P 73 MOPPEBVCAD HYBRID CT ± LIMITED RT IN ADVANCED OR UNFAVORABLE HODGKIN'S DISEASE.

P. G. Gobbi, C. Pieresca, M. Federico, N. Di Renzo, F. Narni, E. Iannitto, G. Grignani, L. Cavanna, P. Avanzini, G. Partesotti, V. Pitini, E. Ascari, V. Silingardi, C. Mauri for the Gruppo Italiano per lo Studio dei Linfomi (GISL).

Clin. Medica II, Univ. Pavia; Catt. Oncologia and Catt. Ematologia, Univ. Modena; Ematologia, S. Giovanni Rotondo (FG); Clin. Medica, Univ. Palermo; I Div. Medica, Osp. Civ. Piacenza; I Div. Medica, Osp. S.M. Nuova, Reggio Emilia; Div. Medicina, Osp. Civ. Sassuolo (MO); Clin. Oncologica, Univ. Messina, Italy.

A new CT regimen, MOPPEBVCAD was derived through hybridization, shortening and intensification of a corresponding 10-drug alternating schedule, CAD/MOPP/ABV, effective in advanced Hodgkin's disease adults.
In the original CAD/MOPP/ABV regimen the sequence CAD (day 1), MOPP (day 36), ABV (day 64) was alternated three times (9 cycles in all), with an interruption between the 6th and 7th cycles for RT to all the nodal regions initially involved with disease. In the hybrid MOPPEBVCAD the following 28-day schedule was repeated 6 times (doses in mg/m²): mechloretamine, 6, i.v., 1° (cycles 1, 3 and 5); lomustine, 100, oral, 1°, (cycles 2, 4 and 6); vindesine, 3, i.v., 1°; alkeran, 6, oral, 1°-3°; prednisone, 40, oral, 1°-14°; epidoxorubicin, 40, i.v., 8°; vincristine, 1.4, i.v., 8°; procarbazine, 100, oral, 8°-14°; vinblastine, 6, i.v., 15°; bleomycin, 10, i.v., 15.
The average projected drug dose during the 6 cycles was increased 42%, corresponding to an overall 1.54 dose intensification (epidoxorubicin was substituted for doxorubicin at equivalent tumoricidal doses). RT was limited and optionally reserved to those sites either more heavily involved at onset or in partial remission after CT.
Eighty evaluable patients with previously untreated, advanced or unfavorably presenting Hodgkin's disease were treated between 1988 and 1991.
RT was delivered in 22 patients; in only 1 was it applied to an incompletely remitting site after CT. Remissions were complete (CR) in 75 patients (93%), partial in 3 (4%), null in 2 (3%). The median relative dose intensity was 0.71 for the overall regimen. The 5 patients who failed to achieve CR were all symptomatic and 3/5 received lower relative dose-intensity cycles; the 4 who relapsed showed initial clinical characteristics at variance, but only 2 of them had relative dose intensities clearly lower than the median. Nonhematological toxicity was acceptable, but there was considerable hematological toxicity (leukopenia < 2.0 x 10^9/L and/or thrombocytopenia < 50 x 10^9/L were recorded in 77% and 60% of the patients, respectively). Fatal gastrointestinal bleeding was seen in 1 patient. One case of Pneumocystis carinii pneumonia was diagnosed and successfully cured.
Caution is needed due to the short median follow-up: 25 months from the start of therapy, 18 months from the end of it. However, the following remarks are possible: 1) the results were reached through abbreviation, intensification and hybridization of an existing and well-known alternating regimen; 2) RT had limited use in this program, hopefully contributing to lower the risk of second tumors seen when it is associated with alkylating agents; 3) the results were obtained in a multicentric study, a condition often impairing results from clinical trials.

P 74 ALTERNATING MOPP/ABVD Vs. OPP/ABVD CHEMOTHERAPY IN ADVANCED STAGE HODGKIN'S DISEASE.

A.P. Anselmo, C. Cartoni, A. Cafolla, MT. Bove,* R. Maurizi Enrici * A. Capua, * C. Biagini, F. Mandelli. Hematology, Department of Biopathology. * Inst. of Radiology, University "la Sapienza" of Rome, Italy.

