Recent developments have clearly shown that bone marrow transplantation (BMT) has a place in the treatment of lymphoproliferative disorders. We report our experience in the last 3 years. 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 (62 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 vincristine, cyclophosphamide and methotrexate. She is 6 months past BMT in complete remission with persisting panhypopituitarism, free of infections but dependent on occasional blood transfusions. The second patient, a 29 year old man, had 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 lymphocytic leukemia (CLL) diagnosed 2 years before transplantation. Before BMT the marrow was still heavily 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 can 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 the time of transplantation and the optimal conditioning regimen needs yet to be defined.

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 years 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 to 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 1 (25%) survived 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 = 0.671) although these patients with CNS involvement at ABMT have poor survival.
ABSTRACTS - Third International Conference on Malignant Lymphoma, Lugano

T 157 AUTOTOLOGOUS BONE MARROW TRANSPLANTATION IN MALIGNANT LYMPHOMA:
High dose combination chemotherapy versus total body irradiation. C. Karaman, V. Ratanachartvorn, W. Sharma, L. Lewko, A. Al-Katib, V. Negendank. Division of Hematology-Oncology, Wayne State University School of Medicine, Detroit, Michigan.

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/M² IV on day 1, Cytosine arabinoside 100 mg/M² IV every 12 hours on day 2-5, Cyclophosphamide 1.5 g/M² IV on day 2-5 and 6-THDP 1.0 g/M² IV every 12 hours on day 2-5. Regimen B consisted of Cyclophosphamide 60 mg/kg/d IV on day 1-6; rest on day 7-14 followed by total body irradiation 230 rad twice a day on day 1, 2, 3.

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 NHL, 4 DML, 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 a 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 NHL, 6 DML, 1 LCL, 1 L.C cell). There were six complete remission (54.5%), 7 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, 4, 6 and 9 months.

Even though the number of patients is small, our study suggests that high dose combination chemotherapy (RTCT) 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.


Lymphoplasmocellular 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 immunohistochemistry, the plasma cell populations comprised mainly monotypic cells with cytoplasmic light chain and either $\alpha$, $\gamma$, or $\epsilon$ heavy chain expression. These monotypic plasma cell populations did not exhibit features of plasmacytoma or myeloma. In one other patient plasmacellular 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 infection. 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-positive cells, fields with IgM-positive cells and areas with mixed populations.

Southern-blotting analysis using $\lambda$-gene segment specific probes did not indicate the presence of clonally-restricted B-lymphocytes.

We conclude that lymphoplasmocellular hyperplasia after ABMT is the result of expansion of a restricted number of B-lymphocyte clones.
ABSTRACTS - Third International Conference on Malignant Lymphoma, Lugano

T 145 MITOXANTRONE AND HIGH-DOSE CYTARABINE (HAOC) FOR THE TREATMENT OF REFRACTORY MALIGNANT LYMPHOMA. A.D.Ho, B.Döken, L. Musch, M. Hufner, W. Kunstein, University Hospital of Heidelberg and Bonn, F.R. Germany

Both mitoxantrone (Novantrone) and high-dose cytarabine (Ara-C) have been shown in monotherapy trials to be effective in pretreated non-Hodgkin's 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 (ex. Chlorambucil + Prednisone, COP, LNHV=16) and in patients with high-grade NHL, resistance or relapse after at least 2 different chemotherapy regimens (ex. CDP or COP-BLAM, LNHV=16 or ProMACE-MOPP). The regimen consists of high-dose Ara-C 3g/m^2/12h 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/m^2/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 0-3), 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 x 10^9/l) after therapy was 7 days and that with severe thrombocytopenia (<20 x 10^9/l) 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.


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 98%.

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

T 147 MITOXANTRONE, VINDESINE AND DEXMETHASONE IN ADVANCED NON-HODGKIN'S LYMPHOMA: A PILOT STUDY. T.M. Loeffler, F.W. Weber, T.U. Haussmann, Medical Center Dortmund, Department of Internal Medicine, 4600 Dortmund, West-Germany

15 patients (pts) with advanced non-Hodgkin's NHL (NHL) were treated with mitoxantrone 12 mg/m^2 day 1 as short-time infusion, vindesine 1.2 mg/m^2 day 1 - 5 as long-time infusion and dexamethasone 30 mg/m^2 day 1 - 5 as short-time infusion. Therapy was recycled on day 28.


Median age was 56 years.


Pts with relapsed high grade NHL: CR 3/8, PR 4/8, NC 1/8. All responding pts are still in remission.


Nausea and vomiting was not observed.

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

T 148 5-EDR ANTRACYCLINE, (2'RI)-4'-TERT-BUTYLPHENYL ADRIAMYCIN (THP-ADM) IN MALIGNANT LYMPHOMAS. K. Nishina, Medical Oncology Division, Chiba Cancer Center, Chiba 260, Japan

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 alopecia dose limiting toxicity. The marrow suppression was more severe than ADM. The NTD was considered to be 75mg/m^2. The phase II clinical studies were conducted with administration schedules 75mg/m^2 every 3 weeks. 1/14, 2/14, 3/14, 5/14, 3/14, 4/14, 3/14 divided in 3-5 days 1/14, 2/14, 3/14 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 lymphomas with two above mentioned schedules were carried out. Sixty-eight NHL and 84 cases were studied with response rate of 16.2, 50.0% CR and 46.8, 75.0% CR & PR respectively. There was no statistical difference between two schedules. Another study for virgin cases, 5 CR and 1 PR in 4 NHL 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. The cases had received between 900 and 1,000mg/m^2 as a cumulative dose and had revealed no signs or symptoms of cardiac failure. Above these doses, two cases had received 1,500mg/m^2 and 1,500mg/m^2 as the highest total dose of these trials. The former patient had not revealed any signs or symptoms of cardiac toxicity, however, the latter patient had 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/m^2 in these administration schedule and the total dose between 900mg/m^2 and 1,000mg/m^2 is the turning point of THP-ADM cardiotoxicity. Further, the cardiotoxicity incidence increases dramatically above a total dose of 1,400mg/m^2. Nevertheless, this fact indicated usefulness 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 MALIGANCY IN CHILDREN
C.R. PINKERTON, J.M. MCBRIDE, J. MACCOY
Dept Haematology and Oncology, Hospital for Sick Children Great Ormond Street, London.

A short duration, high dose intensity, 4 drug regimen devised for the treatment of high risk B cell NHL (multicyclosin Stage 3, Stage 4) and B ALL. Fractionated cyclophosphamide (1.25g/m2), Adriamycin (60mg/m2), was alternated with cytarbine arabinoside (120mg/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 folic 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 Ara-C, cyclophosphamide, TBI and bone marrow transplant but all others received cycles of chemotherapy in 4-7 months.

3 had relapsed after standard therapy and of these 1 (CNS relapse off treatment) remains in remission.

6/7 Stage 3 cases with marrow disease are disease free 6-29 months off treatment. 1/3 with advanced Stage 3 disease is alive. None of the Stage 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 151
PURGING OF A PERIPHERAL BLOOD DERIVED STEM CELL AUTO-GRRAFT
R. H. KELLY, S. KIESEK, K. HENDRICK, C. KIRKLAND, B. DILLON, W. HUNSTEIN, Director of Internal Medicine, University of Heidelberg, F.R.G. and German Cancer Research Center, Heidelberg, F.R.G.

The autologous bone marrow transplantation (ABMT) 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, Kirkland 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 therapeutic strategy in a patient suffering from a non-Hodgkin’s lymphoma (centrocytic-anaplastic in accordance 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 assessed morphologically by bone marrow biopsy aspiration and indirect immunofluorescence was around 30%. 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 10^6 cells/ml. The cocktails 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 (Peli-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 1440 rad and chemotherapy with 200 mg/kg of cyclophosphamide. A total of 3.8 x 10^6 cells/kg or 2 x 10^7 mononuclear cells/kg were transplanted. The total number of GFP-CM was 1.5 x 10^7/kg. 14 days post transplantation an engraftment could be demonstrated by bone marrow aspiration. On day 33 no B-cells could be detected by immunoenzymatic technique (APAAP). Now, on day 45 the peripheral white blood 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 lymphohematopoietic system. In conclusion the use of peripheral blood derived bone 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.

