. PR 25%). There was 3 PD with protocol 1 (50%), and 3 PD in protocol 2 (21%). All CR was observed with protocol 2. 2 pts were not evaluable for toxicity. Major toxicity is hematological: 15 pts OMS grade >2 for PMN and platelets, essentially with protocol 2. All presented infectious problems (no death). 10 pts have presented a grade 2 mucite, all with protocol 2. Alopecia was present in most of the pts, and more marked with protocol 2. No cardiac, hepatic, or renal toxicity was encountered. 19 had received prior treatments with adriamycine.

Overall response rate is important for relapsed pts. Protocol 1 is less toxic but far less active than protocol 2. Updated results with duration of the response will be presented.

T 143 RESULTS OF A NEW COMBINATION CHEMOTHERAPY (ETOPOSID-IFOSFAMID-MITOXANTRONE-BLEOMYCIN,VIM-BLEO) IN ADVANCED NON-HODGKIN LYMPHOMAS.

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51 patients (median age 53 years) with NHL of high or intermediate grade malignancy received a new combination consisting of VP 16 (100 mg), Ifosfamid (1 g) Mitoxantrone (3 mg/m^2) and Prednisone (60 mg/m^2) given on 3 consecutive days. On day 15 Bleomycin (15 u) was given. All but 2 of the 33 pretreated patients had had anthracycline containing, regimens. 47 patients were evaluable for response, 4 early deaths, were excluded. Objective response rate in pretreated patients was 48% (6 CR, 8 PR). In addition 6 patients showed MR with significant prolongation of survival. 13/18 of the patients receiving the new schedule in first line therapy responded (73% objective response rate). Dose limiting toxicity was granulocytopenia. In 33/172 evaluable cycles WBC were below 1000/mm^3. 29 septic episodes required hospitalization of the patients. Thrombocytopenia was seen in 10/172 cycles. In 2 of the 4 patients dying after the first cycle bone marrow aplasia was the main cause of death. Despite the comparable low dosages of Ifosfamid and VP 16 dosis modification seems to be necessary due to the bone marrow depressive effect of Mitoxantrone. No cardiac side effects were seen. It seems note worthy that this new combination is not cross resistant to other anthracycline containing regimens, so that it seems useful in anthracycline pretreated patients. Whether an alternating administration (CHOP-VIM) can improve results in first line therapy should be investigated in future.

T 144 CLINICAL EVALUATION OF EPIRUBICIN IN ADVANCED MALIGNANT LYMPHOMAS.

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A prospective study was carried out using CEOP regimen (CTX 600 mg/m^2 I.V. day 1,8; epirubicin 30 mg/m^2 I.V. day 1,8 or 50 mg/m^2 day 1; VCR 1.4 mg/m^2 I.V. day 1,8 and PDN 100 mg P.O. days 1 to 5, every 3-4 weeks,evaluate after 2 cycles, when stable or proggression, stop treatment; when with response, continue CEOP for total 6 cycles). All patients with histologic proof of intermediate and high-grade malignant lymphomas were eligible; patients shall be without prior treatment; age of patients shall be under 65, and performance status score above 50. Up to December of 1986, 96 patients have been entered and 92 of them are evaluable. Among them, 40 achieved CR, 38 PR, 9 stable, and 5 progression. Their pathological types are as following:

Types	No.Pts	CR	PR	S+I	Response Rate
Hodgkin's disease					
MC	7	6	1		100%
LP	1		1		
NHL					
Intermediate grade:					
Small cleaved	6	3	2	1	
Mixed	10	4	4	2	84.6%
Small noncleaved	11	3	5	2	
Large noncleaved	12	6	6		
High grade:					
Immunoblastic	10	6	4		
Lymphoblatic	12	4	5	3	83.3%
Burkitt's	6	4		2	
T-cell	8	1	6	1	
Mycosis fungoides	4	1	2	1	
Unclassified	5	2	2	1	
Total	92	40	38	14	84.8%

Most patients tolerated this regimen well, and the duration of remission was longer than other regimen used in this institute. It is concluded that CEOP regimen is an effective regimen for induction of remission of malignant lymphomas.

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T 129 ARE THE NEW LYMPHOMA REGIMENS TRULY SUPERIOR TO CHOP?

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The CHOP regimen or one of its variants is one of the most widely used treatments for high-grade lymphoma. CHOP produces complete response (CR) rates ranging from 40% to 87% in reported series, with the higher response rates generally being reported from small single institution studies. Recently there have been a number of new regimens developed which claim to be superior to CHOP in terms of CR rates and long-term survival. Examples of CR rates from these uncontrolled single institution studies include COP-BLAM (73% to 86%), M-or m-BACOD (73%-75%), ProMACE-MOPP (72%-74%), ProMACE-CytaBOM (80%) and MACOP-B (84%). These pilot studies vary considerably in important prognostic factors such as stage and age. The relationship of these prognostic factors to outcome is illustrated by the observation that CHOP produces a 60% CR rate and 55% long term survival in patients less than age 55 with Stage III and IV large cell lymphoma, compared to significantly worse results in older patients. Similarly for patients with Stage I or II lymphoma, CHOP produces CR rates of 95-97% with 80-90% long term survival and these results are significantly better than those observed in Stage III and IV disease.

Although the new regimens seemingly are superior to CHOP, the inclusion of patients of lesser stage or younger age would certainly influence the apparent effectiveness of the new treatment program. Since only one of these regimens has been evaluated in a prospective trial (ECOG tested CAP-BOP versus COPA with equivalent results) and since toxicity associated with these regimens is greater (up to 10% mortality in some series), it is imperative to conduct appropriate controlled randomized trials, stratifying for important prognostic factors such as age, stage and tumor bulk, before these new regimens are accepted as standard treatment.

T 130 PIME therapy for refractory lymphoma.

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Combination chemotherapies with Ifosfamide and VP-16 has shown to be effective as a salvage therapy for refractory non-Hodgkin's lymphoma. We have tested PIME combination therapy on 22 patients with refractory non-Hodgkin's lymphoma and three with Hodgkin's disease. All the patients with non-Hodgkin's lymphoma were either resistance to or relapsed from the CHOP therapy with or without other combination chemotherapies. Ten patients had been given radiotherapy as well. Three patients with Hodgkin's disease were resistant to or relapsed from both MOPP and AVBD therapies.

PIME therapy consisted of Procarbazine 100mg/m2/day p.o. on days 1 though 7, Ifosfamide 1200mg/m2/day i.v. on days 1 through 3, Methotrexate 150mg/m2/day i.v. on days 3 and 10, Etoposide 120mg/m2/day i.v. on days 1 through 3, and Leucovorin 25mg/m2 q6hx4 p.o. on days 4 and 11. The therapy was repeated every 4 weeks, for 6-8 times, then the therapy was discontinued after confirming complete remission by the re-staging. Focal radiotherapy was added to 6 patients with bulky mass at the initiation of PIME therapy.

To date, 21 patients are evaluable. Eight patients (38%) had complete response (CR) which was confirmed by the re-staging following 6th PIME, and eight patients responded partially (PR). Relapsed patients achieving CR were 4 out of 9 (44%). Refractory patients achieving CR were 4 out of 12 (33%). Response according to the histology was: LBL 1/2, IBL 3/3, DL 6/7, DM 1/2, DSC 2/2, FL 1/1, FM 0/1, HD 3/3. Median duration of survival after initiation of PIME therapy was 15 months. Median duration of complete remission was 25 months.

The toxicities of this regimen have been myelosuppression, nausea, vomiting, hair loss and hemorrhagic cystitis.

This combination chemotherapy has major activity in patients with lymphoma which was refractory to or relapsing form the combination chemotherapy containing adriamycin. This regimen may not be cross-resistant with CHOP or AVBD chemotherapy regimen and may be useful as an alternating regimen for the therapy previously untreated patients.

T 131 INTENSIFICATION OF THERAPY IN THE TREATMENT OF NON-HODGKIN'S LYMPHOMA WITH UNFAVOURABLE HISTOLOGY.

