ABSTRACTS - Fifth International Conference on Malignant Lymphoma, Lugano

T214 INTENSIFICATION OF THE CHOEP REGIMEN FOR HIGH-GRADE NON-HODGKIN'S LYMPHOMAS BY G-CSF: FEASIBILITY OF A 14-DAY REGIMEN
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The efficacy of chemotherapy protocols of high-grade Non-Hodgkin's lymphomas (NHL) has not been significantly improved during the last decade. The CHOEP 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. The goal of the research was to determine the efficacy of the combined chemotherapy regimen CHOEP and G-CSF in the treatment of patients suffering from chemotherapy resistant NHL. The patients were distributed into two groups, one with and one without G-CSF. The results showed that the combination of chemotherapy and G-CSF was more effective in terms of complete and partial remissions than the chemotherapy alone. This study suggests that the combination of chemotherapy and G-CSF is a promising approach for the treatment of chemotherapy resistant NHL.

T215 CLINICAL EFFECT OF INTERLEUKIN-3 (IL-3) ALONE AND COMBINATIONS OF IL-3/GM-CSF AND IL-3/SCF IN NON-HODGKIN LYMPHOMA
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42 previously untreated patients with newly diagnosed Non-Hodgkin's lymphoma were treated with standard CHOEP chemotherapy in combination with cytokines. In 24 patients IL-3 was used as monotherapy for 14 days following CHOEP cycle 2 and 4 and after cycle 6 in combination with GM-CSF (3 µg/kg); four different 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 (0.5 µg/kg) were studied. Besides this, new drugs, efficacy of the CHOEP 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 CHOEP 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/m^2 L.v. day 1, doxorubicin 50 mg/m^2 L.v. day 1, vincristine 1.4 mg/m^2 L.v. day 1, etoposide 100mg/m^2 L.v. day 1 to 3, prednisolone 100 mg p.o. days 1 to 5, and G-CSF 300 µg s.c. 4 days to 10 days. Etoposide 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 available for evaluation. The regimen was well tolerated in all patients, except for one who stopped G-CSF treatment due to bone pain and fever. Leucocyte counts < 1000 mm^3 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 patient with epistaxis and fever was obtained with neutropenia. Leukocyte counts < 1000 mm^3 occurred in 25%, thrombocytopenia < 50 000/mm^3 only in 1 patient. No bleeding episodes were observed and no platelet transfusions were necessary. As nausea, that required in 4 patients as monotherapy, was treated with the start of Hb > 10/g/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 interval. A randomized trial will show whether an additional significant increment in dose intensity translates into increased remission rates and/or longer remission durations.
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T216 Dose-Intensification of Chemotherapy (NOSTE) with rituximab- and GC-CSF (G-CSF) (Filgrastim) Support in Advanced Low and Intermediate Grade Non-Hodgkin Lymphomas \( (NHL)\)


For treatment of low and intermediate grade NHL, the combination of mitoxantrone and prednisomine was proven equally effective but less toxic regarding nausea, emesis, and alopecia than other standard chemotherapy regimens. However, hematological toxicities are dose-limiting, particularly granulocytopenia WHO grade III 1/2 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/m² (day 1 and 2) and prednisomine 100 mg/m² (day 1-5) for up to 6 cycles given every 3 weeks in patients with low and intermediate grade NHL.

10 patients, receiving a total of 50 cycles, have completed treatment at the time of this interim-analysis. In patients, neutrophil counts were >2 x 10⁹/l on day 20 of each cycle and only in 2 cycles chemotherapy had to be delayed due to thrombocytopenia (WHO grade I and II, respectively). 3 patients were withdrawn prematurely: 1 patient with progressive disease after presentation with complicating spontaneous fever after 3 cycles switched to a different therapy with curative intent, and 1 patient who refused transfusions was withdrawn due to thrombocytopenia and anaemia. Bleeding or infectious complications did not occur. Apart from benign pain in 2 patients (moderate and moderate) and in 4 patients (1 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.

T217 SEQUENTIAL COMBINATION CHEMOTHERAPY (CEOPPVIML), G-CSF AND RADIOThERAPY IN PATIENTS WITH HIGH GRADE MALIGNANT NON-HODGKIN'S LYMPHOMA (NHL)

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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 μg/kg/d, days 11-20) when severe and/or prolonged neutropenia, and/or infectious complications were present. In pts with stage I disease and in pts with primarily bulky disease, additional radiotherapy (40 Gy) was given after completion of chemotherapy. Chemotherapy was started with a combination of Cyclophosphamide (400 mg/m², days 1,2), Epirubicin (40 mg/m², days 1,2), Bleomycin 30 mg/m², days 1,10, Vincristin (2 mg/m², days 1,10), Prednisone (100 mg/m²/d, days 1-10), and Procarbazine (60 mg/m²/d, days 1-10) (CEOPPVIML). Treatment was repeated every 3 weeks. In pts with complete response (CR) after a maximum of 4 cycles of CEOPPVIML, 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), Melphalan 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 Epstein-Barr-co-infection, a chemotherapy was started with VIML together with Vincristin (2 mg/d, days 1,10) and Prednisone (80 mg/m²/d) (VIMPLOM). Between 11/1996 and 197/1992, a total number of 40 pts (19 males, 21 females) were treated. The median age was 52 yrs (range 20-72). 7 pts had stage I, 12 stage II, 9 pts stage III, and 7 pts stage IV disease. 12 pts had bulky disease (>10 cm) in 16 pts, and extranodal involvement in 15 pts. Histologic types of the tumours (Ki-1 positivity) were: mantle cell 30, lymphoepithelioma-like and unclassified large cell 8. Major toxicities (WHO grade III/IV) of therapy other than total alopecia were leukopenia in 46%, thrombocytopenia in 0%, and anemia in 5% of pts. Mild and moderate effects were nausea and vomiting 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 34 months and 34 months with CR. This points to promising to have continued CR at 30 months. In conclusion, the therapeutic concept used appears to be applicable in a significant proportion of pts, and it also appears promising with regard to the long-term disease-free survival, when the rate of relapses during the first 2 yrs is considered.

T218 EFFECT OF RECUMBLINT HUMAN GRANULOCYTE-MACROPHAGE COLONY STIMULATING FACTOR (r-mHuGM-CSF) AFTER INTENSIVE CHEMOTHERAPY IN ADVANCED CLINICAL STAGE LYMOPHOMAS. FIRST EXPERIENCE IN VENICE.

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To determine whether r-mHuGM-CSF (LICOMAX) can reduce the duration of leukopenia and granulocytopenia as well as the risk of infection after intensive chemotherapy we performed an open randomized clinical trial in 12 patients (pts) 6 male, 6 female, age 40±12 yrs (median 38 yrs). All pts had lymphoma or leukemia WHO stage III-IV (NHL) and 7/12 (5%) had Hodgkin's disease (NHL). All pts received salvage treatment after first relapse with MD soc (Mesna 1,3g/m² i.v. daily 1,4,7,10), Ifosfamide 1,3g/m² i.v. daily 1,4,7,10, MEL (Mesna 50 mg/kg i.d. daily 1,4,7,10), Vincristine 0.8 mg/m² i.d. daily 1,4,7,10, Solomedrol 500 mg/m² i.d. daily 1,4. All pts received chemotherapy at a dose of 5/5μg/kg/day during 5 days, 24 hours after the last dose of chemotherapy a total of 25 cycles were given to our pts.

All pts had a white blood cell count (WBC) below 2.0x10⁹/l and a absolute neutrophil count (ANC) below 1.0x10⁹/l before starting chemotherapy with r-mHuGM-CSF.

We found that the average recovery time for leukopenia and neutropenia was 72 hours after the first r-mHuGM-CSF dose. The mean values of the ANC and ANC in each patient (pts) before and after r-mHuGM-CSF were statistically significant (ANC 0.66±0.40 μg/10⁹/l and 35.95±15.60 μg/10⁹/l; p<0.01). There was not statistically significant changes in the mean values of hemoglobin (Hb), hematocrit (Hct) and platelet (plt) count before and after r-mHuGM-CSF (Hb, 9,9±2.1 g/dl and 9,9±2.1 g/dl; Hct 32.5±1.8 and 32.5±1.9%, plt 100±50 x 10⁹/l and 122±50 x 10⁹/l; p>0.05). Only 3/12 (25%) of the pts required aseptic febrile neutropenia with more than 50% of leukocytes, and within 6 months following chemotherapy. We conclude that the use of r-mHuGM-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 Vincristine and Dexamethasone. Reductions in the number of days of neutropenia may prove of benefit in terms of both hospital costs and the morbidity of chemotherapy.