T 150
HIGH-DOSE CHEMOTHERAPY FOLLOWED BY AUTLOGOUS BONE MARROW RESCUE IN MALIGNANT HISTIOCYTIC TUMORS
C. Meloni, G. Sanoretti, A. De Fabritiis, F. Giannieris, V. Guglielmi, G. Pulsoni, A. Molleti, M. Mandelli, F., Institute of Hematology, University ”La Sapienza” Rome, Italy.

Patients with neoplasms arising from true histiocytes treated with conventional chemotherapy may 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 years) (2 M, 2 F) and 1 in CR and 4 in PR. Of the 4 patients, 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 (Cyclophosphamide, Doxorubicin, Vinristine, Dexamethasone, Oncovin, Cytarabine) followed by ABMT. One patient was lost to follow-up after another autologous bone marrow transplantation.

The results of the 4 patients treated with autologous bone marrow transplantation are listed below. By definition none of the patients have relapsed in the tumor free period after autologous bone marrow transplantation.

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T 152
HIGH DOSE CHEMOTHERAPY AND AUTLOGOUS BONE MARROW REINFUSION IN PATIENTS WITH REFRACTORY MALIGNANT LYMPHOMAS
S. F. Williams, J. D. Bitran, H. M. Golomb, J. E. Ullmann, R. L., Section of Hematology/Oncology, University of Chicago and Michael Reese Medical Centers, Chicago, IL 60637 USA.

These studies were undertaken to determine the toxicity and efficacy of high dose chemotherapy in patients with disseminated malignant lymphomas. Five heavily pre-treated patients with non-Hodgkin’s lymphomas were treated in phase 1/11 studies of multi-alkylator therapy. One patient received high dose cyclophosphamide (CPA) and thiotepa (TT) (biallykylator) and four patients received high dose CPA, TT and oral melphalan (MEL) (triallykylator). Two of the five patients obtained a long-term, 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 biallykylator, one triallykylator. Remission duration was 14, 37 weeks respectively. Both patients progressed in areas of previous disease. One patient died suddenly on day 7 of probable acute pericarditis/cardio-myopathy. The two responders showed evidence of engraftment but one patient had prolonged thrombocytopenia. Major toxicities were mucositis and infections. Three patients, all failed MOPP/AVD regimens, with refractory Hodgkin’s disease, were treated with high dose CPA, carmustine (BONUS) (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 was 24 and 28 weeks off the CR. 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 treatment for malignant lymphomas. A transplant protocol with refractory lymphomas, both Hodgkin’s and non-Hodgkin’s. Further clinical investigation in this area is warranted.
T 137 ETOPSIDES IN COMBINATION CHEMOTHERAPY FOR DIFFUSE LARGE CELL Lymphoma, P Jacobs, M.S King, D. M Dent, Lymphoma Clinic, University of Cape Town and the Groote Schuur Hospital, Observatory 7925, Cape Town, South Africa.

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 of over 80% in the RICOCHET and 50% of the patients. However disease-free survival was superior with the latter combinations and to determine whether this was attributable to improved response to population or drug interactions was prospectively undertook in BACOD in a pilot study. 39 patients with clinical stage III and IV diffuse large cell lymphoma (median 40 years, 5 consecutive days) with doxorubicin (40 mg/m2 on day 1) followed by 9 day rest period (group 1: n=17), the same schedule of etoposide but with cyclophosphamide (20 mg/m2 on day 1) followed by 9 day rest period (group 2: n=8) or etoposide (3: n=14). In a) 3 groups responding patients received 6 cycles of etoposide. The complete response rates were respectively 26%, 25% and 20% with further good partial remissions in 41%, 29% 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 52% of the patients, to extensive gastrointestinal 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 may have some anti-tumour activity. The response rates are inferior to those previously reported and reflect the poor performance status of the patients. The unique challenge of these populations is to predict the remission and to develop future combinations and to further the role of etoposide in these tumours.

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

T 138 TREATMENT OF REFRACTORY OR RECURRENT MALIGNANT Lymphomas WITH A COMBINATION OF ETOPOSIDE (VP-16), IFOSFAMIDE, METHOTREXATE AND BLEOMYCIN (VIBM) M.R. Nowroussian, B. Schoetensack, C. Andersen, A. Niendorf, R. Feller, M. Eichenbronn, Schmidt, Department of Internal Medicine (Cancer Research), University of Essen, 4300 Essen, P.R.G.

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 VIBM (40 mg/m2/day x 5 days, 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, VIBM 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. Histologi- cal types of the tumors (Ricci classification) were: Lymphoblastic 3, immunoblastic 2, immunoblastic-centroblastic 1, centroblastic 6, undifferentiated large cell 4, plasmablastic 2, centrocytic 2, centrocytic-centroblastic 3, Lymphoplasmacytoid I and Hodgkin's disease 11. An overall response rate of 83% was achieved including 34% complete responses, 43% partial responses and 8% minor responses. The median relapse-free interval was 6 months in pts with partial responses 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 has not yet been reached in pts with complete responses. The probability of survival at 22 months for pts with partial remissions or minor responses was 22% (trial not yet complete).

On the basis of these results, VIBM combination appears to be effective in pts with refractory or relapsed lymphomas, particularly for the 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 (IEBP): SALVAGE COMBINATION CHEMOTHERAPY IN CHOP-RESISTANT NON-HODGKIN-LYMPHOMAS, K. Breuer, Division of Hematology and Oncology, Augusta-Franken-Anstalt, 4610 Bochum, W.-Germany.

Since the CHOP regimen has been one of the most frequently used initial remission induction combination chemotherapy in intermediate and high-stage malignant non-Hodgkin’s lymphoma (NHL), the majority of NHL with CHOP relapse or fail to attain complete remission (CR) on CHOP chemotherapy remains a therapeutic problem. Therefore, 10 cases of 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 (IEBP regimen) to investigate this 4-drug chemotherapy combination as a potential 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 1 pt) have been treated with the IEBP regimen:

- 40 mg ifosfamide/kg iv. d 1, 5 with meams prophylaxis,
- 15 mg bleomycin im. d 1, 8, 15 and 21,
- 120 mg etoposide d 1, 3 and 5,
- 200 mg procarbazine po. d 1, 14,
- repeated d 28.

After 1-3 (median 2) IEBP chemotherapy courses in 5 pts a CR and in 7 pts a PR has been achieved with median remission duration of 10 months and 3 months respectively; in the remaining 3 pts no change was observed.

Because of the IEBP regimens could induce CR and PR in the majority of these pts, it proved the potential of non-cross-resistance to CHOP. Therefore, the IEBP regimen represents not only an effective salvage chemotherapy for resistant NHL, but also in contribute a significant improvement of the initial chemotherapy of high-grade NHL by rapidly alternating to CHOP and IEBP regimen as two non-cross-resistant chemotherapy combinations.