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Two hundred forty seven patients with unfavourable histology non-Hodgkin's lymphoma observed from 1978 to 1985 were retrospectively analyzed. Over the study period three therapeutic programs have been experienced: 1) conventional treatment by the use of ciclic combination chemotherapy CHOP or BACOP, 2) intensive induction therapy followed by maintenance therapy as in L_2-LSA_2 regimen, and more recently 3) aggressive therapy which included high dose chemotherapy and TBI followed by autologous bone marrow transplantation as hematologic rescue. Patients were not randomly assigned to the therapeutic protocol; in order to ensure more homogeneous characteristics of each group, patients over 60 years and those with bone marrow involvement were eliminated from the study. 162 patients entered the conventional, 62 the intensive and 23 the aggressive treatment. Remission rate was 45.6%, 53.2% and 69.5% respectively. The probability of survival at 5 years was 30%, 38% and 58% respectively ($p < 0.05$). Disease-free survival at 5 years was 30% in the group treated with conventional, 34% in intensive and 58% in aggressive treatment ($P < 0.005$). The enhancement of survival and disease-free survival was particularly evidend in patients with more aggressive histologies, in patients with bulky disease and in patients treated in relapse. Lymphoblastic, Immunoblastic and True histiocytic lymphoma appear benefited more than other histologies by aggressive therapy with 55% probability of survival at 5 years with respect to 32% with intensive and 20% with conventional therapy ($P < 0.05$). The probability of survival at 5 years of patients with bulky disease was 52%, 28%, and 10% respectively ($P < 0.005$). Finally, patients treated in relapse had 42%, 15% and 8% probability of survival at 4 years by aggressive, intensive and conventional therapy, respectively ($P < 0.05$). In conclusion, our study demonstrates that intensification of therapy produced a general improvement of survival and disease-free survival, however it should be noted that intensification of treatment may be particularly indicated in increasing the cure rate of patients with worse histology and bulky disease in which conventional treatments seems to be less efficacious. In other patients may be hazardous to expose the patients to the risk of aggressive therapies but may be advantageous to propose it in patients relapsed or resistant to the conventional treatments.

T 132 CYCLOPHOSPHAMIDE, ADRIAMYCIN, VINCRISTINE AND PREDNISONE (CHOP) versus CYCLOPHOSPHAMIDE, MITOXANTRONE, VINCRISTINE AND PREDNISONE (CNOP) IN NON-HODGKIN'S LYMPHOMA: A PHASE III RANDOMIZED STUDY.

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From Nov. 1984 to Apr. 86, we have conducted a phase III randomized study to compare the efficacy and toxicity of mitoxantrone versus doxorubicin in advanced diffuse non Hodgkin's lymphomas (NHL). Doxorubicin (50 mg/m^2 i.v., day 1) was employed in the CHOP regimen (every 21 days), with cyclophosphamide (750 mg/m^2, i.v., day 1), vincristine (1.4 mg/m^2, i.v., day 1) and prednisone (50 mg/m^2, for 5 days). Mitoxantrone (10 mg/m^2, i.v., day 1) was associated with the same drugs in substitution of doxorubicin (CNOP regimen). Thirty five patients with stage II - III - IV diffuse NHL classified according to the Working Formulation entered the study: 20 patients were randomized for CHOP and 15 for CNOP. The median age was significantly lower in the CNOP group (47 vs 57 years; $p < 0.02$). Twenty four patients belonged to the intermediate-grade malignancy and 11 to the high-grade malignancy group. Advanced stages accounted for 90% and 60% of total CHOP and CNOP cases. Other patient characteristics including sex, histology, E lesions, bulky disease, LDH score, and symptoms were balanced between the two groups. The complete remission (CR) rate after three cycle of therapy was 50% and 61% for CHOP and CNOP, respectively (not different); after 6 cycles, it was 70% and 66%. The 12-month relapse-free survival was 71 and 65%, for the CHOP and CNOP regimen, respectively. The mean nadir of granulocytes ($1072 \cdot 10^9/l$) was significantly lower ($p < 0.03$) for CNOP, without severe infections. Gastrointestinal toxicity was observed in 90% of CHOP and 73% of CNOP patients. Cardiac toxicity, evaluated by a more than 10% decrease of left ventricular ejection fraction was noted in 47% and 7% of CHOP and CNOP patients, respectively ($p < 0.039$). Cardiac dysrhythmias were noted in four patients; all had been given adriamycin (median dose: 250 mg/m^2). In conclusion, the efficacy of CHOP and CNOP chemotherapy in diffuse NHL was equivalent in term of CR rate; a longer follow-up is necessary for comparison of relapse-free survival. No episodes of heart failure or therapy-related deaths were registred. The clinical relevance of left ventricular ejection fraction reduction in absence of symptoms and of dysrhythmias as cardiac toxicity manifestation remains to be elucidated.

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T 133 TREATMENT OF HIGH AND INTERMEDIATE GRADE MALIGNANT LYMPHOMAS WITH CCNU,ARACYTINE,6-THIOGUANINE,L-ASPARAGINASE,METHOTREXATE AND LEUCOVORINE RESCUE (CATAM) IN RELAPSE OR REFRACTORY TO INTENSIVE CHEMOTHERAPY REGIMENS.

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Non Hodgkin's Lymphomas relapsing after intensive chemotherapy regimens as B-CHOP,BACOP or m-BACOD are usually refractory to most schemes used,their disease free survival is very limited and their bone marrow reserves are poor.As these patients tend to relapse just before next scheduled treatment we decided to use less myelotoxic drugs given at shorter intervals.Our chemotherapy regimen consists of CCNU 70mg/m² Day 1,Aracytine 120mg/m² sq Days 2-7 and 22-27,6-Thioguanine 100mg/m² po Days 2-7 and 22-27,L-Asparaginase 10000 units im Days 12,14,16,18,20,22,24,26,28,30 of the first cycle only,Methotrexate 500mg/m² over 6 hours iv Days 8 and 28,Leucovorin 15mg qid im Days 9 and 29 and po Days 10,11,30 and 31.Treatment was repeated every 42 Days.
Eight patients entered the protocol so far.All were in relapse 2-9 months after been in Coplete Remission with B-CHOP (2 patients), BACOP (1 patient),m-BACOD (2 patients),cisPlatin-Vindesine-Etoposide-Methotrexate-Leucovorin (2 patients),cisPLatin-Hexamethylmelamine-VM 26 (1 patient).All patients had stage IV disease and bone marrow was involved in 6,Waldayer's ring in 4,Liver in 3,Skin in 1 and Stomach in 1.Two patients have had life threatening septicaemias while in myelosuppression with previous chemotherapy regimens.Patients received 1 to 4 cycles of treatment and 3 of them are currently alive without any evidence of disease 52+,24+ and 8+ months after they stopped treatment.Survival for the remaining patients was 6,7,10,10 and 11 months from entering remission.Partial remission was achieved in 3 patients and Complete remission in 5.Chemotherapy was well tolerated and toxicity was minimal.Although leucocyte count nadirs were between 1800 and 2800 no septicaemia related deaths occured.The high percentage of Complete remission achieved and the long disease free survivals we observed suggest that the chemotherapy regimen we used may be capable of producing higher percentage of cures if tried earlier in the course of the disease or if it is enbodied in the initial treatment schedules.

T 134 RESULTS OF T.P.L. 84 (TOURS-POITIERS-LIMOGES) PROTOCOL IN STAGE III-IV UNFAVORABLE NON HODGKIN'S LYMPHOMAS (NHL).

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Intensive chemotherapy has proved effectiveness in term of long term complete remission in stage III-IV non hodgkin's lymphomas. The TOURS-POITIERS-LIMOGES protocol was initiated in february 1984 and 232 consecutive patients were enrolled. We reported here actual results of 57 previously untreated patients with stage III-IV unfavorable NHL. At presentation 19 patients were stage III and 38 patients were stage IV. Histologic subtypes were diffuse mixed (13), diffuse large cell (24) and immunoblastic (20). Two different regimens were used according to age. 15-60 years of age (31 patients) were treated with regimen A : 1) 3 courses of CHEP-Bléo : Cyclophosphamide (C) 1,2 g/m2, Doxorubicin (H) 75 mg/m2, Vindésine (E) 3 mg/m2 and Bléomycine (Bléo) 10 mg/m2 on day 1 ; Vindésine 3 mg/m2 and Bléomycine 10 mg/m2 on day 5 ; and Prednisolone (P) 50 mg/m2/day, day 1-10 2) 3 courses of VAMA with VM 26 (V) 80 mg/m2 on day 1, Cytosine Arabinoside (A) 200 mg/m2/day on day 1-5, L Asparaginase (A) 1000 UI/kg/day on day 6-10 and Methotrexate (M) 1,2 g/m2 on day 21 ; 3) 3 more courses of CHEP-Bléo. Regimen B was given in 26 patients over 60 years of age or less than 60 years of age with bad performance status (52-75). It consisted of ten courses of CAVP-Bléo : Cyclophosphamide (C) 500 mg/m2, Doxorubicin (A) 50 mg/m2, Vindésine (V) 3 mg/m2 and Bléomycine (Bléo) 10 mg/m2 on day 1 ; Vindésine 3 mg/m2 and Bléomycine 10 mg/m2 on day 5, Prednisolone (P) 50 mg/m2/day on day 1-10. In patients treated with regimen A, we observed 5 toxic deaths, 24 CR/26 (92 %). With a median of follow up which exceeds 12 months, 7/24 CR have relapsed. Actually 20/31 patients (64 %) are alive without disease, 17 first remission and 3 in second remission after autologous bone marrow transplantation. Among the regimen B patients, there was 20 RC/27 (74 %), 7 relapses which occured earlier than with regimen A. 12 patients (44 %) are alive without disease.