T219 CAN G-CSF BOOST THE DOSE-INTENSITY OF STANDARD CHEMOTHERAPY?

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As G-CSF reduces hematological toxicity, the objective of this study was to evaluate whether in patients whose dose-intensity of G-CSF was adjusted according to current criteria or delayed until day 35. A total of 15 patients (2 Hodgkin's disease and 13 non-Hodgkin's, median age 57.4 years, range 27-85, 5 female and 10 male) have been enrolled. All but one patient had relapsing or refractory disease at enrollment 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 secondary asymptomatic 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 (3) and 4th (1) cycle. Two responsive patients (1 CH, 1 PR) refused further therapy after the 1st cycle because of extrahematological and the other because of hematological toxicity of the other 6 responsive patients. Only 3 of the 8 planned cycles, the 4th and the 3rd (these 3 last patients are continuing therapy). Of the 12 patients who completed at least 1 cycle (GI), 7 and after the 2nd cycle (GII). G-CSF reduced the incidence of leukopenia and neutropenia and this was more evident after the 2nd cycle. G-CSF and granulocyte counts were compared. The myeloprotective effect of G-CSF also seemed to be delayed after the last granulocyte nadir. As shown by the ANC and neutrophil values documented in GI patients after the 2nd chemotherapy cycle G-CSF did not significantly increase the myelosuppression. It would be, however, of great importance to determine whether G-CSF should allow the dose intensity of standard chemotherapy to be increased, at least in the first 3 cycles.
T 220 S-CSF FOR CHEMOTHERAPY-RELATED LEUKOPENIA IN PATIENTS AFFECTED BY ADVANCED LYMPHOMAS. M. Bonfichi, I. Bellantuno, E.P. Alessandini, P. Bernasconi, G. Pagnucco, E. Brusamolino E. Morra, C. Castagnola, G. Bernasconi. Cattedro di Ematologia, Università 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 22-52) affected by Hodgkin HL(5 cases) and non Hodgkin (mH/L)(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 mortality. 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 until 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 222 TREATMENT OF HIGHLY AGGRESSIVE LYMPHOMAS WITH MACOP-B OR VACOP-F FOLLOWED BY AUTOLOGOUS BONE MARROW TRANSPLANTATION IN FIRST REMISSION L. M. Jost, E. Jacky, M. Reisch, 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-F 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 DWF 1 and 7 as DWF 0 (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-F 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 hemophagocytic 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.


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/m2 on day -4; Ara-C, 150 mg/m2 every 12 h from day -5 to -2; VP-16, 150 mg/m2 every 12 h from day -5 to -2; Cyclo, 45 mg/Kg/day from day -3 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 refractory). Mean follow-up is 34.5 months (1-126). 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. Nerve VOD non-severe intestinal 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 extramedullary toxicity and is worthy of being used as conditioning regimen for ABMT in NHL.
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T 224 AUTOLOGOUS BONE MARROW TRANSPLANTATION FOR NON-HODGKIN’S LYMPHOMA: A REPORT OF 31 CASES FROM THE SPANISH GEL/TAMO COOPERATIVE GROUP.


The role of autologous bone marrow transplantations (ABMT) in patients with poor-risk non-Hodgkin’s lymphomas (NHL) in first remission is being investigated. It has been suggested that patients with adverse features for long-term outcome of chemotherapie (lymphocy toplastic index, advanced stage, 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 1995, 51 were transplanted while in first complete remission (CR). Their main characteristics at diagnosis were: mean age 30 years (range, 3-59), male/female ratio 31/49, intermediate grade/high-grade histology 10/41 (7 lymphoblastic), stage I: 3 patients, II: 15, III: 7, IV: 36, bulky disease 38 out of 46 cases, mean/SD serum LDH 1,063±455 IU/L (range, 95-2,400). 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, 55-93%) and 10% (95% CI, 4-18%), respectively. Toxic death occurred in 14% cases.

In the multivariate analysis of the prognostic factors, only LDH at diagnosis showed independent prognostic significance for DFS after transplant (p=0.015), the best discriminant level being 100 IU/L. Intensifying the histology, clinical stage, number of nodes needed to achieve the remission, interval between complete remission and ABMT, and conditioning regimen were of no predictive value.

This study concludes that in patients with NHL in first CR, ABMT is feasible and curative, at least in those with high risk. The toxicity to the procedure may not be negligible. Not of, a well-known prognostic parameter at diagnosis (LDH level) that identifies patients not likely 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 GROUP “Santos”, A.M.M.


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Up to January ’92, 100 adult intermediate and high-grade NHL (F.O.H.L./i.g.w) 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). Prior had a mean age of 32 years (range 10-55); 68 were males and 32 females. At initial diagnosis 11 were stage II bulky > 10 cm, 14 stage III, 73 stage IV; poor prognostic factors were present as follow: bulky disease in 61 pts, LDH > 200 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 regimens before ABMT rescue, seventy-four pts received Cytoxan (60mg/kg x 2 days) + Total Body Irradiation (10 Gy in a single dose) and 26 higher polychemotherapy only. Procedure related deaths were 11: 6 due to cerebral haemorrhage, 2 to cardiac failure, and 3 to sepsis, trisomcepenemia and venoocclusive disease respectively. The overall probability of survival and DFS, at 4 to 7 yrs, according to the status at ABMT, are as follows:

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<tr>
<th>Status at ABMT</th>
<th>1st CR %</th>
<th>2nd CR %</th>
<th>1st PR %</th>
<th>PD %</th>
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<tr>
<td></td>
<td>57</td>
<td>53</td>
<td>56</td>
<td>16</td>
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To conclude our experience suggests that first CR’s are the most favourable moment for performing 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 benefits 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.


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7 patients with Hodgkin’s Disease (HD) and 8 with non-Hodgkin Lymphomas (NHL) (3 of these High Grade), mean age 31 years (14-47), received intensive therapy followed by autologous transplantation (AT) either with the narrow (NM) or peripheral blood stem cells (PBSC), 6 to 184 months (mean 41 months) after initial diagnosis. Their clinical status at the time of AT was as follows: 1st CR, 5 1st Response lek refractory HD 0 3 NHL 2 (RG) 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, 1.5 g/m and 300 mg/m); 5 received PBSC-AT 250–300 x 10^6/kg PBSC harvested in anid nitrogen but 1 BM AT that was kept 52 hours at 4°C. BM-AT contained a mean of 3.0±1x10^7/kg (2-4.4) nucleated cells and a mean of 0.3±0.1x10^7/kg CFU-GM (4.27-23). PBSC were collected following chemotherapy (CT) in 2 patients and after CT followed by G-CSF in J; the mean of nucleated cells auto-grafted was 6.8±1x10^7/kg (4.6-15.7) and the mean of CFU-GM 35.8±1x10^7/kg (5-87.78). 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 enerygation. Mean time until neutrophils >5x10^7/l and platelets >5x10^9/l were 15.4 (9-27) and 29.4 (9-95) days (18.6 and 22.6 days for those receiving PBSC-AT).

13/15 patients are alive with a median follow-up time after AT of 21 months (2.6-80). 8 are in CR, 1 in CR having relapsed 6 m. after AT (a new CR was obtained with CTX and CNT, who had refractory disease at the time of AT, with active disease). The 4 patients who died were the high grade NHL (2 treated in their 1st CR and 1 in his 3rd) and 2 of the 2 NHL patients who had a refractory disease: 1 of death was infection in 2 days (+90 and +90) and relapse in the other 2 days (+69 and +110). Actuarial survival is 65% and DFS 24 months. For the 5 patients with HD the corresponding data are 86% and 48%.

CTX=Cyclophosphamide; BUS=Busulfan; TBI=total body irradiation.
The lymphomas are chemosensitive malignancies, with a clear dose-response relationship. High dose chemotherapy with autologous bone marrow transplantation (ABMT) improves outcomes in patients with refractory lymphomas compared to conventional chemotherapy treatment with less effective 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 study and experience at our 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 regimens beyond 300mg/m² is associated with a significant increase in mortality from pneumonitis (Wheeler,1990; Zultan,1989), and we have thus pilot escalation doses of Etoposide in the BEAM protocol in an attempt to improve response rates.