Fortysix previously untreated patients with high malignant Non-Hodgkin-Lymphomas stage I-II received cyclophospha- mid 750 mg/m2 iv day 1, vincristine 2 mg iv. day 1, prednisolone 100 mg po day 1-5 and doxorubicin 100 mg iv day 3-5 (CHOP-IEBP) after courses of this regimen an involved field irradiation with a total dose of 25 Gy was employed and was followed by an additional courses of IEBP (14 patients) or an additional courses of IEBP and ifosfamide (26 patients). The CR response rate was 91% with 82 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 (49%), neutropenia (76%), and leukopenia (61%). All patients this result is seen. The results of this study demonstrate that this combined modality treatment produces high complete re- mission rates and a high radiation response rate of majority of these patients achieves long term complete remission of these diseases.
New salvage therapy with methyVL-GAG, H.D. Aron-C, M.Akwa and Iosofand (MAM) for poor prognosis malignant lymphoma

Relapsed or refractory malignant lymphomas have poor prognosis. This group of patients had already received the best conventional treatment including anthracyclines, etoposide and radiotherapy. Now, new salvage therapy is needed to remit disease and select patients for myeloablative treatment with high dose chemotherapy followed by autologous bone marrow transplantation. MethyVL-gag, Ara-C, M.Akwa and Iosofand have shown antitumor activity as single drugs in malignant lymphomas with no cross resistance to drugs used in conventional treatment. MAM protocol was administered as follows: MethyVL-gag 400 mg/m^2 on days 1 and 4 and Ara-C 2 g/m^2 every 2 nd or 3rd days, 1, 2, 3 i.Akwa 80 mg/m^2 or 120 mg/m^2, days 1, 2, 3 Iosofand 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 years (13-58), 8 male, 4 female. Diagnosis were: Hodgkin disease (HD); 3: non-Hodgkin lymphomas (NHL), Diffuse large cell, 6; lymphoblastic lymphomas (LL), Stage at diagnosis was 1: 2 bulky stage II, 3 stage III and 7 stage IV.

Patients were heavily treated previously with 9 different drugs as a median (4-10) and 3 patients received radiotherapy. Median time between diagnosis and MAM was 13 months (4-84) and clinical status at the moment of MAM protocol was 1: 6 refractory disease, 2 first relapse, 2 second relapse.

Hematological toxicity was universal with 11 days (7-14) median granulopenia (0-10^9/L) and 5.5 days (2-16) median thromboctopenia (0-10^7/L). Infectious complications were characterised by fever of unknown origin in 8 patients, 2 pneumonias and 1 candida endocarditis.

Non-hematological toxicity was mainly nausea and vomiting (1), mucositis (9), abnormal liver biochemistry (3), hemoptysis (1) and transitory Iosofand 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: MAM is a pilot study showing an acceptable tolerance in this group of heavily pretreated patients. High anti-tumor response has been observed in relapsed refractory patients with malignant lymphoma. MAM protocol should be introduced early for this type of poor prognosis patients.


22 patients (pts) with ML have been treated with 2 protocols. Protocol 1, 6 pts: MXT 14 mg/m^2, vincristine 1.8 mg/m^2, etoposide 300 mg/m^2 all day 1. Protocol 2, 16 pts: MXT 12 mg/m^2 d1. melphalan 100 mg/m^2 d1 & 2, melphalan 100 mg/m^2 d3. prednisolone 40 mg/m^2 d1 to d3, metotrexate 200 mg/m^2 d8. In all patients 1 pt in situ inceptible, 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.

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11 pts responded (55%, CR 30%, PR 25%). There was 3 PD with protocol 1 (50%), and 3 FD in protocol 2 (21%). All CR was observed with protocol 2. 2 pts were not evaluable for toxicity. Major toxicity was hematological in 10 pts grade 2 or 3 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. Leukenia 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 2 is less toxic but far less active than protocol 1. Updated results with duration of the response will be presented.


51 patients (median age 53 years) with NHL of high or intermediate grade or lymphoma received a new combination consisting of VP-16 (100 mg/m^2), Ifosfamid (1 g) Mitoxantrone (3 mg/m^2) and Bleomycin (50 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 chemotherapy containing, regimes. 47 patients were evaluable for response, 4 early deaths, were excluded. Objective response rate in pretreated patients was 48% (5 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 HBC were below 1000/mm^3. 29 septic episodes required hospitalization of the patients. Thromboctopenia 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 seemed 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 chemotherapy containing regimes, so that it seems useful in anthracycline pretreated patients. Whether an alternating administration (CTP-VIM) can improve results in first line therapy should be investigated in future.

CLINICAL EVALUATION OF TENIPRIMUM IN ADVANCED MALIGNANT LYMPHOMAS. Y. Sun, P.Y. Peng, J.W. Wang, J.C. Zhou, G.L. Wang, S.S.Dong. Cancer Institute & Hospital, Chinese Academy of Medical Sciences, P.O. Box 2259, Beijing, China.

A prospective study was carried out using CHOP regimen (CTX 600 mg/m^2, V.A. 1.5 g/m^2, d1; cyclophosphamide 30 mg/m^2, V.A. 1.5 g/m^2, d1, 15 g/m^2, V.A. 1.5 g/m^2, d1, every 3 weeks, evaluate after 2 cycles) and prednisone, azathioprine, etc. In total, 70 patients fulfilled entry criteria, 40 were evaluable for response. 50% patients achieved CR, 13% PR, 2% complete remission, 6% stable disease, 10% progression, 22% SD. 14 patients died of disease progression. Most patients tolerated this regimen well, and the duration of remission was longer than that in previous regimens used in this institute. It is concluded that CHOP regimen is an effective regimen for induction of remission of malignant lymphomas.
ABSTRACTS - Third International Conference on Malignant Lymphoma, Lugano

T 129 ARE THE NEW LYMPHOMA REGIMENS SUPERIOR TO CHOP? 
Stephen E. Jones, M.D., Charles A. Sammons Cancer Center, Baylor University Medical Center, Dallas, Texas 75246 USA

The CHOP regimen or one of its variants is one of the most widely used treatments for high-grade lymphomas. CHOP produces complete response (CR) rates ranging from 60% to 87% in reported series, with the higher response rates generally being reported from small single institution studies. Over the last number of years a number of 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-BALAM (73% to 86%), M- or e-BACOD (73%-75%), ProMACe-NOPP (72%-74%), ProMACe-CycloBO (80%) and MACH-1 (86%). 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 60% CR rate and 50% 5-year survival in patients less than age 55 with Stage III and IV large cell lymphoma, compared to significantly worse results in older patients. Similarly some 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-BOPP 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.


Combination chemotherapy with ifosfamide and VP-16 has shown a salvage effect in non-Hodgkin's lymphoma and in Hodgkin's lymphoma. We have tested PIME combination therapy on 12 patients with refractory lymphoma. Two patients with non-Hodgkin's lymphoma and three with Hodgkin's lymphoma were either resistant 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 AVH therapy.

PIME therapy consisted of Procarbazine 1000mg/m²/day p.o. on days 1 through 7, ifosfamide 1200mg/m²/day i.v. on days 1 through 3, Methotrexate 150mg/m²/day i.v. on days 3 and 7, Rifampicin 1200mg/day orally on days 1 through 4, and continuous infusion of VP-16 g/m² qday 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 nodal 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 12(33%). Retractory patients achieving CR were 4 out of 12(33%). Response according to the histology were, L1:1/2, M2:3/3, B1:6/7, EM1:1/2, EM2:2/2, PL1/1, FM1/1, HD:3/3. Median duration of survival after initiation of PIME therapy was 15 months. Median duration of complete remission was 6 months.

The toxicities of this regimen have been myelosuppression, nausea, vomiting, and hair loss. This combination chemotherapy has major activity in patients with lymphoma which was refractory to or relapsed from the other combination chemotherapy containing Adriamycin. This regimen may be not cross-resistant with CHOP or AVH chemotherapy regimens 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. Massimo Paletti G. Fiandrino P.L. Ferro, L. Curzi S. Institute of Haematology "L. e A. Scaglioni" - University of Bologna, Italy.

