T 212 HIGH-DOSE CHEMOTHERAPY WITH G-CSF SUPPORT AS PRIMARY TREATMENT FOR POOR PROGNOSIS NON-HODGKIN'S LYMPHOMA.

Gunnar Juliusson.
Division of Clinical Oncology and Hematology, Department of Medicine, Karolinska Institute at Huddinge Hospital, S-141'86 Huddinge, Sweden.

Dose intensity is critical for the cure rate in aggressive non-Hodgkin's lymphomas, to avoid selection of resistant tumor subclones. High-dose chemotherapy is well established when followed by autologous or allogeneic stem cell support, but the highest tolerable doses of combined chemotherapy without stem cells have not been assessed.

We therefore initiated a dose escalation trial with high dose combined chemotherapy and subsequent G-CSF in repeated courses as primary treatment for high-grade malignant lymphoma with poor-risk features in patients 65 years or less.

Six patients were newly diagnosed and three had relapses off therapy. Base-line dose was doxorubicin 90 mg/sqm, cyclophosphamide 1800 mg/sqm, and etoposide 450 mg/sqm, all drugs given by short-term infusions in equally divided doses over three consecutive days. G-CSF (Neupogen®) was given in a high-dose, 20 μg/kg/day by continuous subcutaneous infusions through a portable infusion device from day 4 until neutrophil recovery. All patients received oral prophylaxis with ciprofloxacin, acyclovir and amphotericin. One to four such courses were given. Some patients subsequently had involved field radiotherapy or autologous transplant.

Six patients entered on base-line level, and three on a level with a 30% higher dose of cyclophosphamide and etoposide, but an unchanged doxorubicin dose. Toxicity is shown below. Mucositis was a consistent toxicity, and parenteral nutrition for 7 to 14 days per course was generally needed. One patient required respiratory aid because of severe mucositis, but recovered. Tumor response was rapid. Seven patients had complete and 2 partial remissions. One patient died in CR from cerebral hemorrhage following his second course when he simultaneously developed septicaemia with strepococci and thrombocytopenia. No patient has relapsed from complete remission.

	First Course			Second Course		
Mean value, *range*	Baseline	Dose 2	*Range*	Baseline	Dose 2	*Range*
Number of patients	6	3		5	2	
Neutrophils <1x10(9)/l, *days*	8.8	9.3	*6-11*	7.4	6.5	*2-12*
Platelets <20x10(9)/l, *days*	4.0	6.0	*1-10*	3.8	4.5	*0-8*
Fever >38°, *days*	6.8	4.7	*0-13*	2.6	1.5	*0-6*
Neutropenic fever, *days*	4.5	5.7	*0-8*	1.8	3.5	*0-7*
Erytrocyte transfusions, *units*	1.8	2.7	*0-5*	3.2	3.0	*2-6*
Platelet transfusions, *units*	15.0	16.0	*6-30*	10.8	15.0	*0-24*
Intravenous antibiotics, *days*	11.3	8.7	*0-20*	5.2	6.5	*0-11*

This high-dose protocol requires a substanitial amount of supportive care, but produces rapid and seemingly durable responses in patients with poor-prognosis high-grade malignant lymphoma. Interestingly, the second course has given shorter cytopenias and less infections than the first one, but following the third course thrombocytopenia was more pronounced. The higher dose level was not more toxic than the base-line level. A further dos-escalation is ongoing.

T 213 THE USE OF FILGRASTIM (AMGEN) TO INCREASE DOSE INTENSITY IN PATIENTS WITH POOR PROGNOSIS NHL.

D.N.Carney, P.Lonergan, B.Jenkins, B.Otridge. Depts. of Medical Oncology and Haematology, Mater Misericordiae Hospital, Dublin, Ireland.

While approximately 50% of all patients (pts) with intermediate grade and high grade NHL may be cured of their disease, the 5 year disease free survival for patients with stage 111/1V disease, bulky disease, multiple sites of extra nodal disease, or high grade morphology (including lymphoblastic or immunoblastic NHL), is approximately 20%. For such poor prognosis pts a study using a multidrug programme analogous to that used in acute leukaemia has been carried out.

Pts were treated with 2 courses of modified CHOP (Cyclophosphamide 1000mg/m², Doxorubicin 50mg/m², Vincristine 2mg, all iv day 1 and Prednisolone 40mg/m², po x 5 days, q 3 weeks) followed by 4 courses of an ALL intensification regimen, (Daunorubicin 45mg/m² iv day 1 and 2, Vincristine 2mg iv day 1, Etoposide 100mg/m² iv days 1-5, Cytosine Arabinoside 100mg/m² iv bd days 1-5, Thioguanine 80mg/m² and Prednisolone 40mg/m² po days 1-5). The interval between each course was scheduled to be 21 days.

This regimen has previously been associated with marked myelosuppression, prolonged neutropenia and frequent delays in treatment due to neutopenia. In this study 20 pts self-administered filgrastim (Amgen) 5μg/kg/day sc between chemotherapy courses. The median age was 48 years (range 27-60 years). A total of 94 courses were administered. Of the 77 courses of chemotherapy that could have been delayed, 72 courses (94%) were administered on schedule. Fourteen (70%) patients were able to receive all 6 courses of chemotherapy and 10 (50%) patients received all 6 courses without any dosing delays or dose reduction. The median duration of in-patients hospitalisation over all courses of chemotherapy was 64 days.

The only common filgrastim-related adverse event was mild to moderate bone pain in 5 (25%) patients. One patient had an acute episode of dyspnoea following administration of filgrastim and declined further therapy. Of 18 evaluable patients the overall response rate was 17/18 (94%) with 15/18 (83%) obtaining a complete response. Although filgrastim enabled 70% of pts to receive the full scheduled chemotherapy regime, whether such a regimen would significantly improve the long term outcome of high risk pts with NHL remains to be determined.

T 214 INTENSIFICATION OF THE CHOEP REGIMEN FOR HIGH-GRADE NON-HODGKIN'S LYMPHOMAS BY G-CSF: FEASIBILITY OF A 14-DAY-REGIMEN.

M. Pfreundschuh, L. Trümper, A. Engert, V. Diehl, P. Koch. Med. Klinik, Universität des Saarlandes, D-6650 Homburg

The efficacy of chemotherapy protocols of high-grade Non-Hodgkin's lymphomas (NHL) has not been significantly improved during the last decade. The CHOP protocol which was developed nearly twenty years ago, remains the standard, despite the development of aggressive multi-drug regimens of the second and third generation. For the time being, etoposide (E) is the only cytotoxic drug that may add to the efficacy of the combination of cyclophosphamide, doxorubicin, vincristine and prednisone used in the CHOP regimen. Indeed, excellent results have been obtained with the etoposide-containing CHOP-VP16 or CHOEP combination (Koeppler et al., Br. J. Cancer 60: 79-82, 1989). Besides the addition of new drugs, efficacy of the CHOP protocol might be increased by the augmentation of dose intensity either by increasing the doses of cytotoxic drugs or by decreasing chemotherapy intervals. With the advent of hematopoietic growth factors this has become a realistic goal. To test the feasibility of both adding etoposide and decreasing the time interval of the CHOP regimen, we started a phase I/II study of the CHOEP protocol with G-CSF given in 14-day cycles. The CHOEP protocol consisted of cyclophosphamide 750 mg/m² i.v. day 1, doxorubicin 50 mg/m² i.v. day 1, vincristine 1.4 mg/m² i.v. day 1, etoposide 100mg/m² i.v. day 1 to 3, prednisolone 100 mg p.o. days 1 to 5, and G-CSF 300 μg s.c. days 4 to 13. The cycles were repeated on day 15 and patients received 6 cycles followed by irradiation of bulky disease with 35 Gy. To date, 12 patients in stages II to IV (age range 29 to 79 years, median 67 years) with high-grade NHL according to the Kiel classification have been treated and a total of 54 CHOEP cycles are evaluable for toxicity. The regimen was well tolerated in all patients except for one who stopped G-CSF treatment due to bone pain and fever. Leukocytopenia < 1000 /mm³ occurred in 30% of the cases, but never persisted for more than 4 days. White blood cell counts recovered fully by day 14 in all cases. One two-day episode of fever was observed during leukocytopenia. Thrombocytopenia < 100 000/mm³ occured in 25%, trhombocytopenia < 50 000/mm³ only in 1 patient. No bleeding episodes were observed and no platelet transfusions were necessary. Anemia that required transfusion was observed in 4 patients, all of whom had started therapy with Hb < 10g/dl. Other toxicities were WHO-grade-2 mucositis, which was observed in 3 patients and WHO-grade-2 polyneuropathy in 2 patients. We conclude that G-CSF-supported CHOEP can be given safely in 14-day intervals even to elderly patients. A randomized trial will show whether this significant increment in dose intensity translates into increased remission rates and/or longer remission durations.

T 215 CLINICAL EFFECT OF INTERLEUKIN-3 (IL-3) ALONE AND COMBINATIONS OF IL-3/GM-CSF AND IL-3/G-CSF IN NON-HODGKIN LYMPHOMA.

D. Hovgaard, N.I. Nissen, Dept. of Hematology, Rigshospitalet, Copenhagen Denmark.

42 previously untreated patients with newly diagnosed non-Hodgkin lymphoma were treated with standard CHOP chemotherapy in combination with cytokines. In 24 patients IL-3 was given s.c. as monotherapy for 14 days following CHOP cycle 2 and 4 and after cycle 6 in combination with GM-CSF (3 μg/kg). Four dose levels of IL-3 were examined, 0.5, 1.0, 5.0 and 10 μg/kg. In groups of 6 patients, combinations of IL-3 (7.5 μg /kg) and GM-CSF (3 μg/kg) and IL-3 (7.5 μg/kg) and G-CSF (3 μg/kg) either as sequential or simultaneous administration were examined.
Monotherapy with IL-3 was well tolerated with minor to moderate side effects, fever, chills, cutaneous reactions and flu-like symptoms. These were more pronounced following combination therapy. Preliminary results showed an increase on day 5 (mean) of WBC, espec. neutrophils, following monotherapy of IL-3 and all the different combinations. The counts at the nadir, day 9 (mean) were higher, in particular following IL-3 and G-CSF. Day of nadir was earlier during cytokine therapy compared to control cycles and the neutropenic period was reduced in cycles with cytokines. An increase on day 15 of WBC and neutrophils compared to control cycles was noted during cytokine therapy, espec. for combinations including G-CSF. Recovery from day 15-22 of WBC and neutrophils was also increased, espec. after IL-3 monotherapy or combinations of IL-3 and GM-CSF. Platelet counts were increased in the recovery period day 15-22, when IL-3 was administered alone or combinations of IL-3 and GM-CSF.

T 216 Dose-Intensification of Chemotherapy (NOSTE) with r-metHuG-CSF (Filgrastim) Support in Advanced Low and Intermediate Grade Non-Hodgkin Lymphomas (NHL)

H. Wandt*, S. Wachsmann*, K. Bench*, W.M. Gallmeier*, A. Münz‡, T. Zwingers¥. *5. Medizinische Klinik und Institut für Medizinische Onkologie/Hämatologie, Klinikum der Stadt Nürnberg; ‡Amgen GmbH München; ¥bias GmbH München

For treatment of low and intermediate grade NHL, the combination of mitoxantrone and prednimustine was proven equally effective but less toxic regarding nausea, emesis, and alopecia than other standard chemotherapy regimen. However, hematological toxicities are dose-limiting, particularly granulocytopenia WHO grade III and IV, causing treatment delays of planned 4 weekly intervals and/or dose reduction in about 40-50 % of the patients.

In order to overcome treatment delays due to myelotoxicity we used filgrastim (5 µg/kg/day s.c., day 6-19) as an adjunct to chemotherapy consisting of mitoxantrone 8 mg/m^2 (day1 and 2) and prednimustine 100 mg/m^2 (day 1-5) for up to 6 cycles given every 3 weeks in patients with low or intermediate grade NHL.

10 patients, receiving a total of 50 cycles, have completed treatment at the time of this interim-analysis. In all patients, neutrophil counts were > 2.0 x 10^9/l on day 20 of each cycle and only in two cycles chemotherapy had to be delayed because of thrombocytopenia (WHO grade I and II, respectively). 3 patients were withdrawn prematurely: 1 patient with progressive disease; 1 patient with complete response after cycle 3 switched to a different therapy with curative intent; and 1 patient who refused transfusions was withdrawn because of thrombocytopenia and anemia. Bleeding or infectious complications did not occur. Apart from bone pain in 2 patients (mild and moderate) and dizziness in 1 patient (mild) there were no filgrastim-related adverse events.
In conclusion, filgrastim-support facilitated safe and well tolerated dose on time delivery of chemotherapy in a 3 weekly NOSTE regimen in an outpatient setting.

T 217 SEQUENTIAL COMBINATION CHEMOTHERAPY (CEBOPP/VIML), G-CSF AND RADIOTHERAPY IN PATIENTS WITH HIGH GRADE MALIGNANT NON-HODGKIN'S LYMPHOMA (NHL)

Nowrousian M.R., Mengelkoch B., Kleine-Herzbruch R., Bauer R., Eberhardt W., Reiter W., Müller M., Kasper C., Schlenger L., Budach W., Leder L.D., Sack H., Seeber S. Department of Internal Medicine (Cancer Research), Department of Radiotherapy, Institute for Pathology, West German Tumor Centre, University of Essen, F.R.G.

In patients (pts) with aggressive NHL, the outcome of chemotherapy appears to be related to the dose intensity of drugs. In the present study, an intensified sequential combination chemotherapy was used together with G-CSF (5 ug/kg/d, days 11-20) when severe and/or prolonged neutropenia, and/or infectious complication were present. In pts with stage I disease and in pts with primarily bulky disease, additional radiotherapy (40 Gy) was given to the involved field after completion of chemotherapy. Chemotherapy was started with a combination of Cyclophosphamide (400 mg/m2/d, days 3,4), Epirubicin (40 mg/m2/d, days 1,2), Bleomycin 30 mg/d, days 1,10), Vincristin (2 mg/d, days 1,10), Prednisone (100 mg/m2/d, days 1-10), and Procarbazine (60 mg/m2/d, days 1-10) (CEBOPP). Treatment was repeated every 3 weeks. In pts with complete response (CR) after a maximum of 4 cycles of CEBOPP, this regimen was continued for a total of 6 cycles. In pts with progressive disease or with only a partial response, therapy was switched to a combination of VP-16 (130 mg/m2/d, days 1,3,5), Ifosfamide (1300 mg/m2/d + Mesna, days 1-5), Methotrexate 70 mg/m2/d, days 1,5), and Leucovorin (15 mg, 24, 30, and 36 h after each dose of MTX) (VIML). In pts with Epirubicin contraindication, chemotherapy was started with VIML together with Vincristin (2 mg/d, days 1,10) and Prednison (100 mg/m2/d, days 1-10) (VIMLOP). Between 11/1990 and 7/1992, a total number of 40 pts (19 males, 21 females) were treated. The median age was 52 yrs (range 20-87). 12 pts had stage I, 12 pts stage II, 9 pts stage III, and 7 pts stage IV disease. B-Symptoms were present in 15 pts, bulky disease (> 10 cm) in 16 pts, and extranodal involvement in 15 pts. Histologic types of the tumors (Kiel classification) were: centroblastic 30, immunoblastic 2, and undifferentiated large cell 8. Major toxicities (WHO grade III+IV) of therapy other than total alopecia were leukocytopenia in 46%, thrombocytopenia in 6%, and anemia in 5% of chemotherapy cycles. Infection occured in 41%, and peripheral neuropathy in 3% of pts. There was a toxic death rate of 6%. 89% of pts achieved complete remission (CR). With a median follow-up of 14 months, the projected survival is 85% at 34 months, and 88% of pts with CR are predicted to have continued CR at 30 months. In conclusion, the therapeutic concept used appears to be highly effective in inducing CR. It also appears to be promising with regard to the long-term disease-free survival, when the low rate of relapses during the first 2 yrs is considered.

T 218 EFFECT OF RECOMBINANT HUMAN GARANULOCYTE-MACROFAGE COLONY STIMULATING FACTOR (rhGM-CSF) AFTER INTENSIVE CHEMOTHERAPY IN ADVANCED CLINICAL STAGE LYMPHOMAS. FIRST EXPERIENCE IN VENEZUELA.

R. Somoza, G. Acquatella, J. Desenne, C.D'Jongh, M. Salomón, E. Tovar, M. Hernandez, E. Perdomo. National Center for Oncology-Hematology, and Lymphoma Clinics, Caracas Univesity Hospital, Caracas, Venezuela.

To determine whether rhGM-CSF (LEUCOMAX) can reduce the duration of leukopenia and granulocytopenia as well as the risk of infection after intensive chemotherapy in Lymphomas, we performed a nonrandomized clinical trial in 12 patients (pts) 6 male, 6 female, mean age 46 (26-67) years, with advanced clinical stage (StIV) Lymphomas. 7/12 (58%) had non Hodgkin's Lymphoma (NHL) and 5/12 (42%) had Hodgkin's disease (H.D.). All pts received salvage treatment after first relapse with MINE (Mesna 1.3g/m^2/d I.V. days 1→3, Ifosfamide 1,3g/m^2/d I.V. days 1→2, Novantrone 8 mg/m^2/d day 1, Etoposide 65 mg/m^2/d I.V. days 1→3) ESAP (Etoposide 60 mg/m^2/d I.V. days 1→4, Solumedrol 500 mg/m^2/d/I.V. days 1→4, Ara-C 2 g/m^2/d I.V. day 1, Platinum 100 mg/m^2/d I.V. days 1→4), four alternate cycles. The rhGM-CSF was given subcutaneosly at a dose of 5/Ug/kg/day during 5 days, 24 hours after the last dose of chemotherapy; a total fo 25 cycles were given to our pts.
All pts had a white blood cell count (WBCC) below 2.0x 10^9/l and a absolute neutrophil count (ANC) below 1.0x10 ^{9}/l before starting therapy with rhGM-CSF.
We found that the average recovery time for leukopenia and neutropenia was 72 hours after the first rhGM-CSF dose. The mean values of the WBCC and ANC in each patient (pt) before and after rhGM-CSF were statistically significant (WBCC 0.66+/-0,40 x 10 ^{9}/l and 35.55 +/- 15.60 x 10^9 /l; p= < 0.01). There were not statistically significant changes in the mean values of hemoglobin (Hb), Hematocrit (Hct) and platelet (plt) count before and after rhGM-CSF (Hb. 9.95 +/- 1.3 g/dl and 9.7 +/-1.8 g/dl, Hct 32 +/- 4% and 30 +/- 5%, plt 104+/-50 x 10^9/l and 122 +/- 48x10^9/l; p=>0.05). Only 3/12 (25%) of the pts required antibiotic treatment for associate infection. We observed minimal adverse reaction to rhGM-CSF in 3 pts characterized by rash in one of them and fever in the other two. 3/12 (25%) of the pts died during last chemotherapy cycle, 4/12 (33%) are in complete remission, 3/12 (25%) are in parcial remission (PR) of more than 50% and 2/12 (17%) are in PR of lees than 50%,6 months after finishing chemotherapy. We conclude that the use of rhGM-CSF has been of great help in our country since it allowed us to increase the dose intensity of cytotoxic drugs, particularly those with myelosuppressive dose-limiting toxicity such as VP16, Platinum and Novantrone. Reductions in the number of days of neutropenia may prove of benefit in terms of both hospital costs and the morbility of chemotherapy.

T 219 CAN G-CSF BOOST THE DOSE-INTENSITY OF STANDARD CHEMOTHERAPY?