26 patients have received 400mg/m² of Etoposide daily for 4 days, and 13 patients 400mg/m², with standard doses of Carmustine, Cytoxan and Melphalan, 23 subjects had refractory Hodgkin's disease, and 16 non-Hodgkin's lymphoma. No significant cardiovascular or respiratory complications occurred at either dose, and bacteraemia recovery rates were similar to standard dose BEAM, but increased gastrointestinal (GI) toxicity was noted. 9 patients in the 400mg/m² group suffered grade III to IV mucositis, with severe diarrhoea (13%), and 3 patients haemorrhage occurred in 3. One death occurred due to intracerebral haemorrhage in a platelet refractory patient, all of the 13 patients achieving 600mg/m² 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 meningitis, and 7 required TPN. 21 patients from the 400mg/m² 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 400mg/m² patients was 89% of 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/m², 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-HODGKIN'S LYMPHOMAS.

We report the results obtained in 51 non Hodgkin's lymphomas (NHL) autologous bone marrow purging with immunomagnetic beads. 21 patients with lymphoblastic lymphoma (LB) in stage IB - IIB and one patient with centrocytic 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 cocktails immunomagnetic beads conjugated with monoclonal antibodies directed towards CD 19, 20, 7, 37 and 34. The 14 T cell lymphomas were purged with immunomagnetic beads directed towards CD 3, 5, 7, 45, 47. At time of harvesting, four patients (two B cell and two T cell lymphomas) had 5 - 20% tumour cells in the bone marrow. After purging, no tumour cells were detectable in the BM examination. The pretransplant regimen consisted of hyperfractionated 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 lymphomas had a CR at 3 months. 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 septicaemia and nine in relapse. The lymphoproliferative 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 promising.

T 230 TOTAL BODY IRRADIATION AND BONE MARROW TRANSPLANTATION IN FIFTY PATIENTS WITH HAE摩ELOGICAL MALIGNANCIES USING COMPUTER PLANNING
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The first 50 patients with a variety of haematological malignancies were treated using total body irradiation (TBI) using CT/computer dose calculation prior to bone marrow transplantation (BMT). Accurate planning and dose distribution to organs at risk to these patients are possible with this system. Patients are treated using parallel opposed lateral beams in the supine position using MV photons. Since 1989 33 males and 17 females have been treated (age range 9-51 years). There were 44 ALL, 6 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/m² with TBI doses of either 12 Gy in 6/3/4 days (35 patients) or 16.4 Gy in 5/3/4 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 59%. The 2 year actuarial relapse-free survival was 65% with 7 deaths from leukemic 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 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 5 were CMV related. With longer follow-up accurate long-term data will be available. It will be possible to relate late radiation effects such as cardiac formation and endocrine abnormalities to the actual doses received by such tissues.


From September '91 to December '92, 15 patients (pts) with B lymphoma, either limited or advanced, Stage I-IV, with or without extranodal involvement, were transplanted with autologous peripheral blood stem cells (PBSC) after HD-CY+G-CSF primed mobilization. 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/mlc WBC. Median number of apheresis was 6 (range 4-12); median collected cells were 6.9 x 10^9/kg (range 2.72-13.2); median of CPU-GM was 10.6 x 10^6/kg (range 0.70-6) and median of CD34+/CD33- was 4.9 x 10^6/kg (range 0.17-4.2). In 13 pts phenotypic analysis of collected cells showed values to be within the normal range (CD104: 0.2%; CD19: 15%). In one pt, a clonal B lineage population developed (CD19+ 24.4%; CD19- 36.5%). In another patient, peripheral and BM progression occurred during collection. After a conditioning regimen (Melphalan + TBI), 13 pts received PBSC rescue, and all were 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-term engraftment (> 3 months) showed peripheral pancytopenia in 3 and BM hypopcellularity in five pts. Statistical analysis was made on 9 pts in CR: 5 (group A) with poor engraftment (peripheral pancytopenia and BM hypopcellularity), and 4 (group B) with sustained engraftment. A significant difference was found to exist between groups A and B in terms of CPU-GM (3.58 vs 28.1; p=0.02), and infused colony forming units vs 9.6 vs 9.8; p=0.04). Overall procedure was well tolerated. Four pts died in CR (2 of broncospasmonea at +2, 5 months; 1 of pancytopenia at +6 months and 1 of lung fibrosis at 9 months after rescue). 7 pts. relapsed at +8 and +9 months. Up to now 3 patients are in CR at +3, +6, +8 months after PBSC rescue.

Eighteen patients with malignant lymphoma, 10 non Hodgkin’s and 8 Hodgkin’s, were treated with high-dose CBV (cyclophosphamide 4 x 1.5 g/m²; etoposide 4 x 250-400 mg/m²; BCNU 1 x 150 mg/m²), 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 ≥ 0.5 x 10⁹/l polymorphonuclear cells (PMN) and ≥ 50 x 10⁹/l platelets was 13 days for both lines in PBSC autografted patients, and respectively 20 and 28 days in BM autografted patients. A significant advantage of PBSC over BM was found for time to recovery either PMN ≥ 0.5 x 10⁹/l (p=0.011). Autograft-related toxicity consisted mainly of moderate-severity interstitial pulmonary (3 patients), and one MDS (1 patient) that resolved completely. Of 6 of 18 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 probability of progression-free survival is over 50% at 3 years with a significant difference between patients with sensitive and resistant disease (p=0.01). The efficacy and low-toxicity of CBV suggest that autograft with PBSC may be proposed for the primary treatment of poor prognosis malignant lymphomas.

T233 High-dose Radiochemotherapy with Peripheral Blood Stem Cell Support in Low-Grade Non-Hodgkin’s Lymphoma. R.Haas, R. Rhoderich, H. Goeldschmidt, W. Delbo, 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 1992, 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 leukaphereses a sufficient number of peripheral blood stem cells could be harvested. A threshold quantity of 5 x 10⁹ 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 extremely low content of CD19+ B-cells (less than 0.2% of the total nucleated cells).

So far, 6 patients 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 10⁹/l neutrophils and 9 days (range 6-12) for 20.0 x 10⁹/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 thera- peutic upfront 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.

T234 PERIPHERAL BLOOD PROGENITOR CELL (PBPC) PLUS AUTOLOGOUS BONE MARROW TRANSPLANTATION (ABMT) SIGNIFICANTLY SHORTENS TIME TO ENSACTERPATHY IN PATIENTS WITH NON-HODGKIN’S LYMPHOMA (NHL) AND HODGKIN’S DISEASE (HD). Kazane, C, Ratnashandarath, V, Ubhori, JP, Abin, E, Liu, LG, and Isenbrenner, 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/m² was given subcutaneously for 9 days with leukapheresis on days 6, 8 and 9. BM was then harvested during stable phase hematopoiesis. Cyclophosphamide 300 mg/kg and total body irradiation 300 cGy were administered on days 4 to 5 and days 4 to 1 respectively. Pts with prior mediastinal or abdominal radiation > 2000 cGy received cyclophosphamide 1.8 g/m², VP16 400 mg/m² on days -7 to -4 and CRF 600 mg/m² on day -3. PBPC and BM were infused on Days 0 and 1. GM-CSF 250 mcg/m² was given SQ daily after BM infusion on Day +1 until PMN > 1000/mm³ x 3 days. The time to engraftment, duration of antibiotic and hospital stay were compared to 60 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 BMCT.