Two hundred forty seven patients with unfavourable histology non-Hodgkin's lymphomas observed from 1970 to 1985 were retrospectively analysed. Over the study period three therapeutic programs have been experienced: 1) conventional treatment by the use of combination chemotherapy CHOP or BACOP, 2) intensive induction therapy followed by maintenance therapy as in L-lymphoma, and were recently 3) aggressive therapy which included high dose chemotherapy and 180 followed by autologous bone marrow transplantation as haematologic 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, 92 the intensive and 23 the aggressive treatment. Remission rate was 45.8%, 53.2% and 85.3% respectively for the probability of achieving CR. The probability of disease-free survival at 5 years was 30% in the group treated with conventional, 44% in intensive and 60% in aggressive treatment (P<0.005). The enhancement of survival and disease-free survival was particularly evident in patients with more aggressive histologies. In patients with bulky disease and in patients treated in relapse, lymphoblastic, immunoblastic and true histiocytic lymphomas appear benefited more than other histologies by aggressive therapy with 50% probability of survival at 5 years with respect 70% in CR with intensive and 20% with conventional therapy (P<0.005). The probability of survival at 5 years of patients with bulky disease was 58%, 20% and 10% respectively (P<0.005). Finally, patients treated in relapse had 80% probability of survival at 5 years by aggressive intensive and conventional therapy, respectively (P<0.005). In conclusion, our study demonstrates that intensification of therapy produced a general improvement of survival and disease-free survival, however it is not indicated in increasing the cure rate of patients with bulky 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.


The present analysis involves a randomized study in which 394 patients with histologically proven non-Hodgkin's lymphomas were enrolled as part of a randomized trial comparing cyclophosphamide, Adriamycin, vincristine and prednisone (CHOP) versus cyclophosphamide, mitoxantrone, vincristine and prednisone (CNP). Two hundred forty patients entered stage II and stage III and IV diffuse NHL classified according to the Working Formulation entered the study: 20 patients were randomized for CHOP and 15 for CNP. The mean age was significantly lower in the CHOP group (67 vs 77 years; p < 0.02). Twenty four patients belonged to the intermediate-grade malignancy and 11 to the high-grade malignancy. Advanced stages accounted for 70% and 60% of total CHOP and CNP 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 CNP, respectively (P = 0.047); after 6 cycles of chemotherapy the percentage of patients in complete remission was 71% and 65%, for the CHOP and CNP regimen, respectively. The mean number of granulocytes (107/mm3) was significantly lower (P = 0.058) in CHOP patients, 60% compared to 80% of CNP patients. Gastrointestinal toxicity was observed in 90% of CHOP and 73% of CNP patients. Cardiac toxicity, evaluated by echocardiography, was more frequent in CHOP group (P < 0.039). Cardiac dysrhythmias were observed in 67% of CHOP patients and in 38% of CNP patients (P = 0.0477). Cardiac toxicity manifestations were more severe in CHOP group than in CNP patients (P < 0.039). In conclusion, the efficacy of CHOP and CNP chemotherapy in diffuse NHL was equivalent in term of CR rate; a lower toxicity profile was followed using CNP regimen. No episodes of heart failure or therapy-related deaths were registered. The clinical relevance of left ventricular ejection fraction reduction, absence of dysrhythmias as cardiac toxicity manifestation remains to be elucidated.
T 133

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


Non-Hodgkin’s Lymphomas relapsing after intensive chemotherapy regimens as B-CHOP, DACOP or M-CHOP 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, L-asparaginase 1200U/m² on Days 2-7 and 22-27, 6-Thioguanine 1000mg/m² on Days 2-7 and 22-27, L-Asparaginase 1000 units on Days 12, 14, 16, 18, 20, 22, 24, 26, 28, 30 of the first cycle only, Methotrexate 500mg/m² over 6 hours on Days 6 and 20, Leucovorin 15mg qd im Days 9 and 29 and po Days 10,11,12,13,14,15 and 31. Treatment was repeated every 42 Days.

Eight patients entered the protocol so far. All were in relapse 2-9 months after being in Complete Remission with B-CHOP (2 patients), DACOP (1 patient), M-CHOPCO (2 patients), cisPlatin-Vindesine-Etoposide-Methotrexate-Leucovorin (2 patients), cisPlatin-Hexamethylmelamine-VN 26 (1 patient). All patients had stage IV disease and bone marrow involvement in 6, Nadalayar’s ring in 4, Liver in 3, Kidney in 1 and Stomach in 1. Two patients have had life threatening septicaemia while in myelosuppression with previous chemotherapy regimens. Patients received 1 to 4 cycles of treatment and 3 patients are currently alive more than 6 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 leucopenia count nadirs were between 800 and 2000 no sepsisemia related deaths occurred. 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 prolonging cures if trialed earlier in the course of the disease or if it is embodied in the initial treatment schedules.

T 134

RESULTS OF T.P.L. 84 (TOURS-POTIERS-LIMOGES) PROTOCOL IN STAGE III-IV UNRESECTABLE NON-HODGKIN’S LYMPHOMAS (NHL).


Intensive chemotherapy has proved effectiveness in terms of long term complete remission in stage III-IV non-Hodgkin’s lymphomas. The TOURS-POTIERS-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 inoperable NHL. At presentation 18 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 CEP-Bleo: Cyclophosphamide (C) 1.2 g/m², Doxorubicin (A) 75 mg/m², Vindesine (E) 3 mg/m² and Bleomycin (Bleo) 10 mg/m² on day 1; Vindesine 3 mg/m² and Bleomycin 10 mg/m² on day 5; and Prednisolone (P) 50 mg/m²/day, day 1-10. 2) 3 courses of VAP with VM 26 (V) 80 mg/m² on day 1, Cytoxan Arabinoside (A) 200 mg/m²/day on day 1-5, L Asperaginase (A) 1000 UI/kg/day on day 6-10 and Methotrexate (M) 1.2 g/m² on day 21; 3) 3 more courses of CEP-Bleo. Regimen B was given in 26 patients over 60 years of age or less than 60 years of age with bad performance status (50-75%). It consisted of ten courses of CAVP-Bleo: Cyclophosphamide (C) 500 mg/m², Doxorubicin (A) 50 mg/m², Vindesine (V) 3 mg/m² and Bleomycin (Bleo) 10 mg/m² on day 1; Vindesine 3 mg/m² and Bleomycin 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 CN/26 (92 %), with a median of follow up which exceeds 12 months. 24/26 CR have relapsed. Actually 20/23 patients (84%) 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 NC/27 (74 %), 7 relapses which occurred earlier than with regimen A. 12 patients (44%) are alive without disease.

T 135

COMBINED ADRIAMYCIN, VINCristine, Prednisolone and Etoposide (ADVP) IN THE TREATMENT OF DIFFUSE LARGE CELL NON-HODGKIN’S LYMPHOMA.


We have treated 51 patients with diffuse non-Hodgkin’s lymphoma of centroblastic/centrocytic, large cell/centroblastic or large cell (unspecified) histiologic type at anatomical site II or worse with a combination of intra-venous Adriamycin (30 mg/m²) and vincristine (1mg) on days 1 and 15 and of oral prednisolone (40 mg/day) and etoposide (100 mg/m²/day) 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 years. Comparing a single unrelated death in remission actuarial duration of remission in 35 patients is 90% at 3 years. All relapses are at under 1 year.

In the "intermediate grade" (centroblastic/centrocytic) group (n = 22) actuarial survival is 97% at 3 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 99% 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 elderly and bone-marrow infiltration and in disease. Patient acceptance and tolerance are very high.

T 136

SEXUAL DISTRIBUTION REGARDING CERVICAL ETIOLOGY FOR INTERMEDIATE AND HIGH GRADE NON-HODGKIN’S LYMOPHIA.