Background and methods. In order to improve the overall survival and disease-free survival achieved with the use of standard alternating MOPP/ABVD, 8 courses of this regimen have been randomly compared in 240 patients affected by advanced stage Hodgkin's disease (HD) to 8 courses of alternating OPP/ABVD (vincristine 1.4 mg/sqm on days 1 , 8 and 15, procarbazine 100 mg/sqm orally on days 1-21, prednisone 40 mg/sqm orally on days 1-14 followed by standard ABVD on day 28). Withdrawal of mechlorethamine was performed to reduce the iatrogenic delayed toxicity. Patients in complete remission (CR) after the stop of chemotherapy received 20 Gy involved field consolidation radiotherapy combined with 40 Gy splenic irradiation. From May 1983 to December 1993, 218 new patients with stage IIB, IIIB and IV HD are evaluable for response, duration of CR and survival (106 in MOPP/ABD arm and 112 in OPP/ABVD arm). The clinical characteristics were equally distributed in both arms.
Results. CR was 91% in the MOPP/ABVD group and 88% in the OPP/ABVD group, with 75% and 78% of patients alive in continuous CR, respectively. The corresponding ten-years overall survival was 76% and 82% (p >.05). Ten-years disease-free survival was respectively 77% and 83% (p >.05). The median follow-up was 58.1 months. Gonadal function impairment was characterized by 79% of males with azoospermia studied in MOPP/ABVD group and 78% in the other arm; amenorrhea developed respectively in 48% and 63% of fertile women. Four secondary tumours occurred in the MOPP/ABVD arm (3.7%) and 2 in OPP/ABVD arm (1.8%).
Conclusions. Both regimens appear equally effective in inducing and maintaining the CR. A longer follow-up is required to assess differences in late complications.

P 75 MOPP/CVPP VERSUS (VS) ABVPP IN PATIENTS WITH STAGE IV HODGKIN DISEASE (HD): LONG TERM RESULTS OF THE LMS 80 PROTOCOL.

D. Assouline, C. Sebban, P. Adeleine, J. Jaubert, J.A. Gastaud, Y. Carcassone, M. Blanc, C. Martin, P.Y. Peaud, B. Coiffier J.J. Viala and D. Fière. Department of Hematology, Hôpital E. Herriot, 69437 Lyon Cedex 03, France.

To assess the efficacy and toxicity of an anthracycline containing regimen for stage IV HD, we analyzed the results of a prospective multicentric study initiated in 1980. Staging laparotomy (with splenectomy and liver biopsies) was performed at diagnosis for all clinical stages I, II or IIIA. For clinical stages IIIB and IV, laparoscopy was recommended with liver biopsies. 334 patients (pts) were enrolled in this study, and after clinical and surgical staging, 89 pts were classified as stage IV. Median age was 47 (16-68). The treatment was randomized between R1: 12 alternate MOPP/CVPP (MOPP: chlormethine 6 mg/m² at d1 and d8, vincristine 1.4 mg/m² at d1 and d8, procarbazine 100 mg/m² and prednisolone 40 mg/m² from d1 to d14 / CVPP: lomustine 75 mg/m² at d1, vinblastine 4 mg/m² at d1 and d8, procarbazine 100 mg/m² and prednisolone 40 mg/m² from d1 to d14) (46 pts) or R2: 12 ABVPP (adriamycine 30 mg/m² at d1, bleomycine 5 mg/m² and vinblastine 5 mg/m² at d1 and d8, procarbazine 100 mg/m² and prednisolone 40 mg/m² from d1 to d14) (43 pts). 70 pts/89 (79%) entered in complete remission (CR) at the end of the treatment, 19 pts (21%) were refractory to treatment and died from HD. 19 pts/70 (27%) relapsed within a median of 20 months, 13 pts/19 died from HD. 3 secondary malignancies occured in pts treated with MOPP therapy. In this group of 89 stage IV HD, with a median follow-up of 8 years, overall survival (OS) is 59% in R1 group vs 65% in R2 group, and disease-free survival (DFS) is 66% vs 73%, without any statistical difference. In this prospective study, ABVPP regimen led to the same results as the classical association MOPP/CVPP with likely decreased risk of secondary malignancies.

P 76 RESPONSE TO MOPP/ABV CHEMOTHERAPY IN ADVANCED STAGES HODGKIN'S DISEASE : THE EORTC LYMPHOMA COOPERATIVE GROUP AND GROUPE PIERRE-ET-MARIE-CURIE EXPERIENCE.