T 135 COMBINED ADRIAMYCIN, VINCRISTINE, PREDNISOLONE AND ETOPOSIDE (HOPE) IN THE TREATMENT OF DIFFUSE LARGE CELL NON-HODGKIN'S LYMPHOMA.

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We have treated 51 patients with diffuse non-Hodgkin's Lymphoma of centrocytic/centroblastic, centroblastic, lymphoblastic, histiocytic and large cell (unspecified) histologic types at anatomical stage II or worse with a combination of intra-venous adriamycin (30 mgs/m²) and vincristine (2mgs) on days 1 and 14 and of oral prednisolone (40 mgs daily) and etoposide (100 mgs/m², daily) on days 1 to 5 of a 28-day cycle for 6 courses. 46 patients are fully evaluable. Age range is 23 to 81 years (median 63). Male:Female ratio is 3:1.

35 of 46 (76%) achieved complete remission and 9 of 46(19.5%) partial remission (ECOG criteria) by 2 to 4 cycles of therapy. Overall actuarial survival is 78% at 3.5 years. Censoring a single unrelated death in remission actuarial duration of remission in 35 patients is 90% at 3.5 years. All relapses are at under 1 year.

In the "intermediate grade" (centroblastic/centrocytic) group (n = 22) actuarial survival is 87% at 3.5 years while in the "high grade" (all other histologies) group (n = 29) it is 72% at 3 years (p = 0.195, not significant). In those under 60 years of age (n = 22) actuarial survival is 88% at 3 years and over 60 years of age (n = 29) it is 71% (p - 0.217, not significant).

This is a simple and easily managed out-patient schedule with low toxicity and very few brief delays due to therapy-related cytopenia. It is effective in both skeletal and bone-marrow infiltration and in gut disease. Patient acceptance and tolerance are very high.

T 136 SIX DRUG INDUCTION REGIME CONTAINING ETOPOSIDE FOR INTERMEDIATE AND HIGH GRADE NON-HODGKIN'S LYMPHOMA.

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Thirty patients with intermediate and high grade Non-Hodgkin's lymphoma received 4 x 42 day cycles of Adriamycin 50 mg/m² i.v. day 1, Vincristine 1 mg/m² i.v. day 1, Methotrexate 200 mg/m² i.v. days 8, 15, 28, 35, Etoposide 120 mg/m² i.v. days 21-23, Cyclophosphamide 600 mg/m² i.v. day 21 and oral EC Prednisolone 10 mg qds days 1-7 and 21-28. Four patients had received prior radiotherapy but none had received cytotoxic chemotherapy. The mean age was 48.8 (range 22-70) and all were ECOG performance status 0-2. Three patients were Stage 1. 12 Stage II, 6 Stage III and 9 Stage IV. Twenty- five patients have completed 3 or 4 cycles and 26 are evaluable for response. The overall response rate was 96% with 18 CR (69%), 7 PR (27%) and 1 SD. One patient in PR was converted to CR by involved field radiotherapy. Four patients have relapsed at 8, 9, 12 and 14 months. There was one death in which haematological toxicity may have been a contributory factor. Two patients have died of progressive disease and one of mesenteric artery thrombosis. Nephrotoxicity was not observed, and mucositis was the other main toxicity seen. Median follow-up is 18 months, and 8 patients are relapse free at more than two years. This intensive regime with weekly scheduling of 6 cytotoxic drugs produces a high initial response rate with acceptable early treatment failure and toxicity.

ABSTRACTS - Third International Conference on Malignant Lymphoma, Lugano

T 121

MACOP-B: High toxicity in the treatment of Malignant Lymphoma (ML) Froimtchuk, M, Olivatto, L.O., Gil, R.A., Allan, S.E., Carriço, M.K. and the Lymphoma Group of the Instituto Nacional de Cancer Rio de Janeiro, Brasil.

A total of 51 previously untreated pts received MACOP-B for the treatment of ML. Median age was 50 yrs (range 16-78). All pts had performance status greater than 50 (Karnofsky scale). Toxicity was high: 53% of pts presented granulocyte count of less than 500/mm³ and all pts developed anemia, 29% of them requiring blood transfusions; infection was detected in 32 pts (23% minor and 39% major); severe mucositis was observed in 49%; nausea and vomiting of moderate to severe intensity was reported in 82% of pts. Fever due to Bleomycin, nurologic and skin toxicities were of mild intensity and were observedin 12%, 31% and 10% respectively. 30 pts had one or more week delay in their treatment due to toxicity. Overall mortality rate was 13.7%. All deaths were due to sepsil and were associated with severe musositis (100%) and severe leucopenia (50%) autopsy was performed in these seven pts confirming sepsil. No Pneumocystis catinii was evidenced. This highly effective 12 wks chemotherapy combination proved to be extremely toxic. Most of the toxicity was related to the use of moderate dose of Methothrexate (MTX) in spite of adequte rescue. New programs using lower MTX dose or its replacement should be evaluated.

(MACOP-B Ann. Intern. Med. 1985; 102:596-602)

T 122

PHASE III COMPARATIVE TRIAL ADRIAMYCIN VS NOVANTRONE (m BACOD vs. m-BNCOD) IN THE TREATMENT OF NON-HODGKIN'S LYMPHOMAS WITH UNFAVOURABLE HISTOLOGY. Gherlinzoni F.*, Guglielmi C.**, Mazza P.*, Lauria F.*, Zinzani P.L.*, Tura S.*, Amadori S.**, Mantovani L.**, Martelli M.**, Mandelli F.**.

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From August 1984 to July 1986 70 previously untreated patients with high or intermediate grade non-Hodgkin's lymphoma (NHL) according to Kiel classification entered a phase III comparative trial of Adriamycin (ADR) vs. Novantrone (NOV) (CYANAMID - LEDERLE) in the protocol m-BACOD The study included patients with stage II-IV, performance status 0-2 and with normal cardiac function at diagnosis. They were randomly assigned either to m-B-ADR-COD or to m-B-NOV-COD. Patients responding to treatment received 10 cycles of chemotherapy and then were restaged. 49 patients (70%) were males, 21 (30%) females; median age was 50.4 yrs 54 patients (77%) had no clinical symptoms at diagnosis; 37 patients (53%) had intermediate grade NHL, 33 patients (47%) had high grade NHL. 15 patients (21%) had bulky disease. 35 patients were randomized with Adr and 35 with Nov. At the time of this writing, 59 patients are evaluable, 29 treated with NOV, 30 with ADR. CR was achieved in 19 over 29 patients (65,5%) treated with NOV, and in 21 over 30 patients (70%) treated with Adr. 7 patients relapsed (17.5%) (4 NOV and 3 ADR) and 12 patients (20%) failed to respond,9 patients (15%) (2 NOV and 7 ADR) died for progression of the disease. Side effects included nausea and vomiting, alopecia, peripheral neurotoxicity which were more severe in patients treated with ADR. Haematological toxicity, including neutropenia and/or thrombocytopenia, required only temporary interruption of treatment. Cardiac toxicity was recorded in 6 patients (2 NOV and 4 ADR) and 1 patients had to interrupt defenitively the treatment.

Preliminary data indicate that Novantrone is highly effective in inducing CR in unfavourable histology NHL, with a low incidence of clinical toxicity, especially cardiac.

T 123

MACOP-B CHEMOTHERAPY FOR UNTREATED AND RELAPSED INTERMEDIATE GRADE B-CELL LYMPHOMA. PRELIMINARY RESULTS: DECEMBER 1984 - DECEMBER 1986. E. Gallo, D. Ferrero, R. Badoni, M. Scassa*, A. Pileri, C. Tarella, Cattedra di Ematologia di Torino e Ospedale Civile di Asti.