Thirty patients with intermediate and high grade Non-Hodgkin’s lymphomas received 4 x 42 days 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 histopathological 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 regimen 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). From the Hospital Clinic of Lugo, Spain

A total of 51 previously untreated pts received MACOP-B for the treatment of ML. Median age was 50 yrs (range 16-70). All pts had performance status greater than 50 (Karnofsky scale). Toxicity was high: 53% of pts presented granulocytopenia count of less than 500/mm^3 and 11 developed anemia. 29% of them requiring blood transfusions: infection was detected in 32 pts (23% minor and 9 major); severe mucositis was observed in 49%: nausea and vomiting of moderate to severe intensity was reported in 62% of pts. Fever due to Blemming and mucosal ulceration and toxicities of mild intensity were observed in 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 sepsis and were associated with severe mucositis (100%) and severe leucopenia (30%) autopathy was performed in these seven pts confirming sepsis. No pneumocystis carinii was evidenced. This highly effective 12 ws chemotherapy combination proved to be extremely toxic. Most of the toxicity was related to the use of moderate dose of Methotrexate (MTX) in spite of adequate rescue. New programs using lower MTX dose or its replacement should be evaluated.


T 122

PHASE III COMPARATIVE TREATMENT TRIAL OF NON-HODGKIN'S LYMPHOMA (NHL) ACCORDING TO KIEL CLASSIFICATION: AN OPEN AND RANDOMIZED STUDY IN URBAN AND RURAL AREAS GROUNDED ON COMPARISON OF KIEL AND ROME CLASSIFICATION

From August 1984 to July 1986 70 previously untreated patients with NHL according to Kiel classification entered a phase III comparative trial of Adriamycin (ADR), Vinblastine (VBL), Cyclophosphamide (CTX) and Prednisone (PRED). The study included patients with one or more than one large mass as per CT scan and with normal cardiac function at diagnosis. They were randomly assigned either to ADR+CTX+VBL+PRED or to ADR+CTX+PRED. Patients responding to treatment received 1 cycles of chemotherapy and were then re-staged. 49 patients (70%) were evaluable. 21 (42%) females; median age was 59 yrs (range 8%); 54 patients (70%) had no clinical symptoms at diagnosis: 25 patients (55%) had intermediate grade NHL, 33 patients (48%) had high grade NHL. 15 patients (25%) had bulky disease. 35 patients were randomized with ADR and 35 with VBL. At the time of this writing 8 patients are evaluable. 28 treated with ADR, 30 with VBL. CR was achieved in 19 over 20 patients (65%). CR was achieved in 7 (50%) treated with ADR, 7 patients relapsed (17.5%) (4 ADR and 3 VBL) and 11 patients (50%) failed to respond. 3 patients (3%) (2 ADR and 1 VBL) died due to progression of the disease. Side effects included nausea and vomiting, alopecia, peripheral neuropathy which were more severe in patients treated with ADR. Haematological toxicity, including neutropenia and thrombocytopenia, required temporary interruption of treatment. Cardiac toxicity was recorded in 6 patients (2 ADR and 4 VBL) and 2 patients had to interrupt definitively the treatment. Haematological toxicity indicates that Adriamycin is highly effective in inducing CR in unfavourable histology NHL, with a low incidence of clinical toxicity, especially cardiac.

T 123


MACOP-B is an innovative chemotherapeutic 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 pts with grade I (2 pts with grade I, 1 pt with grade II), granulocytopenia (5 pts with WBC < 1000/mm^3), anemia (6 pts with Hb < 10 g/dl) and peripheral neuropathy (2 pts with grade II, 2 pts with grade I). One pt developed a herpes zoster infection requiring therapy 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+70%). 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 7 months of follow-up. Two of the 16 pts who achieved CR while in follow-up after completion of MACOP-B therapy. None of the pts with osteosclerotic infiltrate (grade D or E histology) achieved CR, for the persistence of bone marrow involvement, in absence of clinical significative localizations of the disease. These pts received four additional courses of chemotherapy without any clinical improvement. In four of the seven pts in CR, a disease progression occurred at 1 months after completion of MACOP-B. Of the nine previously treated pts (stage III and IV) who achieved remission MACOP-B therapy at the second 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 histology but not for those with D or E subtypes, in particular when bone marrow involvement was present. Poor response to MACOP-B was employed as salvage regimen.

Supported by a grant of the Italian National Research Council, Special Project "Oncology" contract 86.4094.66

T 124

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

Mohamed E. Mamou, M.D., Nazif Byad-Ji-Hakmi, M.D., Heba El-Zawahry, M.D., Zikri Khalid, M.D., Musalufa El-Sirafi M.D., Ahmad Al Khedri, M.D., Hussein Khalid, M.D., and Fayda A. Mohamed, M.D.

CAIRO, EGYPT

Eighty-seven patients with non-Hodgkin's lymphoma (NHL) were consecutively treated with combination chemotherapy regimens (TOP) (52 patients) and (CHOP + weekly VCR) regimen (35 patients). Patients were 60 males and 27 females with no prior therapy (chemotherapy, 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 staging I patients were stage I, 46 stage III and 34 stage IV. All patients who received TOP (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 (PR) in 13 patients and no response in 9 patients, an over all response of 82.7%. The overall survival of the whole group was 76% with median survival 13 months. Nine patients relapsed after a median of 13 months. The survival rate among those achieving CR was 90% and among PR it was 79%. The overall survival rate was 89% among the CR patients.

Group B: Complete response (CR) was achieved in 17 patients (PR) 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 of 21 months. Nine patients relapsed after a median of 13 months. The survival rate among those achieving CR was 90% and among PR it was 79%. The overall survival rate was 89% among the CR patients.
T 125 EVALUATION OF B-COPH REGIMEN IN NON-HODGKIN Lymphomas (NHL) INTERMEDIATE AND HIGH-GRADE MALIGNANCY. G. Sallavalle, L. Tedeschi, E. Arnoldi, P. Fraschini, R. Labianca, G. Beretta, G. Lupini - Medical Oncology Dept. S. Carlo Borrromeo Hospital, Milan (2013 Italy). In NHL with intermediate and high-grade histology, B-COPH, firstly proposed by Cabanillas and Coll, in 1977 (Blood, 49, 1977), is reported as an active (CR: 48-87%) and well tolerated regimen. Since, in 1977 in the Italian cooperative (EORTC) combination (B=bleo+cytoxan 10mg/m2/d, days 1 and 5 + 4-Cylophosphamide 750mg/m2/d, days 1 and 5 + Adriamycin 50mg/m2/d, day 1 + vincristine 1mg/m2/d, days 1 and 5 + prednisone 100mg/m2/d, 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, 20 pts are now evaluable (WHO criteria, Cancer 47,207-214, 1981) and 6 pts are too early for evaluation. Our data are the following:

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<thead>
<tr>
<th>No. Eval. pts</th>
<th>CR(%)</th>
<th>PR(%)</th>
<th>No. Response</th>
<th>CPR (%)</th>
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<tbody>
<tr>
<td>Intermediate</td>
<td>19</td>
<td>50</td>
<td>21</td>
<td>21</td>
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<tr>
<td>High</td>
<td>10</td>
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| 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 male and female and high histology; the median survival time is 16 months (range 8-30 months). Toxicity was moderate and usually reversible.

We gratefully acknowledge the fact that this regimen is active in NHL with intermediate and high-grade malignancy, with acceptable toxicity (no sepsis or drug-related myelosuppression). It is used as a primary treatment for intermediate and high-grade histology patients. Our results indicate that this regimen is active in NHL with intermediate and high-grade malignancy, with acceptable toxicity (no sepsis or drug-related myelosuppression). It is used as a primary treatment for intermediate and high-grade histology patients.

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T 126 CDOP VERSUS M-CHOP - CDOP IN ADVANCED INTERMEDIATE AND HIGH-GRADE DIFFUSE NON-HODGKIN'S LYMPHOMAS (I & HG-NHL). G. Gomez, T. Han, E. Henderson, Department of Hematologic Oncology, Roswell Park Memorial Institute, Buffalo, New York, U.S.A.