<table>
<thead>
<tr>
<th>Group</th>
<th>Total Pts</th>
<th>NHL/HD</th>
<th>Median Age</th>
<th>Days PNM &gt;0.5</th>
<th>Days PNM &lt;1000</th>
<th>Days PNM &lt;2000</th>
<th>Days PNM &gt;5000</th>
<th>Days PND &gt;0.5</th>
<th>Days PND &lt;1000</th>
<th>Days PND &lt;2000</th>
<th>Days PND &gt;5000</th>
<th>Days ATL &gt;0.5</th>
<th>Days ATL &lt;1000</th>
<th>Days ATL &lt;2000</th>
<th>Days ATL &gt;5000</th>
<th>Days in Hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>13</td>
<td>9</td>
<td>47 (18-60)</td>
<td>13 (9-50)</td>
<td>12 (9-50)</td>
<td>11 (9-50)</td>
<td>2.4 (0.3-4.0)</td>
<td>11 (9-50)</td>
<td>3.4 (1.6-7.1)</td>
<td>2.2 (1.1-5.1)</td>
<td>1.4 (1.0-2.5)</td>
<td>1.2 (1.0-2.5)</td>
<td>1.2 (1.0-2.5)</td>
<td>1.2 (1.0-2.5)</td>
<td>1.2 (1.0-2.5)</td>
<td>23 (18-35)</td>
</tr>
<tr>
<td>Group B</td>
<td>58</td>
<td>35</td>
<td>47 (18-60)</td>
<td>13 (9-50)</td>
<td>12 (9-50)</td>
<td>11 (9-50)</td>
<td>2.4 (0.3-4.0)</td>
<td>11 (9-50)</td>
<td>3.4 (1.6-7.1)</td>
<td>2.2 (1.1-5.1)</td>
<td>1.4 (1.0-2.5)</td>
<td>1.2 (1.0-2.5)</td>
<td>1.2 (1.0-2.5)</td>
<td>1.2 (1.0-2.5)</td>
<td>1.2 (1.0-2.5)</td>
<td>23 (18-35)</td>
</tr>
</tbody>
</table>

The recovery time to PMN >500 and >1000 were statistically significantly shorter in pts receiving both PBPC plus ABMT (p=0.001), the duration of thrombocytopenia, anorexia cutaneous and hospital stay were not different. The data confirm that rapid engraftment recovery when adding PBPC to ABMT even in these heavily pretreated group of patients. The follow-up time is too short to compare the difference in the relapse rate and overall survival between the two treatment groups.


Sequential administration of high-dose single drugs concluded by PB and BM autograft (HDSAs) 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 B symptoms); subtype: E (2 pts), F (3 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 debulking purposes. G-CSF (Filgrastim; Anges-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 + BM cells, 1 with BM cells only), 8 (72%) achieved CR. These 8 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.
ABSTRACTS - Fifth International Conference on Malignant Lymphoma, Lugano

T 236 HIGH DOSE SEQUENTIAL CHEMOTHERAPY WITH PB AND BM CELL AUTOGRAFT IN HIGH RISK RELAPSED LYMPHOMAS. D. Caraciolo, P. Gavarrotti, M. Aglietta, P. Bondepan, M. Falda, E. Gallo, F. Locatelli, A. Agnelli, P. Faolini, P. Sanavio, S. Urgesi, U. Vitolo, C. Tarella. Divisioni Universitaria e Ospedaliera di Ematologia, Int.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 extrahematopoietic toxicity. Ten patients completed the program and showed excellent tolerability to the final autografting phase. Eight patients were grafted with BM + PB cells; 5 substantial or 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, +6, +7, +18, 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 REIFUSION OF AUTOLOGOUS PERIPHERAL STEM CELLS (APBS) IN RELAPSED OR REFRACTORY HIGH-GRADE MALIGNANT NON-HODGKIN'S LYMPHOMAS. M. Freude, C. Arzenien, L. J. A. Könette (1). P. Heuener (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-hr infusion, cytoxane-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 1.2 mg/kg G-CSF are given twice daily. Apheresis of APBS is done on days 5 + 6. APBS are harvested with the high-dose chemotherapy and G-CSF is given at a dose of 5 mu/kg. With WBC rising to >1,000/μl repeated aphereses are performed. Thirteen patients have 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 centraloblastic NHL, the others each a large cell medistinal B-NHL, a high-grade pleomorphic T-NHL and a high-grade not classifiable NHL. All patients had extensive disease (B3 stage). They received massive pretreatment (2 schedules or more in all patients, radiotherapy in 5 patients, and another patient with preexisting autologous bone-marrow transplantation). Four patients have been refactory to pretreatment; the others had a 2nd and 3rd relapse. Granulocytes grade 4 WHO was present in all patients but hematopoetic recovery occurred after a median of 8 days after course 1 and after a median of 4 days after course 2. Median duration of neutropenia was 5 and 4 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 disease. We conclude that MTX-based high-dose chemotherapy is tolerable and effective when given with APBS 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 AND FOR ACCELERATING GRAFT AFTER MYELOABLATIVE THERAPY. A. Cocciferri, R. Campanero, M. Monti, M. Orlandini, C. Olivi, G. Cerri, A. Tedeschi, H. Zierari, P. Leonz, Clin. Haematol, University of Ancona, Italy. Twelve patients with malignant lymphoma were transplanted with Autologous Peripheral Blood Stem Cells (PBSC) when 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 means of a Filanwil 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: Granulocyte Growth Factor - G-137- 200 μg/m2/day) starting from the 2nd day from the 2nd day of the 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 12.9±19/kg CD34+ cells; we reinseated a mean of 15x10^6 to 19x10^6/kg in 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, subcutaneously, until reaching the threshold of 500 WBC/mL. The take occurred very quickly, both for neutrophils (>5000/μl) at day 15, and for platelets (>200.000/μl) at day 15, without transfusions; immunological recovery was also rapid (total lymphocytes count >1000/μl at day 50), 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 or 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 hospitalization 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 79%.

Our experience shows that the utilization of PBSC collected after G-CSF and their association with the G-CSF after myeloablative regimen is followed by fast and complete hematologic 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.


PBSC and G-CSF are known to shorten duration of aplasia in patients receiving high dose chemotherapy with haemopoietic stem cell rescue. We evaluated the impact of these two techniques in 67 lymphoma patients who have been in our institution since 01/89. Twenty two patients (group I) received G-CSF for collection of PBSC 5 μg/kg daily (Schering Plough-Sandost) and after stem cell injection 5 μg/kg daily until achievement of 500 PFC/μL3 on 3 consecutive days and were compared with three historical groups: bone marrow stem cells + G-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-Hodgkin's Lymphoma (NHL) including lymphocytic small cell and mixed follicular, Exudat 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 TH2 in 14 patients.

Two toxic deaths were observed in groups I and IV. At this time 11 median of new second group I, days (9±18) in group II, 15 days (10±18) in group III and 16 days (11±7) in group IV (p < 0,001) - 2) G-CSF shortens duration of neutropenia (~50 ± 30% in group I and II and 5 ± 3 days in group III and IV (p < 0,05) - 3) a significant 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 circulating stem cells (CSC) in 1/3 of patients at the University of Largo, Italy.

T 241  G-CSF ADMINISTERED DURING RADIATION-INDUCED GRANULOCYTOPENIA PREVENTS DISCONTINUATION OF RADIOTHERAPY: A PHASE II STUDY. A. Magni, W. M. Herbst, and F. V. A. Hoek. Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA, USA.

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 lymphoma), 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 be discontinued for 3-6 weeks in half of the patients and definitively stopped in the other half. On radio logical 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) 60 Gy to still be delivered at the time granulocytopenia occurred (≤ 1.5 x 10⁹/l) and 3) platelets ≥ 75 x 10⁹/l. G-CSF was given at a dose of 5 µg/kg/d s.c. until the granulocyte count was ≥ 2 x 10⁹/l. RT was only discontinued if granulocytes and platelets decreased below 1.0 x 10⁹/l and 40 x 10⁹/l, respectively. Of 30 patients treated with G-CSF, 22 received a normal dose of RT and 8 patients had partial RT dose reductions due to hematologic toxicity. Of 5 patients who had been treated with G-CSF, 6 received a partial RT dose reduction.

BONE Marrow TRANSPLANTATION (BMT) IN ADULTS' Lymphomas.