A.M.Liberati, S.Filippo, F.Di Clemente, S.Sacchi,* F.Di Costanzo#, M.Brugia#, B.Biscottini. Clinica Medica I Perugia, *Clinica Medica II Modena, #Servizio Oncologico Terni Italia

As G-CSF reduces hematological toxicity, the objective of this study was to ascertain whether when 5µg/kg/day G-CSF was associated with a CECP regimen (80mg/m² CCNU, 60mg/m² VP16, 30mg/m²chlorambucil and 32mg/m² methylprednisolone) it allowed the 4-week intercycle chemotherapy interval to be respected or shortened to 3 weeks without reducing the dose. During the 1st cycle, 50% patients were randomized to receive chemotherapy plus G-CSF and 50% chemotherapy alone. The treatment was reversed in the 2nd cycle and from the 3rd cycle on all patients were administered chemotherapy plus G-CSF, which was given from the day one after CECP was terminated until granulocytes reached >1000/ml on two consecutive days or WBC ≥3000/ml, but not for more than 23 days. CECP was administered every 21 days if granulocytes were >1000/ml and/or WBC ≥3000/ml and platelets≥100000/ml. If these values have not been achieved by the 28th day, chemotherapy was continued but at a reduced dose (according to current criteria) or delayed until day 35. A total of 15 patients (2 Hodgkin's disease and 13 low-grade non-Hodgkin's lymphomas, median age 57.4 years, range 22-70, 5 female and 10 male) have been enrolled. All but one patient had relapsing or refractory disease at enrollement in the study. Three patients received only one cycle . One patient, randomized to receive chemotherapy alone in the 1st cycle interrupted the treatment because of pulmonary aspergillosis and two randomized to receive G-CSF during the 1st cycle died shortly after the completion of the 1st cycle, one due to progressive disease and the other to infectious complications. Another 4 non-responders discontinued treatment after the 3rd (1), 4th (2) and 5th (1) cycle. Two responsive patients (1 CR and 1 PR) refused therapy after the 2nd and the 3rd cycle, one because of extrahematological and the other because of hematological toxicity. Of the other 6 responsive patients, 3 (1 CR and 2 PR>75%) have completed the 6 planned cycles, one the 4th and 2 the 3rd (these 3 last patients are continuing therapy). Of the 12 patients who have completed at least two cycles, 5 received G-CSF after the 1st (GI) and 7 after the 2nd cycle (GII). G-CSF reduced the incidence of leukopenia and neutropenia and this was particularly evident in Group II when the post 1st and 2nd cycle WBC and granulocyte counts were compared. The myeloprotective effect of G-CSF also seemed to persist after the 1st administration period, as shown by the WBC and neutrophil values documented in GI patients after the 2nd chemotherapy cycle. G-CSF did not significantly altered the platelet counts. It would, therefore, seem that G-CSF should allow the dose intensity of standard chemotherapy to be increase, at least in the first 3 cycles.

T 220 G-CSF FOR CHEMOTHERAPY-RELATED LEUKOPENIA IN PATIENTS AFFECTED BY ADVANCED LYMPHOMAS.

M. Bonfichi, I. Bellantuono, E.P. Alessandrino, P. Bernasconi, G. Pagnucco, E. Brusamolino E. Morra, C. Castagnola, C. Bernasconi. Cattedra di Ematologia, Universita' di Pavia - Divisione di Ematologia, Policlinico S. Matteo IRCCS, 27100 Pavia, Italy

Recombinant human granulocyte colony stimulating factor (G-CSF) has been reported to increase the leukocyte count following cancer chemotherapy.
We have treated with G-CSF 15 patients (8 male, 7 female; median age 34 yrs. range 22-62) affected by Hodgkin (HL)(5 cases) and non Hodgkin (NHL)(10 cases) lymphomas after conventional or high-dose chemotherapy; besides three out of 4 HL pts were submitted to autologous BMT to reduce morbidity and morbility.
All patients had an antecedent clinical history characterised by prolonged cytopenia with severe infectious diseases (4 cases: lung aspergillosis, anal abscess, 2 bacterial pneumonia) or long period of fever (> 39°C) of unknown origin after the previous courses of chemotherapy.
G-CSF (5 mg/kg iv daily) was administered after a mean time of 5 days (range 1-16) from the end of the chemotherapy untill the neutrophils were more than 1500.
The neutrophil recovery was evaluated with or without G-CSF. With G-CSF the mean period of leukopenia was shorter: 13.8 days (range 2-21) vs 28.3 (range 20-37)
All patients but two tolerated the therapy well. Two pts, both suffering from HL with lung infections (respectively mycotic and bacterial), presented a severe distress respiratory syndrome when leukocytes increased to over 10 x 10 ^{9}/l. In the first one bone pain responsive only to morphine was observed. Two patients, with 100 % bone marrow involvement, did not show any advantage with the growth factor therapy.
In conclusion G-CSF treatment in patients without bone marrow failure reduced the period of leukopenia and consequently the duration of hospitalization. No increase of the neoplastic disease was ever observed.

T 221 AUTOLOGOUS BONE MARROW TRANSPLANTATION IN POOR RISK HIGH GRADE NON-HODGKIN'S LYMPHOMA IN FIRST COMPLETE REMISSION.

G H Jackson[1], A L Lennard[1], P R A Taylor[1], P Carey[1], B Angus[2],H Lucraft[3], R G B Evans[3], S J Proctor[1] on behalf of the Newcastle and Northern Lymphoma Group, Departments of [1]Haematology, [2]Pathology, [3]Radiotherapy, Royal Victoria Infirmary, Newcastle upon Tyne, NE1 4LP, UK

Thirty patients with high grade poor risk non-Hodgkin's lymphoma (NHL) were considered for ABMT following remission induction according to a standard protocol. Two patients relapsed prior to ABMT. Twenty-eight patients were conditioned with high dose melphalan (HDM). In addition 10 patients received fractionated total body irradiation (TBI), 1 patient hemi-body irradiation and 4 high dose etoposide. Unmanipulated non-cryopreserved autologous marrow was reinfused within 56 hours of harvesting.

Engraftment occurred in all patients with a median of 11 days of neutropenia (<0.5x10^{9}/l), a median requirement for platelet transfusion of 3 days, and packed red cell transfusion of 2 units, with a median of 18 days in hospital post transplant. There was no procedure related mortality and only minor morbidity was observed. Two patients relapsed at 1 and 2 months post transplantation and 1 patient died of squamous cell carcinoma of the lung 33 months after transplantation. The remaining 25 patients remain alive, well and in first complete remission with a median follow-up of 44 months post transplantation. The event free survival at 3 years for all patients considered for ABMT was 83%.

We conclude that ABMT for high grade NHL in CR1 with non-cryopreserved marrow results in rapid neutrophil and platelet recovery without growth factor support. It is a safe procedure and the conditioning treatment is associated with high survival when used as consolidation of CR in high risk patients.

T 222 TREATMENT OF HIGHLY AGGRESSIVE LYMPHOMAS WITH MACOP-B OR VACOP-P FOLLOWED BY AUTOLOGOUS BONE MARROW TRANSPLANTATION IN FIRST REMISSION

L. M. Jost, E. Jacky, M. Reichlin, G. Pichert, H.-P. Honegger, and R. A. Stahel, Division of Oncology, Department of Medicine, University Hospital, Zürich, and Institute of Oncology, City Hospital Triemli, Zürich. Switzerland

We report the results of a phase II study on the treatment of highly aggressive non-Hodgkin's lymphoma of stage II or higher with 12 weeks of chemotherapy using the MACOP-B or VACOP-B regimen followed by dose intensification and autologous bone marrow transplantation (ABMT) in first complete remission. Since December 1987, 17 consecutive patients were included in the study. The median follow-up was 32 (range 4-60) months. Ten patients were classified as having IWF I and 7 as IWF J (Burkitt type) non-Hodgkin's lymphoma. Three patients had stage II, one stage III, and 13 stage IV disease. LDH was elevated in 8 of 14 patients. Five patients had overt bone marrow infiltration, 7 had other extranodal disease (including breast, pericardium and CNS), and 9 presented with bulky lesions over 10 cm. The median age was 27 (range 16-51) years. Six patients received MACOP-B and 11 VACOP-B chemotherapy. Fifteen patients achieved a complete remission, whereas 2 patients had a partial remission or progression during therapy. Two patients in complete remission relapsed within 4 weeks after completion of chemotherapy and 1 patient died without evidence of persisting lymphoma due to refractory bone marrow failure caused by a hemophagocytosis syndrome. The 12 remaining patients with complete remissions underwent bone marrow harvest within a median of 3 (range 1.5-5.0) months and dose intensification with ABMT within a median of 4 (range 2.6-5.8) months after initiation of chemotherapy. Dose intensification consisted of cyclophosphamide combined with total body irradiation for the first 4 patients and of cyclophosphamide, BCNU and etoposide for the remaining 8 patients. Among these 12 patients no toxic deaths occurred. Currently 10 patients are alive and free of relapse. In 2 patients relapse occurred within 12 months after dose intensification. One of these died of progressive tumor and one achieved a second complete remission lasting 42+ months after further salvage therapy. The calculated relapse-free survival at 3 years was 53% (CI: 25-75%) for all 17 patients and 78% (CI: 43-98%) for the 12 patients undergoing dose intensification in first remission. The calculated overall survival at 3-years for all 17 patients was 62% (CI: 30-83%). Highly aggressive non-Hodgkin's lymphomas are conventionally treated with complex chemotherapy regimens lasting for up to 2 years. Our results using 12 weeks of chemotherapy followed by dose intensification in first remission suggest that the duration of treatment can be significantly shortened without compromising relapse free survival.

T 223 AUTOLOGOUS BONE MARROW TRANSPLANTATION (ABMT) IN NON-HODGKIN'S LYMPHOMAS (NHL): BOLOGNA EXPERIENCE USING BAVC AS CONDITIONING REGIMEN.

M.C. Miggiano, F. Gherlinzoni,, G. Visani, P. Ricci, P. Mazza, P.L. Zinzani, M.R. Motta, S. Rizzi, G. Rosti, G. Bandini, S. Tura. Institute of Hematology "L. & A. Seràgnoli", St. Orsola Hospital, University of Bologna, Italy.

From April 1982 48 patients (pts) with high-grade NHL were submitted to ABMT in Bologna. BAVC conditioning regimen includes four singularly active and potentially synergistic drugs, scheduled as follows: BCNU, 200 mg/sm on day -4; ARA-C, 150 mg/sm every 12 h from day -5 to -2; VP-16, 150 mg/sm every 12 h from day -5 to -2; Cyclo, 45 mg/Kg/day from day -5 to -2. Our series comprises 25 males and 23 females; mean age is 27 yrs (14-52). The most frequent histological subtype is anaplastic large cell (ALC) lymphoma (17 pts), followed by centroblastic (9 pts) and lymphoblastic (6 pts) lymphoma. Fourteen pts have been autotransplanted at diagnosis, 9 in partial remission (PR), 6 in complete remission (CR), 6 in responding relapse. 13 pts had an unresponsive disease at ABMT (8 resistant relapse, 5 primary refactory). Mean follow-up is 34.5 months (1-128). Bone marrow purging was not performed.
Results. Actuarial overall survival projected at 10 yrs is 46%, probability of relapse for CR pts is 35%. Latest relapse occurred 26 months after ABMT. No differences have been observed according to sex or to histology, while pts with a low tumor burden at ABMT have a better outcome ($p<0.05$). 2 treatment related deaths occurred (4%), due to septic shock and to myocardial infarction. No liver VOD nor severe interstitial pneumonitis were registered. One pt developed a congestive heart failure, likely due to Cyclophosphamide cardiotoxicity, but completely recovered.
Conclusions. These data confirm that BAVC protocol combines an effective anti-neoplastic activity with a low extrahematological toxicity and is worthy of being used as conditioning regimen for ABMT in NHL.

T 224 AUTOLOGOUS BONE MARROW TRANSPLANTATION FOR NON-HODGKIN'S LYMPHOMA IN FIRST REMISSION. A REPORT OF 51 CASES FROM THE SPANISH GEL/TAMO COOPERATIVE GROUP.

J. Sierra, E. Conde, J. García-Laraña, S. Brunet, A. Iriondo, J. Marín, D. Caballero, F. Martínez, A. León, J. García-Conde, J. Lahuerta, F. Hernández, C. Solano, D. Carrera, C. Richard, J. Zuazu, J. Baro, J. Rifón, J. Díaz-Mediavilla, C. Rozman, E. Montserrat. Spanish Cooperative Group for Bone Marrow Transplantation in Lymphomas (GEL/TAMO).

The role of autologous bone marrow transplants (ABMT) in patients with poor-risk non-Hodgkin's lymphoma (NHL) in first remission is being investigated. It has been suggested that patients with adverse features for long-term outcome with chemotherapy (namely, advanced stage at diagnosis, extranodal disease, poor performance status, or high LDH level) should be treated with ABMT as part of their front-line therapy.

Among 132 patients from the Spanish Cooperative Group autografted for NHL between 1984 and 1992, 51 were transplanted while in first complete remission (CR). Their main characteristics at diagnosis were: mean age 30 years (range, 3-59), male/female distribution 31/20, intermediate grade/high grade histology 10/41 (17 lymphoblastic), stage I: 3 patients, II: 15, III: 7, IV: 26, "bulky" disease 38 out of 46 cases, mean±SD serum LDH 1,065±1455 IU/L (range, 159-9216). Thirty-two patients were conditioned with chemotherapy and radiation and 19 with chemotherapy only.

With a median follow-up of 21 months, 40 patients are alive with a disease-free survival (DFS) and a relapse rate at 8 years of 77% (95% CI, 65-89) and 10% (95% CI, 4-18), respectively. Toxic deaths occurred in 14% of cases.

In the multivariate analysis of the prognostic factors, only LDH at diagnosis showed independent prognostic value for DFS after transplant ($p=0.015$), the best discriminant level being 600 IU/L. Interestingly, age, histology, clinical stage, number of regimens needed to achieve the remission, interval between complete remission and ABMT, and conditioning regimen were of no predictive value.

This study confirms that in patients with NHL in first CR, ABMT is feasible and can produce prolonged DFS, although the toxicity of the procedure may not be negligible. Of note, a well-known prognostic parameter at diagnosis (LDH level) that identifies patients not likely to be cured with conventional chemotherapy is also correlated with a shorter DFS after transplant.

T 225 HIGH-DOSE THERAPY (HDT) WITH AUTOLOGOUS BONE MARROW TRANSPLANTATION RESCUE (ABMT) IN 100 AGGRESSIVE POOR-PROGNOSIS NON-HODGKIN'S LYMPHOMAS. A REPORT OF THE NON-HODGKIN'S COOPERATIVE STUDY GROUP.

G. Santini*, A.M. Congiu, P. Coser, T. Chisesi, A. Contu, A. Porcellini, M.R. Sertoli, O. Vinante, D. Pierluigi, S. Nati, E. Rossi, M. Spriano, L. Miglio, R. Vimercati, E. Damasio, V. Rizzoli. *Department of Haematology, San Martino Hospital, Genoa, Italy.

Up to January '92, 100 adult intermediate and high-grade NHL (F,G,H,I,J/WF) with advanced stage, were treated with HDT and ABMT. 45 pts were in 1st complete remission (CR), 16 in 2nd CR, 21 in 1st partial remission (PR), 18 in progressive disease (PD). Pts' had a median age of 32 years (range 15-55); 68 were males and 32 females. At initial diagnosis 11 were stage II bulky > 10 cm., 14 stage III, 75 stage IV; poor prognostic factors were present as follow: bulky disease in 61 pts, LDH > 500 U/L in 74, B symptoms in 39, BM involvement in 35 and more than 1 extranodal involvement in 29. 1st CR pts were intermediate and high-grade NHL with two or more negative prognostic factors at diagnosis or adult advanced-stage lymphoblastic lymphomas (LBL). In second CR, 1st PR and PD, no additional negative factors were required. As conditioning regimen before ABMT rescue, seventy-four pts received Cytoxan (60mg/Kg x 2 days) + Total Body Irradiation (10 Gy in a single dose) and 26 high-dose poly-chemotherapy only. Procedure related deaths were 11: 6 due to cerebral haemorrage, 2 to cardiac failure, and 3 to sepsis, broncopneumonia and venocclusive disease respectively. The overall probability of survival and DFS, at 4 to 7 yrs, according to the status at ABMT, are as follow:

	1st CR %	2nd CR %	1st PR %	PD %
S	57	53	56	16
DFS	55	54	36	11

In conclusion our experience suggests that first CR's are the most favourable moment to perform HDT followed by ABMT in aggressive NHL with additional negative prognostic factors at diagnosis, or in adult advanced stage LBL. A randomized study is now warranted to evaluate the real benefit of adding ABMT to this category of patients. In 2nd CR or 1st PR pts present results seem to improve survival and DFS. However, also for these pts, randomized studies are requested.

T 226 POOR RISK LYMPHOMAS TREATED WITH INTENSIVE THERAPY AND RESCUE WITH AUTOLOGOUS TRANSPLANT.

P.Llamas, M.G.Gómez-Roncero, V.Carrasco, R.Cabera, C.Regidor, J.L.Díez, R.Forés, M.Briz, I.Sanjuán y M.N.Fernández. Hospital Puerta de Hierro, Universidad Autónoma de Madrid, Spain.

7 patients with Hodgkin's Disease (HD) and 8 with non-Hodgkin Lynphoma (NHL) (3 of these High Grade), mean age 31 years (14-47), received intensive therapy followed by autologous transplant (AT), either bone marrow (BM) or peripheral blood stem cells (PBSC), 6 to 184 months (mean 4.5) after initial diagnosis. Their clinical status at the time of AT was as follows:

	1st CR	CR >1st	Responsive relapse	Refractory
HD	0	4	1	2
NHL	2 (HG)	4	1	1 (HG)

10 patients received TBI+CTX (12 Gy and 120 mg/kg), 3 were given BUS + CTX (16 and 120 mg/kg) and 2 got CTX + VP16 + BCNU (6 g/m, 1.5 g/m and 300 mg/m); 5 received PBSC-AT and 10 BM-AT, all preserved in liquid nitrogen but 1 BM-AT that was kept 52 hours at 4ºC. BM-AT contained a mean of 3.02×10^8/kg (2 - 4.45) nucleated cells and a mean of 10.8×10^4/kg CFU-GM (4.27 - 23). PBSC were collected following chemotherapy (ChT) in 2 patients and after ChT followed by G-CSF in 3; the mean of nucleated cells auto-grafted was 8.6×10^8/kg (4.62 - 15.7) and the mean of CFU-GM 35.8×10^4/kg (5 - 87.76). Following AT, 6 patients received G-CSF and 1 GM-CSF, until recovery of the neutrophil count.

All patients but 1, who died on day +19 with pulmonary aspergillosis, had complete hematopoietic engraftment. Mean time until neutrophils $>0.5 \times 10^9$/l and platelets $>50 \times 10^9$/l were 16.4 (8-27) and 29.4 (9-58) days (18.6 and 22.6 days for those receiving PBSC-AT).

11/15 patients are alive with a median follow-up time after AT of 11.6 months (5.5 - 20): 8 are in CCR, 1 in CR having relapsed 6 m. after AT (a new CR was obtained with ChT) and 2, who had refractory disease at the time of AT, with active disease. The 4 patients who died were the 3 high grade NHL (2 treated in their 1st CR and 1 in his 3rd) and 1 of the 2 patients who had refractory HD; main cause of death was infection in 2 (days +19 and +90) and relapse in the other 2 (days +69 and +130). Actuarial survival is 65 % and DFS 25 % 1 year after AT. For the group of patients with HD the corresponding data are 86 % and 48 %

CTX=Cyclophosphamide; BUS=Busulfan; TBI=total body irrad.

T 227 ESCALATING DOSE OF MITOXANTRONE (MITO) WITH HIGH DOSE CYCLOPHOSPHAMIDE, CARMUSTINE AND ETOPOSIDE (CBV) IN REFRACTORY LYMPHOMA UNDERGOING ABMT.

M. Attal, D. Schlaifer, F. Huguet, P. Canal, G. Laurent, J. Pris - Service d'hématologie - TOULOUSE - FRANCE.

CBV is a standard regimen for patients with lymphoma undergoing ABMT. However, almost all patients grafted in refractory phase of the disease ultimately relapse. MITO is an active drug in lymphoma and was demonstrated to be suitable for dose escalation when supported with ABMT. We thus conducted a dose finding study of MITO associated with CBV and ABMT : MITO, single infusion over 30 min on D-8 ; Cyclophosphamide, 1.5 mg/m^2 every 24 hours for 4 doses on D-7, -6, -5, -4 ; Etoposide, 125 mg/m2 every 12 hours for 8 doses on D-7, -6, -5, -4 ; Carmustine, 300 mg/m^2 in a single bolus infusion on D-4 ; unpurged bone marrow graft was infused on D0. Twenty patients (mean age 38.5 years) with malignant lymphome (HD = 6, NHL = 14) refractory to conventional therapy (primary refractory = 8, refractory relapse = 12) were treated at six dose levels of MITO (15, 30, 45, 60, 75, 90 mg/m^2). Pharmacokinetic results demonstrated a linear relationship between administered dose of MITO and 1) plasma peak value, 2) area under the curve, and 3) D0 plasma concentration of MITO. No toxic death occured. The maximum tolerated dose appeared to be 75 mg/m^2. Indeed 2/5 patients treated with 90 mg/m^2 developped WHO grade toxicity ≥ 3 (1 hepatic, 1 cardiac) versus 0/15 patients treated with doses up to 75 mg/m^2. Furthermore the mean duration of neutropenia was 31.7 days for patients treated with 90 mg/m^2 versus 22.6 days for doses up to 75 mg/m^2 ($p<0.05$). Hematologic toxicity appeared to be due to long terminal plasma half life of MITO resulting in the drug being detectable in the plasma on the day of marrow infusion. A high response rate was observed at each dose level and 60 % achieved CR. The 2 years post ABMT probability of survival was significantly higher for patients achieving CR after ABMT (71 % - 95 % CI = 30 to 99) than for patients who did not (0 %) ($p < 0.001$). Finally, the high rate of CR we observed in such a poor risk population suggests that MITO + CBV may represent an advance in the management of lymphoma.