Forty-five patients with advanced I & HG diffuse NHL were treated by randomization with either CDOP (cyclophosphamide 750mg/m2 iv and doxorubicin 50mg/m2 iv on day 1, vincristine 1mg/m2 on days 1 and 8 and prednisone 100mg/m2 x 5 days). This treatment was given every 21 days, or with M-CHOP (oral R 30mg/m2 q 6 h for 4 days x 4 followed after the last dose by oral leucovorin 10mg/m2 q 6 h 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 8 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 18 patients (7 in the M-CHOP) were found to have follicular architecture. All of these 5 achieved CR and are at present free of disease. Of the remaining, 20 patients received M-CHOP and 19 CDOP. The CR rate was 82% and 82%, respectively (p=0.1). There were no significant differences in remission duration (p=0.74) or in survival (p=0.77) between the 2 treatments. Fifty percent and 43% 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 CDOP respectively (p=0.01). Two patients in the M-CHOP arm and 1 in the CDOP arm died with cytophenia and infection during treatment.

T 127 HIGH DOSE M-CHOPRETREATMENT DELIVERED BETWEEN CYCLES OF THE FIRST GENERATION REGIMEN CDOP IN CHOP IN INTERMEDIATE AND HIGH-GRADE MALIGNANT LYMPHOMAS: G. Rosenberg, K. Kohnen, F. Wiernik, E. Henderson, Z. Hehlmann, E. G. Visscher, T. Oosterwegel, E. Heim, H. H. Krüger (1), H. Arnold (2), A. Kraft (2), M. E. Hein (3), E. Günther (4), Medizinische Universität zu Köln, 7500 Tußlingen (1), Medizinische Universität zu Köln, 7800 Freiburg (2), Onkol. Forschungszentrum, 6800 Mannheim (3); Kreiskrankenhaus Böblingen (4). 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 cycle. We have treated 19 patients with advanced intermediate and high-grade malignant lymphomas with a CHOP-MTX regimen. Chemotherapy was given every 3 weeks starting with CHOP (Cyclophosphamide 750mg/m2, Adriamycin 50mg/m2, vincristine 14mg/m2, day 1, and Prednisone 60mg/m2, day 1-5); on day 10 MTX 1g/m2 in 500 ml saline was given in 1h. Hydration with 3 l fluid per day was maintained until serum MTX level decreased to 1x7.5. Leucovorin rescue started after 24h. 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 1/16, narrow involvement 4/16, extranodal involvement 9/16. Evaluable data are available for 11 patients (2 patients on therapy, one patient died after 1 cycle, not therapy related). Results: CR after 4 courses: 11/13 (85%), CR after 6 courses: 12/13 (92%). relapse: 1/11 (28%). Two patients were subsequently transplanted. The disease free survival of patients in CR after 4 cycles is 90% (10/11). Median follow up was 5 months. The toxicity of this regimen was very low. Full blood counts (fbc) in 3 patients, no thrombocytopenia (<50% fbc), 1 patient with severe neutropenia (fbc) and 1 patient with major infection (candidiasis). 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 toxicity and high complete response rate this is an important advantage of this regimen.

T 128 RESPONSE-ORIENTED THERAPY IN HIGH-GRADE MALIGNANT NON-HODGKIN'S LYMPHOMAS (I&HG-NHL) WITH CHOP AND VIM-BLDO B. Stenke (1), H. Krüger (1), H. Arnold (2), A. Kraft (2), M. E. Hein (3), E. Günther (4), Medizinische Universität zu Köln, 7500 Tußlingen (1), Medizinische Universität zu Köln, 7800 Freiburg (2), Onkologisches Zentrum, 6800 Mannheim (3); Kreiskrankenhaus Böblingen (4). 24 patients (male 15, female 8, 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, 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 overall complete remission rate was 21/24 (88%). With a median follow up of 22 months, 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 response-oriented 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.
T 113


Between January 1974 and December 1983 113 patients with localized high grade NHL were treated at this centre. Histological material was classified into histopathological groups (MHG) according to Rappaport, and 56 were DDL, 48 DLH and 7 DM or unspecified. Staging included clinical examination, chest a-v, bone marrow aspirate and lymphography, computerized tomography abdominal scan or laparotomy; 62 were stage I and 51 stage II. Treatment was surgical excision alone (2 patients) or excision/ectomy 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 61.8% at 5 years and 52.5% at 10 years. For patients with stage II and bulky (5 cm) stage I disease there was significant improvement (p<0.05) in relapse-free survival (RFS) and a non-significant trend towards improved overall survival for those treated with chemotherapy alone or together with irradiation, compared with irradiation alone. This trend was seen in both major MHG. 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 42 Gy (98%) and 52 Gy (100%) with 4 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 MHG as independent variables. Patients with localized NHL and treated with radiotherapy was 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-COM COMBINATION CHEMOTHERAPY. S. Jell, V. Vouvanot, V. Kovinov, N. Buvovit, and M. Hillevoll. Institut for Onkologi og Radiologi, Belgradje, Yugoslavia

50 patients with stage IIB, IV NHL lymphomas, 12 central reticulum non cleaved, 8 central reticulum-centrocytic, 7 centrocytic -cleaved, 11 lymphocytic including 7 T-types, 9 others - entered the study. 67 were completely untreated, 13 were previously treated (9 CHOP, 2 Adriablastine-Toepoidea-Cyclophosphamide, 3 COPP/MMOP, 4 CHOM). Median age was 63 years, range 30-79 years.

Chemotherapy consisted of treatment courses of T-COM monthly for 6 months and also included chemotherapy of the lymphoma. 66 patients had complete remission, 25.5% of patients received chemotherapy alone (Adriablastine 50 mg/m² iv day 1, Teniposide 140 mg/m² iv day 1, Cyclophosphamide 300 mg/m² iv 2h iv days 3-5, Methotrexol (isol) 20 mg/m² iv days 2-4). Followed by monthly maintenance with COM (Cyclophosphamide, Oncovine, Methotrexol) all day), every fourth COM being replaced by T-COM (equimolar equivalent of Adriablastine), for 3 years.

In the whole group, complete remission (CR) was achieved in 50 patients, partial remission (PR) in 9, progressive disease was observed in 7% (PD); remission rate (RR) was 93%. Different histological types responded:

- Lymphoblastic: CR 61.5%, PR 30.6%, PD 7.4%, RR 99.8%, mean response duration (MRD) 13.6 months, only 4/13 still in remission 4.5, 5.5, 24, 35 months; no plateau in remission duration curve; leukemic transformation in 1 patient.

- Central reticulum: CR 66.3%, PR 30.6%, RR 96.8%, MRD 16.3 months, all patients still in remission lasting 12-24 months 6/12, over 24 months in 4/12.

- Centrocytic: CR 85.8%, PR 14.2%, RR 95.8%, MRD 16.1 months, all patients still in remission lasting 8-24 months 14/18, over 24 months in 5/14.

- Centrocytic-centroblastic: CR 62.3%, PR 25.8%, RR 54.9%, MRD 12.7 months, only 7/8 still in remission; no plateau in remission duration curve; 2 pleomorphic lymphoid immunoblastic transformation (1). Lymphocytic: CR 27.5%, PR 55%, PD 17.5% (both T), RR 62.9%, MRD 15.4 months, 6/7 patients still in remission (4/5 patients in remission lasting 12-24 months, 2 patients underwent T-COM).

Either CR or PR was achieved in all patients resistant to COPP or splenic hyperplasia response to initial treatment of T-COM in the T-CAR combination. The regimen seems very active for centroblastic and centrocytic-cleaved NHL lymphoma, less so for lymphocytic, and is probably not the best choice for lymphoblastic and centroblastic-centrocytic NHL lymphoma.