MACOP-B is an innovative chemoterapeutic program which is effective for the treatment of diffuse large cell lymphoma. Between december 1984 and december 1986 we treated with this regimen 16 pts with intermediate grade B-cell lymphoma at diagnosis and 9 pts with relapsed lymphoma. The newly diagnosed, untreated pts had a median age of 51 years (range, 24 to 71 years). Their clinical stage was documented with standard procedures, including bone marrow biopsy and computerized tomographic scans of the chest and abdomen. Nine pts had stage II disease, 5 with bulky masses; 3 pts had stage III disease, 1 with bulky mass and 4 pts had stage IV disease with bone marrow involvement. The histologic subclassification (Working Formulation system) was as follows: D, three pts; E, four; F, one; G, eight. All the pts completed the 12 courses of chemotherapy. Major toxicities were: mucositis (4 pts with grade III, 12 with grade I and II),granulocytopenia (5 pts with WBC < 1000/mm³), anemia (6 pts with Hb < 10 g/dl) and peripheral neuropathy (2 pts with grade III, 2 with grade II). One patient developed a herpes zooster infection requiring theraphy discontinuation for 2 weeks. Complete remission (CR) was achieved by the patient with F subtype and by 6 out of 8 pts with G subtype (overall CR for G and F=77%). Among the 7 pts with D or E subtype, only two (29%) were in CR after the MACOP-B chemotherapy. Partial response (PR) was observed in all the other pts. No pts had progression of the disease during treatment. All the pts who achieved CR are in actuarial disease free survival at 2-16 months from the completion of the MACOP-B. None of the pts with osteomedullary infiltration (grade D or E histology) achieved CR, for the persistence of bone marrow involvement, in absence of other manifested localizations of the disease. These pts received four additional courses of chemotherapy without any clinical improvement. In four of the seven pts in PR, a disease progression occurred at 1-4 months after completion of MACOP-B. Of the nine previously treated pts (stage III and IV) who underwent MACOP-B therapy at their first or second relapse, only one achieved complete remission(actuarial DFS:16 + months). Short lasting PR were observed in the other 8 cases.

In conclusion, MACOP-B was an effective treatment for pts with intermediate grade lymphomas of G and F histology but not for those with D or E subtypes, in particular when bone marrow involvement was present. Poor results were obtained when MACOP-B was employed as salvage regimen.

Supported by a grant of the Italian National Research Council, Special Project "Oncology", contract n.86.00424.44

T 124

LONG-TERM RESULTS OF TWO COMBINATION CHEMOTHERAPY REGIMENS IN THE TREATMENT OF NON-HODGKIN'S LYMPHOMA

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CAIRO NCI - CAIRO - EGYPT

Abstract:

Eighty-seven patients with non-Hodgkin's lymphoma (NHL) were consecutively treated with combination chemotherapy regimens (IOP) (52 patients) and (CHOP + weekly VCR) regimen (35 patients). Patients were 60 males and 27 females with no prior therapy (chemotherapy, or radiotherapy). Their ages ranged 17-71 years, "mean 45 years". They were pathologically classified according to the working Formulation: Low-grade 11, intermediate grade 49, and high grade 27 patients. According to the clinical stagining; 7 patients were stage II, 46 stage III and 34 stage IV. All patients who received IOP (group A) were evaluable for response. While only 30 of the 35 patients of those who received CHOP + weekly VCR were evaluable for response.

Group A:

Complete response ,(CR), was achieved in 20 patients, partial response (P.R.)in 23 patients and no response in 9 patients, an over all response of 82.7%. The overall survival of the whole group was 78% with median survival 21 months.; Nine patients relapsed after a median of 13 months. The survival rate among those acheiving CR was 90% after 33 months of follow-up.Disease free survival rate was 89% among the CR patients.

Group B:

Complete response (CR) was acheived in 17 patients (P R) in 10 patients and 3 showed no response, an overall response of 90%. The survival of the whole group was 47% with a median survival 27 months the overall survival among (CRS)was 61% with the disease free survival 80%.

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T 125 EVALUATION OF B-CHOP REGIMEN IN NON-HODGKIN LYMPHOMAS (NHL) (INTERMEDIATE AND HIGH-GRADE MALIGNANCY).

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In NHL with intermediate and high-grade histology, B-CHOP, firstly proposed by Cabanillas and Coll. in 1977 (Blood, 49, 1977), is reported as an active (CR: 48-87%) and well tolerated regimen.
Since 1984 in our Center we treated with this combination (B=Bleomycin 10 mg/mq/i.m. days 1 and 5 + C=Cyclophosphamide 750 mg/mq/i.v. day 1 + H=Adriamycin 50 mg/mq/i.v. day 1 + O=Vincristin 1.4 mg/mq/i.v. days 1 and 5 + P=Prednisone 100 mg/p.o. days 1 to 5; every 21 days x 8 courses) 35 patients (pts) in all stages.
25 pts were male and 10 female with a median age of 51.8 years (range 20-70); 20 with intermediate, according to Working Formulation and 15 with high grade malignancy. 29 pts are now evaluable (WHO criteria, Cancer 47:207-214, 1981) and 6 pts are too early for evaluation.
Our data are the following:

	No. Eval. pts	CR(%)	PR(%)	No. Response (<PR %)
Intermediate	19	58	21	21
High	10	60	20	20

4 pts in CR stopped treatment after 3 or 4 courses due to treatment refusal or other medical reasons, and are at present free of disease. Of the 19 pts who completed the treatment 14 (74%) are in CR (range 4^+-23^+ months) with no differences between Intermediate and high histology; the median survival time is 16^+ (range 8^+-30^+) months.
Toxicity was moderate and always reversible:

WHO grade	1	2	3
Myelosuppression	30%	33%	5%
Nausea & Vomiting	25%	20%	25%
Mucositis	45%	10%	5%
Hair loss	5%	43%	33%
Neurotoxicity	28.5%	38%	14%

Our results indicate that this regimen is active in NHL intermediate and high grade malignancy, with acceptable toxicity (no sepsis or drug-related cardiotoxicity, nor drug-related death)
At our Center, B-CHOP regimen appears to be superior in terms of clinical activity than the previously used non-adriamycin containing regimen (COP, CVP). A more prolonged observation is needed to assess if this activity can produce a definitive improvement in overall and disease free survival. More aggressive and perhaps active regimens will be investigated, from the current year.

T 126 CHOP VERSUS METHOTREXATE - CHOP IN ADVANCED INTERMEDIATE AND HIGH GRADE DIFFUSE NON-HODGKIN'S LYMPHOMAS (I & HG-NHL).

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Forty five patients with advanced I & HG diffuse NHL were treated by randomization with CHOP, (cytoxan 750 mg/m^2 iv and Doxorubicin 50mg/m^2 iv on day 1, Vincristine 1/mg/m^2 on days 1 and 8 and oral prednisone 100mg/m^2 x 5 days). This treatment was given every 21 days, or with M-CHOP (oral M 30mg/m^2 q 6 hours (h) x 4 followed after the last dose by oral leukovorin 10mg/m^2 q 6h x 4 on days 1 and 8 followed on day 15 and 22 by CHOP as in the above program. This treatment was repeated every 28 days). Six cycles of CHOP or of M-CHOP were planned. None of the 45 patients had previous chemotherapy, 17 had received previous radiation therapy. The age range was 24 to 76 years (median 61 years). Both treatment groups were comparable in histology and clinical features (age, sex, presence of B symptoms, large intra-abdominal tumor, sites of extranodal involvement). The median follow-up on study was 58 months (range 47 to 78 months). One patient was lost to follow up. On later review 5 patients (2 in the M-CHOP) were found to have follicular architecture. All of these 5 achieved CR and are alive. Of the remaining, 20 patients received M-CHOP and 19 CHOP. The CR rate was 60% and 63% respectively (p:1.0). There were no significant differences in remission duration (p:0.74) or in survival (p:0.78) between the 2 treatments. Fifty one percent and 47% of the patients treated with CHOP and with M-CHOP respectively were alive at 6 years. Severe hematologic toxicity was observed in 14% and 10% of cycles of M-CHOP and of CHOP respectively (p:0.51). Two patients in the M-CHOP arm and 1 in the CHOP arm died with cytopenia and infection during treatment.

T 127 HIGH DOSE METHOTREXATE DELIVERED BETWEEN CYCLES OF THE FIRST GENERATION REGIMEN CHOP IN INTERMEDIATE AND HIGH GRADE MALIGNANT LYMPHOMAS.