J.M.M. Raemaekers, J.M.V. Burgers, A-M. Mandard, U. Tirelli, P. Carde, A. Hagenbeek, W.P.M. Breed, R. De Bock, M. Vovk, J. Thomas, A. Van Hoof, A. Pinna, J. Marnay and M. Henry-Amar. Department of Haematology, University Hospital Nijmegen, PO Box 9101, 6500 HB Nijmegen, The Netherlands.

From September 1989 to December 1992, 234 clinical stage III-IV Hodgkin's disease patients from 36 centres in 7 european countries were prospectively enrolled in an ongoing phase III trial (EORTC protocol # 20884). After initial MOPP/ABV courses patients in complete remission (CR) were randomized for additional radiotherapy (RT) to involved areas, or no RT. Patients in partial remission (PR) were all given RT. The present abstract reports response to MOPP/ABV only. Usual staging procedures were performed including lymphangiography, but no laparotomy. Treatment response was assessed after 4 and 6 courses. Early CR patients (after 4 courses) were given 6 courses overall, whereas late CR patients (after 6 courses) were administered 8 courses.
Patients were 63% males (sex ratio 1.7). Mean age at diagnosis was 36.4 years (range 15 to 72). There were 28% stage IIIA, 32% stage IIIB, 14% stage IVA and 26% stage IVB. Of the 93 stage IV patients, 32 (34%) had disease localized above the diaphragm, and 58 (62%) patients presented with one extra nodal localization only. Lymph node involvement was present in 95% of the patients (12% with 1-2 nodes, 59% with 3-5 nodes, 24% with 6-11 nodes). Mediastinal involvement was present in 84% of the patients, 41% presenting with a M/T ratio ≥ 0.33. After review (179 cases) by the histology panel, 92% of the cases were considered true Hodgkin's disease, 5% were doubtful, 1% were unconclusive specimen, and 2% were classified as non-Hodgkin's lymphomas. Of the 165 true Hodgkin's disease cases, 1% were lymphocytic predominant, 80% were nodular sclerosing, and 19% were mixed cellularity type. Among the 133 nodular sclerosing cases, 57% were classified as grade 1 of the BNLI classification, 38% were grade 2, whereas 5% were borderline cases.
Of the 205 patients who completed 4 courses, 76 (37%) were early CR, whereas 4 (< 2%) did not respond or progressed. After 6 courses, 123 of 188 (65%) were in CR (of whom 56 were PR after 4 courses), 63 (34%) in partial remission and 2 (1%) had progressed. Factors predicting for early or late complete response were assessed through a logistic regression model which included age, gender, stage, systemic symptoms, topography, number of nodal and extra nodal localizations, mediastinal bulk, and biological parameters as dependent variables. An early CR was associated with younger age ($p<0.05$), absence of B symptoms ($p<0.05$), < 5 nodal areas involved ($p<0.05$), and absence of bulky mediastinal involvement ($p<0.05$). Stage, histologic type, or biologic parameters did not correlate with a high rate of early CR in this series. A late CR was associated with the same factors and also to disease limited to one side of the diaphragm.

P 77 IMPROVED SELECTION OF POOR RISK HODGKIN'S DISEASE PATIENTS FOR EARLY THERAPY INTENSIFICATION USING THE SCOTLAND AND NEWCASTLE PROGNOSTIC INDEX IN PLACE OF CLASSICAL STAGING.

S J Proctor[1], P R A Taylor[1], R Prescott[2], M Mackie[3] on behalf of the SNLG, [1]Department of Haematology, Royal Victoria Infirmary, Newcastle upon Tyne, NE1 4LP, [2]Medical Statistics Unit, University of Edinburgh, [3]Department of Haematology, Western General Hospital, Edinburgh, UK

Classical staging (Ann Arbor) is of great clinical value though it consistently fails to predict sufficiently accurately stage IIIB and IV patients who are destined to perform satisfactorily on four drug schedules. The Scotland and Newcastle Lymphoma Group (SNLG) index objectively using the poor prognostic factors relating to age, haemoglobin, absolute lymphocyte count and bulk disease plus staging enhances the ability to select chemotherapy failure in patients at diagnosis (Proctor et al, Eur J Cancer, 1991, 27:624-629). For 165 of 455 patients with stages IIIB and IV the index predicted 45% of such patients in a poor risk category and the remainder in good risk category. The low index patients (good risk) had a four year survival of 80% and the high index patients a survival of 25%. Further evaluation of the index on a geographically based population has further confirmed that the index will predict only 50% of the stage IIIB and IV as being truly poor risk. The SNLG Hodgkin's index is a far more accurate predictor for selecting patients for autotransplantation in first remission. A randomised controlled trial of autotransplant with melphalan/VP16 pre-conditioning versus a hybrid schedule in first remission is being conducted utilizing this selection process.