T 115

TOXICITY OF A COMBINATION OF ABVD AND MEDIASTINAL IRRADIATION FOR HODGKIN'S DISEASE PATIENTS WITH MASSIVE INITIAL MEDIASTINAL INVOLVEMENT. J.L. Legrange, A. Thysa, C. Calzani, R.J. Bensadoun, M. Méry, M. Schneider, Centre Lacsassas, Nice, France

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 were obtained for treatment of such patients by radiotherapy (RT), either by administering lung RT systematically as a principle, or by progressively expanding the volume irradiated, in the hope of reducing the toxicity of such treatments and the severity of such pathologies. Initial treatment by chemotherapy is often offered, for example, the EORTC HDNII trial compares a 3 MOPP-RT±3 MOPP association with 3 ABVD-RT for these cases. One aim of this trial is to compare the toxicity; Fucail et al. (J. Eur. Radiother. 1981;3:169-176) reported that 49% of patients treated by ABVD-RT presented respiratory sequels versus only 15±2% of patients treated with MOPP-RT. From 1981 to 1982, we used an ABVD-RT combination to treat five patients (aged 17 to 35 years) with type 2 HD (stage II, stage III) who had an MT ratio of 0.43±0.57. Histic local irradiation consisted of 40 Gy given in 10-20 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 MED 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 various other symptoms, such as uropathy, periapical pain, anergy, fatigue, adynamia, bone loss 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. R.-P. Muller, R. Pottet, Department of Radiotherapy, Universities of Koin and Munster (Germany)

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 institute. According to the Ann Arbor staging system, 14 pts were in stage I, 19 in stage II, and 8 in stage III. Histologically 15 cases were classified as low malignancy and 9 as high malignancy. According to the old German classification, all were classified as low malignancy. The treatment plans were based on individual CT scans and calculated by a computer planning system. The lens was shielded whenever possible. Initial local control was achieved in 93% of stage I, and 90% of stage II pts. 63% for stage III, 17% for stage IV NHL lymphoma. (13 lymphoblastic, 12 centroblastic, 6 centrocytic, 1 B-cell). In stage III, 12/14 pts. respectively, "all local recurrences." The rate of side effects was insignificant, one patient developed an entropi of the lower lid, another a slightly dry eye. In the two cases the lens had to be removed because 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 dissemination of primary localized tumors, which occurred in 8 pts before initial treatment. In stages I and II, according to histological subtypes, we saw no differences in local control.
**ABSTRACTS - Third International Conference on Malignant Lymphoma, Lugano**

**T 117** **ADJUVANT CHEMOTHERAPY IN THE TREATMENT OF LOCALIZED WALDEYER'S RING NHL. J. Itami, S. Morii, W. Arikawa, 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 the 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), results concerning indication and optimal regimen remain unclear. We have treated 65 patients with histologically confirmed WR-NHL with RT and/or with or without CT. Duration of chemotherapy was 6 months. The stage I was further classified into stage I-I and I-II (2 according to Musshoff et al.). Relapse rate and actuarial survival (AS) at five years are presented in the table:

<table>
<thead>
<tr>
<th>Stage</th>
<th>I-I</th>
<th>I-II</th>
</tr>
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<tbody>
<tr>
<td>5-Y-AS (%)</td>
<td>78</td>
<td>73</td>
</tr>
<tr>
<td>5-Y-RPS (%)</td>
<td>61</td>
<td>55</td>
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</table>

**T 118** **CONCURRENT CHEMOTHERAPY-RADIOTHERAPY FOR STAGE I AND II INTERMEDIATE AND HIGH GRADE NON-HODGKIN LYMPHOMAS. J.J. Mearwald and W. Slod, 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 were excluded, 11 patients, too early for evaluation. 26 Pts were stage I, 14 st. II; 17 patients had extranodal presentations (stomach, thymus, skin). 12 Pts had intermediate, 28 high grade malignancy. Following 4 courses of CHOP 7 pts reached a PM and 3 a CR. Following 4 courses of CHOP and alimentherapy 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.

**T 119** **ALLEVIATION OF POST CHEMOTHERAPY NEUTROPENIA AND SEPTICEMIA WITH LITHIUM CARBONATE IN PATIENTS WITH ADVANCED MALIGNANT LYMPHOMAS. N. Papadakis, M. Boukis, E. Vokariolou, C. Coutoumas, P. Pili, S. Panagos, Department of Medical Oncology, A. Papanicolaou Hospital of Kifisia, 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. 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 single wide spectrum antibiotics and Lithium Carbonate given by mouth (200mg tid) for 7 days. Nadir leukocyte counts were 1541±356 for the first group and 1502±250 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. Lithium carbonate was 11.2244.88 days and 7.158.08 days for the 2 groups respectively, while duration of fever was 12.254.00 days and 4.505.66 days respectively. In the non treated group 57% of septic deaths occurred 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 infection 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 in parallel with peripheral blood leukocyte count increase or several days thereafter. As to 4 days are needed to observe increase of granulopoiesis after Lithium treatment we currently plan to start Lithium administration one to two days before the expected granulocyte nadir day in the absence of any sign of infection in those patients with heavy leukocytosis in peripheral blood and leukocytosis in peripheral blood lymphocytes and preferentially in refractory patients after extensive radiotherapy or 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 K. 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, CVOP, VMOP or VMOP/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 0.6 x 10^9/l) during the three weeks following the second injection. Two of these patients also developed profound thrombocytopenia (platelets less than 20 x 10^9/l), although no patient became thrombocytopenic in the absence of neutropenia. The blood counts were charted on semilogarithmic paper (ordinate 4.8 log cycle; abscissa 3 cycles per 30 days). 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 50%. Of these 25, seven (28%) subsequently became neutropenic and (two of them also thrombocytopenic). On the remaining 390 courses of treatment only six (1.5%) subsequently became neutropenic.

By studying the relative 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 receive 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.
ABSTRACTS - Third International Conference on Malignant Lymphoma, Lugano

T 105
PRIMARY GASTROINTESTINAL (GI) NON-HODGKIN’S LYMPHOMA (NHL): EVALUATION OF 36 PATIENTS (P2B).
From 1973 to 1984, 36 pts with primary GI-NHL were staged and treated at our institution. Histologic diagnosis was reviewed according to the Working Formulation (W.F.). Median age was 50.6 years. Primary site of involvement were: stomach (19 pts=52%), intestine (17 pts=47%). 13 pts had stage I, 6 pts stage II, 11 pts stage III, and 6 pts stage IV. 4 pts had low grade (LC), 16 pts Intermediate Grade (IG) and 11 pts High Grade (HG). 5 cases were not available for histologic review. 9/13 pts in stage I and 1/6 in stage II, were managed with surgical resection only. All others were treated with chemotherapy + surgery. Median follow-up of all groups of pts was 58 months. Overall complete response (CR) rate was 88% (31 pts). A good prognostic factor for CR was gastric involvement (CR in gastric NHL was 94 vs intestinal 76%, p=0.02). The overall survival was 60% at 8 years. Prognostic Factors for survival: Histology (8-year survival: LG = 90% vs HG<52%, p=0.04); and stage (100% survival for stage I vs 94% for stage II, p=0.04). There was no difference in survival in localized lymphomas (stage I-II) treated with surgery alone or surgery plus chemotherapy (85% at 8 years for both groups). Among localized stages (I + II), HG NHL, even if treated with surgery plus chemotherapy (CHOP) had a significant worse survival than LG or HG NHL (3-year survival: LG = 100% vs HG 84%, p=0.006).
Form these results, the use of aggressive chemotherapy, such as third generation regimens, after adequate surgical resection is advisable in high grade GI NHL, also in localized cases.