T 228 DOSE INTENSIFICATION OF ETOPOSIDE IN THE BEAM ABMT PROTOCOL FOR LYMPHOMA : TOXICITY ANALYSIS

W Mills, J Strang, J A Arnold, K Patterson, D C Linch, A H Goldstone
University College Hospital, Gower Street, London

The lymphomas are chemosensitive malignancies, with a clear dose-response relationship. High dose chemotherapy with autologous bone marrow transplantation (ABMT) improves outcome in patients with refractory lymphoma compared to conventional dose treatment and with regimens such as BEAM, long term disease free survival rates of approximately 50% in subjects with chemosensitive tumours can be achieved (Linch, 1993), albeit at the cost of significant mortality and morbidity. The BNLI miniBEAM-BEAM study and experience at our own centre (Chopra et al,1991) demonstrate that the dose intensity - response curve may not have plateaued even at this end of the spectrum. Increasing the Carmustine dose in ablative regimes beyond 300mg/m^2 is associated with a significant increase in mortality from pneumonitis (Wheeler,1990; Zulian,1989), and we have thus piloted escalated doses of Etoposide in the BEAM protocol in an attempt to improve response rates.

26 patients have received 400mg/m^2 of Etoposide daily for 4 days, and 13 patients 600mg/m^2, with standard doses of Carmustine, Cytarabine and Melphalan. 23 subjects had refractory Hodgkin's disease, and 16 nonhodgkin's lymphoma. No significant cardiovascular or respiratory complications occurred at either dose, and haematological recovery times were similar to standard dose BEAM, but increased gastrointestinal (GI) toxicity was noted. 9 patients in the 400mg/m^2 group suffered grade III to IV mucositis, with severe diarrhoea (35%), and GI haemorrhage occurred in 3. One death occurred due to intracerebral haemorrhage in a platelet refractory patient. 10 of the 13 patients recieving 600mg/m^2 of Etoposide suffered grade III to IV mucositis with severe, prolonged diarrhoea (78%), and significant GI haemorrhage occurred in 5. One patient died from complications of toxic colitis, and 7 required TPN. 21 patients from the 400mg/m^2 group have been evaluated for response at 3 months post ABMT; 14 achieved CR and 4 PR, with an overall response rate of 86%. Overall response in the 600mg/m^2 patients was 89%; of 9 assessed, 5 attained CR and 3 PR. From this study we conclude that, although the escalation of Etoposide has not lead to a significant increased early mortality, the maximum tolerated dose within the BEAM protocol is 400mg/m^2, and we are now using this dose in all patients undergoing BEAM ABMT. The initial response rates compare favourably with our previous BEAM results, but ultimate proof of the efficacy of such dose escalation will require a randomised trial and long term follow up.

T 229 ABMT IN NON HODGKINS LYMPHOMAS.

Bone marrow purging with immunomagnetic beads.

Kvaløy S, Kvalheim G, Jakobsen E, Beiske K, Langholm R, Høiby A, Funderud S, Fodstad Ø, Smeland E, Jetne V, Olsen D, Foss Abrahamsen A, Høst H, Vorkinn E & Holte H.
The Norwegian Radium Hospital, 0310 Oslo, Norway

We report the results obtained in 51 non Hodgkins lymphomas (NHL) autotransplanted with bone marrow purged with immunomagnetic beads. 21 patients with lymphoblastic lymphoma (LB) in stage IB - IVB and one patient with centroblastic lymphoma were transplanted in first remission. 31 patients (14 low grade and 17 high grade) were transplanted in second or later remission. 44 patients were in complete remission (CR) and 7 in partial remission (PR) at the time of ABMT. The bone marrow from all 37 patients with B cell lymphomas were purged with coctail immunomagnetic beads conjugated with monoclonal antibodies directed towards CD 19, 20, 21, 23, and 37. The 14 T cell lymphomas were purged with immunobeads towards CD2, 3, 4, 5, and 7. At the time of harvesting, four patients (two B cell and two T cell lymphomas) had 5 - 20% tumor cells in the bone marrow. After purging, no tumor cells could be detected by immunohistochemical examination.The pretransplant regimen consisted of hyper-fractionated TBI (1.3 Gy x 2/5 days) and CY 60 mg/kg/2 days. 8/9 (89%) of the B lymphoblastic NHL and 8/12 (67%) of the T cell lymphoblastic NHL are in CR with a median observation time of 18 mos. (mean observation time 27 mos.). Of those who underwent ABMT in 2. or later remission, 10/14 (71%) low grade and 8/15 (53%) high grade are in CR, respectively (median observation time 9 mos., mean 14 mos.). Except for one patient, granulocyte engraftment (> 0.5x10^9/L) was observed on day 24 (median). Platelet recovery (> 20x10^9/L) was observed on day 34 (median). However, one patient had a late recovery of platelets (8 mos.), and in another patient the platelets are still not recovered after 12 mos. 11 patients have died, two in septicemia and nine in relapse. The lymphoblastic group has at our institution a very poor prognosis (historical control). Despite a certain selection bias, we consider that the results of ABMT in lymphoblastic lymphomas are promisisng.

T 230 Total body irradiation and bone marrow transplantation in fifty patients with haematological malignancies using CT based planning

P. J. Barrett-Lee*, A. M. Cassoni, W. Mills, A. H. Goldstone.

Dept. of Clinical Oncology and Haematology, Middlesex and University College Hospital, London W1N 8AA.

The first 50 patients with a variety of haematological malignancies have been treated with total body irradiation (TBI) using CT/computer dose calculation prior to bone marrow transplantation (BMT). Accurate planning and display of dose distributions to critical structures is possible with this system. Patients are treated using parallel opposed lateral beams in the supine position using 8 MV photons. Since 1989 33 males and 17 females have been treated (age range 9-51 years). There were 14 cases of AML, 16 with ALL/T cell lymphoblastic lymphoma, 11 with NHL, 6 with CML and 3 patients had solid tumours. The majority of patients received conditioning with either Cyclophosphamide 60 mg/kg or melphalan 110 mg/m^2 with TBI doses of either 12 Gy in 6F/3 days (35 patients) or 14.4 Gy in 8F/4 days (14 patients). With follow-up time ranging from 5-43 months there have been 16 deaths in total (32%) with an actuarial 2 year survival of 55%. The 2 year actuarial relapse-free survival was 65% with 7 deaths from leukaemic relapse at 2-9 months after BMT. In addition 9 patients died from treatment related toxicity including two with veno-occlusive liver disease, two with aspergillosis and two with chronic GVHD. In all 14 patients had significant pulmonary toxicity (28%) which was fatal in 5 cases. Eight patients showed evidence of pneumonitis based on pre- and post-treatment lung function tests (16%) of which 50% were CMV related. With longer follow-up and accurate knowledge of TBI dosimetry it will be possible to relate late radiation effects such as cataract formation and endocrine abnormalites to the actual doses received by such tissues.

T 231 HIGH-DOSE CYTOXAN (HD-CY) + G-CSF PRIMED PERIPHERAL BLOOD STEM CELL AND AUTOGRAFT FOR NHL WITH PERSISTENT BONE MARROW INVOLVEMENT.

G. Santini, A.M. Congiu, T. Chisesi, E. Rossi, M. Spriano, M. Vespignani, S. Nati, M.R. Sertoli, L. Miglio, D. Pierluigi, G. Piaggio, M.R. Raffo, M. Podestà, E. Damasio. Department of Haematology, San Martino Hospital, 16100 Genoa, Italy.

From September '91 to December '92, 15 patients (pts.) with B phenotype, intermediate or high-grade non-Hodgkin's lymphomas, pretreated with a median of two combination chemotherapy regimens (range 1-4), underwent HD-CY (7 gr/mq single dose) and G-CSF infusion (5 mcg/Kg/day, continuous infusion), in order to reduce tumor burden and to collect Peripheral Blood Stem Cells (PBSC). The median age of pts. was 42 yrs. (range 28-54); 6 pts. were males and 9 females. All pts. presented BM involvement, ranging from 10 to 50%, and eleven nodal disease. Performance Status was 0-2. The collection began with a median number of about 1.000/mcl WBC. Median number of apheresis was 6 (range 4-12); median collected cells were 6.9 x 10^8/Kg (range 2.72-13.2); median of CFU-GM was 10.8 x 10^4/Kg (range 0-70.6) and median of CD34+/CD33- was 4.93 x 10^6/Kg (range 0-17.4). In 13 pts. phenotypic analysis of collected cells showed values to be within the normal range (CD10+: 0.2%; CD19+: 1%). In one patient, a clonal B lineage population developed (CD10+: 24-43%; CD19+: 36-54%). In another patient, peripheral and BM progression occurred during collection. After a conditioning regimen (Melphalan + TBI or BEAM), 13 pts. received PBSC rescue, and 11 are evaluable for response. Nine out of 11 pts obtained BM and nodal complete remission, while two pts. entered PR. A good short-time engraftment (1 month) was observed in ten pts. Long-time engraftment (> 3 months) showed peripheral pancytopenia and BM hypocellularity in five pts. Statistical analysis was made on 9 pts in CR: 5 (group A) with poor engraftment (peripheral pancytopenia and BM hypocellularity), and 4 (group B) with good engraftment. A significant difference seems to exist between groups A and B in terms of CFU-GM (5.38 vs 28.1; p=0.02), and infused cells (5.6 vs 9.8; p=0.01 average number). Overall procedure was well tolerated. Four pts. died in CR (2 of broncopneumonia at +2, +5 months; 1 of pancytopenia at +6 months and 1 of lung fibrosis at + 9 months after rescue). Two pts. relapsed at +8 and +9 months. Up to now 3 patients are in CR at +3, +6, +8 months after PBSC rescue.

T 232 HIGH-DOSE CYCLOPHOSPHAMIDE, ETOPOSIDE AND BCNU (CVB) WITH AUTOLOGOUS STEM CELL RESCUE IN MALIGNANT LYMPHOMAS.

Caterina Patti, Ignazio Majolino, Rosanna Scimè, Alessandro Indovina, Stefania Vasta, Grace Liberti, Serena Gentile, Alessandra Santoro, *Roberto Pisa, and Francesco Caronia. Dipartimento di Ematologia e Unita' Trapianti di Midollo Osseo, and *Servizio di Istopatologia, Ospedale V. Cervello, Palermo, Italy.

Eighteen patients with malignant lymphoma, 10 non Hodgkin's and 8 Hodgkin's, were treated with high-dose CVB (cyclophosphamide 4 x 1,5 g/m^2; etoposide 4 x 250–400 mg/m^2; carmustine 4 x 150–200 mg/m^2), and received autologous peripheral blood stem cells (PBSC, 13 patients) or bone marrow (BM , 5 patients) for transplantation. At time of autograft 6 patients were in complete remission (CR), 3 in partial remission, 4 in sensitive relapse, 1 in resistant relapse and 4 with progressive disease. CR patients all had poor prognostic features at presentation. PBSC were collected at time of rapid hematologic recovery after intense chemotherapy by use of a cell separator. All patients engrafted. Median time to achieve $\geq$ 0.5 x 10^9/l polymorphonuclear cells (PMN) and $\geq$ 50 x 10^9/l platelets was 13 days for both lines in PBSC autografted patients, and respectively 20 and 28 days in BM autografted patients. A significative advantage of PBSC over BM was found for time to recover either PMN $\geq$ 0.5 and PMN $\geq$ 1 x 10^9/L (p=0.01). Autograft-related toxicity consisted mainly of moderate-severity interstitial pneumopathy (3 patients), and VOD (1 patient) that resolved completely. Of the 12 patients autografted with detectable disease, 5 (41%) obtained a CR. Seven out of the 18 autografted patients (39%) had disease progression 1 to 5 (median 3) months after autograft. The projected progression-free survival is over 50% at 3 years with a significative difference between patients with sensitive and resistant disease (p=0.01). The efficacy and low toxicity of CVB suggest that autograft with PBSC may be proposed for the primary treatment of poor prognosis malignant lymphomas.

T 233 High-dose Radiochemotherapy with Peripheral Blood Stem Cell Support in Low-grade Non-Hodgkin's Lymphoma.

R.Haas, R. Ehrhardt, H. Goldschmidt, W. Hunstein.
Dept. of Internal Medicine V, Univ. of Heidelberg, Germany

Patients with stage IV low-grade non-Hodgkin's lymphoma (NHL) may be considered for dose-escalated cytotoxic therapy and stem cell support, because long-term disease-free survival is rarely achieved with conventional chemotherapy. Since 1/92, 10 patients (median age: 39 years, range 29 - 51) with centrocytic (2) or follicular (8) NHL were included into our pilot study. Following "remission" induction with first-line regimens such as CHOP or Promace-MOPP, the patients received one course of consolidation therapy with high-dose ara-C/mitoxantrone plus G-CSF (Neupogen, Amgen). With a median number of 3 leukapheresis a sufficient number of peripheral blood stem cells could be harvested. A threshold quantity of 5x10^{6}CD34+ cells/kg bw necessary for rapid and sustained engraftment following myeloablative conditioning therapy was obtained with one single leukapheresis in 5 of the 10 patients. More important, compared with bone marrow, the blood-derived autografts were characterized by an extremly low content of CD19+ B-cells (less than 0.2% of the total nucleated cells).
So far, 6 pts underwent myeloablative conditioning therapy with hyperfractionated total body irradiation (14.4 Gy) and cyclophosphamide (200 mg/kg). Following the reinfusion of G-CSF-exposed PBSC, rapid engraftment was achieved with a median time of 11.5 days (range 11 - 15) to reach 0.5 x 10^9/l neutrophils and 9 days (range 6 -12) for 20.0 x 10^9/l platelets. No hematopoietic growth factors were given post-transplantation. The treatment-related toxicity was low with a median hospitalization of only 20 days. All patients are still in remission with a median follow-up of 4 months (range 2 - 6). The low toxicity of this therapeutic "up-front" approach reflects a patient recruitment at a time when the hematopoietic reserve is not compromised by repeated cycles of chemotherapy. The incorporation of new ex-vivo strategies such as the CD34+ cell enrichment in the cytokine-mobilized autografts is then feasible to reduce the potential risk of reinfusing clonogenic tumor cells.

T 234 PERIPHERAL BLOOD PROGENITOR CELL (PBPC) PLUS AUTOLOGOUS BONE MARROW TRANSPLANTATION (ABMT) SIGNIFICANTLY SHORTENS TIME TO ENGRAFTMENT IN PATIENTS WITH NON-HODGKIN'S LYMPHOMA (NHL) AND HODGKIN'S DISEASE (HD).

Karanes, C, Ratanatharathorn, V, Uberti, JP, Abella, E, Lum, LG, and Sensenbrenner, LL. Wayne State University, Detroit, Michigan, U.S.A.

Between 10/91 and 1/93, 13 pts underwent GM-CSF primed PBPC plus ABMT (Group A) for NHL and HD. Daily GM-CSF at the dose of 250 mcg/M^2 was given subcutaneously for 9 days with leukapheresis on days 6, 8 and 9. BM was then harvested during stable phase hematopoiesis. Cyclophosphamide 50 mg/kg/d and total body irradiation 300 cGy were administered on days -8 to -5 and days -4 to -1 respectively. Pts with prior mediastinal or abdominal radiation >2000 cGy received Cyclophosphamide 1.8 gm/M^2/d, VP16 400 mg/M^2/d on days -7 to -4 and BCNU 600 mg/M^2 on day -3. PBPC and BM were infused on Days 0 and +1. GM-CSF 250 mcg/M^2 was given SQ daily after BM infusion on Day +1 until PMN >1,000/cu.mm. x 3 consecutive days. The time to engraftment, duration of antibiotics and hospital stay were compared to 69 historical control patients who received only ABMT for NHL and HD (Group B) as shown below. All pts had been previously treated with chemotherapy with a median of 1.5 regimens (range 1-6). 31 pts received prior radiation therapy and 21 received booster radiation to the area of bulky disease prior to BMT.

	PSPC+ABMT	ABMT	
total #pts	13	69	
NHL/HD	8/5	37/32	p=0.82
median age	47 (18-60)	37 (13-60)	p=0.18
CY-TBI/CVB	9/4	34/35	
PSC cell dose(x10^6/kg)	5.44(1.67-6.7)	-	
BM cell dose(x10^8/kg)	2.2 (0.4-3.5)	2.5 (0.82-6.0)	p=0.34
purging	4 (31%)	11 (16%)	p=0.38
Days PMN<500	13 (9-59)	22 (9-72)	p=0.001
Days PMN<1000	15 (12-63)	30 (10-208)	p<0.001
Days PLT<25,000	24 (7-65)	31 (1-204)	p=0.35
Days PLT<100,000	40 (13-68)	60 (13-482)	p=0.254
days of antibiotics	25 (0-77)	27 (12-58)	p=0.73
days in hospital	33 (24-85)	37 (23-76)	p=0.44

The recovery time to PMN >500 and >1,000 were statistically significantly shorter in pts receiving both PBPC plus ABMT (p=0.001), the duration of thrombocytopenia, intravenous antibiotic and hospital stay were not different. The data confirm the rapid neutrophil recovery when adding PBPC to ABMT even in these heavily pretreated group of patients. The followup time is too short to compare the difference in the relapse rate and overall survival between the two treatment groups.

T 235 G-CSF AND HIGH DOSE SEQUENTIAL CHEMOTHERAPY WITH PB AND BM CELL AUTOGRAFT AS FIRST LINE TREATMENT FOR ADVANCED-STAGE NON-HODGKIN'S LYMPHOMAS.

C. Tarella, D. Caracciolo, P. Gavarotti, P. Bondesan, C. Cherasco, P. Zanon*, E. Gallo, A. Pileri. Divisione Universitaria di Ematologia; Ospedale Molinette, Torino, Italy and *Amgen Italia.

Sequential administration of high-dose single drugs concluded by PB and BM autograft (HDSA) has been proposed by Gianni et al. from the Milan Cancer Institute. We employed the HDSA scheme as first line treatment in 11 lymphoma patients with particularly poor prognosis. Clinical features included: median age of 47 years (range 26-57); stage III in 3 pts, stage IV in 8 (5 with BM involvement); subtype: E (2 pts), F (4 pts), T-Aild type (1 pt), "discordant" G or H (4 pts). The scheme was preceded by 1-2 APO courses and 1-3 DHAP for debulkying purposes. G-CSF (Filgrastim; Amgen-Roche) was given to 10 pts after high-dose (HD) CTX and VP16. G-CSF shortened the neutropenic phase (1st day to > 500 ANC/mmc: +12 for both HD-CTX and HD-VP16; median duration of ANC < 500/mmc: 4 and 3 days, for HD-CTX and HD-VP16, respectively) and amplified the extent of progenitor mobilization. In fact, higher peak values of circulating CFU-GM were recorded after the first high-dose course compared to the second course (median CFU-GM peak values = 23,644/ml vs. 3,757/ml), independently of the drug employed. There was one toxic sudden death in a patient waiting for autograft, while in CR; one patient with pericardial lymphoma, refractory to most attempted treatments, including RT, died for disease progression 10 mos. from diagnosis. Of 9 pts completing the scheme (8 autografted with PB $\pm$ BM cells, 1 with BM cells only), 8 (72%) achieved CR. These pts are in continuous CR, at a median follow up of 18 mos. Thus, HDSA with G-CSF proved to be a well tolerated scheme; appropriate timing of drug delivery with G-CSF allows collection of large amounts of circulating progenitors; HDSA supported by growth factor may be effective in lymphoma patients with limited life expectancy.

T 236 HIGH DOSE SEQUENTIAL CHEMOTHERAPY WITH PB AND BM CELL AUTOGRAFT IN HIGH RISK RELAPSED LYMPHOMAS.