Between 1983 and 1992, 35 adults patients with LL received BMT (autologous = 26, allogeneic = 9). They all priory received prospective randomized chemotherapy protocols for acute lymphoblastic leukemia (LALL, LAL), 84% of patients were conditioned with cyclophosphamide and etoposide (Cy/VE), 20% with Cy/VE and total body irradiation (Cy/VE and TBI), 16% with Cy/VE alone, and 16% with Cy/VE and TBI. All patients were conditioned with Cy/VE and TBI. The mean age was 38 years. At the beginning of RT, 22 patients (53%) were conditioned with Cy/VE and TBI. The staging at diagnosis showed: Stage I = 3, Stage II = 6 (4 bulky), Stage III = 4, Stage IV = 23. Twenty-one patients were given autologous BMT, 1 patient was given allogeneic BMT, and 1 patient was given autologous BMT as first complete remission (CR1) at a median time of 5 months (autologous = 6 months, allogeneic = 4 months). Six patients received autologous BMT in second CR (CR2) or third CR (CR3) complete remission at a median time of 13 months (range 6 to 66 months) and 1 patient was allografted in CR3 at 8 months. The 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 patients) or MELPHALAN (9 patients).

The 7 patients who received BMT in CR1 are alive and well in continuous CR (CCCR): 5/7 autografts with a median follow-up of 13 months (range 9 to 107 months) and 2/7 autografts with a median follow-up of 27 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 allogeneic 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 30 months (allogeneic) after BMT. 1/5 patient who received autologous BMT in RA 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 develop such a procedure after induction-consolidation chemotherapy of adult LL.
SURVEY OF BURKITT LYMPHOMA IN SERBIA 1981-1992

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The first HIV I infection was registered in Serbia in 1983. The Burkitt lymphoma is one of the commonest neoplasms 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 Serbia in patients in 1981-1992 using the national cancer register. The HIV I testing included detection of anti HIV I antibodies with the Pivazmy anti-HIV ELISA test and HIV I antigen with the Abbott ELISA test. Confirmatory tests included the Abbott 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 in the next years, 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 913 neoplastic disorders registered in this population. At the moment of diagnosis of Burkitt lymphoma the patients were positive either for GP41 and GP42 antibodies or for GP41 antibody and HIV I antigen; at least one HIV I positive patient during the whole period lost the antigen and development GP42 antibodies. Among HIV I positive patients 2 were in clinical stage IIIE, in 1 case III and 5 in IIIS, I and 5 with bone marrow infiltration. Among the HIV I positive cases 2 were in stage IIIE and 3 in IIIS, I, with bone marrow infiltration. The HIV I negative cases were treated either by the ProMAC and 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 MAC/SLICE regimen, intrathecal therapy with 3/5 complete responses, and no CNS localizations were detected until now. The survey is still ongoing.

We evaluated the clinical features of presentation, the morphologic and immunohistochemical pattern, the modality of spread, and the response to therapy of 38 consecutive pts (34 M, 16 F, median age 28) with primary mediastinal B-cell lymphomas with sclerosis, a recently documented subtype of non-Hodgkin's lymphomas (NHL). The clinical aspects were subdivided into 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 41%. 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 centrocyte), diffuse, centroblastic (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 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 48% at 3 year resp., P = 0.06). After a 13/15 remitters 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 years survival is 39% for all pts and 78% for remitters. In conclusion, this study shows that primary mediastinal B-cell lymphomas with sclerosis is a distinctive subtype of NHL. Its unique clinicopathologic aspects and aggressive behaviour demand separate consideration among NHL. Intensive chemotherapy, followed by consolidation RT, may delay a long survival in a good proportion of cases. Some pts, however, are expectedly 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., as possibly cytokine release by the tumor suggested by the presence of a heavy inflammatory infiltrate) may explain the highly aggressive behaviour of this lymphoma.


In a multicentric randomized trial on aggressive non-Hodgkin's lymphomas comparing MACOP-B vs F-MACHOP (September 1988 - August 1991), 69 examples of anaplastic large cell lymphoma (ALCL) were recorded. In this study, we evaluated these cases after 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 Blaut's 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 vs 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 (66%). On the other hand, ALCL-CT revealed a mediastinal mass in 57% of cases, rare bulky tumour (18%) and non-evident stage distribution (II, 46%; III, 34%; IV, 19%). 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 37 ALCL-CT and with ALCL-HR, respectively, are alive; the relapse-free survival is 79% for ALCL-CT and 68% for ALCL-HR, respectively, at a mean follow-up of 28 months (range, 15 to 66 months). Our data confirm that ALCL represents a peculiar clinicopathologic entity, which can benefit from third generation chemotherapy regimens for high-grade non-Hodgkin's lymphomas. Moreover, it is possible to differentiate ALCL based on the 2 ALCL histologic subtypes: CT and HR - for clinical features of presentation (age, bulky disease, stage and involved sites) and for relapse-free survival.

T 249 PRIMARY MEDIASTINAL LYMPHOMA: EXPERIENCE AT MD ANDERSON CANCER CENTER (MDACC), J. Rodriguez, W. C. Pugh, F. B. Hagemeister, M. McLaughlin, M. A. Rodriguez, J. B. RomaguetF, Swan, F. Cabañas. UT MDACC, Houston, TX.

PML has been described as a different B-cell lymphoma with CD19(+)/CD21(-) phenotype and a lack of HLA class-I surface molecules. From 1985-90 thirty-five patients were presented to MDACC with PML. Median age was 33 years with a predominance of females (59%). 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 III/IV. 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 masses. Six patients died during initial treatment 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 251 Ki-1 Non-Hodgkin's Lymphoma: King Faisal Specialist Hospital & Research Centre 2 Year Experience. A. Ezzat, M. Raja, S. Bazaz, S. El Azkouni, R. Weinicki, M. Dalarak, A. Abu El-Walid, 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 immunohistochemical criteria are presented. The patients are two males and ten females in 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 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 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 actuarial survival is 78% and disease free survival is 30%. 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.
ABSTRACTS - Fifth International Conference on Malignant Lymphoma, Lugano


Clinical and immunohistochemical features of 50 patients (pts) with anaplastic Ki-1 positive lymphoma (Ki-1-LNH) 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% of all pts), malignant histiocytosis (6), anaplastic large cell lymphoma (7) and acromegaly melanoma (1). Immunohistotype 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 (LN) 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 IIa, 16 stage IIb, 11 stage III and 8 stage IV. Constitutional symptoms were present in 20 cases and compressive or constrictive extension in 16 cases while 4 pts had a cutaneous rash. 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 (11), malignant lymphoma (19) or malignant histiocytosis (4) with MPV, CVMP, ABVD, EBVP or CHOP-like regimens. A complete remission was observed in 34/45 pts (76%), 17/34 pts relapsed (50%) after CR in LN (9 cases), skin (3 cases), lung (2 cases), bone (2 cases), 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 75% at 3 years 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 stage (4-60 years) showed no significant difference, but the survival was statistically better in negative leucocyte common antigen cases (p<0.01) and in stages III vs I/IV (p<0.02). Ki-1-positive NHL appears as a high grade lymphoma with high initial failure, poor prognostic and frequent cutaneomuscular involvement or relapses.


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 WHO working formulation, 7 large cell, immunoblastic and 2 diffuse large cell; according to the Ki67 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 involvement (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 in undergoing induction therapy, and one failed induction. The latter patient achieved a CR after salvage treatment with involved field radiation and DNR (doxorubicin, cisplatin, and cytarabine) and remains disease free 2 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 mitoxantrone, ifosfamide, etoposide, and dexamethasone and will 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 or extranodal involvement, response to chemotherapy at both presentation and in relapse.

T 254 HISTOLOGIC AND CYTOLOGIC ASPECTS OF CHILDHOOD NON-HODGKIN’S LYMPHOMAS TREATED WITH SPOP LBMB99 AND LBMB99 Regimen: Survey of Pediatric Oncology.


Since 1989, 87 and cell childhood non-Hodgkin’s lymphoma (NHL) accepted 47 cases of anaplastic large cell NHL have been treated with LBMB99 and LBMB99 regimens. Initial material from 203 cases were reviewed by a panel of pathologists and cytopathologists. 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 cytopsines from pleural or ascitic effusions. Cases were classified according to the criteria of the up-dated iHL 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, inconsiderable nucleolus and narrow pale or basophilic cytoplasm. A good agreement was obtained between pathologists and cytopathologists, some cases with discrepancies were discussed to come to a consensus, but the “atypical medium-sized cell” category was recognized by both. The distribution of cases according to the histological and cytopsietic aspects have shown: 13 centrolsbile (CB) NHL, or large cells (LC), 129 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 LA and all the “atypical medium-sized cell”), 11 cases were T-cell (5 LB, 2 peripheral pleomorphic medium cell).