T 106
PRELIMINARY RESULTS OF MODIFIED PRIMADEC, MOPP (W) CHEMOTHERAPY (CT) FOR GASTROINTESTINAL LYMPHOMA (GIL).
From January to December 96 we treated 13 patients (pts) with GIL by 5 by 8 cycles of MOPP: day 1 Etoposide 120mg/m2, Doxorubicin 25 mg/m2, Cyclophosphamide 500 mg/m2, day 2 Vinblastine 1.4 mg/m2, Deoicretus 5 mg/m2, Vinocrin 4 mg/m2, Oncovar 25 mg/m2, Cyclophosphamide 500 mg/m2, day 4 Vinyseline 1.4 mg/m2. MOPP was repeated 5 by 8 cycles of MOPP: day 1 Etodolac 800 mg/m2 + Melfalic Acid, day 1 to 4 Procarbazine 100 mg/m2, Melfalic Acid 60 mg/m2. 7 pts had gastric lymphoma (LG): 4 stage IE, 3 stage III, 5 high grade (HG). 2 intermediate grade (IG). 6 pts had intestinal lymphoma (IL): 2 stage IIE, 1 stage IIIE, 1 IG. 1 IL, 2 stage IIE (IL), 1 HG, 1 LG, 1 stage IIE (IL), 1 IG, 1 LG. 1 stage IIIE, 1 IG, 1 LG.
All pts received a complete remission (CR) after initial treatment (1 PT alone, 1 CR + abdominal irradiation). 2 pts (1 LG, 1 IL) had a previous history of supra diafragmatic Hodgkin’s disease treated 9 and 17 years before by mantle field irradiation and CT.

PATIENTS POPULATION

<table>
<thead>
<tr>
<th>GASTRIC</th>
<th>INTESTINAL</th>
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<tr>
<td>7</td>
<td>6</td>
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</tbody>
</table>

Results: 3 pts in complete remission (CR) after initial surgery: LG not available, 1 pt with documented partial remission (PR) after 2 cycles relapsed after 16 cycles and died of disease; 2 pts (1 LG stage IIE IL, 1 LG stage III IL) are in PR after 4 cycles and currently pursuing LT. 7 pts are in CR: 5 with LG, 4 after 2 cycles, 1 after 4 cycles (bulky IIE immunoblastic), 2 with IL after 2 cycles (1 relapsed IIE IL, 1 bulky HG IIE IIE with contiguous hepatic extension). Toxicity was hematologic (2 WAC grade 4 neutropenia) without any life threatening infection, digestive (vomiting WHO grade 1 to 3) and ocular (conjunctivitis mild constant).

Concl: modified MOPP 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 (LCHL) OF WALDEYER’S RING.
Radiation therapy alone for localized large cell lymphoma has proved to be curative in 40 - 60% of patients, with the best result 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 1989, in a series of 24 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. 8 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 alive, 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 LYMPHOMA: DURING TREATMENT, V. Josi, S. Papadou, V. Popovit, R. Han, R. Banjocci; Institute for Radiology and Oncology; Dept. of Hematology; Dept. of Endocrinology; Laboratory for Radiographic Investigation, Belgrade.
We have investigated the occurrence of thyroid gland dysfunction in patients with lymphoma initially treated with chemotherapy alone. Twenty patients were included: 10 with Hodgkin’s disease (HD) and 10 with non-Hodgkin’s lymphoma (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, T3g, thyrotropin, antithyroglobulin antibodies (anti-Tg Ab) and antithyroid microsomal antibodies (anti-TPO Ab). The types of therapeutic regimens were: MOPP, COPP, CHOP, CHIVP 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. Antibodies to thyroglobulin antibodies were elevated in 10 (50%) cases before chemotherapy and were normalised 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 lymphoma in the early course of chemotherapy. The elevated values of anti-Tg Ab before therapy could be interpreted as nonspecific finding i.e., a part of general immunological abnormalities in patients with lymphoma 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.
T 110


From 1/1970 to 6/1985 32 pts affected by stage I-II primary non-Hodgkin lymphoma of bone were observed. Before 1976 12 pts had a clinical staging (CS) (clinical evaluation, chest X-ray, X-ray of the involved bone); after 1976 10 pts had a pathologic staging (PS) (bone scan, lymphangiography, bone marrow, clinical examination). The incidence of bone metastases was compared in 24 pts (CS:12pts; PS:12pts); stage I occurred in 9pts (P:5pts; CS:4pts). Receiving radiation therapy (RT) alone and 14pts received RT and adjuvant chemotherapy (CT). RT was administered with a Cobalt Unit to a target volume of larger than the involved bone. The 5-year overall and disease-free survival of pts was 64% (40-0) with conventional fractionation. Adriamycin 50mg/m2, Vincristine 1.5mg/m2, Etodolac 600mg/m2 every 3wks for 6pts were employed as adjuvant regimen. Median follow-up was 40ets (10-190). Results analysed for RT and chemotherapy staging and PS are presented:

<table>
<thead>
<tr>
<th>SITE OF PRIMARY</th>
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<th>THERAPY</th>
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<tbody>
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15/6/5 19/4/5 19/9/7 15/11/7 32/20/7

20/2pts (62.5%) are disease free (DF); 7/20pts (35%) are alive (+) for overall disease and 6pts (11%) are alive with relapse of 3 local and 3 distant. Our data suggest that a higher staging affects significance of survival (73.5% 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 prognostic independent of the stage 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 18.3mths respectively. We can not evaluate the prognostic significance of PS for stage for the incidence of understaging and site of primary in our da ta.

T 111

PROGNOSTIC SIGNIFICANCE OF THE DURATION OF FIRST DISEASE-FREE SURVIVAL IN NON-HODGKIN'S LYMPHOMA CHEMOTHERAPY. R.A. Abdyldeyev, G.V. Kruglova, Kirghis Research Institute of Oncology & Radiotherapy, Frunze, USSR.

Prognostic significance of the duration of first disease-free interval (DS) was studied in 43 previously untreated non-Hodgkin's lymphoma (NHL) patients. Chemotherapy was a primary therapy for all patients: 159 pts were treated with single-agent chemotherapy and 284 patients - with chemotherapy. The ages ranged from 14 to 82 (median, 45). In majority of patients (58.06%) the primary sites of tumour growth were the lymph nodes, and in the other (41.94%) - extralymphatic 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 IV) stages of the process.

It has been indicated that the length of the first complete DS does not depend on the morphologic type of NHL (P>0.05). The duration of the first complete DS precisely correlates with the lifetime of patients: the longer DS (more than 2 months), for the longer time patients live, i.e., for 5 years 60.4% survived versus 6.8% with short DS (less than 2 months) (P<0.0001). Partial DS 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 DS is longer and the difference is significant: 43.9% and 18.2% patients lived for 5 years, respectively (P<0.0001). Last, these NHL patients should be treated for the achievement of complete and most stable therapeutic results. In NHL patients who achieved the partial DS need the adjuvant maintenance chemotherapy.

T 112


A retrospective analysis for pretreatment prognostic variables on complete response (CR) rate and disease-free survival (DFS) was performed on 66 patients affected by clinically localized (Ann Arbor I and II) diffuse large cell (DLC) or undifferentiated (UD) lymphoma treated with combination chemotherapy. The following variables were included: age, primary site (non-germinal sinus or non-sinus); type of combination chemotherapy (ProveClif vs F-MABCDP or m-BACOD); a lower CR rate was registered in pts with M infectious (43%) or with bulky disease (35%), or with N-illness (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, PD had a CR rate of 95% and a 67M long term DFS as opposed to a CR rate of 45% and a 760 long term DFS for PP pts. The proportion of PP pts was 54% among those treated with ProveClif and 61% among pts treated with F-MABCDP; the response rate was 97% in pts treated with ProveClif and 92% in pts treated with F-MABCDP. The rate of combination chemotherapy did significantly influence CR rate and duration in only 25 pts, with good, poor and achieved hypothesis with log-rank test. According to the results the best results of less intensive chemotherapy (ProveClif) did not result in a significantly lower CR rate and DFS with comparable survival with DFS.

<table>
<thead>
<tr>
<th>Type of Chemotherapy</th>
<th>Total CR</th>
<th>Total DFS</th>
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<tr>
<td>ProveClif</td>
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<td>58</td>
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<tr>
<td>F-MABCDP/m-BACOD</td>
<td>26</td>
<td>73</td>
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Supported by a grant CNR, PFO, Contract no. 86.00466.44 and MI 40%.