D. Caracciolo, P. Gavarotti, M. Aglietta, P. Bondesan, M. Falda, E. Gallo, F. Locatelli, A. Novarino, F. Paolino, F. Sanavio, S. Urgesi, U. Vitolo, C. Tarella. Divisioni Universitaria e Ospedaliera di Ematologia, Ist.Radioterapia, Clin.Medica I; Osp. Molinette, Torino, Italy.

Feasibility and efficacy of the innovative regimen based on the sequential administration of high-dose single drugs followed by myeloablative treatment with BM+PB cell rescue (HDSA) was tested in 14 patients with relapsed or refractory lymphoma and very poor prognostic features, i.e. histological switch, marrow invasion, low performance status. There was one treatment-related death during the high-dose phase; three more patients did not complete the program due to disease progression or extrahemopoietic toxicity. Ten patients completed the program and showed excellent tolerability to the final autografting phase. Eight patients were grafted with BM + PB cells; a substantial increase in progenitor cell mobilization was documented in 6 patients following high-dose chemotherapy. A durable response was documented in 11 patients; CR was reached in 10 patients. A high tumor response was already seen following HD-CTX in the 3 patients presenting with massive BM involvement and leukemic spread of small lymphocytes. Median overall survival (OS) was 27 months and median failure-free survival (FFS) was 12 months. In a comparable group of 26 patients treated during the same period with conventional therapies median OS was 8 months and median FFS was 4 months, thus shorter than in the HDSA group ($p=0.06$ for OS and $p=0.03$ for FFS). Four patients treated with HDSA are currently in continuous CR at +7, +16, +28, and +44 months. Thus, in poor-prognosis, heavily pretreated patients HDSA is feasible, it gives superior results than conventional therapies, it allows a prolonged survival and it might offer a chance of cure in some patients; in addition, HD-CTX should be considered as a very effective, alternative approach for the management of patients with small lymphocytic marrow invasion.

T 237 HIGH-DOSE CHEMOTHERAPY WITH G-CSF AND REINFUSION OF AUTOLOGOUS PERIPHERAL STEM CELLS (APBSC) IN RELAPSING OR REFRACTORY HIGH-GRADE MALIGNANT NON-HODKGIN'S LYMPHOMAS.

M. Freund (1), J. Andres (2), L. Arseniev (1), A. Könneke (1), P. Heußner (1), M. Kahrs (1), H.-D. Kleine (1), H.-J. Schmoll (1), and H. Link (1). (1) Department of Haematology and Oncology, and (2) Blood Bank, Hannover Medical School, W-3000 Hannover, Germany

The prognosis of relapsing and refractory high-grade malignant non-Hodgkin's lymphomas is poor. Only few patients will enter a stable complete remission. With high-dose chemotherapy and autologous bone marrow transplantation continuous complete remissions can be achieved in 20 to 40% of the patients depending on the entry criteria. On this background a positive dose-response relationship may be postulated.

To overcome the shortage of facilities for autologous bone marrow transplantation we are developing a novel high-dose protocol to be given on open ward. Treatment is started with a pre-phase of VCR 1.4 mg/m² (max. 2 mg) IV days 1, 8 and prednisolone 60 mg/m² PO days 1 - 10. The high-dose chemotherapy consists of prednisolone 60 mg/m² PO days 1 - 4, ifosfamide 1,500 mg/m² IV days 1 - 4, methotrexate 5,000 mg/m² day 1 as a 24 h-infusion, cytosine-arabinoside 1,000 mg/m² IV days 3 + 4, and etoposide IV days 3 + 4. The dose of etoposide has been escalated from 170 mg/m² to 500 mg/m² at the present time. The high-dose chemotherapy is repeated 4 times. During the pre-phase 12 µg/kg G-CSF are given twice daily. Apheresis of APBSC is done on days 5 - 7. APBSC are reinfused after the high-dose chemotherapy and G-CSF is given at a dose of 5 µg/kg. With WBC rising to >1,000/µl repeated aphereses are performed.

Thirteen patients habe been enrolled. 6 patients (age 22-55 years) are evaluable for response and toxicity, the other patients are still under treatment. 3 patients had a centroblastic NHL, the others each a large cell mediastinal B-NHL, a high-grade pleomorphic T-NHL and a high-grade not classifiable NHL. All patients had extremely advanced disease (5 stage IV, 1 stage III) with massive pretreatment (2 schedules or more in all patients, radiotherapy in 5 patients, and another patient with preceeding autologous bone-marrow transplantation). Four patients have been refractory to pretreatment, the others had a 2nd and 3rd relapse.

Granulopenia grade 4 WHO was present in all patients but hematopoietic recovery occurred after a median of 8 days after course 1 and after a median of 4 days after course 2. Medians for critical thrombopenia were 5 and 2 days respectively. Further toxicities consisted mainly in musositis, nausea, vomiting and diarrhea. Two patients achieved a complete and 3 a partial remission. 1 patient had progressive desease. We conclude that MTX-based high-dose chemotherapy is tolerable and effective when given with APBSC rescue. A further dose-escalation of ifosfamide is currently on its way.

T 238 PERIPHERAL BLOOD STEM CELL TRANSPLANTATION IN 12 PATIENTS WITH HIGH RISK LYMPHOMA: UTILIZATION OF G-CSF BOTH DURING MOBILIZATION AND FOR ACCELERATING GRAFT AFTER MYELOABLATIVE THERAPY.

A. Olivieri., R. Centurioni, M. Montillo, M. Offidani, L. Ciniero, A. Tedeschi, H. Ziarati, P. Leoni. Clinic of Haematology, University of Ancona, Italy.

Twelve patients with malignant lymphoma were transplanted with Autologous Peripheral Blood Stem Cells (PBSC); 8 were affected by high risk non-Hodgkin Lymphoma and 4 by very high risk Hodgkin Lymphoma.The median age was 35 years, ranging from 22 to 56; seven were female and five were male. Peripheral blood stem cells were collected by leukapheresis with a Fenwall CS 3000 blood separator, after mobilization with very high doses of chemotherapy (Cyclophosphamide: 7g/m² or VP-16: 2,5 g/m²), followed by Granulocyte Colony Stimulating Factor (G-CSF: Granulokine - Roche S.p.A.). The myeloablative regimen was BEAM for Non-Hodgkin Lymphomas and CVB for Hodgkin Lymphomas. At the time of transplant four patients were in first CR, four in second Cr and four in Relapse with chemosensitive disease.

We needed an average 3,5 leukapheresis for each patient, collecting $12,9x10^6$/kg CD34+ cells; we reinfused a mean of $15x10^4$ CFU-GM/kg per patient; all patients, except two with bone marrow involvement, received autologous back-up bone marrow. After receiving PBSC the patients were treated with G-CSF at the dosage of 5 µg/kg/die, subcutaneously, until reaching the threshold of 5000 WBC/µl.

The take occurred very quickly, both for neutrophils (>500/µl at day +10) and for platelets (>20.000/µl at day +15, without transfusions); immunologic recovery was also rapid (total lymphocyte count >1000/µl at day +20), but not complete, with an inverted CD4+/CD8+ ratio in all patients.

Immediate post-transplant clinical progress was good: we did not observe transplant related deaths nor interstitial pneumonia or veno-occlusive disease; the mean period of neutropenia was seven days, with an average of 2 days of fever >38°C (range 0-6); the mean hospitalisation time, from starting of the conditioning regimen, was 20 days. The follow-up ranges from two to nineteen months (median six months), with an overall survival of 92% and a DFS of 75%.

Our experience shows that the utilisation of PBSC collected after G-CSF and their association with the G-CSF after myeloablative regimen is followed by fast and complete haematologic recovery, without severe complications during the aplastic period; additional benefits include reduced morbidity, mortality, along with lower overall costs.

Lastly, although the median follow-up is too short, there is as yet no evidence that transplantation of PBSC increases the risk of relapses.

Key words:
PBSC: Periferal Blood Stem Cells; G-CSF: Granulocyte Colony Stimulating Factor.

T 239 VALUE OF GM-CSF ON COLLECTION OF PERIPHERAL BLOOD STEM CELLS (PBSC) AND HEMATOPOIETIC RECONSTITUTION IN PATIENTS UNDERGOING HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR LYMPHOMA

Ph. COLOMBAT, M. DELAIN, Ph. LANOTTE, B. CORET, I. DESBOIS, J. DOMENECH, E. BERGER, C. LINASSIER, J.P. LAMAGNERE
C.H.R.U. Bretonneau, TOURS - Schering Plough-Sandoz Laboratories PARIS - FRANCE

PBSC and GM-CSF are known to shorten duration of aplasia in patients receiving high dose chemotherapy with hematopoietic stem cell rescue. We evaluated the impact of these two technics in 67 lymphoma patients grafted in our institution since 01/89.
Twenty two patients (group I) received GM-CSF for collection of PBSC 5 µg/kg daily (Schering Plough-Sandoz) and after stem cell infusion (5 µg/kg daily until achievement of 500 PMN/mm3 on 3 consecutive days) and were compared with three historical groups : bone marrow stem cells + GM-CSF post autologous bone marrow transplantation (ABMT) (n = 1 ; group II)), peripheral blood stem cells collected and infused without growth factor (n = 6) ; group III), ABMT without growth factor (n = 28 ; group IV).

There were 46 males and 21 women with a median age of 41 years (range : 12-66) Histology was Hodgkin's Disease in 27 patients, low grade non Hogkin's Lymphoma (NHL) (including lymphocytic small cell and mixed follicular, diffused small cleaved cell lymphoma) in 18 patients, intermediate or high grade NHL (except for diffused small cleaved cell lymphoma) in 22 patients.

Conditioning regimen was chemotherapy alone in 53 patients (BEAM, n = 47 ; CBV, n = 6) or included TBI in 14 patients.

Two toxic deaths were observed in groups I and IV. At this time : 1) median of neutropenia is 12 days (4-33) in group I, 13 days (9-18) in group II, 15 days (10-18) in group III and 16 days (11-57) in group IV ($p < 0.0001$) - 2) GM-CSF shortens duration of thrombocytopenia (< 50 000/mm3) (group I + II/groupe III + IV) ($p < 0.05$) - 3) a significative reduction of duration of hospitalization is observed when we compared group I + II to group III + IV ($p < 0.0001$).

T 240

Single intermediate-dose (4g/m²) cyclophosphamide and G-CSF for mobilization of circulanting stem cells (CSC) on an outpatient basis (*).

G.Libertì, A.Indovina, F.Buscemi, S.Gentile, R.Scimé, C.Malleo, S.Vasta, M.Pampinella, V.Cappuzzo, A.Santoro, I.Majolino.
Dipartimento di Ematologia ed Unità Trapianti di Midollo Osseo, Ospedale Cervello, Palermo, Italy.

Single high-dose cyclophosphamide (HD-CY) is effective in producing high levels of CSC in patients with lymphoma, myeloma or solid tumors, but retains a certain toxicity. We used a single intermediate-dose (4 g/m²) cyclophosphamide (ID-CY) followed by G-CSF (5-10 mcg/kg) until the end of the collections in 6 patients with intermediate or high grade non-Hodgkin's lymphomas.
Their median age was 42 (range 36-48), with 4 females and 2 male. Only 1 out of 4 patients with stage IV, presented bone marrow involvement at collections. The peak level of peripheral CD34+ occurred at 9-10 days (median 9,5) after ID-CY, generally coinciding with the peak of CFU-GM. With ID-CY+G-CSF we did not observe neutropenia <0,5, fever or infections. No transfusional support was required. All the patients were treated on an outpatient basis. The patients underwent 2-5 (median 3) apheretic collections with a median yield of CFU-GM 42,0 x 10^4/kg (8-105.1) and CD34+ 2.9 x 10^6/kg (12-25). 4 patients were autografted, 3 with CSC and 1 with CSC+BM. All engrafted rapidly, with 8-14 (median 13) days to ANC>0,5 and 9-19 (median 14) to platelets >50.0. In conclusion, ID-CY+G-CSF produces high levels of CSC, the toxicity is absent and allows the treatment to be performed outpatiently. Moreover, the collections are easy to plan, with a peak of CD34+ generally on day +9 from CY administration. (*) *Work in part supported by the associazione Italiana per la Ricerca sul Cancro.*

T 241

G-CSF ADMINISTERED DURING RADIATION-INDUCED GRANULOCYTOPENIA PREVENTS DISCONTINUATION OF RADIOTHERAPY: A PHASE II STUDY.

W. Mellink[1], J. Wielenga[2]. [1]Dept. of Radiation Oncology, The Dr. Daniel den Hoed Cancer Center, Rotterdam; [2]Dept. of Hematology, University Hospital, Rotterdam, The Netherlands.

Myelosuppression is a well-known side effect of most chemotherapeutic agents. In clinical practice of locoregional radiotherapy (RT) severe (grade III/IV) granulocytopenia and/or thrombocytopenia are very rare, due to compensatory mechanisms of the bone marrow (BM) outside the treatment volume. However, it may occur in patients who are irradiated on large volumes (e.g. in the lymphomas), in particular when BM reserve is impaired due to previous myelotoxic chemotherapy and/or old age.
Retrospective studies in patients with Hodgkin's disease indicate that if cytopenia occurs during RT, treatment has to discontinued for 3-6 weeks in half of the patients and definitively stopped in the other half. On radiobiological grounds it can be assumed that this discontinuation most likely impairs curability. Although there is extensive experience with growth factors in patients treated with chemotherapy, hardly any clinical data are available on their efficacy during myelotoxic RT.
A prospective phase II study was initiated to evaluate the efficacy of G-CSF in preventing discontinuation of RT in patients with radiation-induced granulocytopenia. Eligibility criteria to start with G-CSF were: 1) RT with curative intent; 2) at least 6.0 Gy still to be delivered at the time granulocytopenia occurred (≤ 1.5 x 10^9/l); and 3) platelets > 55 x 10^9/l. G-CSF was given at a dose of 5 µg/kg/day s.c. until the granulocytes were > 10^9 x 10^9/l. RT was only discontinued if granulocytes and/or platelets decreased below 1.0 x 10^9/l and 40 x 10^9/l, respectively.
As per February 1, 1993, 5 patients have been treated with G-CSF so far; 4/5 were diagnosed with lymphoma and all patients had previously received chemotherapy. Granulocytopenia (≤ 1.5 x 10^9/l) occurred after a radiation dose which varied from 10.0-32.0 Gy. G-CSF resulted in a significant increase in the number of granulocytes after the first administration and prevented the interruption of RT in all cases. The total number of G-CFS administrations varied from 4-12 during RT and from 0-6 after RT. Finally, in all patients G-CSF-independent levels of granulocytes > 2.0 x 10^9/l and platelets > 100 x 10^9/l were reached 3-8 weeks after cessation of RT.
In conclusion, G-CSF administered during radiation-induced granulocytopenia successfully prevented temporary or definitive discontinuation of RT, which might enhance the chance of cure. A prospective, multi-institutional study is currently under way in The Netherlands.

T 242

BONE MARROW TRANSPLANTATION (BMT) IN ADULT'S LYMPHOBLASTIC LYMPHOMA (LL) R. Bouabdallah, D. Blaise, A.M. Stoppa, L. Xerri, D. Sainty, J. Camerlo, J.A. Gastaut, D. Maraninchi Institut Paoli-Calmettes, Marseille, FRANCE

Beetween 1983 and 1992, 35 adults patients with LL received BMT (autologous = 26, allogenic = 9). They all priory received prospective randomized chemotherapy protocols for acute lymphoblastic leukemia (LAL 80, LAL 84, LAL 87, LAL90). The mean age was 38 years in autologous BMT and 22 (15-40) in allogenic BMT. The staging at diagnosis shows : St I = 2, St II = 6 (4 bulky disease), St III = 4, St IV = 23. Twenty three patients were grafted (autologous = 15, allogenic = 8) in first complete remission (CR1) at a median time of 5 months (autologous = 6 months, allogenic = 4 months). Six patients received autologous BMT in second (CR2) or third (CR3) complete remission at a median time of 13 m (range 6 to 66 months) and 1 patient were allografted in CR3 at 8 months. The 5 remaining patients were considered as Refractory Disease (RD) with a median follow-up of 10 months (range 4 to 16 months) when they received autologous BMT.
A total body irradiation was performed for nearly all the patients (n=28) in association with CYCLOPHOSPHAMIDE (19 pts) or MELPHALAN (9 pts).
17/23 patients who received BMT in CR1 are alive and well in continuous CR (CCR) : 9/15 autografts with a median follow-up of 43 months (range 9 to 107 months) and 8/8 allografts with a median follow-up of 72 months (range 4 to 114 months). Five patients relapsed after autologous BMT at a median time of 5 months (4 - 10 months) and died from lymphoma, and 1 patient who was autografted died at 51 months in CCR. No relapse after allogenic BMT in CR1 was observed.
For the 7 patients who received BMT in CR2 or CR3, 2 are alive in CCR at 42 months (autologous) and 50 months (allogenic) after BMT.
1/5 patient who received autologous BMT in RD is alive in CCR (11 m+).
Overall this results confirm that BMT is partially efficient in patients failing to first line therapy with only 3/12 patients alive in CCR. The excellent results achieved when BMT is given during first CR (17/23 patients in CCR) invite to developp such a procedure after induction-consolidation chemotherapy of adult LL.

T 243

ALLOGENEIC OR AUTOLOGOUS BONE MARROW TRANSPLANTATION (BMT) AS CONSOLIDATION THERAPY IN LYMPHOBLASTIC LYMPHOMA (LBL) IN FIRST COMPLETE REMISSION (CR). Morel P, Brice P, Lepage E, Dupriez B, Marolleau JP, Jouet JP, Bauters F, Gisselbrecht C. Service des Maladies du Sang CHRU, Lille and Institut d' Hèmatologie, Hôpital Saint Louis, Paris, France

From January 1985 to April 1992, we treated 28 LBL patients (pts) aged 15 to 47 years (median 28, M/F=3) with an intent of autologous or allogeneic BMT as consolidation therapy. Criteria for intent of BMT was bone marrow involvement in the 4 first pts. The 24 remaining pts were prospectively treated with an intent of BMT if they fulfilled at least one of the following criteria: high-risk LBL according to Coleman index (J Clin Oncol, 1986, 4, 1628) (17 pts), intermediate or high risk LBL according to the LNH84 index (J Clin Oncol, 1991, 9, 211) (18 pts), or pts with unknown initial LDH and at least one of the other adverse prognostic factor included in these indexes (6 pts).
Induction regimen was: 6 cycles of CHOP: 1 pt, the LNH-84 protocol: 17 pts or ALL induction regimen: 10 pts. 15 pts had bone marrow involvement, 3 had CNS involvement. Ann Arbor stage was IV in 22 pts. LDH was normal in 4 pts, >1 to 2xN in 4 pts, >2xN in 11 pts and unknown in 9 pts. 12 pts had high- or high-intermediate risk LBL, 8 pts had low- or low-intermediate risk LBL according to the international prognostic index. This index was not determined in 8 pts. Twenty-five pts achieved a CR, 2 pt achieved a PR, 1 had stable disease. Five of the 25 CR pts relapsed before BMT. 4 of these pts underwent BMT during a second CR. However, only 1 of them is alive at 30 months. Twenty of the 25 CR pts underwent BMT (12 of them had initial BM involvement) 3 to 8 months after diagnosis (median 5 months). 4 pts received allogeneic BMT. 2 pts received syngeneic BMT. Five pts received autologous BMT with purged marrow rescue, 9 pts received autologous BMT without purged marrow rescue. Conditioning regimen included total body irradiation and chemotherapy in 18 pts, chemotherapy alone in 2 pts. No toxic death, no severe GVHD (grade 3 or 4) occurred. Seven pts relapsed 3 to 9 months after BMT (2 allogeneic, 1 syngeneic, 4 autologous BMT). Actuarial disease free survival of the 20 pts grafted in first CR was estimated 43% at 36 months, with 7 pts alive in first CR for at least 24 months. Actuarial disease free survival of the 25 CR pts was estimated 36% at 30 months. Overall survival was estimated 41% at 30 months. BM involvement, Coleman index, international prognostic index had no prognostic value for DFS and overall survival of the 28 patients.
Our results confirm that allogeneic or autologous BMT may prevent late relapse in pts with LBL in first CR. Furthermore, we could not identify a subset of LBL patients that may be selected for BMT. Large randomized study will identify LBL pts requiring BMT.

T 244 LYMPHOBLASTIC LYMPHOMA (LBL): CURABLE DISEASE WITH INTENSIVE TREATMENT.