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The prognosis of lymphomas of unfavourable histology improved with the recent introduction of regimens characterized by an increasing number of drugs given more frequently while non marrow toxic drugs are added to suppress tumor growth during the cytopenic phase of the treatment cycles. We have treated 16 patients with advanced intermediate and high grade malignant lymphoma with a CHOP-MTX regimen. Chemotherapy was given every 10 days starting with CHOP (Cyclophosphamide 750 mg/m^2, Adriamycin 50 mg/m^2, Vincristine 14 mg/m^2, day 1, and Prednisone 60 mg/m^2, day 1-5); on day 10 MTX 1 g/m^2 in 500 ml saline was given over 1 h. Hydration with 3 l fluid per day was maintained until serum MTX level decreased to 1 x 10^{-7} M. Leucovorin rescue started after 24 h. Urinary alkalization was achieved by sodium bicarbonate. Six of these CHOP-MTX cycles were delivered with tumor response evaluation after 4 and 6 courses. Patients not in complete remission (CR) after 4 courses were subsequently transplanted. Patient characteristics are as follows: males 10/16, mean age 51 yrs, stage II 3/16, stage III 1/16, stage IV 12/16, marrow involvement 4/16, extranodal involvement 9/16. Evaluable data are available for 13 patients (two patients on therapy, one patient died after 1 cycle, not therapy related).
Results: CR after 4 cycles: 11/13 (85%), CR after 6 cycles: 12/13 (92%), relapse: 1/11 (9%). Two patients were subsequently transplanted. The disease free survival of patients in CR after 4 cycles is 90% (10/11). Median follow up was 9 months. The toxicity of this regimen was very low: leucocytopenia (<1.10^9/l) in 3 patients, no thrombocytopenia (<50.10^9/l), moderate mucositis and neurologic toxicity occurred in respectively 3 and 5 patients, major infection (campylobacter sepsis) occurred in 1 patient. The drug doses were not modified, no delay in treatment was allowed.
Although the data are preliminary, in this small group they are very promising and deserve further study. The addition of high dose MTX may reduce CNS relapse; together with the low toxicity and high complete response rate is this an important advantage of this regimen.

T 128 RESPONSE-ORIENTED THERAPY IN HIGH-GRADE MALIGNANT NON-HODGKIN'S LYMPHOMAS (NHL) WITH CHOP AND VIM-BLEO

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24 patients (male 10, female 14, median age 52 years) with high-grade malignant NHL (centroblastic 12; immunoblastic 6; high-grade malignant, not further defined 6) were treated in a multicenter study. 8 patients had stage II, 4 stage III and 12 stage IV disease. Treatment was initiated according to the CHOP protocol. Patients reaching at least a partial remission after 2 and a complete remission after 4 cycles were continued on CHOP to a total of 9 cycles. Patients not meeting these criteria were switched to a combination therapy with etoposide, ifosfamide, methotrexate and bleomycin (VIM-Bleo). With the CHOP treatment, 16 patients (67 %) achieved a complete remission. Of the remaining 8 patients, 1 died with progressive disease before change of treatment. 7 were treated with VIM-Bleo, of these, 5 achieved a complete remission. Thus, the overal complete remission rate was 21/24 (88%). With a median follow up of 22 month, 6 patients had relapses, the projected 2-year disease-free survival rate is 64 %. 5 of the 6 relapses occurred in patients treated only with CHOP. We conclude, that with this form of therapy good remission rates can be achieved; however, there is a significant rate of relapses especially in patients treated with CHOP as the only form of chemotherapy. Consolidation therapy is necessary also in patients with a rapid response to CHOP.

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T 113 DISEASE-FREE SURVIVAL AND PROGNOSIS IN STAGES I AND II HIGH GRADE NHL - THE IMPACT OF CHEMOTHERAPY.

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Between January 1974 and December 1983 113 patients with localised high grade NHL were treated at this centre. Histological material was classified into histopathological groups (HPG) according to Rappaport, and 58 were DPDL, 48 DHL and 7 DM or unclassified. Staging included clinical examination, chest x-ray, bone marrow aspirate and lymphography, computed tomography abdominal scan or laparotomy; 62 were stage I and 51 stage II. Treatment was surgical excision alone (2 patients) or excision/biopsy combined with irradiation (72 patients), chemotherapy (19 patients) or both (20 patients). 41 presented with nodal and 72 with extranodal disease (including 27 with gastrointestinal, 16 with Waldeyer's ring and 13 with thyroid NHL).

Actuarial survival for stage I patients was 68.3% at 5 years and 65.5% at 10 years, and for stage II patients 61.2% at 5 years and 52.2% at 10 years. For patients with stage II and bulky (>5 cm) stage I disease there was a significant improvement (p=0.05) in relapse-free survival (RFS) and a non-significant trend towards improved overall survival for those treated with chemotherapy; either alone or together with irradiation, compared with irradiation alone. This trend was seen in both major HPGs. For patients responding completely to chemotherapy, irradiation of bulky sites did not appear necessary.

For irradiated patients local control was achieved in 78/92 (85%) patients, and for those with bulky disease, 31/40 (77.5%) treated with <40 Gy and 6/6 (100%) with ≥ 40 Gy. There was no significant difference in RFS for those treated with extended compared with involved fields.

Survival was significantly prolonged ($p < 0.001$) for patients responding completely to primary therapy. There was no significant difference in survival for patients with nodal compared with extra-nodal presentation.

A multivariate analysis of survival data identified age and HPG as independent variables of prognostic significance. Although radiotherapy is an effective treatment for high grade NHL, we recommend treatment with primary chemotherapy for patients presenting with stage II or bulky stage I disease.

T 114 DETECTION OF NON HODGKIN (NH) LYMPHOMA HISTOLOGICAL TYPES RESPONSIVE TO T-CAM COMBINATION CHEMIOTHERAPY

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6o patients with st. IIB-IV NH lymphoma (13 lymphoblastic, 12 centroblastic non cleaved, 8 centroblastic-centrocytic, 7 centrocyti-cleaved, 11 lymphocytic including 2 T-types, 9 others)- entered the study. 47 were previously untreated, 13 were previously treated (4 CHOP, 2 Adriablastine-Etoposide-Cyclophosphamide, 3 COPP/MOPP, 4 Chl rambucil). Median age was 63 years, range 3o-79 years.

Treatment consisted of 8 T-CAM induction cycles at monthly intervals (Adriablastine 5o mg/m² iv day 1, Teniposide 14o mg/m² iv day 2 Cyclophosphamide 3oo mg/m²/24 h iv days 3-5, Methylprednisolone loo mg/m²/24 h, days 3-6), followed by monthly maintenance with COM (Cyclophosphamide, Oncovine, Methylprednisolone, all day 1), every fouth COM being replaced by T-CEM reinduction (equimolar Epirubicine substituting Adriablastine), for 3 years.

In the whole group, complete remission (CR) was achieved in 58% patients, partial remission (PR) in 35%; progressive disease was observed in 7% (PD); remission rate (RR) was 93%. Different histologic types responded:

Lymphoblastic: CR 61,5%, PR 3o,8%, PD 7,7%, RR 92,3%, mean response duration (MRD) 13,6 months; only 4/13 still in remission 4+, 6 15+, 33+ months; no plateau in remission duration curve; leucaemic transformation in 2patients.

Centroblastic: CR 66,3%. PR 3o,8%, RR loo%. MRD 16,3 months, al patients still in remission lasting 12-24 months 6/12, over 24 month in 4/12.

Centrocytic, cleaved: CR 85,7%, PR 14,3%, RR loo%, MRD 16,7 mon hs, 6/7 patients still in remission lasting 7-33 months.

Centroblastic-centrocytic: CR 66,3%. PR 25%, PD 12,5%. RR 87,5% MRD 12,7 months, only 3/8 still in remission; no plateau in remissic duration curve; 2 patients underwent immunoblastic transformation (I

Lymphocytic: CR 27,5%, PR 55%, PD 17,5% (both T), RR 82,5%, MR 15,4 months, 6/11 patients still in remission, (4/11 patients in remission for 2o+, 23+, 23+, 45+ months), 2 patients underwent it.

Either CR or PR was achieved in all patients resistent to CHOP or a similar Etoposide containing regimen, indicating a critical pla of Teniposide in the T-CAM combination. The regimen seems very activ for centroblastic and centrocytic-cleaved NH lymphoma, less so for lymphocytic, and is probably not the best choice for lymphoblastic and centroblastic-centrocytic NH lymphoma.

T 115 TOXICITY OF A COMBINATION OF ABVD AND MEDIASTINAL IRRADIATION FOR HODGKIN'S DISEASE PATIENTS WITH MASSIVE INITIAL MEDIASTINAL INVOLVEMENT.

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The presence of a large mediastinum (MT ratio ≥ 0.35) in patients with Hodgkin's disease (HD) is an adverse factor that is often associated with other indicators of a poor prognosis. Good results have been obtained for treatment of such patients by radiotherapy (RT), either by administering lung RT systematically as a principle, or by progressively reducing the volumes irradiated. Owing to the lung toxicity of such treatments and the severity of such pathologies, initial treatment by chemotherapy is often offered. For example, the EORTC H6U trial compares a 3 MOPP-RT-3 MOPP association with 3 ABVD-RT-3 ABVD for these cases. One aim of this trial is to compare the toxicity; Zucali et al. (J. Eur. Radiother. 1981,3,169-176) reported that 49% of patients treated by ABVD-RT presented respiratory sequela versus only 15%-20% of patients treated with MOPP-RT. From 1981 to 1983, we used an ABVD-RT combination to treat five patients (aged 17 to 35 years) with type 2 HD (3 stage II, 2 stage III) who had an MT ratio of 0.43-0.57. Mantle field irradiation consisted of 40 Gy given in 16-20 fractions over 28-47 days. Three patients received 6 courses of ABVD, 1 patient received 10 courses, and 1 received only 3 courses. Four patients are currently NED for their HD; 1 patient has died. All 5 patients presented signs of toxicity: 3/5 had a severe respiratory syndrome, 2/5 had mediastinitis, responsible for the one death, and venous thrombosis of the upper limbs. The role of adriamycin, bleomycin and irradiation as the causes of toxicity are discussed. The ABVD-RT combination should be avoided for these HD patients, or the number of ABVD courses and/or the irradiation dose must be reduced.