Cytogenetic studies were performed in 28 classified cases showing t(9;14) or (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 cytopsietic approaches were in agreement and complementary to characterize childhood NHL recognizing in addition to classical NHL, some atypical lymphoid types with other abnormalities in 4 cases out of 7 showing morphologic features between lymphoblastic and SNCC non BL categories.


There were 56 children with newly diagnosed non-Hodgkin’s lymphoma (NHL) treated at our Department from 87 till 97. 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 85 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:
-30 days chemotherapy extending 30 days starting in the first month of therapy

-temoporary or permanent change of protocol

The results of treatment were as follows: Survival (2 years, 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 58%, B NHL 71% non-B-NHL 57%, protocol patients 68% non protocol 54%.
ABSTRACTS - Fifth International Conference on Malignant Lymphoma, Lugano

T 256


The efficacy of a response-adapted 7 cycle chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisolone [COP]; bleomycin, vincristine, prednisolone, mitoxantrone [BLAM]; and ifosfamide, melphalan, etoposide, prednisolone, vincristine, doxorubicin, mitoxantrone, cisplatin [IMVP-16]) in high-grade malignant NHL was evaluated in a prospective multicenter trial. From 1986-1989, 356 evaluable patients (pts) were recruited with a median age of 56 (range 16-75) years, presenting with stage II/III/IV disease in 345/29/4 cases, B-symptoms in 51%, extranodal disease in 61%, serum LDH > 240 U/l in 50% and lymph nodes > 25 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 survival (RFS) survival were 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<0.001 each) with comparable results for RFS (Ki n.s.). Contrary to common expectations DI was critically important; 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<0.01). These results were confirmed if either the given dose or the time were introduced as independent variables in the model. RFS was not affected. Accordingly to these data the prognosis of high-grade malignant NHL pts is negatively correlated with tumor load, but cxt of high DI may not be advantageous.

T 257


We reviewed the records of 962 pts with NHL diagnosed and treated at our institution between 1976 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 (C0: 0-5%, C1:5-15%, C2: >15%). It was detected at diagnosis in 340 pts (35%): in 207/405 (51%) low-grade (LG), in 73/258 (25%) intermediate-grade (IG), and in 60/168 (37%) 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), 8% of HG NHL (LG vs HG, P<0.001). 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 HG-NHL, BM+ (especially C2-M) and PB+ whenever they occurred, were significantly associated with poor outcome. In HG-NHL, pts BM+ at diagnosis did worse than BM- (P<0.05), but 50% of pts with C2-M 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

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

T 258


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 β3 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 CD457 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. non-bulky disease and high vs. low level of fever, 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 SETA-2-MICROGLOBULIN IN NON-HODGKIN'S LYMPHOMAS. S. Packer, M. Elashoff, H. Zhong, E. Beyers, S. Hambardzumyan, A. Bailer, H. Hladik, B. Storveth. "Tumor Parker" Oncology Research Unit and Chest Department AI-Dade, 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. 90 individuals were included; 20 with lymphoma, 10 with bronchial carcinoma, 10 with non-malignant lung disease and 10 normal healthy controls. Serum B2-M was determined using the phakocyte B2-Micro test supplied by Pharmacia Diagnostics. 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. 10/40 of patients with bronchial carcinoma, 7/30 of patients with lymphoma and 3/30 of patients with benign lung diseases showed levels above the cut-off value in the normal healthy controls (3.8 kg/l). Serum B2-M was correlated with the clinical state of lymphoma patients during therapy.
ABSTRACTS - Fifth International Conference on Malignant Lymphoma, Lugano


Background. Analysis of prognostic factors in 59 patients with primary extranodal NHL observed in a single institution during a 9-year period (1984-1993).

Methods. Inclusion criteria were the presence of NHL at one or more extranodal sites with or without 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 prognostic: age, sex, constitutional (B) symptoms, site of involvement, bulky disease, histology (Working Formulation), (Ann Arbor system with Musshof'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 preceded 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 14, whereas 9 were unclassified. The extension of NHL was: 1, 10 cases; 1, 19; 2, 8; 3, 7; 4, 9; 3 and IV, 7.

Complete response was attained in 31 of 32 evaluable cases (97%) (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 died, overall survival (OS) being 45% at 5 years. In the multivariate analysis three variables had an adverse influence in DFS: extensive disease (III, IV or IV) (p<0.001), LDH level (p<0.04), and aggressive histology (p<0.03). 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<0.001) and extranodal involvement (p<0.03). When HIV-positive patients were excluded from the model, bulky disease emerged as the most unfavourable variable for OS (p<0.03).

Conclusions. 1. - The frequency, localization, histological subtypes and response to treatments are similar to that 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.


The level of the enzyme deoxy-thymidine kinase in serum (S-DT/K) 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-DT/K levels, and to study if C-TK and tumour burden also carries prognostic information. More than 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-DT/K 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 cm3) were retrospectively estimated from the statements in the patient files.

In the entire material, a correlation between S-DT/K and tumour volume, but not between S-DT/K and MI was seen. However, when dividing the tumour volumes into three categories; small (< 30 cm3), medium (30-60 cm3) and large (> 60 cm3), a correlation between S-DT/K and C-TK within each category was not found within the different clinical stages, according to Ann Arbor. C-TK correlated well with the S-DT/K and MI. The S-DT/K and C-TK tumour burden all carried prognostic information. In low grade NHL, C-TK had additional information to S-DT/K. A multivariate analysis in high grade NHL, tumour burden had no prognostic information whereas the clinical stage had no prognostic information. S-DT/K 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-DT/K, reflecting tumour-cell proliferation rate and the tumour-cell proliferation rate and the tumour burden. Since the stage and levels in separate experiments increase considerably the data 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.


GRUPO ONCOLÓGICO DE LINFOMAS (GOLI). 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 biochemical variables at diagnosis were correlated with the overall survival. The analysis for the variance (ANOVA) was used to compare the data.

RESULTS: there were 258 males and 273 females, with a median age of 58.5 years (11-87). Histology according Working Formulation was: A 36.34%, B 31.59% and C 22.14%, not determined 9.96%. Clinical stages were: 1 - 113 patients, II - 90, III - 81 and IV - 248. Performance status (ECOG scale) was: 0 - 65.3%, 1 - 27.5%. Systemic symptoms were present in 147 patients at diagnosis. The primary location was nodal in 179 cases (33.0%), extranodal in 110 (22.5%) and combined in 253 (46.67%). The most frequent nodal location was abdominal (45.9%), followed by cervical (41.3%) and axilar and inguinal (32%) each. The erythrocyte 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 (1-147 months).

The following factors were found to decrease survival in the univariate analysis: 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 LYMPHOMAS (NHL) WITH A LONG FOLLOW-UP FROM A SINGLE INSTITUTION.


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 follow-up was 6.5 years (range: 1 to 21 to 85). M/F ratio: 79/64. Median follow-up: 6.5 years (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 survival: 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=89) the only significant parameter was performance status (p<0.007). When the focus of 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), FR (p=0.003), and absence of B-symptoms (p=0.014).

In conclusion, in 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 variable, with those achieving a CR having a longer survival than those in PR or failing to respond.
ABSTRACTS - Fifth International Conference on Malignant Lymphoma, Lugano


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:

\[ 0.038\text{Age} + 0.4\text{Stage} - 1 + 0.03\text{WCC} + 0.10\text{Age} + 0.07\text{If } B\text{ symptoms are present.} \]

Cut off points were <2 for the best prognostic group and >3 for the worst prognostic group.

<table>
<thead>
<tr>
<th>SURVIVAL</th>
<th>% IN GROUP</th>
</tr>
</thead>
<tbody>
<tr>
<td>median 5 Yr</td>
<td>10 Yr</td>
</tr>
<tr>
<td>stage IV</td>
<td>6.5 mm</td>
</tr>
</tbody>
</table>

Best Group (25%) (1)
123 mm 86% 69%
Intermediate Group (50%) (2)
123 mm 86% 69%
Worst Group (25%) (3)
123 mm 86% 69%

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 x10^9 (53%) were in Group 3. Using this simple clinical index, we can use simple clinical assessments from the SNLG database, 11% (58/513) of patients with follicular lymphoma who are under 40 years old and have a particularly poor survival, and should thus be considered for more intensive or experimental treatment.