GA Pangalis, G. Paterakis, VA Boussiotis, P Panayiotidis, S Lafioniatis, M Angelopoulou, Ch Kittas, K Papavassiliou. Lymphoma Clinic, University of Athens School of Medicine, Laikon General Hospital, Athens, Greece.

Lymphoblastic lymphoma is an aggressive tumor for which the best treatment is not known yet. In the present study we report our experience in 31 patients with LBL, who have been treated in our Unit with the L-17M protocol of the Memorial Sloan Kettering Cancer Center. 20 of them were male and 11 female with a median age of 26 years (14-68). 7 patients had clinical stage I, 5 II, 1 III and 18 IV. 6 patients presented with B symptoms. Mediastinal mass (d> 8cm) was evident in 12 (39%), bone marrow infiltration in 20 (64.5%), CNS involvement in 4 (13%), pericardiac or pleural infiltration in 9 (29%) and elevated LDH serum levels in 8 (26%) patients. Complete remission (CR) was achieved in 23 (74%) patients. This was confirmed in all but one at the end of the induction phase. The analysis of our results, as far as survival and clinical correlations are concerned is based on 24 patients who have already completed the treatment protocol (2 1/2 years). The median survival of the 17 patients in whom CR was observed, was found to be 38 mo (2-100+). Five (29%) of them relapsed in a median time of 24 mo after CR was documented. Relapse was allocated in the CNS and bone marrow in 2 patients, CNS in 1, bone marrow in 1 and mediastinum in 1. 7 non-responding patients had clinical stage IV disease with bone marrow involvement. In addition, 4 of the 5 patients who relapsed had bone marrow infiltration at diagnosis. The percentage of bone marrow infiltration however did not have any prognostic value regarding the possibility of CR or relapse. CNS infiltration, and pericardiac and pleural involvement were also negative factors concerning achievement of CR, while patient's age, presence or size of mediastinal mass and serum LDH level were not. Among the 24 patients who had completed the treatment protocol 12 deaths (50%) were observed. 7 of them concerned the patients who did not enter CR, 3 patients who relapsed after achieving CR, and 2 patients who died because of treatment toxicity in CR, (one of septicemia and toxic shock and the other of acute hepatic failure). We concluded from our trial that LBL may be considered as a currable disease in 50% of the patients, if intensive chemotherapy is administered. Factors that were found to have poor prognostic significance were bone marrow involvement (indepently from percentage) CNS, pleural and pericardiac infiltration.

T 245 MULTIAGENT CHEMOTHERAPY IN ADULT'S BURKITT LYMPHOMA.

R. Bouabdallah, A.M. Stoppa, L. Xerri, D. Sainty, J.A.Gastaut, D. Blaise, D. Maraninchi, Institut J. Paoli-I. Calmettes, Marseille, France.

Objectives : To evaluate the protocol from the French Pediatric Oncology Society in adults Burkitt lymphoma, we have treated 19 patients in our institution beetween 1984 and 1992.

Patients and methods : The mean age was 32 years (14-74); Murphy's statification shows : St.I = 1, St. II = 3, St. III = 2, St. IV = 13 (3 ALL_3). An abdominal bulky disease was present in 7 patients. The most frequent extra-nodal disease was : gastro-intestinal tract (5 pts), bone marrow (4 pts), central nervous system (CNS) (3 pts), bone (3 pts) and liver (2 pts).

This regimen includes : one course of COP with 300 mg/m^2 of CYCLOPHOSPHAMIDE (CPM) on day (D) 1, 2 mg of VINCRISTINE (VCR) on D1, 60 mg/m^2/d of PREDNISOLON (PDN) D1 to D5, followed by two courses of COPADM (CPM 500 mg/m^2/D D2 to D4, VCR 2 mg D1, PDN 60 mg/m^2/d D1 to D5, ADRIAMYCINE (ADM) 60 mg/m2 D2, METHOTREXATE (MTX) 3 g/m^2 D1. Doses of CPM and VCR are two fold in the second COPADM. This regimen ends by two courses of CYM with CYTARABINE (ARA-C) 100 mg/m^2/D D2 to D6 and MTX 3 g/m^2 D1. Four intra-thecal injections of MTX with or without ARA C are used during the chemotherapy regimen which not exceds 4 months.

ABMT conditioning by TBI and CPM or MELPHALAN was performed in 9 patients in first complete remission.

Results : 14/19 patients (73%) achieved a complete remission (CR), 2 were in partial remission (PR) and there was 3 failures. 12 out of 14 patients achieving a CR are still alive and well in continuous CR with a median follow up of 39 months (range 13 to 83 months). Two patients who were in first CR relapsed and died two months after ABMT (1 CNS relapse, 1 nodal relapse). All PR or failures (n = 5) died from lymphoma, 2 to 6 months from initiation of chemotherapy (median : 3 months).

Conclusion : This regimen gives a high rate of CR and disease free survival (DFS) in a high grade non hodgkin lymphoma. Moreover such chemotherapy gives an efficient CNS prophylaxis, without CNS irradiation. No difference in DFS was observed in patients who underwent ABMT, so, like in pediatric patients, the use of such procedure remains questionnable.

T 246 SURVEY OF BURKITT LYMPHOMA IN SERBIA 1981-1992

V. Kovčin, S. Jelić, I. Filipović, M. Đorđević

Institut za onkologiju i radiologiju, Belgrade, Yugoslavia (Serbia)

The first HIV I infection was registered in Serbia in 1983. The Burkitt lymphoma is one of the commonest neoplasias in HIV I positive population and is considered to represent a criterium for diagnosis of AIDS. Thus we have analyzed the incidence of Burkitt lymphoma in patients over 18 years in Serbia from January 1981 to December 1992 using the national cancer register. The HIV I testing included detection of anti HIV I antibodies with the Plivazym anti-HIV ELISA test and HIV I antigen with the Abbot ELISA test. Confirmatory tests included the Abbot ENVACOR test and the Western-Blot test Dupont. In 1981 and 1982 no cases of Burkitt lymphoma were recorded. In 1983 there were 2 cases, in 1984, 1 case, and in 1985, 5 cases. The number increased the next year, 5 cases being recorded in 1986. There were 7 cases in 1987, and among those cases the first HIV I positive patient was recorded. No new cases were detected in 1988 and 1989, and 1990 yielded 5 new cases all of them HIV I positive. In 1991 and 1992, 1 new case per year was recorded, both cases being HIV I negative. It is noteworthy that most HIV I positive patients in Serbia are recruited from the population of intravenous drug abusers. The Burkitt lymphoma accounted for 5/13 neoplastic disorders registered in this population. At the moment of diagnosis of Burkitt lymphoma the patients were positive either for GP41 and GP24 antibodies or for GP41 antibody and HIV I antigen; at least one HIV I positive patient during treatment lost the antigen and development GP24 antibodies. Among HIV I negative patients 2 were in clinical stage IIE, 1 in C.S.III and 16 in C.S.IV, 5 of then with bone marrow infiltration. Among the HIV I positive cases 2 were in stage IIE and 3 in C.S.IV, 1 with bone marrow infiltration. The HIV I negative cases were treated either by the ProMACE or LAL-18 regimen, including intrathecal therapy. The complete response rate was 10/18, and death due to CNS involvement accounted for 7/16 deaths in this group. The HIV I positive cases were treated with ProMACE regimen without intrathecal therapy with 3/5 complete responses, and no CNS localizations were detected until now. The survey is still ongoing.

T 247 MEDIASTINAL LARGE CELL LYMPHOMA WITH SCLEROSIS:24 CASES TREATED WITH MACOP-B REGIMEN.

R.Freilone,M. Bertini,L.Orsucci,U.Vitolo,A.Levis,G, Todeschini,V. Meneghini,D.Novero,C.Tarella,E.Gallo,G.Luxi,M.Pizzu ti,A.Novarino,A.Urgesi for the MRSGNHL Division of Hematology,Ospedale Molinette Torino (Italy)

In a series of 225 patients with diffuse large cell lymphoma (DLCL) treated,from June 1986 till December 1990,with MACOP-B,24 (9%) were defined as having a stage II large B-cell lymphoma with sclerosis of the mediastinum.This type of lymphoma has been reported to have a highly aggressive behaviour and special histological and clinical features.

Nineteen (79%) patients were younger than 50 years,18 (75%) were female and 9 (37%) symptomatic at diagnosis.Elevated LDH levels were found in 13 patients (57%).All patients had mediastinal involvement and 21 (88%) had a bulk mediastinum.10 patients had E lesion. 21 patients(88%) achieved CR,1 (4%) PR and 2 (8%) NR. A comparison was made between patients with DLCL in stage II of our series.

Lymphoma type	pz	LDH >500	Bulky	CR	DFS	Surv.
a) with sclerosis and mediastinum	24	57%*	88%*	88%	79%	90%
b) without scler. and with med.	30	34%	73%	70%	70%	80%
c) without scler. and without med.	42	23%	50%	81%	67%	67%

(* p<0,01)(5 year DFS and Survival)

The group of patients with sclerosis had prognostic parameters significantly worse ,namely, elevated LDH and bulky disease.

There were no differences in the three groups (with a median follow up of a 54 months) in CR rates in 5-year survival rates and in 5-year DFS rates.

MACOP-B chemotherapy has been proven effective in this subgroup of lymphoma patients with sclerosis that had thus far been reported to have a poor prognosis.A longer follow up and an extension of our study will enable us to confirm our encouraging results.

T 248 PRIMARY MEDIASTINAL B-CELL LYMPHOMA WITH SCLEROSIS: AN AGGRESSIVE TUMOR WITH DISTINCTIVE CLINICAL AND PATHOLOGIC FEATURES.

M. Lazzarino, E. Orlandi, M. Paulli*, E. Boveri*, E. Morra, E. Brusamolino, S. Kindl*, R. Rosso*, M. C. Buonanno, C. Astori, U. Magrini*, C. Bernasconi. Cattedra di Ematologia, Divisione di Ematologia, Sezione di Anatomia Patologica*, Università di Pavia, Policlinico S. Matteo IRCCS, Pavia, Italy

We evaluated the clinical features of presentation, the morphologic and immunohistochemical pattern, the modality of spread, and the response to therapy of 30 consecutive pts (14 M, 16 F, median age 26) with primary mediastinal B-cell lymphoma with sclerosis, a recently documented subtype of non-Hodgkin's lymphoma (NHL). The clinical aspects were largely homogeneous: 93% presented as an acute or subacute oncologic emergency due to a rapidly enlarging mass of the anterior mediastinum. The tumor was bulky in 73% and accompanied by superior vena cava syndrome in 57%. Using CT scan, the incidence of caval compression reached 80%. Intrathoracic extension to adjacent organs was documented in 47%. Despite its invasive behaviour, the disease was confined to the mediastinum and contiguous structures in 86% of pts. The tumor presented heterogeneous morphologic features consistent in most cases with "follicular-derived lymphoma": centroblastic-centrocytic (large centrocytes), diffuse, in 2; centrocytic (large) in 4; centroblastic in 17. In 7, the neoplastic population was composed mainly of centrocyte-like cells with abundant clear cytoplasm not morphologically referable to any known B-cell lymphoma subtype. All cases were characterized by huge sclerosis. Of 28 pts evaluable for response (14 treated with CHOP, 14 with MACOP-B or VACOP-B), 15 (54%) achieved CR, with a trend, not statistically significant, towards a better response to MACOP-B/VACOP-B than to CHOP (71% vs 36% CR rate, P = 0.06). After CT, 13/15 remitters received consolidation radiotherapy to the mediastinum. In this series we could identify no clinical, biological, or histopathologic features significantly correlated with poor response. The actuarial 3-yrs survival is 39% for all pts and 78% for remitters. In conclusion, this study shows that primary mediastinal B-cell lymphoma with sclerosis is a distinctive subtype of NHL. Its unique clinico-pathologic aspects and aggressive behaviour demand separate consideration among NHL. Intensive chemotherapy, followed by consolidation RT, may ensure long survival in a good proportion of cases. Some pts, however, are extremely refractory to first- and second-line treatments, with a very poor survival. Conventional prognostic factors seem inadequate to identify these very poor-risk cases. Peculiar biologic characteristics (e.g. an uncontrolled cytokine release by the tumor, suggested by the presence of a heavy inflammatory infiltrate) may explain the highly aggressive behaviour of this lymphoma.

T 249 PRIMARY MEDIASTINAL LYMPHOMA(PML)-EXPERIENCE AT MD ANDERSON CANCER CENTER (MDACC).

J. Rodriguez, W. C. Pugh, , F.B. Hagemeister, P. McLaughlin, M.A. Rodriguez, J. E. RomagueraF. Swan, F. Cabanillas. UT MDACC. Houston, TX.

PML has been described as a different B-cell lymphoma with CD19(+)CD21(-) phenotype and a lack of HLA class-1 surface molecules. From 1985-90 thirty-five patients presented to MDACC with PML. Median age was 33 yrs with a predominance of females (69%). Most (83%) presented with dyspnea, cough, or chest pain and 29% with superior vena cava (SVC) syndrome due to the mediastinal involvement. Eighty-eight percent were Ann Arbor stages I-II. CD21 was (-) in 9/9 cases studied and CD19 was positive in 15/15 cases. Serum lactate dehydrogenase (LDH) was elevated in 73% but beta 2 microglobulin (B2M) was normal in 94% despite having bulky mediastinal disease. This correlates with the lack of HLA class-1 surface molecules and suports the concept of a different biological entity. Most patients received an Adriamycin-containing regimen with involved field radiotherapy. Sixty-three percent had a complete remission and, in the group of patients initially treated at MDACC (17 of 35), the survival was 70% with a median follow-up of 42 months. As a whole, six patients received salvage ABMT of which 4 are alive with no evidence of disease. We conclude that Adriamycin containing regimens with additional involved field radiotherapy offered a rate of complete remission and survival comparable to that of other non-mediastinal B-cell diffuse large cell lymphomas.

T 250 CLINICO-PATHOLOGIC STUDY OF 69 PATIENTS WITH ANAPLASTIC LARGE CELL LYMPHOMA (ALCL).

M. Bocchia, P. L. Zinzani, F. Gherlinzoni, E. Sabattini, P. Mazza, S. Poggi, B. Falini*, C. D. Baroni**, S. Pileri, S. Tura. Institute of Hematology "L. e A. Seràgnoli" and Hemolymphopathology Unit - Bologna University; * Institute of Hematology, Perugia University - Italy; ** 2nd Chair of Pathologic Anatomy, Sapienza University - Rome.

In a multicentric randomized trial on aggressive non-Hodgkin's lymphomas comparing MACOP-B versus F-MACHOP (September 1988 - August 1991), 69 examples of anaplastic large cell lymphoma (ALCL) were recorded. In this study, all these cases are regarded as being homogeneously treated, since no significant differences between the 2 protocols arose from the trial. ALCLs represented 26% of all the analyzed lymphomas. They were subdivided into 2 groups according to Stein: common type (ALCL-CT) (41 cases) and Hodgkin-related (ALCL-HR) (28 cases). Immunohistochemistry showed that the T-cell phenotype was the most commonly observed (58%) in both groups, followed by the B-cell (29%) and null (13%) ones. On clinical grounds, ALCL-HR diverged from ALCL-CT in the mean age of patients (27 yrs versus 34 yrs) and the type of presentation. In particular, ALCL-HR always showed involvement of the mediastinum, frequent bulky disease (57%) and predilection for stage II (68%). On the other hand, ALCL-CT revealed a mediastinal mass in 57% of the cases, rare bulky tumour (18%) and more widespread stage distribution (II: 46%, III: 34%; IV: 20%). The chemotherapeutic choice was homogeneously distributed: ALCL-CT (16 MACOP-B and 25 F-MACHOP) and ALCL-HR (13 MACOP-B and 15 F-MACHOP). 28/41 (68%) ALCL-CT patients went into complete remission, and 10/41 (24%) obtained partial remission with slow response to therapy, and only 1 was resistant; at the same time, in the ALCL-HR group, 19/28 patients (68%) obtained a CR and 4/28 (14%) showed a PR. It is noteworthy that patients with ALCL-CT who obtained CR showed a higher probability of relapsing disease: 9/28 (32%) versus 4/19 (21%) of the ones with ALCL-HR. At the present time, 68% and 66% of the patients with ALCL-HR and ALCL-CT, respectively, are alive; the relapse-free survival is 79% for ALCL-HR and 68% for ALCL-CT, respectively, at a mean follow-up of 28 months (range, 12 to 46 months). Our data confirm that ALCL represents a peculiar clinico-pathologic entity, which can benefit from third generation chemotherapy regimens for high-grade non-Hodgkin's lymphomas. Moreover, it is possible to differentiate the 2 ALCL histologic subsets - CT and HR - for clinical features of presentation (age, bulky disease, stage and involved sites) and for relapse-free survival.

T 251 Ki-1 Non-Hodgkin's Lymphoma: King Faisal Specialist Hospital & Research Centre 2 Year Experience.

A. Ezzat, M. Raja, S. Bazarbashi, S. El-Akkad, R. Wierzbicki. M. Dalmark, A. Abd. El-Warith, F. Khalifa, Department of Oncology, King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia

Abstract:

Twelve consecutive patients with Ki-1 positive non-Hodgkin's lymphoma by morphologic and immunophenotypic criteria are presented. The patients had an age range of 6-53 years with a median of 20, and the sex distribution was equal. The median duration of symptoms before diagnosis was 3 months with a range of 2-6. Nine patients presented with disease in the lymph nodes, including 5 and 3 with abdominal and mediastinal involvement respectively, and 4 of these 9 also had extra nodal disease. Three patients presented with extra nodal disease as the sole site of involvement. Bone was the commonest site of extra nodal involvement, and none of the patients had skin involvement. Of the 12 patients, 7 had B symptoms. Seven patients had stage I/II disease and 5 had stage IV disease. Immunophenotyping was available in 10 patients, of which 5 were T-cell, 2 B-cell, and 2 Null-cell types respectively, and 1 could not be categorised. All 12 patients received combination chemotherapy with varying but standard protocols, and 5 had additional consolidation radiotherapy. Seven patients achieved complete remission (CR), 3 had partial remission (PR), 1 died of progressive disease (PD) two weeks after commencing therapy, and 1 patient is not evaluable and is still on treatment. Six out of 7 who had initial CR remain disease free including one successfully salvaged with second line chemotherapy and radiation therapy. Three out of 12 have died due to PD. With a median follow-up of 11 months (1-29 months), 5/7 patients with stage I/II remain disease free and 1/5 with stage IV is disease free; overall acturial survival is 67% and disease free survival is 50%. We conclude that Ki-1 positive lymphoma has a diverse clinical presentation, variable immunophenotype, and the only identifiable adverse prognostic factor appears to be advanced stage at presentation.

T 252 ANAPLASTIC Ki-1-POSITIVE NON-HODGKIN'S LYMPHOMA CLINICAL FEATURES AND PROGNOSTIC FACTORS IN A COHORT OF 50 PATIENTS.

H. Eghbali, M. Trojani, I. de Mascarel, J.M. Coindre, P. Soubeyran, F. Bonichon and B. Hœrni. Fondation Bergonié, 180, rue de Saint-Genès 33076 Bordeaux Cedex (France)

Clinical and immunohistological features of 50 patients (pts) with anaplastic Ki-1-positive lymphoma (Ki-1-NHL) were reviewed. These pts represent 4 % of 1200 cases of previously untreated lymphomas managed in the same institution. They include 27 males and 23 females of 10 to 82 years (median 41). In 29 cases, the previous diagnosis was Hodgkin's disease (15 cases), malignant histiocytosis (6), anaplastic carcinoma (7) and achromic melanoma (1). Immunophenotype study on paraffin embedded materials of 25 cases showed 4 cases of B, 8 cases of T, 13 null phenotype and was not specified in 25 cases. Thirty-nine pts displayed lymphadenopathy as initial site, 7 exclusive cutaneous lesions, 2 gastro-intestinal masses and 2 bone involvement. Twelve pts with lymph nodes (L.N.) had also cutaneous (6 cases), bone marrow (2), bone (1), thyroid (1), pleura (1) and bronchial involvement (1). According to Ann Arbor classification, there were : 15 stage I (4 stage I0), 16 stage II, 11 stage III and 8 stage IV. Constitutional symptoms were present in 20 cases and compressive or contiguous extension in 16 cases while 4 pts had a cutaneous rush. Five pts had no treatment : 2 died soon after diagnosis, 3 were in complete remission (CR) after biopsy (one with lymph node, 2 with skin lesions). Three pts were irradiated with a previous diagnosis of anaplastic carcinoma. Forty-two pts had initial chemotherapy either for anaplastic carcinoma (4 pts), Hodgkin's disease (15), malignant lymphoma (19) or malignant histiocytosis (4) with MOPP, CVPP, ABVD, EBVP or CHOP-like regimens. A complete remission was observed in 34/50 pts (68 %), 17/34 pts relapsed (50 %) after CR in L.N. (9 cases), skin (3 cases), lung (2 cases), bone, liver and stomach (1 case each). Twenty-two pts died of relapse or lymphoma progression and 6 with unrelated causes. With a median follow-up of 7.2 years, according to Kaplan Meier method and Log rank test, the disease-free survival is 65 % at 3 yèars and 45 % at 10 years, whereas freedom from progression (FFP) is 50 % and 30 %. The analysis of FFP and survival according to compressive behaviour, constitutional symptoms, cutaneous involvement, epithelial membrane antigen, granulocyte-macrophage antigen (CD15) and age (± 40 years) showed no significant difference, but the survival was statistically better in negative leukocyte common antigen cases (p=0.01) and in stages I/II vs III/IV (p=0.02). Ki-1-positivie NHL appears as a high grade lymphoma with high rate of initial failure, poor prognosis and frequent cutaneo-mucous involvement or relapses.