T 116 RADIOTHERAPY OF ORBITAL NON-HODGKIN LYMPHOMAS

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Non-Hodgkin lymphomas of the orbit occur infrequently and are rare. Since 1965, 41 patients with histologically proven Non-Hodgkin lymphomas (NHL) have been irradiated at our institutions.

According to the Ann Arbor staging system, 14 pts. were in stage I_E, 19 in stage II_E, and 8 pts. in stages III_E/IV_E. Histologically 15 cases were classified as low malig nant and 9 as high malignant. According to the old Germar classificatin, the other cases were 15 reticulum cell sarcomas and 2 lymphosarcomas. The patients were given radiation doses between 26 and 46 Gy, using individualize treatment techniques. Since 1978, treatment plans were based on individual CT scans and calculated by a computec planning system. The lens was shielded whenever possible. Initial local control was acchieved in 93% of stage I_E and 9o% of stage II_E patients, 63 % for stage III_E/IV_E pts. respectively. All local recurrences(6 pts.) occure within 18 months. The ultimate local control rate ammount ed 71% in stage I_E(10/14 pts.) and 76% (13/17 pts.) in stage II_E. Median observation time was 36 months for all patients.

The rate of side effects was insignificant, one patient developed an entropium of the lower lid, another a slight ly dry eye. In two cases the lens hd to be removed becaus of progressive cataract.

In our opinion, radiotherapy is the treatment of choice for orbital Non-Hodgkin lymphomas, resulting in a high local control rate and low morbidity. The course of the disease is mainly influenced by the tendency of dissemina tion of primary localized tumors, which occured in 8 pts. beeing initially in stages I_E/II_E. According to histologically subtypes, we saw no differences in local control.

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T 117 MILD ADJUVANT CHEMOTHERAPY IN THE TREATMENT OF LOCALIZED WALDEYER'S RING NHL. J. Itami, S. Mori, N. Arimizu, Dept. of Radiol., Chiba Univ., Chiba, Dept. of Pathol., Institute of Med. Science, Tokyo Univ., Tokyo, Japan.

One of the most frequent presentations of the non-Hodgkin's lymphoma (NHL) in head and neck region is the involvement of the Waldeyer's ring (WR). WR-NHL in stage I and II has been treated by radiation therapy (RT), although recent studies suggest improvement of prognosis with adjuvant chemotherapy (CT). But the indication and optimal regimen remain undefined. We have treated 43 patients with histologically confirmed WR-NHL with RT with or without mild VEMP adjuvant chemotherapy. The stage II was further classified into stage II-1 and II-2 according to Musshoff et al. Relapse free survival (RFS) and actuarial survival (AS) at five years are presented in the table.

		5-Y-RFS (%)		5-Y-AS (%)	
Age	<60	61	p=0.55	76	p=0.12
	≥60	13		47	
Stage	I	79	p=0.10	100	p=0.05
	II-1	41	p=0.09	65	p=0.01
	II-2	12		12	
Grade	low	75	p=0.06	100	p=0.11
	intermediate	33	p=0.41	57	p=0.53
	high	75		75	
CT	No	30	p=0.26	80	p=0.30
	Yes	50		61	
RT Field	IF	45	p=0.27	63	p=0.50
	EF	57		69	

Multivariate analysis by Cox was also performed to see the correlation of possible prognostic factors. Only the stage showed statistical significance with RFS and AS as end points. These results clearly indicate limited usefulness of VEMP regimen not including Adriamycin. This retrospective study revealed the possibility that the stage I and II-1 might be cured in a considerable percentage with RT alone if intensive staging and RT are performed, while stage II-2 WR-NHL needs to undergo aggressive CT with or without consolidating RT.

T 118 COMBINED CHEMOTHERAPY-RADIOTHERAPY FOR STAGE I AND II INTERMEDIATE AND HIGH GRADE NON-HODGKIN LYMPHOMAS. J.H. Meerwaldt and W. Sizoo, The Dr Daniel den Hoed Cancer Center, Rotterdam, The Netherlands

Between January 1983 and January 1987 51 patients were randomized in this study. Treatment consisted of 4 courses of CHOP, followed by involved field radiotherapy. Patients in CR were then randomized to receive either no further treatment until relapse or another 4 courses of CHOP. 40 Patients are evaluable, 2 patients excluded, 11 patients, too early for evaluation.
26 Pts were stage I, 14 st. II; 17 patients had extranodal presentations (stomach, mamma, testis and skin). 12 Pts had intermediate, 28 high grade malignancy. Following 4 courses of CHOP 7 pts reached a PR and 33 a CR. Following 4 courses of CHOP and radiotherapy all 40 patients obtained a CR.
19 Patients received another 4 courses of CHOP, 21 patients no further treatment.
Up to now, with a mean follow-up of 20 months, 7 relapses have been noted, 3 in stage I and 4 in stage II. 2 Patients received 8 courses of CHOP, 5 only 4 courses. Increased relative hazard rates of around 2 were calculated for stage, malignancy grade, initial response following 4 courses of CHOP and for the treatment following randomization.
Conclusion of these preliminary results:
For stage I 4 courses of CHOP with involved field radiotherapy is an acceptable treatment.
Stage II will best be included with stage III and IV, to receive more agressive treatment.

T 119 ALLEVIATION OF POST CHEMOTHERAPY NEUTROPENIA AND SEPTICAEMIA WITH LITHIUM CARBONATE IN PATIENTS WITH ADVANCED MALIGNANT LYMPHOMAS. M.Papadakou,H.Boukis,E.Voskaridou,T.Coutsouradis, P.Pipis,G.Panagos. Department of Medical Oncology,"A.Anargiri" Oncological Hospital of Kifisia,N.Kifisia,Athens 14564,Greece

Seventy six patients with non-Hodgkin's Lymphomas and six with Hodgkin's Disease were followed in our Department for advanced, relapsing or refractory disease and they received 297 courses of chemotherapy. Thirty eight patients developed 74 episodes of severe neutropenia and fever following chemotherapy. Twenty one of them had stage IV disease with bone marrow involvement in 14,while six had stage II and 11 stage III disease. In 28 episodes patients received combinations of 2 to 4 antibiotics but no Lithium Carbonate while in 46 episodes patients were treated with the same antibiotic combinations or sigle wide spectrum antibiotics and Lithium Carbonate given by mouth (300mg tid) for 7 days.Nadir Leucocyte counts were 1541± 586 for the first group and 1590±570 for the Lithium treated group. Nadir Granulocyte counts were from less than 100 to 750 for the non treated group and from less than 100 to 650 for the Lithium treated group. Duration of Leucopenia was 11.22±4.98 days and 7.1±5.08 days for the 2 groups respectivelly,while duration of fever was 12.72±9.00 days and 4.90±5.66 days respectivelly. In the non treated group five septic deaths occured 1 to 12 days after septicaemia started. There were no septic deaths in the Lithium treated group.
As there were no differences between the two groups in disease characteristics,demographic data or prior chemotherapy and radiation treatment,the benefits observed in the Lithium treated group have to be attributed only to stimulation of Leucopoiesis by the drug. Indeed,we observed that fever usually subsided 1 to 2 days before any increase of granulocytes in peripheral blood after Lithium, while in the non treated group fever subsided together with peripheral blood leucocyte count increase or several days thereafter. As 2 to 4 days are needed to observe increase of granulopoiesis after Lithium treatment we currently plan to start Lithium administration earlier and preferably one to two days before the expected granulocyte nadir day in the abscence of any sign of infection in those patients with heavy infiltration of bone marrow by Lymphoma and ,also,in refractory patients after extensive radiotherapy or/and chemotherapy.With the present experience we expect that this 2 poor risk groups of patients will have the opportunity to be treated with more aggressive chemotherapeutic regimens and,probably,to achieve complete remissions.

T 120 PREDICTING NEUTROPENIA AFTER CHEMOTHERAPY FOR LYMPHOMA. Sylvia M.Watkins, A.D.White, Department of Oncology, Lister Hospital, Stevenage, U.K.