P 78 ADVANCED HODGKIN' S DISEASE TREATED WITH THE ALTERNATING MOPP AND ABVD REGIMEN: ANALYSIS OF LONG-TERM RESULTS, TOXICITY AND PROGNOSTIC FACTORS.

E.Brusamolino, E.Orlandi, M.Lazzarino, E.Morra,, G.Pagnucco, A.Livraghi, A.Santagostino, C.Astori, M.Bonfichi, G.Castelli,, C.Bernasconi. Cattedra di Ematologia, Università di Pavia; Divisione di Ematologia , Policlinico San Matteo IRCCS, 27100 , Pavia, Italy.

Purpose: a) To test the long-term results and toxicity of alternating MOPP-ABVD chemotherapy (CT) in advanced Hodgkin's disease (HD) b) To assess the prognostic value of selected pretreatment variables and drug dose-intensity.
Patients and Methods: This study included 138 consecutive patients with previously untreated advanced HD.(median age: 31 yrs; median follow-up of patients alive: 55 mos). Patient selection included stages IIB (33% of total), IIIB (26%), IV (25%) and stages II-IIIA (16%) with bulky disease and polmonary hilus involvement. Nodular sclerosis was the commonest histology (53%); B symptoms were present in 62%, bulky disease in 32% and bone marrow in 10% of patients. The alternating MOPP-ABVD chemotherapy was delivered as originally described (NEJM 1982; 306:770) in an overall 8-month program. Adjuvant RT on sites of bulky disease was delivered in 24 patients (18 in CR and 6 with residual disease after CT). Factors for the probability of CR were determined using Pearson χ^2 tests and factors for RFS and overall survival (OS) using log-rank tests. Coviariates were analyzed with the Cox proportional hazard regression model. Dose intensity for each drug was calculated according to Hryniuk.
Results: Complete remission after 8 courses of therapy was obtained in 106 (77%) patients; six cases entered CR after additional RT with an overall rate of 81%. Partial response was obtained in 16% and only 6 patients progressed during the therapy. Significant factors for CR in univariate analysis were stage (II vs IV, p=.039), histology (NS vs others, p=.045), B symptoms (p=.0025),and bone marrow involvement (p=.0017). In multivariate analysis, only bone marrow (p=.026) and histology (p=.036) retained significance. The actuarial 5-yr RFS was 84%; in univariate analysis, significant factors for RFS were bulky disease and age≤20 years (p=.045), in the Cox model, only a negative trend (p=.08) was observed for the group (albeit small) of patients under 20.strongly correlating with bulky disease. The 5-yr OS and freedom from tumor mortality were 79% and 76%, respectively. A prognostic significance for OS was observed for B symptoms (p=.0092), nodular sclerosis vs. others (p=.002), Hb level below 12g/dL (p=.04) and bone marrow involvement (p=.01). In multivariate analysis, only B symptoms and histology retained significance.(Hb correlated with B symptoms by median and γ test). The median % of relative dose intensity after 8 cycles were as follows: adriamycin 86, mechloretamine 85, vincristine 73, vinblastine 84, bleomycin 79, procarbazine 74, dacarbazine 81. This analysis did not show any significant association between the rates of drug delivery and clinical outcome. Long-term complications occurred in five patients: two myelodysplasias, one acute leukemia and two solid tumors (lung and larynx).
Conclusions: Alternating MOPP/ABVD cured more than 65% of patients with advanced HD, with neglegible acute and late toxicity. Prognostic analysis may define subgroups with low chance of cure deserving a more intensive approach.

P 79 EPIRUBICIN,BLEOMYCIN,VINBLASTINE, ETOPOSIDE AND PREDNISONE (BEVEP) IN HODGKIN DISEASE (HD)

F.Ferrara, A.De Renzo*, A.D'Arco^, L.Prossomariti, R.Cimino and B.Rotoli*. Division of Hematology, Cardarelli Hospital, Naples; *Division of Hematology, University of Naples Medical School, ^Medical Division, Cava dei Tirreni Hospital, Italy.