T 253 CLINICOPATHOLOGIC FEATURES AND TREATMENT OUTCOME OF CHILDREN WITH LARGE CELL LYMPHOMA AND THE t(2;5)(p23;q35).

J. Sandlund, C-H Pui, M. Roberts, H. Mahmoud, C. Berard, R. Hutchison, W. Crist, M. Rafferty, S. Raimondi. St. Jude Children's Research Hospital, Memphis, TN., SUNY-HSC, Syracuse, NY.

The t(2;5)(p23;q35) chromosomal rearrangement was detected in 9 children with large cell lymphoma treated at St. Jude Children's Research Hospital. When classified according to the NCI working formulation, 7 were large cell, immunoblastic and 2 diffuse large cell; according to the Kiel classification system, 6 were anaplastic large cell, 2 immunoblastic and 1 centroblastic. CD30 expression was documented in 6 of 8 cases tested. The clinical presentation included nodal ± extranodal (bone in 4 cases and skin in 3) disease sites. Seven presented with stage III disease, and one each with stage II and IV. All patients were treated with regimens containing cyclophosphamide, Adriamycin, and prednisone. Seven had a complete response (CR); one is undergoing induction therapy, and one failed induction. The latter patient achieved a CR after salvage treatment with involved field radiation and DHAP (dexamethasone, cisplatin, and cytarabine) and remains disease free 2½ years from diagnosis. Three children relapsed within 24 months from the time of diagnosis. Two of these are disease-free after salvage treatment with DHAP and autologous bone marrow transplantation (ABMT), and the third achieved a second CR after treatment with methotrexate, ifosfamide, etoposide, and dexamethasone and will soon undergo ABMT. Of the five event-free patients, two are off therapy (49+ and 75+ months from diagnosis) and three are still undergoing primary therapy. In summary, the t(2;5)(p23;q35) is associated with both anaplastic and non-anaplastic histologic subtypes, both $CD30^+$ and $CD30^-$ phenotypes, and with nodal ± extranodal involvement responsive to chemotherapy at both initial presentation and in relapse.

T 254 HISTOLOGIC AND CYTOLOGIC ASPECTS OF CHILDHOOD NON HODGKIN'S LYMPHOMAS TREATED WITH SFOP LMB89 AND LMT89 REGIMENS (French Society of Pediatric Oncology).

M.J. TERRIER-LACOMBE, M. RAPHAEL, J. DUMONT, C. BAYLE, O. GENTILHOMME, F. BERGER, P. FELMAN, C. PATTE.
Histopathologie A, Institut Gustave Roussy Villejuif France.

Since 1989, B and T cell childhood non Hodgkin's lymphoma (NHL) excepted 47 cases of anaplastic large cell NHL have been treated with LMB89 and LMT89 regimens.
Initial material from 203 cases were reviewed by a panel of pathologists and cytologists. Paraffin embedded material was obtained in 100 cases, in 44 cases, in addition to paraffin sections, imprints or smears were obtained and in 59 cases only smears or cytospins from pleural or ascitic effusions.
Cases were classified according to the criteria of the up-dated Kiel classification and its equivalents to the working formulation (WF). One subtype termed "atypical medium-sized cells" was added to characterize medium sized cells having irregular nuclear shape, intermediate features between fine and coarsely reticulated chromatin, inconspicuous nucleolus and narrow pale or basophilic cytoplasm.
A good agreement was obtained between pathologists and cytologists, some cases with discrepancies were dicussed to obtain a consensus, but the "atypical medium-sized cell" category was recognized by both.
The distribution of cases according to the histological and cytological aspects have shown : 13 centroblastic (CB) NHL or large cells (LC), 128 small noncleaved cell (SNCC) with 62 cases of typical Burkitt's lymphoma (BL) and 66 atypical BL or SNCC non BL, 30 lymphoblastic (LB), 7 cases classified as "medium sized cells", and 2 peripheral pleomorphic medium cell NHL. 23 cases remained unclassified for technical reasons.
The immunophenotype was determined in 147 cases. 136 cases were B-cell type (13 LC, 110 SNCC BL or non BL, 6 LB and all the "atypical medium-sized cell"). 11 cases were T-cell (9 LB, 2 peripheral pleomorphic medium cell).
Cytogenetic studies were performed in 26 classified cases showing t(8;14) or t(8;22) in 19 cases of SNCC (BL or non BL),in 2 "atypical medium-sized cell" and in 1 LC. Other cytogenetic abnormalities were observed in 2 "atypical medium-sized cell", 1 LB in 1 LC.
The histologic and cytologic approaches were in agreement and complementary to characterize childhood NHL recognizing in addition to classical NHL some atypical cases which are B cell type with cytogenetics abnormalities in 4 cases out of 7 showing morphologic features between lymphoblastic and SNCC non BL categories.

T 255 INFLUENCE OF ADHERENCE TO PROTOCOL ON TREATMENT RESULTS ON EXAMPLE OF NON-HODGKIN'S LYMPHOMA PATIENTS TREATED AT SINGLE INSTITUTION FROM 1987 TILL 92.

A. Dłużniewska, T. Depowska Sz. Skoczeń. Department of Haematology, Polish - American Children's Hospital, Cracow, Poland.

There were 58 children with newly diagnosed non Hodgkin's lymphoma (NHL) treated at our Department from 87 till 92. There were 9 patients of stage I or II, 36 of stage III and 13 of stage IV. 31 children were classified as B -NHL and 27 as non B NHL.
All patients were supposed to be treated according to NHL-BFM 86 protocol. Analysis of adherence to protocol as well as evaluation of treatment results was performed. A group of "non protocol patients" was selected according to following criteria:
-pretreatment
-gaps in chemotherapy exceeding 30 days starting in the first month of therapy
-temporary or permanent change of protocol
The results of treatment were as follows:
Survival(two year, plateau after two years):
whole group 68%, B NHL 68% non B NHL 64%, protocol patients 71% non protocol patients 54%.
EFS (2-year, plateau after two years): whole group 65%, B-NHL 71% non-B-NHL 57%, protocol patients 68% non protocol 54%.

T 256 A DOSE INTENSITY (DI) AND RISK FACTOR ANALYSIS OF 556 PATIENTS TREATED WITH COP-BLAM/IMVP-16 FOR HIGH-GRADE MALIGNANT NON-HODGKIN LYMPHOMAS (NHL).

H.H. Gerhartz, W. Wilmanns, Ü. Aydemir, N. Brack, G. Brittinger, W. Dornoff, M. Engelhard, A. Engert, W. Enne, R. Fuchs, W. Gassmann, J. Heise, D. Huhn, K. Kabelitz,, R. Kuse, E. Lengfelder, F. Ludwig, P. Meusers, M. Nahler, H. Radtke, C. Schadek, W. Schneider, C. Schöber, W. Siegert, U.W. Spann, H. J. Staiger, E. Terhardt, E. Thiel, T. Wagner, M. Tiemann, K. Lennert. Med. Dept. III, Klinikum Großhadern, D 8000 Munich 70, FRG for the German BMFT Study.

The efficacy of a response-adapted 7 cycle chemotherapy (ctx) (COP-BLAM, 3-5 cycles, followed by IMVP-16, 2-5 cycles) in high-grade malignant NHL was evaluated in a prospective multicenter trial. From 1986-1989, 556 evaluable patients (pts) were recruited with a median age of 56 (range 16-75) years, presenting with stage II/III/IV disease in 36%/23%/41%, B-symptoms in 51%; extranodal disease in 61%, serum LDH ≥240 U/l in 50% and lymph nodes ≥5 cm in 44% of the cases. Early CR after 3 cycles of ctx was achieved in 45%, total CR after completion of ctx in 62% of all pts. Overall (OS) and relapse free (RFS) survival are 58% and 57% at 3 years. The prognostic relevance of various parameters was studied including dose intensity (DI) which was calculated as average given DI in % of scheduled DI per cycle. Thus, 4 DI groups were formed: maximal, score >90; good, score 75-89; moderate, score 50-74; insufficient, score <50. By multivariate analysis the major risk factors for OS were identified to be age, LDH and Karnofsky index (KI) (p=0.0001 each) with comparable results for RFS (KI n.s.). Contrary to common expectations DI was only of minor importance: it was not the subgroup of maximal DI but of moderate DI that had a marginally better OS (p=0.04, in pts with at least 4 courses P=0.07). These results were confirmed if either the given dose or the time were introduced as independent variables in the model. RFS was not affected. According to these data the prognosis of high-grade malignant NHL pts is negatively correlated with tumor load, but ctx of high DI may not be advantageous.

T 257 LONG-TERM PROGNOSTIC EFFECT OF BONE MARROW (BM) AND PERIPHERAL BLOOD (PB) INVOLVEMENT IN NON-HODGKIN'S LYMPHOMAS (NHL). ANALYSIS OF 962 PATIENTS.

E. Morra, M. Lazzarino, A. Castello*, G. Pagnucco, E. Brusamolino, P. Bernasconi, A. Santagostino, A. Livraghi, A. Corso, C. Castagnola, E. Orlandi, C. Astori, M.C. Buonanno, M. Bonfichi, U. Magrini*, and C. Bernasconi. Cattedra di Ematologia, Divisione di Ematologia, Sezione di Anatomia Patologica*, Università di Pavia, Policlinico San Matteo IRCCS, 27100 Pavia, Italy.

We reviewed the records of 962 pts with NHL diagnosed and treated at our Institution between 1975 and 1991, to evaluate the impact on survival of BM and PB involvement, present at diagnosis (early) or occurring during the course of the disease (late). BM infiltration (BM+) was graded according to its extent (<25%, 25-75%, >75%). It was detected at diagnosis in 340 pts (35%): in 207/405 (51%) low-grade (LG), in 73/289 (25%) intermediate-grade (IG), and in 60/268 (22%) high-grade (HG) NHL (LG vs IG and HG, P<0.0001). Late BM+ was found in 39 further pts (4%): 11 LG, 11 IG, and 17 HG-NHL. PB involvement (PB+) was present at diagnosis in 104 pts (11%): in 16% of LG, 6% of IG (LG vs IG P<0.001), 9% of HG NHL (LG vs HG P<0.01). A late leukemic phase occurred in 69 pts (7%): 24 LG, 20 IG, and 25 HG NHL. In LG-NHL, presence and degree of BM+ as well as PB+ at presentation did not affect the outcome, while late development of BM+ and PB+ carried a poor prognosis. In IG-NHL, BM+ (especially >75%), and PB+, whenever they occurred, were significantly associated with poor outcome. In HG-NHL, pts BM+ at diagnosis did worse than BM- (P=0.06), but 50% of pts with <25% BM+ are surviving at 10 yrs. BM+ occurring late, and PB+ in any phase of the disease, predicted short survival. The table shows the actuarial survival at 5, 10, and 15 years, according to the presence of BM+ and PB+ at diagnosis or during the course of the disease.

PROPORTION SURVIVING

Grade	Low				Intermediate				High			
At years	5	10	15		5	10	15		5	10	15	
BM-	64	42	42		59	40	40	***	29	25	25	
BM+ early	60	38	38	**	37	20	0		20	14	14	*
BM+ late	18	9	-		22	22	-		0	0	0	
PB-	73	50	48		52	38	36	**	30	24	24	***
PB+ early	69	46	40	***	23	23	0		6	6	6	
PB+ late	32	7	0		22	10	6		0	0	0	

* P <0.05 ** P <0.01 *** P <0.001

T 258 Integrin β_2 chain (CD18) expression correlates with prognosis in malignant B cell lymphomas.

B.K. Erikstein, H. Holte, S. Kvaløy, E. Hannisdal and E.B. Smeland. Department of Immunology and Department of Oncology; The Norwegian Radium Hospital and The Norwegian Cancer Society, 0310 Oslo, Norway.

Several studies have shown that cell cycle related parameters including DNA synthesis and activation antigen expression can predict patient survival in lymphoma patients. In this clinical study of 69 malignant B cell lymphomas (52 with low grade and 17 with high grade malignancy) we have examined viable lymphoma cells for cell surface expression and positivity of several cell interaction and activation molecules by flow cytometry. Expression of CD18 (integrin β_2 chain) was found to correlate strongly with patient survival (median follow up 50 months) even when adjusting for other important prognostic factors (P=0·0001). The percentage of cells positive for both CDw75 and MHC class II, proved important both as single parameters and in the multivariate analysis (CDw75). Histology, classified as low versus high grade malignancy, bulky vs. not bulky disease and high vs. low thymidine incorporation, were also found to correlate with prognosis in this study. The results on CD18 expression must be interpreted with caution and need confirmation in new prospective studies.

T 259 PROGNOSTIC VALUE OF BETA-2-MICROGLOBULIN IN LYMPHOMA.

Omar El-Ahmady*, Mohamed Esmat Mahmoud, Abu Baker Helal El-Asmar, Ezzat Atwa. *Tumor Marker Oncology Research Unit and Chest Department Al-Azhar University, Cairo, EGYPT.

Serum B2-Microglobulin is frequently elevated in patients with lymphoproliferative disorders including lymphoma. This study was conducted to evaluate the diagnostic and prognostic value of B2-Microglobulin (B2-M) in patients with lymphoma and bronchial carcinoma. 50 individuals were included; 20 with lymphoma, 10 with bronchial carcinoma, 10 with non-malignant lung diseases and 10 normal healthy controls. Serum B2-M was determined wsing the phadezym B2-Micro test suplied by Pharmacia Diagnostice. Results of this study revealed that serum B2-M was significantly elevated in bronchial carcinoma and lymphoma compared to either patients with non-malignant lung diseases or normal healthy controls. 10/10/of patients with bronchial carcinoma, 17/20 of patients with lymphoma and 3/10 of patients with benign lung diseases showed levels above the cut-off value in the normal healthy controls (3.8 mg/l). Serum B2-M was correlated with the clinical state of lymphoma patients during therapy.

T 260 PRIMARY EXTRANODAL NON-HODGKIN'S LYMPHOMAS (NHL): A MULTIVARIATE ANALYSIS OF PROGNOSTIC FACTORS IN 59 PATIENTS FROM A SINGLE INSTITUTION.

JM Ribera, A Oriol, M Batlle, A Flores, G Las Heras, J Juncà, J Roncalés, M Pujol, F Millá, E Feliu. Service of Hematology. Hospital Universitari Germans Trias i Pujol. 08916 Badalona, Barcelona, Spain.

Background. Analysis of prognostic factors in 59 patients with primary extranodal NHL observed in a single institution during a 9-year period (1984-1992).
Methods. Inclusion criteria were the presence of NHL at one or more extranodal sites with or without minor (<25%) nodal component after routine staging procedures. Primary NHL of the Waldeyer's ring were excluded from the study. The following data were recorded and evaluated for prognosis: age, sex, constitutional (B) symptoms, site of involvement, bulky disease, histology (Working Formulation), staging (Ann Arbor system with Mushoff's modifications), and the main hematological and biochemical parameters. Due to the diversity of sites involved, treatment of the patients was not uniform, but usually consisted in chemotherapy preceeded by surgery when appropriate. Statistical analysis was performed using SPSS and BMDP packages.

Results. The frequency of extranodal NHL was 22%. The gastrointestinal tract was the most common site of extranodal involvement (33 cases). Eight cases were infected by HIV, the NHL was bulky in 18 patients and B symptoms were present in 20. NHL was of low-grade in 11 cases, intermediate in 24 and high in 15, whereas 9 were unclassified. The extension of NHL was: I_E 30 cases, II_{E1} 10, II_{E2} 9, III 3 and IV 7.

Complete response was attained in 32 of 52 evaluable cases (61%) (4 patients are still on treatment). Eight cases have relapsed. The probability of disease-free survival (DFS) was 60% at 5 years. Twenty-five patients have died, overall survival (OS) being 45% at 5 years. In the multivariate analysis three variables had an adverse influence in DFS: extensive disease (II_{E2}, III or IV) (p=0,003). LDH value (p=0,04), and aggressive histology (p=0,02). This results were not influenced by the exclusion of HIV-positive patients from the analysis. On its turn, the main parameters negatively affecting OS were aggressive histology (p=0,008) and extradigestive involvement (p=0,03). When HIV-positive patients were excluded from the model, bulky disease emerged as the most unfavourable variable for OS (p=0,003).

Conclusions. 1.- The frequency, localization, histological subtypes and response to treatment of the patients of this series are similar to those of other single-institution or population-based series. 2.- The main prognostic factors identified in nodal NHL can also be applied to primary extranodal NHL.

T 261 RELATIONS BETWEEN, AND PROGNOSTIC INFORMATION FROM, THE LEVELS OF DEOXY-THYMIDINE KINASE IN SERUM, IN TUMOUR CELLS AND THE TUMOUR BURDEN IN NON-HODGKIN LYMPHOMAS.

Suzanne Rehn[1], Bengt Glimelius[1], Simon Gronowitz[2], Claes Källander[2], and Christer Sundström[3]. Departments of Oncology[1] and Pathology[3], Akademiska sjukhuset, S-751 85 Uppsala and Research unit of Replication enzymology[2], Biomedical Center, University of Uppsala, S-751 23 Uppsala, Sweden.

The level of the enzyme deoxy-thymidine kinase in serum (S-TK) is shown to be of great prognostic importance in non-Hodgkin lymphomas (NHL). It has been assumed that the serum level reflects both tumour-cell proliferation rate (levels of TK in the tumour-cells (C-TK)) and the tumour burden. This study was performed in order to assess the relative contribution of tumour burden and tumour-cell proliferation rate to the S-TK levels, and to study if C-TK and tumour burden also carries prognostic information.

One hundred and five patients with NHL, 50 with high grade NHL and 55 with low grade NHL, was investigated for the levels of C-TK at diagnosis. In 89 patients, 41 with high grade NHL and 48 with low grade NHL, S-TK was available at diagnosis. Measurements of the fraction of cells in S-phase and mitotic index (MI) were available in 89 and 87 patients, respectively. The tumour volumes (in cm^3) were retrospectively estimated from the statements in the patient files.

In the entire material, a correlation between S-TK and tumour volume, but not between S-TK and C-TK was seen. However, when dividing the tumour volumes into three categories; small (< 50 cm^3), medium (50-500 cm^3) and large (> 500 cm^3) tumour volumes, there was a correlation between S-TK and C-TK within each category. This was not found within the different clinical stages, according to Ann Arbor. C-TK correlated well with the S-phase rate and MI.
S-TK, C-TK and tumour burden all carried prognostic information. In low grade NHL, C-TK had additional information to S-TK in a multivariate analyses. In high grade NHL, tumour burden had a strong prognostic information whereas the clinical stage had no prognostic information. S-TK and tumour burden never gave additional prognostic information to each other, whereas C-TK and tumour burden always did.

The serum level of TK depends upon both the tumour burden and the tumour-cell proliferation rate, thus confirming our assumption. Both S-TK, C-TK (reflecting tumour-cell proliferation rate) and tumour burden have prognostic importance. Since the S-TK levels in separate experiments increase considerably the days after cytostatic treatment, it is likely that the levels of the enzyme reflect the number of proliferating cells that has died the days before sampling.

T 262 ANALYSIS OF PROGNOSTIC FACTORS IN LOW-GRADE NON-HODGKIN'S LYMPHOMAS.(NHL) PRELIMINARY RESULTS.