The records of 29 patients with Hodgkin's disease and 41 with non-Hodgkin lymphomas were studied. These patients were all receiving treatment with CHOP, COP, LOPP, CVP, MVPP or MOPP/BLEO. All had blood counts sufficiently high to receive the full recommended doses of chemotherapy on day 1 and day 8 in a total of 418 courses of treatment. Nevertheless, there were 13 episodes of neutropenia (neutrophils less than $0.8 \times 10^9/l$) during the three weeks following the second injection. Two of these patients also developed profound thrombocytopenia (platelets less than $20 \times 10^9/l$), although no patient became thrombocytopenic in the absence of neutropenia.

The blood counts were charted on semilogarithmic paper (ordinate 4.8cm per log cycle; abscissa 3cm per 30 days). In 25 courses of treatment there was a drop in the neutrophil and/or platelet count represented by a fall of more than 45° on the semilogarithmic chart (representing an actual drop of approximately 30%). Of these 25, seven (28%) subsequently became neutropenic (and two of them also thrombocytopenic). Of the remaining 393 courses of treatment only six (1.5%) subsequently became neutropenic.

By studying the angle of fall of the neutrophil and platelet counts on a simple chart after the first week of chemotherapy, it is possible to identify about half the lymphoma patients at risk of developing clinically significant neutropenia if they recive full doses of cytotoxic drugs on day 8. We suggest that, having identified such patients, they should receive modified doses of chemotherapy on day 8 in order to avoid such life-threatening complications.

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T 105 PRIMARY GASTROINTESTINAL (GI) NON-HODGKIN'S LYMPHOMA (NHL): EVALUATION OF 36 PATIENTS (PTS).

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From 1973 to 1984, 36 pts with primary GI-NHL were staged and treated at our institution. Histologic diagnosis was reviewed according to the the Working Formulation (W.F.). Median age was 50.6 years. Primary sites of involvement were: stomach (19 pts=53%),intestine (17 pts=47%). 13 pts had stage I, 6 pts stage II_1, 11 pts stage II_2 and 6 pts stage III and/or IV. B symptoms were observed in 19 cases. 4 pts had Low Grade (LG), 16 pts Intermediate Grade (IG)and 11 pts High Grade(HG)NHL. 5 cases were not avalaible for histologic review. 9/13 pts in stage I and 1/6 in stage II_1 were managed with surgical resection only. All others were treated with chemotherapy $\pm$ surgery.
Median follow-up of all groups of pts was 58 months.
Overall complete response (CR) rate was 86% (31 pts). A good prognostic factor for CR was gastric involvement (CR in gastric NHL was 94 vs intestinal 76,p=0.05) and localized lymphoma (I + II vs III + IV,p=0.0). The overall survival was 60% at 8 years. Prognostic factors for survival was Histology (8-year survival: LG + IG=78% vs HG=52%, p=0.04)and stage (I 100% survival at 8 years vs II. median survival= 94 mo vs III + IV median survival = 44 mo , p=0.006).
There was no difference in survival in localized lymphoma (stage $I+II_1$) treated with surgery alone or surgery plus chemotherapy (85% at 8 years for both groups).Among localized stages (I + II_1),HG NHL, even if treated with surgery plus chemotherapy (CHOP) had a significant worse survival than LG + IG NHL (8-year survival: LG + IG=100% vs HG median survival 30 mo, p=0.0015).
Form these result the use of aggresive chemotherapy,such as thind generation regimens,after adequate surgical resection is advisable in high grade GI NHL, also in localized cases.

T 106

PRELIMINARY RESULTS OF MODIFIED PROMACE MOPP (MPM) CHEMOTHERAPY (CT) FOR GASTROINSTESTINAL LYMPHOMA (GIL).

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From january to december 86 we treated 13 patients (pts) with GIL by 6 to 8 cycles of MPM : day 1 Etoposide 120mg/sqm, Doxorubicin 25 mg/sqm, Cyclophosphamide 650 mg/sqm, day 8 Vincristine 1,4 mg/sqm, Mechlorethamine 6 mg/sqm, Day 14 Methotrexate 500 mg/sqm + Folinic Acid, Day 1 to 14 Procarbazine 100 mg/sqm, Prednisone 60 mg/sqm. 7 pts had gastric lymphoma (GL) : 4 stage IE, 3 stage IIE, 5 high grade (HG), 2 intermediate grade (IG). 6 pts had intestinal lymphoma (IL): 2 stage IIE ileal, 1 HG, 1 IG, 2 stage IIE jejunal, 1 HG, 1 low grade (LG), 1 stage IIE caecal HG, 1 stage IIE sigmoidian HG. 2 pts with IL (1 LG, 1 IG) had a relapse 4 years after initial treatment (1 CT alone, 1 CT + abdominal irradiation). 2 pts (1 IL, 1 GL) had a previous history of supra diaphragmatic Hodgkin's disease treated 9 and 17 years before by mantle field irradiation and CT.

PATIENTS POLPULATION

	7 GASTRIC	6 INTESTINAL	
HG	3 II E + 2 I E	3 II E + 1 I E	9
IG	1 II E + 1 IE	1 II E	3
LG		1 II E	1

Results : 3 pts in complete remission (CR) after initial surgery are not evaluable, 1 pt with a documented partial remission (PR) after 2 cycles relapsed after his 6th cycle and died of disease. 2 pts (1 IG stade IIE GL, 1 LG stage IIE IL) are in PR after 4 cycles and currently pursuing CT. 7 pts are in CR : 5 with GL, 4 after 2 cycles, 1 after 4 cycles (bulky IIE immunoblastic), 2 with IL after 2 cycles (1 relapsed IIE ileal IG, 1 bulky HG IIE caecal with contiguous hepatic extension). Toxicity was hematologic (2 WHO grade 4 neutropenia) without any life threatening infection, digestive (vomiting WHO grade 1 to 3) and ocular (conjunctivitis almost constant).

Conc : modified MPM CT yields a high response rate in GIL with limited toxicity. Duration of response can only be evaluated through longer follow up.

T 107 PRIMARY CHEMOTHERAPY FOR LOCALIZED LARGE CELL NON-HODGKIN'S LYMPHOMA (NHL) OF WALDEYER'S RING.

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Radiotherapy alone for localized large cell lymphoma has proved to be curative in 40 - 60% of patients, with the best results in stage I or IE. Combination chemotherapy, proven to be effective in advanced stages of the disease, should be administered before radiotherapy in order to obtain an early systemic control and prevent relapses. Between 1976 and 1985, in a series of 34 patients with localized large cell NHL of Waldeyer's ring observed at the Institut Curie, 8 were treated by radiotherapy alone : 4 furtherly developed gastric relapses. 6 were treated by radiotherapy followed by chemotherapy : 5 developed relapses (3 out of 5 were gastric). 20 additional patients were treated by primary combination chemotherapy using the CHOP regimen, followed by radiotherapy : 19 achieved a complete remission before radiotherapy. Only one relapse was observed, non gastric, 4 years after the initial treatment. All other patients are alived, free of disease, with a median follow-up of 5 years. Primary chemotherapy, followed by radiotherapy, is associated in this group of NHL with a very good prognosis and no secondary gastric localization.

T 108 THYROID GLAND FUNCTION IN PATIENTS WITH LYMPHOMAS DURING TREATMENT.

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We have investigated the occurence of thyroid gland malfunction in patients with lymphomas initialy treated with chemotherapy alone. Twenty patients were included: 10 with Hodgkin's disease (HD) and 10 with non-Hodgkin's lymphomas (NHL). There were 10 women and 10 men. We used the following parameters for evaluation of the thyroid gland function: T3, T4, TSH, free T4, TBG, thyroglobulin, antithyroglobulin antibodies (anti-Tg Ab) and antimicrosomal antibodies (anti-Mc Ab). The types of therapeutic regimens were: MOPP, COPP, HCOP, ChlVPP and COP. All parameters were tested before and after 3 cycles of chemotherapy. Statistical analysis shows that there is no significant difference in any of parameters studied except for anti-Tg Ab. Antithyroglobulin antibodies were elevated in 10 (50%) cases before chemotherapy and were normalized in all patients after 3 cycles of chemotherapy. The results of our investigation indicate that there is no change in the thyroid gland function in patients with lymphomas in the early course of chemotherapy. The elevated values of anti-Tg Ab before therapy could be interpreted as a nonspecific finding i.e. a part of general immunological abnormalities in patients with lymphomas or could be a consequence of microinfiltration of the thyroid gland with malignant cells. The normalization of anti-Tg Ab titer could be a consequence of immunosuppressive effect of chemotherapy.