From 08/86 to 10/91 111 patients (pts) with high grade malignant NHL (Kiell-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 CHOEP/VPEP followed by involved field irradiation as published elsewhere. 54 pts (non-study group) did not fulfill study criteria (pre-treatment stage 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) (CHOEP or CHOPEP), 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 49.35%, respectively, at 2 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.

<table>
<thead>
<tr>
<th>CR/PR</th>
<th>OS</th>
<th>RFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>study group</td>
<td>84/12/2</td>
<td>70/25.2</td>
</tr>
<tr>
<td>non-study group</td>
<td>50/12/2</td>
<td>40/20.2</td>
</tr>
<tr>
<td>p-value</td>
<td>0.0002</td>
<td>0.49</td>
</tr>
</tbody>
</table>

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.

Conclusion: Our analysis clearly shows that the results of our clinical NHL-study can be compared 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 CHOEP or CHOEP/VPEP 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 age and performance status > 2 for this unselected group.

T 265 PROGNOSTIC FACTORS AND SURVIVAL IN HIGH-GRADE NON-HODGKIN'S LYMPHOMA. Gy. Varga, Z. Bóboryné, M. Bérczi. 2nd Department of Internal Medicine, Szent-Györgyi Albert Medical School, 6701 Széged, Hungary

In a multicentre study the data of 133 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, 25 % 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 are alive.

At the univariate analysis in high-grade non-Hodgkin's lymphoma 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 a 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.


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 (define as ≤50% response (p=0.002), OR=3.74) and a large tumor burden (p=0.0033, 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=0.011, 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. By univariate analysis, the variables correlated with OS were performance status (ECOG), Ann Arbor stage, bone marrow involvement, number of extranodal disease sites, tumor burden, retraperitoneal involvement, serum albumin, LDL level, alkaline phosphatase and TR. In multivariate analysis, the three variables found to be predictors of OS were TR (p=0.0011; RR=3.70), tumor burden (p<0.003, RR=4.11) and serum albumin (p=0.032, RR=3.20).

If only pretherapeutic variables were included in the analysis, tumor burden (p<0.0001; RR=4.07), Ann Arbor stage (p<0.0001; RR=3.30) and serum albumin (p<0.0001; RR=3.48) were the variables that retained their significance.

Release-free survival (RFS): Estimated 5-year RFS was 61% (95% CI, 51-71%). In multivariate analysis, stage was the best release predictive 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<0.0001), and 5-year RFS was 81%, 44% and 33% (p<0.0001), respectively.
T 268  COMPARISON OF PROGNOSTIC SCORES OF HIGH GRADE NON HODGKIN LYMPHOMAS (NLH)

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3rd Medical Department and Ludwig Boltzmann Institute for Leukemia Research and Hematology, Hanusch Hospital, Vienna, Austria

Institute for Medical Statistical, 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, LDN, extranodal involvement and preexisting 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 lymphomas (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: 16-89 y). Ann Arbor stages were as follows: I/III, II/I, III/II, IV/III2. The bulk size was > 5 cm in 50 pts., > 5 cm in 30 pts. and > 10 cm in 10 pts. The Karnofsky-index was <60 in 54 pts. 44 pts. showed "B symptoms* and the LDH was increased in 42 pts. 50/109 pts reached a CR(54%), 33/109 reached a PR(30%) and 14(16%) pts. were not responders. The different scores with their various advantages, significance and implications for further studies will be presented.

References


Both of LDH and B2M are known of their values to reflect the tumor burden at the 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 CHOPE 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 200ug/ml, the second group were patients with LDH less than 500u/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% attain 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.


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 pathogenetically characterized; whereas, in 49 representative cases the association of EBV was assessed by non-isotopic in situ hybridisation (ISH) and the immunohistochemical demonstration of latent nuclear protein-1 (LMP-1). Most lymphomas were of B-cell derivation and showed a "plastic" 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-1 lymphomas. Combined ISH studies for viral DNA and EBER and immunohistochemical demonstration of LMP-1 suggested that there were differences in viral latent gene expression between ALC Ki-1 or immunoblastic lymphomas (usually EBV-LMP-1 1), and EBV-infected cells of small noncleaved cells lymphomas which did not show LMP-1 expression. Two main groups of HIV-associated systemic NHL, i.e. "plastic" cell and "anaplastic" cell lymphomas, which includes specific cytogenomic 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 "plastic" cell lymphomas.

Acknowledgements: This work was supported in part by the Istituto Superiore di Sanità, AIDS project 1992, Rome, Italy and by the Associazione Italiana per la Ricerca sul Cancro, Milan, Italy.

Service d'Hématologie, Hôtel-Dieu, 75004 Paris (France).

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

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 T cell pts (pts 2) NHLs. BM was involved as diagnosis in all but one case (pt 3). Risk factors for HIV were homosexuality with anal intercourse (1), T4 levels at presentation were above 200U/l in 3 pts (pt 2 with CD4 leaekemia not evaluable). First line reductive regimens were COP and 3 courses of CHOP (pts 1), MACOP-B (pts 2 and 4) or COPd, COPADIM x 2 plus CYME (pts 3 and 4). Complete remission was obtained in all but one case (pt 2). Bone marrow was harvested under sedovide therapy in all pts and purged with monostafmide (pt 1) or anti-T MoAbs (pt 2). Median duration of post-ABMT aplasia (PMN < 500U/l) was 32 days without noticeable morbidity. Hematopoetic recovery was incomplete in the 3 lineages but without prolonged transfusional needs. Pt 1 who demonstrated ganciclovirtreated CMV pneumonitis (d-x1), progressive pancytopenia, and reappearance of P24 ag at d153, died of neurological AIDS 14 months after ABMT without evidence of NHL relapse. Pt 2 did not received sildarafine after conditioning. Pts 2 and 3 died because of NHL respectively at 12 and 2 months post-ABMT with negative P24 antigenemia and stable PMN. 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 hematopoetic recovery, presumably because of previous treatments. BM involvement by NHL and/or HIV-associated dysmyelothropenia. 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.
**ABSTRACTS - Fifth International Conference on Malignant Lymphoma, Lugano**

**T 272 HIGH INCIDENCE OF EPSTEIN-BARR VIRAL DNA IN CRYOPRESERVED AIDS-RELATED LYMPHOMA SPECIMENS.**
M. Samoszuk, B. 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 274 COMPARISON OF HIV-RELATED NON-HODGKIN’S LYMPHOMA (IVL, RNL) AND NON-HODGKIN’S LYMPHOMA IN THE GENERAL ELDERLY POPULATION (AGE > 70 YEARS): NO DIFFERENCE IN RESPONSE RATE AND SURVIVAL.**
U. Tirolt, D. Ermayer, A. Aubert, V. Zagonel, G. Heuzey, P. Poivre, M. Turat, D. Bernardet, E. Vacheret, and S. Monbéjot. *Division of Medical Oncology and AIDS, Division of Pathology, Division of Medical Oncology, C.R.O. Arno-Lietz, Lyon, France*

HIV-related NHL is considered to be more unfavorable NHL, both for the treatment-related survival and for the underlying HIV infection. Although NHL occurring in the population over 70 years of age or more is also considered to be an unfavorable subset of NHL, the aim of this study is to compare the number of 15 pts (age > 70 years) with high-grade Histologic subtypes according to the W.H.O. (1986), with a mean age of 63 years (range 70-26) and with a relatively good PS (50%) according to Karnofsky observed in June 1987 (1987) to February 1994 (Group A) with the outcome of 13 pts see with similar age and with similar PS and NHL characteristics (CNS NHL were excluded) (Group B, observed from July 1979 to May 1993, 1987). All pts were seen and treated at our institution. Pts of group A received the VAMP (VP16, Mesna, Prednisone, Adriamycin) chemotherapy (CT) regimen, specifically designed for our aging pts (Tirolt et al. JCO 1988: 2:236-31, 1992), while pts of group B were treated with a more aggressive third-generation CT regimen, LNH/L жену (Coffner et al, JCO 6: 1018-26, 1989). Progress characteristics and results of this comparison are summarized in the table:

<table>
<thead>
<tr>
<th>Group A</th>
<th>Group B</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N PTS</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Median age (range)</td>
<td>75 (71-86)</td>
<td>75 (71-86)</td>
</tr>
<tr>
<td>Male/female</td>
<td>7/6</td>
<td>7/6</td>
</tr>
<tr>
<td>PS (mean)</td>
<td>70 (50-100)</td>
<td>80 (50-100)</td>
</tr>
<tr>
<td>Histology (W.H.O)</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>H</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Stage</td>
<td>5/13</td>
<td>10/15</td>
</tr>
<tr>
<td>IV</td>
<td>3/13</td>
<td>8/13</td>
</tr>
<tr>
<td>B symptoms</td>
<td>4/13 (31%)</td>
<td>8/13 (62%)</td>
</tr>
<tr>
<td>Median CD4(+) counts/mm (range)</td>
<td>-</td>
<td>235-39 (435)</td>
</tr>
<tr>
<td>Response</td>
<td>CR</td>
<td>CR</td>
</tr>
<tr>
<td>NC</td>
<td>3/12 (23%)</td>
<td>7/13 (54%)</td>
</tr>
<tr>
<td>PR</td>
<td>7/13 (54%)</td>
<td>5/13 (38%)</td>
</tr>
<tr>
<td>PD</td>
<td>0/13</td>
<td>1/13</td>
</tr>
<tr>
<td>Mortality</td>
<td>12/13</td>
<td>10/13</td>
</tr>
</tbody>
</table>

**T 275 TREATMENT OF HIV-RELATED NON-HODGKIN’S LYMPHOMA (IVL, RNL) WITH THE COMBINATION OF DASH (MALE FACTORS) IN THE DAYS OF HOSPITALIZATION AND TOXICITY WITH CONCOMITANT OVERALL REDUCTION IN THE COST.**
U. Tirolt, D. Ermayer, A. Aubert, V. Zagonel, G. Heuzey, P. Poivre, M. Turat, D. Bernardet, E. Vacheret, and S. Monbéjot. *Division of Medical Oncology and AIDS, Division of Pathology, Division of Medical Oncology and AIDS, Division of Medical Oncology, C.R.O. Arno-Lietz, Lyon, France*

Treatment of HIV-related NHL with CT is associated with an increased risk of side effects, particularly bone marrow toxicity. The aim of this study is to compare the toxicity and the use of CT with C-CSF versus CT without C-CSF. We have analyzed 37 consecutive patients (pts) treated with intensive CT regimen of 12 pts (median 30 days, range 21-30 days) between July 1987 and June 1991 with C-CSF (19 pts) and 19 pts (median 30 days, range 21-30 days) between July 1979 and June 1991 without C-CSF. We have found that pts receiving C-CSF showed significantly lower days of hospitalization and toxicity with concomitant overall reduction in the cost. The data were analyzed for 12 pts receiving C-CSF, 5 days/3 days for days of hospitalization and for 19 pts not receiving C-CSF, 7 days/3 days for 30 days of hospitalization.

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U. Tirolt, D. Ermayer, A. Aubert, V. Zagonel, G. Heuzey, P. Poivre, M. Turat, D. Bernardet, E. Vacheret, and S. Monbéjot. *Division of Medical Oncology and AIDS, Division of Pathology, Division of Medical Oncology and AIDS, Division of Medical Oncology, C.R.O. Arno-Lietz, Lyon, France*

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**T 277 HIV-RELATED NON-HODGKIN’S LYMPHOMA IN 81 PATIENTS.**
L. Jahns, C von Gunten, A Bademaker, J. Von Roenn. Northwestern University, Chicago, Illinois, USA

The records of all patients with HIV-related non-Hodgkin lymphoma (NHL) treated at Northwestern Memorial Hospital from 1985 through 1992 were reviewed. Of 81 total patients, 72.5% were male and 7.5% were female. Of 51 patients with adequate records, 52.5% were white, 10.5% black, 6.5% Hispanic, and 4% Asian. The mean age was 38 years (range 22-52). Homosexuality/bisexuality was the risk factor in 52.5% IV drug use in 10%, heterosexual contact in 5% and blood transfusion in 8%. 92.5% 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 128-1798). The mean CD4 lymphocyte count was 118 cells/ml (range 2-600). 52% 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 currently employed classification. Only one patient had small lymphocytic lymphoma (non-Burkitt) in contrast with other published series. Of 24 patients receiving chemotherapy, 74% received CHOP and 18% m-BACOD. 54% received chemotherapy prophylaxis of the CNS. 43% of patients achieved a CR. Mean survival of patients presenting without constitutional symptoms (n=5) was 27.9 months (SEM 7.4). In contrast, those with constitutional symptoms (n=65) had a mean survival of 4.0 months (SEM 0.8, p=0.01). Subgroup analysis and survival curves will be presented.
ABSTRACTS - Fifth International Conference on Malignant Lymphoma, Lugano

T 276 CHOP INDUCTION AND AZT/INTERFERON ALPHA 2B MAINTENANCE THERAPY IN HIV-NON-HODGKIN’S LYMPHOMA.

Induction therapy with CHOP followed by Maintenance therapy with IFN alpha 2b in 24 patients with HIV-associated Non-Hodgkin’s lymphoma.

Methods: Two risk groups were distinguished.

1. Normal risk: 2 of 3 criteria met: CD4+ lymphocytes/µl: WHO act. index 2; opportunistic infection; 2. High risk: 2 of 3 criteria not met.

Excluded 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 WR and prednisolon. Supportive treatment in both groups with aerosol pentamidin and G-CSF according to a fixed scheme depending on leukocyte value.

110 patients from 15 institutions were registered between 1/90 and 10/92. 60 patients were not treated according to protocol: 11 patients with primary CNS lymphoma. 4 patients stage Ia. 13 patients histology other than NHL (N. Hodgkin, multiple myeloma and ALL). 8 patients final stage II, 12 patients interim postmorbid, 5 patients secondary malignancy, in 7 cases no approval could be obtained. 9 patients were treated in the high risk group and 38 patients in the normal risk group. The mean value of CD4+ lymphocytes/µl in high risk patients was 16 in normal risk patients. 102.

Results: Induction and maintenance therapy are well tolerated. In the normal risk group 28/28 (64%) achieved CR and 6/28 PR (21%). 10 patients are too early for evaluation. In the high risk group no remissions were achieved. Median time to progression is 18 months in the normal risk group 61 days. In a Cox regression model 2 risk factors defining poor prognosis could be estimated: CD4 count below 50/µl 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. IAOCACCIO*, G. CARLONI*, M. CARTONETTI, R. RAPATRINTI, 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 develop 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-I 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 antiblastic therapy, M-CHOP, do not affect viremia in these patients. However, in one patient with an HIV-associated NHL, subsequent therapy with high dose cytarabine and etoposide protocol, seems to normalize 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-I 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 AIDS-associated lymphoma, and this kind of analysis appears to be promising for understanding the pathogenic 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. HOFFMAN (*) A. DEVILLE B. SCHMID, C. DOELER (*), J. MICHELS (†), A. THYS (‡).
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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 knowledge, only one case has been reported in child (Peddiar志1990,116: 7-12). We report a second case in a 7 yr 4 mo old boy with bilateral cervical, mediastinal and retropertitoneal involvement but no general symptoms (stage IIIA). Severe thoracic herpes zoster with pulmonary involvement resolved rapidly under acyclovir. The ESR was 57 mm the first hour. Histicologic examination of a cervical lymph node diagnosed Hodgkin’s disease (nodular sclerosis type). HIV antigenemia was negative. CD4 lymphocytes count at 760/mm^3 and hyper IgG of 34 mg/dl. EBV serology was strongly positive: VCA 1/6120, EA 1/2820, EBNA 1/10. In situ hybridization for EBV was positive in Reed-Stemberg cells with Bam H1 and E-Probes. Treatment consisted in 8 alternating courses of MOPP and ABVP followed by irradiation of involved field at 25 Gy. Tolerance of chemotherapy was initially poor with delays and dose reduction, then improved with use of G-CSF. No opportunistic infection occurred 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. Klunk, M. Glass, M. L. Gruber, and F. Hoobberg. 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 histologic subtypes of primary CNS 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. 1992, 10:726-8) 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^2 IV, and vincristine 1.4 mg/m^2 IV day 1. Methotrexate 15 mg/m^2 IV 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 16 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.

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