P. Zamora, P. Menéndez, J. Gómez Codina, J.A. Moreno Nogueira, R. Carrión, J.J. López López, J. Dorta, J. Rifá, E. Murillo, J.L. González Larriba, R. Colomer, M. Constela, J. Belón.
GRUPO ONCOLÓGICO DE LINFOMAS (GOL). SPAIN.

OBJECTIVE: to analyze prognostic factors for survival in patients with low-grade NHL.

MATERIAL AND METHODS: the clinical records of 542 patients with low-grade NHL (groups A, B and C of the Working Formulation) treated in 13 Spanish hospitals between January 1981 and December 1991 were retrospectively analyzed. Sixteen clinical and biological variables at diagnosis were correlated with the overall survival. The analysis for the variance (ANOVA) was used to compute the data.

RESULTS: there were 268 males and 273 females, with a median age of 58.5 years (13-87). Histology according Working Formulation was: A 36.34%, B 31.5% and C 22.14%, not determined 9.96%. Clinical stages were: I - 113 patients, II - 90, III - 81 and IV - 248. Performance status (ECOG scale) was: 0-1 65.3% and 2-3 27.5%. Systemic symptoms were present in 147 patients at diagnosis. The primary location was nodal in 179 cases (33.02%), extranodal in 110 (22.29%) and combined in 253 (46.67%). The most frequent nodal location was abdominal (45.9%), followed by cervical (41.3%) and axillar and inguinal (32% each). The erythocyte sedimentation rate (ESR) was > 25 in 270 patients. The hemoglobin level was < 11 g/dL in 87 patients (16.05%). The lactate dehydrogenase (LDH) level was increased in 136 cases (25.09%). Seventy three percent of patients received chemotherapy as the first line of therapy, 13.9% (71) received radiotherapy and 10.33% (56) were operated. Seventeen patients were initially followed-up without therapy. A complete remission was obtained in 69% of patients after the first line of therapy. The median survival was 45 months (3-147 months).

The following factors were found to decrease survival in the univariate ahalysis: age > 60, stage IV, presence of B symptoms, performance status 2-3, bone marrow infiltration, albumin level < 3.5 g/dL, elevated LDH level, ESR > 25 and the lack of complete response after first line therapy. Sex, histology and hemoglobin level did not have prognostic importance.

T 263 ANALYSIS OF PROGNOSTIC FACTORS IN LOW-GRADE MALIGNANT LYMPHOMA: A STUDY BASED ON 143 PATIENTS WITH A LONG FOLLOW-UP FROM A SINGLE INSTITUTION

A. López-Guillermo, E. Montserrat, P. Marín, F. Bosch, M.J. Terol, J.C. Reverter, L. Escoda, J. Ordi, J. Bladé, E. Carreras, F. Cervantes, B. Nomdedeu, M. Rovira, J. Sierra, A. Urbano-Ispizua, C. Rozman. Postgraduate School of Hematology "Farreras Valentí". Hospital Clínic. University of Barcelona, Barcelona, Spain.

In a series of 143 patients with low-grade lymphoma diagnosed from 1970 to 1991, prognostic analyses have been performed to determine the impact of different variables in survival. Median age: 55 yrs (range, 21 to 85); M/F ratio: 79/64. Median follow-up: 6.5 yrs (range, 1.5 to 20). Overall median survival was 8.6 yrs with a projected survival at 10 yrs of 48% (95% CI: 37.5% - 58.5%). Although a higher number of complete responses (CR) was observed in patients initially treated with combination chemotherapy as compared to those receiving single agents (47% vs 21 %; p=0.013), no differences were observed in survival according to treatment (median survivals: 7.1 vs. 9.1 yrs, respectively). In addition, no survival differences were observed on the basis of histology: small-lymphocytic (52.4%), follicular small-cleaved (43%), follicular mixed (54%) at 10 yrs, respectively.
In the univariate analysis of the whole group variables associated with survival were: performance status, B symptoms, stage, number of lymphnode sites involved, extranodal involvement, bone marrow infiltration, ESR, WBC count, leukemic expression, and serum LDH. In the multivariate analysis of the entire series the only predictive variables were stage (p=0.008) and age (p=0.053). For patients in advanced III/IV stage (n=119) the only significant parameter was performance status (p=0.007). When response to therapy was included in the analysis variables associated with a longer survival, both in the whole group and in stage III/IV patients, were response to therapy: CR (p<0.001), PR (p=0.003), and absence of B-symptoms (p=0.014).
In conclusion, in this low-grade lymphoma series no major differences in outcome have been observed according to the histologic subtype and front-line treatment. However, response to therapy emerges as the most important prognostic parameter, with those patients achieving a CR having a longer survival than those in PR or failing to respond.

T 264 THE IDENTIFICATION OF PROGNOSTIC GROUPS IN YOUNGER PATIENTS WITH FOLLICULAR LYMPHOMA.

D A Cameron, R C F Leonard, J-H Mao, R J Prescott, on behalf of the Scotland and Newcastle Lymphoma Group (SNLG) Therapy Working Party.

Using the SNLG database, 268 patients were identified between 1980 and 1990 who had follicular lymphoma and were under the age of 60 years at presentation. Using a Cox model, a multivariate analysis was carried out for clinical, haematological and pathological data at presentation. A simple formula for calculating a prognostic index was derived, and the patients grouped into 25% and 75% quartiles. The prognostic index is calculated as follows:-

0.036*Age + 0.4*(Stage -1) + 0.03*(White Cell Count ÷ 10^9) + 0.7 if B symptoms are present.

Cut off points were <2.3 for the best prognostic group
and >3.4 for the worst prognostic group.

	SURVIVAL			% IN GROUP		
	median	5 Yr	10 Yr	stage IV	B Sym	>40
Best Group (25%) (1)	>123m	86%	69%	1%	0%	48%
Intermediate Group (50%) (2)	123m	80%	56%	44%	9%	75%
Worst Group (25%) (3)	54m	44%	18%	85%	71%	95%

Groups 1 & 2 had similar survival curves, but Group 3 has a significantly worse survival (p<0.0001). The dominant individual factors are stage and the presence of B symptoms. Although most of the worst prognostic group are over 40 years old, age itself does not necessarily confer a poor prognosis. White blood cell count was well distributed in all prognostic groups, but the majority of counts over 10*10^9 (53%) were in Group 3. Using this simple clinical index, we can using simple clinical assessments identify from the SNLG database, 11% (58/513) of patients with follicular lymphoma who are under 60 years old and have a particularly poor survival, and should thus be considered for more intensive or experimental treatment.

T 265 PROGNOSTIC FACTORS AND SURVIVAL IN HIGH-GRADE NON-HODGKIN'S LYMPHOMA.

Gy. Varga, Z. Borbényi, M. Bérczi. 2nd Department of Internal Medicine, Szent-Györgyi Albert Medical School, 6701 Szeged, Hungary

In a multicentre study the data of 131 consecutive patients were analyzed retrospectively to get informations about the prognostic importance of age, stage of the disease, response to the treatment, extranodal origin, B symptoms and histological subtype. The median age at presentation was 57.3 ± 16.3 years. Sixty five percent of the patients belonged to stage I and II, 35 % to stage III and IV. Patients were treated according to different protocols (CVP, CHOP-Bleo, Pro-MACE-COPP). Remission was achieved in 90 cases. The mean follow-up time was 44 months, the median survival 19.8 months. At seven years 24 % of the patients is alive.

At the univariate analysis in high-grade non-Hodgkin's lymphomas stage of the disease, response to the treatment and extranodal origin were the only prognostic factors. Using the model Cox a multivariate analysis was performed: the most important predictive factors for survival were the stage of the disease and response to the treatment. Only above 70 years gets the age some prognostic relevance.

Our results indicate that the identification of some prognostic characteristics of patients with high-grade non-Hodgkin's lymphoma would allow to identify sub-groups with unique responses to specific therapies.

T 266 TREATMENT OUTCOME AND PROGNOSTIC FACTORS IN 111 UNSELECTED AGGRESSIVE LYMPHOMA PATIENTS: COMPARISION OF THE RESULTS OF PATIENTS FULFILLING STUDY CRITERIA AND THOSE DOING NOT - RETROSPECTIVE SINGLE CENTER ANALYSIS.

H. Wandt, K. Brendel, J. Birkmann, F. Braun and W.M. Gallmeier. 5. Medizinische Klinik und Institut für medizinische Onkologie und Hämatologie, Flurstr. 17, D-8500 Nürnberg 91, Germany.

From 08/86 to 10/91 111 patients (pts) with high grade malignant NHL (Kiel-Classification) stage II-IV were admitted to our regional cancer center. 57 pts (study group) were treated in a randomized multicenter study comparing four intensive consecutive courses of CHOEP to four alternating courses of high CHOP/IVEP followed by involved field irradiation as published elsewhere. 54 pts (non-study group) did not fulfill study criteria (pretreatment before admission to our hospital, age > 70, performance status > 2). These pts were treated according to clinical assessment. 32 of the 54 pts received a comparably intensive chemotherapy (ct.) (CHOP or CHOEP), 60 % of the pts were irradiated (involved field). The other 22 pts got only a dose-reduced regime and/or less than four cycles of ct.. The reduction of intensity of therapy in this subset of pts was mainly due to advanced age and poor performance status.
Remission rate (CR/PR) for all 111 pts was 68/17 %. The overall (OS) and relapse free survival (RFS) was 54,5 % and 69,5 %, respectively, at two years with a median follow-up of 24 months . When we compare CR/PR and OS between the study and the non-study group the differences are highly significant. In contrast the RFS between the two groups did not differ significantly.

	CR / PR	OS	RFS
study group	84 / 12 %	70 %	72,5 %
non-study group	50 / 12 %	40 %	62 %
p-value	0,0001	0,0002	0.49

If we consider in the non-study group only the subset of pts (32 pts), who did get sufficient chemotherapy the differences of the remission rates, OSs and RFSs are no longer significant
In a multivariate analysis for the whole group of 111 unselected pts stage, LDH, old age and performance status are important prognostic factors.
Conclusion: Our analysis clearly shows that the results of our clinical NHL-study can be expanded to a broader group of pts, provided that the non-study pts can tolerate a comparably intensive treatment like a minimum of four courses of CHOP or CHOEP followed by involved field irradiation. Beside the established lymphoma-associated prognostic factors (stage, LDH) we can confirm the prognostic value of patient-related factors like old age and performance status > 2 for this unselected group.

T 267 PROGNOSTIC FACTORS IN PATIENTS WITH AGGRESSIVE NON-HODGKIN'S LYMPHOMA TREATED WITH CHOP.

E. Conde, M. Gandarillas, I. Román, C. Richard, J. Baro, A. Iriondo, MA. Cuadrado, MJ. Rabuñal, M. Recio, R. Rios, J. Garijo, A. Zubizarreta. Servicio de Hematología. Hospital M. Valdecilla. 39008 Santander. Spain.

We have investigated prognostic factors in 114 patients with aggressive non-Hodgkin's lymphoma (NHL), excluding lymphoblastic and Burkitt lymphomas, treated with CHOP between 1978 and 1990. The median follow-up was 24 months.

Tumor response (TR): Complete response (CR) was achieved in 73% and partial response (PR) in 11%. Logistic regression analysis showed that a poor TR after the first three courses, of CHOP (defined as <50% response) (p=0.003, OR=37.24) and a large tumor burden (p=0.0003, OR=7.69) were the best prognostic factors.

If only pretherapeutic variables were included in the analysis, tumor burden (p=0.006, OR=4.31) and bone marrow infiltration (p=0.01, OR=3.42) were retained as independent predictors of TR.
Overall survival (OS): Estimated 5-year OS was 48% (95% CI, 38-58%) with a median OS of 58 months. In univariate analysis, the variables correlated with OS were performance status (ECOG), Ann Arbor stage, bone marrow involvement, number of extranodal disease sites, tumor burden, retroperitoneal involvement, serum albumin, LDH level, alkaline phosphatase and TR. In multivariate analysis, the three variables found to be predictors of OS were TR (p<0.0001; RR=7.30), tumor burden (p<0.003; RR=4.11) and serum albumin (p<0.02; RR=3.20).

If only pretherapeutic variables were included in the analysis, tumor burden (p<0.00001; RR=8.07), Ann Arbor stage (p<0.0001; RR=3.30) and serum albumin (p<0.0016; RR=3.48) were the variables that retained their significance.
Relapse-free survival (RFS): Estimated 5-year RFS was 61% (95% CI, 51-71%).In multivariate analysis, stage was the best relapse predictory variable (p=0.0003; RR=4.74).

In this study, the three clinical features that were identified as independently predictive for survival (tumor burden, stage and serum albumin) were utilized to develop a prognostic factor model that include three risk groups of patients: **Low risk:** Low tumor burden, stage I/II and normal albumin. **Intermediate risk:** Low tumor burden with either stage III/IV or low albumin. **High risk:** Large tumor burden and/or stage III/IV with low albumin.

These 3 risk groups of patients had strikingly different outcome reflected by differences in CR, OS and RFS. CR was achieved in 91%, 70% and 44% of these groups, respectively (p=0.0007). Five-year OS for each group was 71%, 45% and 13% (p<0.00001); and 5-year RFS was 81%, 44% and 33% (p=0.001), respectively.

T 268 COMPARISON OF PROGNOSTIC SCORES OF HIGH GRADE NON HODGKIN LYMPHOMAS (NHL)

R.Heinz, G.Hopfinger-Limberger, B.Schneider* , E.Pittermann
3rdMedical Department and Ludwig Boltzmann Institute for Leukemia Research and Hematology, Hanusch Hospital, Vienna, Austria
Institute for Medical Statistic, University of Vienna, Austria*

Many different risk staging systems to predict prognosis of pts. suffering from NHL have been published.In 1983 we defined a simple score[1] using accepted risk prediction factors such as histology, Ann Arbor-staging B-symptoms,Karnofsky index, BSR,LDH,extranodal involvement and preexsisting organ dysfunction. MD Anderson Hospital[2] assessed a sophisticated system based on tumor burden and LDH. The Dana Farber score[3] considered performance status and number of involved sites. The recently introduced International Index[4], established on a worldwide multicenter study, includes age, Ann-Arbor stage, number of extranodal sites, performance status and LDH.

The above mentioned staging systems served as the basis for our retrospective study. We evaluated 109 patients suffering from highly malignant non-Hodgkin lymphoma (71 centroblastic, 38 immunoblastic, comparable to the diffuse large cell lymphoma). Treatment was administered between 1980 and 1990. All patients were uniformly staged and received the same induction therapy (CHOP). A complete follow up is available. The average age was 70 years (range: 24-89 y). Ann-Arbor stages were as follows: I/36, II/30, III/11 and IV/32. The bulk-size was >5 cm in 50 pts., >7 cm in 30 pts. and >10 cm in 16 pts. The Karnofsky-index was <70 in 54 pts. 84 pts. showed "B symptoms" and the LDH was increased in 42 pts. 58/109 pts reached a CR(54%), 33/109 reached a PR(30%) and 18(16%) pts. were non responders. The different scores with their various advantages, significance and implication for further studies will be presented.

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T 269 The Value of Lactic Dehydrogenase (LDH) and Beta 2 Microglobulin (B2m) as Prognostic Factors in Non-Hodgikn's Lymphomas.

H. EL-Zawahery, M .R. Hamaza, R. M. Gaffer, H. M. Khalid, N. Zakary, S.Shoman, and N Gad-El-mawla. Medical Oncology and Tumor Biology Departments, National Cancer Institute, Cairo .

Both of LDH and B2m are known of their values to reflect the tumor burden at time of presentation, they proved by many series to have a prognostic significance among NHL patients. We tried in this study to correlate between disease progress and response to chemotherapy with the level of LDH and B2M. Sixty three patients with NHL who were properly staged and treated with CHOP protocol of chemotherapy, were evaluated as regard their LDH and B2M Sera level. At presentation LDH and B2M were elevated in 73% of patients (100% of stage IV and 65% of stage III). According to the value of LDH and B2M three group of patients could be identified; the first were those with LDH level less than 350u/ml and B2M less than 200ng/ml, the second group were patients with LDH less than 500/ml and B2M less than 400ng/ml and the third group were those with LDH more than 500u/ml and B2M more than 600ng/ml. There was a definite relation between achieving complete remission CR and the three prognostic groups. In the first group all patients achieved CR and 20% of them relapsed while the other 80% still in CR after a follow up period of 6 months . Among patients of the second group 64% attend CR and 18% attend partial remission PR, after 6 months 36% of CR relapsed . The third group of patients showed the least response; CR 13%, PR 21% while relapses were 50% . In conclusion estimation of LDH and B2m levels at time of patients presentation is helpful for predicting the response to chemotherapy and both of them may be of value in patient's follow up.

T 270 A PATHOGENETICALLY-ORIENTED PATHOLOGIC CLASSIFICATION OF HIV-ASSOCIATED SYSTEMIC LYMPHOMAS.

A. Carbone, U. Tirelli, A. Gloghini, R. Volpe, M. Boiocchi. Centro di Riferimento Oncologico, IRCCS, 33081 Aviano, Italy.

In this paper, a specific pathologic classification of HIV-associated systemic lymphomas, including the association of EBV in different categories, has been formulated.* Eighty-seven HIV-associated NHL were classified according to classic NHL classifications, and a recent description of morphologic variants of high-grade B-cell NHL. Seventy-one cases were immunopheno-genotypically characterized; whereas, in 49 representative cases the association of EBV was assessed by non-isotopic in situ hybridization (ISH) and the immunohistochemical demonstration of latent membrane protein-1 (LMP-1). Most lymphomas were of B-cell derivation and showed a "blastic" cell morphology, with (a) small noncleaved cells (36 cases); (b) large noncleaved cells (10 cases); (c) immunoblasts, usually polymorphic (12 cases). Moreover, twelve cases were classified as anaplastic large cell (ALC) $Ki\text{-}1^+$ lymphoma. Combined ISH studies (for viral DNA and EBER) and immunohistological demonstration of LMP-1 suggested that there were differences in viral latent gene expression between ALC $Ki\text{-}1^+$ or immunoblastic lymphomas (usually EBV^+, $LMP\text{-}1^+$), and EBV-infected cells of small noncleaved cell lymphomas which did not show LMP-1 expression. Two main groups of HIV-associated systemic NHL, i.e. "blastic" cell and "anaplastic" cell lymphomas, which include specific cytomorphologic subtypes, were morphologically recognized. Within the former group, immunoblastic (polymorphic) lymphomas were included as a separate entity because they were different in EBV association and LMP-1 expression from other "blastic" cell systemic lymphomas.

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* "Blastic" EBV^- or EBV^+ $LMP\text{-}1^-$	"Blastic" EBV^+ $LMP\text{-}1^+$ or EBV^-
-centroblastic (G-WF)	-immunoblastic (H-WF)
-small noncleaved cell (J-WF)	
-plasmablastic (plasmacytoma)	"Anaplastic" EBV^+ $LMP\text{-}1^+$
-intermediate features	-anaplastic large cell $Ki\text{-}1^+$
	- ? Hodgkin's lymphoma
Others (rare types)	

T 271 Feasability of autologous bone marrow transplantation (ABMT) in HIV-associated non-Hodgkin's lymphomas (NHLs).

F. Bauduer, B. Rio, G. Andreu, C. Boccaccio, A. Delmer, F. Cymbalista, J. P. Marie, R. Zittoun.
Service d'Hématologie, Hôtel-Dieu, 75004 Paris (France).

HIV patients (pts) have a 60-fold increase relative risk to develop NHLs comparing with the general population. Because of the immune status impairment, these high-grade NHLs which demonstrate a poor prognosis are usually treated with non aggressive chemotherapies. Nevertheless, Burkitt NHLs can develop in non severely immunocompromised HIV pts for whom a curative approach is possible. In addition, the hemopoietic capacity of HIV grafted marrow is not established because of associated dysmyelopoiesis rendering ABMT questionable. We report here our own experience about the feasability of ABMT after cyclophosphamide (60 mg/kg x 2 days) and TBI which is currently proposed in non-HIV Burkitt pts.