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T 109 CHEMOTHERAPY RELATED TOXICITY IN ELDERLY PATIENTS WITH NON HODGKIN LYMPHOMA (NHL)

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Treatment of choise for elderly pts with NHL has not been established. While some authors suggest non aggressive chemotherapy (CT),others contend that dose reduction ensues in response and survival disadvantage. Therefore 2 group of unselected pts with NHL sequentially treated were analyzed. Pts characteristics are the following: group A:21 pts(5 male,16 female);median age 68(r 60-90); histology according to Working formulation High+Intermediate grade 18 pts(85.7%),Low grade 3 pts;clinical stage I 5 pts,II 7,IV 9;first line CT: CHOP 11 pts,BACOP 3,CVP 5,ProMACE/MOPP(P/M) 2;group B 28 pts(17 male,11 female),median age 48(r20-59);histology: High+Int grade 24 pts(85.7%),Low grade 4pts (14.3%);clinical stage I 5 pts,II 7,IV 16;first line CT:CHOP 10 pts, BACOP 4,CVP 4,P/M 10. At a median follow up of 18 months responses to treatment are comparable: group A 12 CR(57%),3 PR,6 SD+P;group B 18CR (64%),5 PR,5 SD+P. The relative dose intensity for each drug was calculated according to Green et al 1980. No significant difference between groups was noted.

	Group A	Group B
EDX	.93	.92
VCR	.77	.80
ADR	.87	.96
PDN	.91	.89
BLM	.75	.93

Dose was reduced in 5 pts in group A and 3 in group B.
Toxicity was analyzed according WHO criteria. P/M treated pts were not considered because group were not balanced. In 2 pts of group B VCR was discontinued for neurotoxicity. In spite of a higher VCR related neurotoxicity and ADR related cardiotoxicity in group A,no treatment discontinuation was required. Treatments were delayed in 3 pts in both groups.

	GB 3-4	Hb 3	NV 2-3	Neur 1-2	Cardiac 3-4
Group A	26.3	5.3	15.7	42.1	15.7
Group B	16.6	5.5	27.7	27.7	5.5

In conclusion our data showing comparable results in term of response rate,relative dose intensity and toxicity, suggest the feasibility to deliver full dose polychemotherapy,even including doxorubicin, in elderly patients with NHL.

T 110 PROGNOSTIC SIGNIFICANCE OF SITE OF PRIMARY AND STAGING IN NON-HODGKIN LYMPHOMA OF BONE.

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From 1/1970 to 6/1985 32pts affected by stage I-II primary non-Hodgkin lymphoma of bone were observed.Before 1976 13pts had a clinical staging (CS) (clinical evaluation, chest X-ray, X-ray of the involved bone); after 1976 19pts had a pathological staging (PS) (bone scan lymphoangiogram,bone marrow biopsy,laparoscopy with liver biopsy).Stage I occurred in 24pts (CS:13pts;PS:11pts); stage II occurred in 8pts (PS).19pts received radiation therapy (RT) alone and 14pts received RT and adjuvant chemotherapy (CT).RT was administered with a Cobalt Unit to a target volume 5 cm larger than tumor volume:the average total dose was 44 Gy (40-50) with conventional fractionation.Adriamycin 50mg/m2,Vincristin 1,5mg/m2,Endoxan 600mg/m2 every 3wks for 6mts were employed as adjuvant regimen.Median follow-up was 46mts (18-180).Results analysed for site of primary,staging and therapy are as follows:

SITE OF PRIMARY	STAGING		THERAPY		N°pts/DF/+
	CS/DF/+	PS/DF/+	RT/DF/+	RT CT/DF/+	
PELVIS	6/1/5	4/ 3/-	5/-/5	5/ 4/-	10/ 4/5
JAW	4/3/-	6/ 5/-	10/8/-	------	10/ 8/-
EXPANDABLE BONE	2/1/1	6/ 4/-	3/1/1	5/ 4/-	8/ 5/1
SHOULDER	1/1/-	2/ 1/1	1/-/1	2/ 2/-	3/ 2/1
VERTEBRA	-----	1/ 1/-	-----	1/ 1/-	1/ 1/-
	13/6/6	19/14/1	19/9/7	13/11/-	32/20/7

20/32pts (62.5%) are disease free (DF);7/32pts (21.9%) are dead (+) for generalized disease and 5/32pts (15.6%) are alive with relapse (1 local and 4 distant).Our data remarks that an adequate staging affects significantly DF (73.7% in the PS group vs. 46.1% in the CS group). Furthermore 3/6 DF in the CS group had the primary in the jaw. This site of primary seems to have a good prognosis indipendent of the staging and after RT alone;only 2/10pts relapsed (one was a local relapse and the other one a distant) and now are again DF from 18,38mts respectively.We can not evaluate the prognostic significance of adjuvant CT and stage for the inference of understaging and site of primary in our data.

T 111 PROGNOSTIC SIGNIFICANCE OF THE DURATION OF FIRST DISEASE-FREE SURVIVAL IN NON-HODGKIN'S LYMPHOMA CHEMOTHERAPY.

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Prognostic significance of the duration of first disease-free survival (DFS) was studied in 443 previously untreated non-Hodgkin's lymphoma (NHL) patients. Chemotherapy was a primary therapy for all patients: 159 patients were treated with single-agent chemotherapy and 284 patients - with polychemotherapy. The ages ranged from 14 to 82 (median, 48). In majority of patients (68.8%) the primary sites of tumour growth were the lymph nodes, and in the others (31.2%) - extranodal sites. High-grade NHL was diagnosed in 282 patients, low-grade NHL was in 161 patients, and only in 40 patients the morphologic type was not verified. By the beginning of the chemotherapy only 49 patients had local (I and II)stages, whereas all the rest patients had generalized (III and IY)stages of the process.

It has been indicated that the length of the first complete DFS does not depend on the morphologic type of NHL (P>0.05). The duration of the first complete DFS precisely correlates with the lifetime of patients: the longer DFS (more than 2 months), for the longer time patients live, i.e., for 5 years 60.4% survived versus 6.8% with short DFS (less than 2 months) (P<0.0001). Partial DFS is fast completed in high-grade NHL and does not much influence on terms of life (P>0.05). On the contrary, in low-grade NHL the terms of the partial DFS appear to be of prognostic significance: 43.9% and 18.2% patients lived for 5 years, respectively (P<0.02).

Thus, high-grade NHL patients should be treated for the achievement of complete and most stable therapeutic results. Low-grade NHL patients who achieved the partial DFS need the adjuvant maintenance chemotherapy.

T 112 PRIMARY CHEMOTHERAPY FOR EARLY STAGES OF DIFFUSE HIGH GRADE LYMPHOMA: ANALYSIS OF PROGNOSTIC VARIABLES

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A retrospective analysis for pretreatment prognostic variables on complete response (CR) rate and disease-free survival (DFS) was performed on 67 adult patients (pts) affected by clinically localized (stage I-II) diffuse large cell (DLC) or undifferentiated (DU) lymphoma treated with combination chemotherapy. We did not include pts with primary gastro-intestinal disease. Patient features were as follows:

Tot pts	Age (yrs) range	med.	Sex M	F	Musshof Stage I	III	II2	Histology IBL	oth.	Bulky > 6cm	B Sympt	Primary Site Abd	Med	oth.
67	18-77	52	41	26	19	7	41	40	27	12	10	14	7	46

Complete response (CR) was achieved by 75% of all pts and 64% of CRs are projected disease-free at 14 years (median follow-up 50 months). We analyzed the following features: histology (immunoblastic vs others), B-symptoms (present vs absent), Musshof stage (I-III vs II2), Ann Arbor stage (I vs II), tumor bulkiness (> 6 cm vs < 7 cm), primary site (abdominal vs mediastinal vs others), type of combination chemotherapy (ProVeCiP vs F-MACHOP or m-BACOD). A lower CR rate was registered in pts with Musshof stage II2 (63%), or with bulky disease (33%), or with B-symptoms (40%). On the basis of the presence of one or more of these bad prognostic features we classified as good prognosis (GP) 22 patients and poor prognosis (PP) the remaining 45 pts. GP had a CR rate of 90% and a 76% long term DFS as opposed to a CR rate of 67% and a 56% long term DFS for PP pts. The proportion of PP pts was 54% among those treated with ProVeCiP and 81% among pts treated with the more intensive regimens. The type of combination chemotherapy did significantly influence CR rate and duration only in PP pts, with better results achieved with adriamycin containing regimens (F-MACHOP or m-BACOD); on the other hand the results of less intensive chemotherapy (ProVeCiP) did not result in a significantly lower CR rate and % DFS for pts with GP disease.

Type of Chemotherapy	Total PP No.pts	% CR	% DFS	Total GP No.pts	% CR	% DFS
ProVeCiP	19	58	38	16	81	71
F-MACHOP/m-BACOD	26	73	78	6	100	100

Supported by a grant CNR, PFO, Contract no. 86.00466.44 and MPI 40%.