The 4 pts were men with a mean duration of known seropositivity of 3 yrs (1-6). The mean age was 37.7 (25-54). They presented with stage IV Burkitt (pts 1, 3 and 4) or peripheral T4 cell (pt 2) NHLs. BM was involved at diagnosis in all but one case (pt 3). Risk factors for HIV were homosexuality (2), toxicomany (1) or both (1). T4 levels at presentation were above 200/ul in 3 pts (pt 2 with CD4 leukaemia not evaluable). First line reductive regimens were COP and 3 courses of CHOP (pt 1), MACOP-B (pt 2) or COP, COPADM x 2 plus CYME (pt 3 and 4). Complete remission was obtained in all but one case (pt 2) Bone marrow was harvested under zidovudine therapy in all pts and purged with mafosfamide (pt 1) or anti-T MoAbs (pt 2). Median duration of post-ABMT aplasia (PMN < 500/ul) was 32 days without noticeable morbidity. Hemopoietic recovery was incomplete in the 3 lineages but without prolonged transfusional needs. Pt 1 who demonstrated ganciclovir-treated CMV pneumonitis (d+75), progressive pancytopenia, and reappearance of P24 ag at d+153, died of neurological AIDS 14 months after ABMT without evidence of NHL relapse. This pt did not received zidovudine after conditioning. Pts 2 and 3 died because of NHL respectively at 12 and 2 months post-ABMT with negative P24 antigenemia and stable P24 Ab. Pt 4, grafted only 15 days ago, is alive in CR.

In conclusion, ABMT seems feasible in HIV pts concerning the aplastic period, nevertheless without subsequent complete hemopoietic recovery, presumably because of previous treatments, BM involvement by NHL and/or HIV-associated dysmyelopoiesis. This type of therapy do not seem to accelerate the course of HIV infection. Interest of such intensive regimens in this field has to be established in more cases.

T 272 HIGH INCIDENCE OF EPSTEIN-BARR VIRAL DNA IN CRYOPRESERVED AIDS-RELATED LYMPHOMA SPECIMENS.

M. Samoszuk, E. Ramzi, and H. Anton-Culver. Departments of Pathology and Medicine, University of California, Irvine, California USA

Epstein-Barr virus (EBV) has been proposed as a possible etiologic agent for AIDS-related lymphomas (ARL). In previous studies, however, EBV has been detected in only approximately half of ARL specimens. In order to determine if tissue fixation alters the ability to detect EBV in ARL, we used the polymerase chain reaction and dot-blotting with a biotinylated probe to identify EBV DNA in normalized amounts of DNA extracted from fixed and unfixed (cryopreserved) ARL specimens. We analyzed 30 lymphoma specimens obtained from AIDS patients, including 17 cases of large cell (immunoblastic) lymphoma, 11 cases of small non-cleaved cell lymphoma, and 2 cases of Hodgkin's disease. Overall, 18 out of the 30 specimens (60%) contained EBV DNA. There were 7 cases in which EBV DNA could not be detected in fixed tissues but was readily detected in unfixed tissues. Only 4 out of 23 (17%) ARL specimens fixed in formalin or B-5 contained detectable EBV DNA. By contrast, 17 out of 18 (94%) unfixed ARL specimens contained EBV. In 2 out of the 17 positive cases, fresh peripheral blood lymphocytes from the same patients were also available for analysis and did not contain EBV DNA. We conclude that the fixation of ARL specimens in B-5 or formalin markedly reduced the ability to detect EBV in ARL by polymerase chain reaction and subsequent dot-blotting. Moreover, we conclude that EBV is detectable in a very high proportion of unfixed ARL specimens and that peripheral blood lymphocytes from the same ARL patients do not necessarily also harbor EBV. These results suggest that tissue fixation is an important variable in interpreting the results of molecular studies of EBV in ARL.

T 273 HIV-RELATED NON-HODGKINS LYMPHOMA IN 81 PATIENTS.

L. Jahnke, C von Gunten, A Rademaker, J Von Roenn. Northwestern University, Chicago, Illinois, USA

The records of all patients with HIV-related non-Hodgkins lymphoma (NHL) treated at Northwestern Memorial Hospital from 1985 through 1992 were reviewed. Of 81 total patients, 92.6% were male and 7.4% were female. Of 51 patients with adequate records, 82% were white, 10% black, 6% hispanic, and 1% asian. The mean age was 38 years (range 22-52). Homosexuality/bisexuality was the risk factor in 82%, IV drug use in 10%, heterosexual contact in 6% and blood transfusion in 2%. 25% had no previous AIDS-defining illness at the time of diagnosis of NHL. ECOG performance status was 0 in 28%, 1 in 36%, 2 in 19%, 3 in 14% and 4 in 6%. The mean serum LDH at diagnosis was 463 mg/dl (range 128-1795). The mean CD4 lymphocyte count was 118 cells/ml (range 2-600). 58% were on no anti-retroviral therapy at diagnosis. 84% had extranodal disease (Ann-Arbor Stage IV) while 15.7% had Stage I disease. There was no predominant extranodal site of presentation. 92% were pathologically classified as immunoblastic or large cell using the Working Classification. Only one patient had small lymphocytic lymphoma (non-Burkitts) in contrast with other reported series. Of 34 patients receiving chemotherapy, 74% received CHOP and 18% m-BACOD. 54% received chemotherapy prophylaxis of the CNS. 41% of patients achieved a CR. Mean survival of patients presenting without constitutional symptoms (n=35) was 27.9 months (SEM 7.4). In contrast, those with constitutional symptoms (n=15) had a mean survival of 4.0 months (SEM 0.9, p=0.01). Subgroup analysis and survival curves will be presented.

T 274 COMPARISON OF HIV-RELATED NON-HODGKIN'S LYMPHOMA (HIV-NHL) AND NON-HODGKIN'S LYMPHOMA IN THE GENERAL ELDERLY POPULATION (AGE≥ 70 YEARS): NO DIFFERENCE IN RESPONSE RATE AND SURVIVAL

U. Tirelli*, D. Errante*, A. Carbone*, V. Zagonel§, G. Nasti*, P. Polizzi*, M. Tavio*, D. Bernardi*, E. Vaccher* and S. Monfardini§. * Division of Medical Oncology and AIDS, °Division of Pathology, §Division of Medical Oncology, C.R.O. Aviano-Italy

HIV-NHL is considered the most unfavourable NHL, both for the aggressiveness of NHL and for the underlying HIV infection. However, NHL occurring in pts of the general population with 70 years of age or more are also considered an unfavourable subset of NHL. The aim of this study is to compare the outcome of 13 pts (age≥ 70 years) with high-grade (H and J histologic subtypes according to the W.F.), stage III or IV NHL and with a relatively good PS (>50 according to Karnofsky) observed from June 1987 to February 1991 (Group A) with the outcome of 13 pts with HIV infection and with similar PS and NHL characteristics (CNS NHL were excluded) (Group B), observed from July 1989 to March 1991. All pts were seen and treated at our institution. Pts of group A received the VMP (VP16, Mitoxantrone, Prednimustine) chemotherapy (CT) regimen, specifically devised for elderly pts (Tirelli et al. JCO 10, 2: 228-36, 1992), while pts of group B were treated with a more aggressive third generation CT regimen, LNH84 (Coiffier et al. JCO 8: 1018-26, 1989). Pts characteristics and results of this comparison are summarized in the table:

	Group A	Group B	P value
N° PTS	13	13	
Median age (range)	75y (71-86)	36y (23-54)	
Male/female	7/6	11/2	
Median PS (range)	70 (50-100)	80 (50-100)	
Histology (W.F.)			
H	11	5	0.13
J	2	8	0.08
Stage			
III	5/13	10/13	0.15
IV	8/13	3/13	0.13
"B" symptoms	4/13(31%)	8/13(62%)	0.18
Median CD4+cell count/mmc (range)	-	235(39-435)	
Response			
CR	3/13(23%)	7/13(54%)	0.17
PR	7/13(54%)	5/13(38%)	0.25
PD	3/13(23%)	1/13(8%)	0.44
Mortality	12/13	10/13	
Cause of death			
NHL progression	11/12	4/10	0.14
NHL progression +O.I.	-	2/10	
Opportunistic Infection	-	1/10	
Other	1/12	3/10	
Median survival (months)	11	10	0.76

With a comparable median PS, histological subtypes and stages at presentation, our data demonstrate that the outcome of HIV-NHL is not different from that of a selected group of NHL of the general population, i.e. pts ≥ 70 years of age. Therefore HIV-NHL, at least with PS > 50, although in advanced stages and unfavourable histology, could be treated with aggressive CT and with response rate and median survival not significantly different from that of elderly (≥ 70 years) pts with NHL from the general population. Supported by grants of CNR '92 and AIRC '92.

T 275 TREATMENT OF HIV-RELATED NON-HODGKIN'S LYMPHOMA (NHL) WITH CHEMOTHERAPY (CT) AND G-CSF: REDUCTION IN THE DAYS OF HOSPITALIZATION AND TOXICITY WITH CONCOMITANT OVERALL REDUCTION IN THE COST.

U. Tirelli, D. Errante, E. Vaccher, M. Tavio, V. Accurso, D. Bernardi, R. Talamini °, M. Spina, R. Foà* and S. Monfardini**. Division of Medical Oncology and AIDS Program, °Epidemiology Unit, C.R.O. Aviano- Italy , *Department of Medical Science and Human Oncology, University of Turin, **Division of Medical Oncology , CRO Aviano - Italy .

Treatment of HIV-related NHL with CT is associated with an increased risk of side effects, in particular bone marrow toxicity. The aim of this study is to compare the toxicity and the cost of CT with G-CSF versus CT without G-CSF. We have analyzed 37 consecutive patients (pts) treated with intensive CT regimens: 19 pts from july '89 to june '91 without G-CSF and 18 pts from july '91 to september '92 with G-CSF, 5 mcg s.c./kg/day starting 24 hours after CT for 13 days in all cycles. The CT regimens employed were the LNH 84 regimen (Coiffier et al JCO 1989, 8:1018-26) composed by Adriamycin, Cyclophosphamide, Vindesine, Bleomycin, and Prendisone and the CHOP-like regimen, CHVmP/VCR-BLM (Carde et al, Ann Oncol 1991, 2:431-6) given for 3-6 cycles. The analysis was performed only for the first 3 cycles of CT. The cost of 1 day of hospitalization in our division is about 450US dollars. Patient characteristics and results of the study are summarized in the table:

	WITHOUT G-CSF	WITH G-CS F	P VALUE
N. PTS	19	18	
MEDIAN AGE (RANGE)	36 (28-59)	32 (18-51)	
MALE/FEMALE	17/2	15/3	
HISTOLOGY (W.F.) G/H/I/J/K	2/4/-/12/1	3/1/1/8/5	
STAGE I/II/III/IV	3/5/1/10	2/2/7/7	
MEDIAN CD4+ CELL COUNT/mmc	235	120	
RESULTS-toxicity			
- Day of Nadir WBC,mean(from CT start)	10.8 (± 2.8)	8.4 (± 1.5)	0.006^
- Nadir WBC/mmc ,mean (all pts)	281 (± 248)	514 (± 439)	0.09^
" " " " (pts with CD4+ ≥ 200)	410	1239	0.009^
-Mean n. of CT cycles /pt	2.7 (± 0.7)	2.4 (± 0.8)	NS^
-Pts with documented infections	11% §	8%	NS*
-Pts with mucositis	47%	22%	0.08*
- Cycles at full dose	88%	86%	NS*
- Mean delay between the CT cycles (days)	9.0 (± 6.4)	4.0 (± 4.7)	0.01^
RESULTS-response			
- Overall response	88%	78%	0.22*
RESULTS-cost			
- Mean toxicity -related days of hospitalization	18.0 (± 13.2)	6.4 (± 9.1)	0.003^
- Mean hospitalization + G-CSF cost/cycle	$ 3232 (± 2282)	$ 2282 (± 1345)	NS^

The side effects of G-CSF were uncommon and mild. We have shown that treatment with G-CSF significantly reduced the nadir WBC in pts with CD4+ ≥ 200, the mean delay between the CT cycles and the mean toxicity-related days of hospitalization.Therefore, by contrast with what one might expect, the cost of CT+G-CSF vs CT alone did not increase, actually it decreased. In addition, a decreased incidence of mucositis was observed, while there is not yet a positive impact on the overall response rate. In conclusion, G-CSF in addition to CT should be preferred in the treatment of pts with HIV related NHL.
§Fatal in 1 pt; ^Mann-Whitney test; *Fisher test chi-square.
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T 276 CHOP-INDUCTION AND AZT/INTERFERON ALPHA 2B MAINTENANCE THERAPY IN HIV-ASSOCIATED NON-HODGKIN'S LYMPHOMA.

C.Scheidegger*, D.Huhn**, R.Weiß**, S.Mitrou**, D.Schürmann**, K.Arasteh**, K.Becker**, J.vanLunzen**, U.Kronawitter**, G.Trenn**.
*I. Med. Dept. Krankenhaus München-Schwabing, 8000 München 40, Germany .**University Hospitals in Berlin, Frankfurt, Hamburg, Essen, München.

Induction therapy with CHOP followed by maintenance therapy with IFN alpha 2b and AZT were evaluated in a pilot study in patients with HIV-associated Non-Hodgkin's lymphomas.
Methods: Two risk groups were distinguished. 1.Normal risk: 2 of 3 criteria met: CD4+ lymphocytes>50/ul; WHO act. index 1+2; no opportunistic infection; 2.High risk: 2 of 3 criteria not met. Excluded were patients with stage Ia of lymphoma and primary CNS-lymphoma. Induction treatment in normal risk consisted of 4-6 cycles of CHOP including CNS prophylaxis followed by maintenance treatment with AZT 500 mg/d and IFN alpha 5 x 10^6 U sc 3 x/w for 12 months. Induction treatment in high risk consisted of weekly VCR and prednisolon. Supportive treatment in both groups with aerosol pentamidin and G-CSF according to a fixed scheme depending on leukocyte value. 107 patients from 15 institutions were registered between 1/90 and 10/92. 60 pat. were not treated according to protocol: 11 pat. with primary CNS lymphoma, 4 pat. stage Ia, 13 pat. histology other than NHL (M.Hodgkin, multiple myeloma and ALL), 8 pat. final stage, 12 pat. diagnosed postmortem, 5 pat. secondary malignancy, in 7 cases no pat. approval could be obtained. 9 pat. were treated in the high risk group and 38 pat. in the normal risk group. The mean value of CD4+ lymphocytes/ul in high risk pat. was 16 in normal risk pat. 193.
Results: Induction and maintenance therapy are well tolerated. In the normal risk group 18/28 (64%) achieved CR and 6/28 PR (21%). 10 pat. are too early for evaluation. In the high risk group no remissions were achieved. Median survival in the high risk group is 82 days, in the normal risk group 641 days. In a Cox regression model 2 risk factors defining poor prognosis could be estimated: CD4 count below 50/ul and WHO act. index >2.

T 277 DETECTION BY PCR OF HIV VIREMIA IN PATIENTS WITH HIV-ASSOCIATED LYMPHOMA AND EFFECT OF ANTIBLASTIC THERAPY.

S. IACOVACCI*, G. CARLONI*, M. CANTONETTI, R. LENTINI, G. PAPA ET AL. Institute of Experimental Medicine, CNR, Rome; Division of Haematology, Ospedale S. Eugenio, Rome, Italy.

Patients with acquired immunodeficiency disease syndrome (AIDS) are at risk for the development of a broad spectrum of opportunistic infections and for the development of cancer. It is estimated that 5% of HIV-infected individuals will develope non-Hodgkin's lymphoma (NHL). C-myc rearrangements and/or a detectable EBV genome are frequently associated with NHL in HIV-infected patients. In addition, although the majority of NHL developed after AIDS or progressive generalized adenopathy, there are many cases that have no prodromes before presenting with lymphoma. This suggests that several distinct mechanisms may be involved in the pathogenesis of HIV-associated NHL. At this regard, it is possible that the link between the two diseases may not be only the immunocompromised state, but also a direct role of HIV or other coinfecting viruses, such as HTLV-1 and EBV. Therefore, we investigated by polymerase chain reaction (PCR) the ability of these viruses to coinfect patients with AIDS-associated lymphoma. HIV provirus actively transcribing in lymphocytes and virionic RNA in sera were found in all the investigated patients. AZT treatment as well as the standard protocol of antiblastic therapy, F-MACHOP, do not affect viremia in these patients. However, in one patient with an HIV-associated NHL a subsequent cycle of therapy, according to the CNOP protocol, seems to negativize HIV-viremia (detected by RT-PCR), although HIV-proviral DNA and RNA still persisted in peripheral lymphocytes. 2 out of 4 NHL patients were also positive by PCR for HTLV-1 provirus in DNA from circulating lymphocytes, and 1 out of 4 tested patients contained EBV genome in these cells. So PCR can be successfully used in detecting replication of HIV and other eventually coinfecting viruses in patients with AIDA-associated lymphoma, and this kind of analysis appears to be promising for clarifying the pathogenetic role of coinfecting viruses in these malignancies.

T 278 HODGKIN'S DISEASE IN AN HIV POSITIVE BOY WITH EBV DETECTION BY IN SITU HYBRIDIZATION

.P. HOFMAN [1] A. DEVILLE [2], J. AUDOUIN [3],C. SOLER [2], J.F. MICHIELS [1], A. THYSS [2].
1 - Laboratoire d'anatomopathologie - Hopital Pasteur - Nice - France
2 - Hopital Lenval - Nice France
3 - Hotel Dieu - Paris - France.

Although not included in the definition of AIDS, Hodgkin's disease is increasingly reported in HIV positive adults . Most of these patients have advanced disease with general symptoms and poor haematological tolerance of treatment : in addition prognosis is not as good as in HIV negative patients. To our knowlege, only one case has been reported in child (J Pediatr,1990,116 - 5 : 735-8). We report a second case in a 7 yr 4 mo old boy with bilateral cervical, mediastinal and retroperitoneal involvement but no general symptoms (stage 3A). Severe thoracic herpes zoster with pulmonary involvement resolved rapidly under acyclovir. The ESR was 37 mm the first hour. Histologic examination of a cervical lymph node diagnosed Hodgkin's disease (nodular sclerosis type).HIV antigenemia was negative with a CD4 lymphocyte count at 760 mm^3 and hyper IgG of 34 mg/l . EBV serology was strongly positive : VCA 1/6120, EA 1/1280, EBNA < 1/10. In situ hybridization for EBV was positive in Reed-Sternberg cells with Bam Hi-w and EBR probes. Treatment consisted in 6 alternating courses of MOPP and ABVP followed by irradiation of involved fieds at 25 Gy. Tolerance of chemotherapy was initially poor with delays and dose reduction , then improved with use of G-CSF. No opportunistic infection occured and the patient is well and in complete remission 8 months after diagnosis. Clinical data will be updated and signification of EBV positivity with in situ hybridization will be discussed.

T 279 TREATMENT OF PRIMARY CNS LYMPHOMA BY COMBINED MODALITY THERAPY WITH M-CHOD FOLLOWED BY CRANIAL IRRADIATION.

C. Shustik, MD, J. Glass, MD, M.L. Gruber, and F. Hochberg, MD; McGill University, Temple University Comprehensive Cancer Center, and Massachusetts General Hospital.

Despite localized disease and radiosensitivity, treatment of primary CNS lymphoma (PCNSL) by whole brain irradiation is associated with predominantly CNS relapse at a median of 12 months in most radiotherapy series. The curability of aggressive histology lymphoma by multi-agent chemotherapy has prompted investigation of combined modality approaches to improve response duration and survival in PCNSL. A multivariate analysis of survival in PCNSL (Blay et al, ASCO Proc. 1078, 1992) identified inclusion of high dose methotrexate in treatment as an important variable. In this phase II trial, seventeen patients with PCNSL were treated with three cycles of M-CHOD every three weeks followed by whole brain irradiation. Eligibility criteria included negative HIV status and negative staging studies for systemic disease with normal renal and cardiac function. Each cycle of chemotherapy consisted of: cyclophosphamide 750 mg/m^2 IV, doxorubicin 50 mg/m^2IV, and vincristine 1.4 mg/m^2IV day 1, dexamethasone 10 mg/m^2orally days 1 - 5; methotrexate 3.5 gm/m^2IV d 15 with leucovorin rescue. Patients with clinical or radiologic progression after one or more cycles of chemotherapy were started on radiotherapy before completion of three cycles. Complete or partial responses of >90% tumour volume were observed in 14 patients with maximum response seen on CT scan prior to the initiation of radiotherapy. Three patients had progressive disease after one cycle of chemotherapy. Treatment was associated with minimal mucositis and grade 3 and 4 neutropenia and thrombocytopenia of limited duration in 19 of 46 cycles. Progression-free survival in the 14 responding patients is 6+ to 32+ months (median 17). M-CHOD is a manageable and well-tolerated regimen producing objective tumour responses in PCNSL and warrants further study.