A combination chemotherapy consisting of epirubicin (40 mg/sqm days 1,15 iv), bleomycin (10 mg/sqm days 1,15 iv), vinblastine (6 mg/sqm days 1,15 iv), etoposide (80 mg/sqm days 1 to 3, 15 to 18 iv), and prednisone (60 mg/sqm 1 to 5, 15 to 20) was administered to 33 patients suffering from advanced HD. As compared to the classical ABVD combination, adriamycin was replaced by epirubicin to reduce the risk of cardiotoxicity and dacarbazine by etoposide with the aim of employing a more active drug (etoposide has been proven to be highly effective in relapsing or refractory patients) as well as of increasing patient compliance. This scheme is expected to be less leukemogenic and less toxic on gonads as compared to MOPP. Patients with bulky disease were programmed to receive additional radiotherapy on involved fields. Five patients were in clinical stage IIA, 11 in IIB, 3 in IIIA, 7 in IIIB, 1 in IVA and 6 in IVB. 26 patients were treated at diagnosis, 7 in late relapse, i.e. more than 12 months after discontinuation of previous treatment. There were 18 males and 15 females, median age was 40 (range 14-73). All patients were treated on outpatient basis. At the time of writing, 20/22 evaluable patients obtained complete remission (CR). Two patients (one refractory to and one relapsing after BEVEP combination) achieved CR following MOPP chemotherapy. Hematologic toxicity was mild: severe leukopenia requiring longer interval between courses occurred in only two patients. All patients experienced transient severe alopecia (grade 3 according to WHO criteria). In one patient a transient increase of SGOT was observed. After a median follow up of 10 months, 19 patients are in continuous CR. We conclude that BEVEP is an effective regimen for HD either at diagnosis or in relapse with minimal acute toxicity; it should be tested in randomized trials versus MOPP or ABVD or MOPP/ABVD combination.

P 80 ALTERNATING COPP+ABVD VERSUS RAPIDLY ALTERNATING COPP+ABV+IMEP FOR HODGKIN'S DISEASE: PRELIMINARY RESULTS OF TWO RANDOMIZED TRIALS FOR INTERMEDIATE (HD5 Protocol) AND ADVANCED (HD6 Protocol) STAGES.

V.Diehl, B.Lathan, M.Löffler, O.Brosteanu, D.Hasenclever, U.Rüffer, M.Pfreundschuh, E.Dühmke, A.Georgii, E.Hiller, P.Koch, G.Dölken, T.Cerny, C.Cartoni, F.Mandelli
for the German Hodgkin's Lymphoma Study Group (GHSG), Cologne, Germany.

To investigate whether developement of tumor resistance might be prevented by rapid application of non cross-resistent drugs, a new 10 drug regimen COPP+ABV+IMEP, repeated every 6 weeks, was compared to conventional alternating COPP+ABVD, given every 8 weeks. From 3/88 to 1/93 the GHSG conducted two randomized multicenter trials for pts. with first diagnosis of HD. 1318 pts. were randomized (HD5: 862; HD6: 556).
Eligibility criteria: HD5: CS/PS I and II with at least one of the following risk factors: massive mediastinal tumor, massive spleen involvement, extranodal disease, elevated ESR (≥ 50 mm/h or ≥ 30 mm/h with B-symptoms) or ≥ 3 lymphnode areas involved; and all CS/PS III A. HD6: CS/PS III B and IV.
Study design: HD5: Randomization to 2 courses of either COPP+ABVD or COPP+ABV+IMEP followed by identical radiotherapy (30 Gy EF+10 Gy bulk).
HD6: Randomization to 4 courses of either chemotherapy regimen followed by IF irradiation in case of initial bulk, slow response, or residual nodal disease.
Arms A: COPP+ABVD every 8 weeks, idential to MOPP+ABVD standard therapy, except that mustargen was substituted by cyclophosphamide (650 mg/m^2 d1+8).
Arms B: COPP+ABV+IMEP every 6 weeks with cyclophosphamide 800 mg/m^2 d1, vincristine 1.4 mg/m^2 d1, prednison 40mg/m^2 d1-15 and d29-35, procarbazine 100 mg/m^2 d1-10, doxorubicin 40 mg/m^2 d15, bleomycin 10 mg/m^2 d15, vinblastine 6 mg/m^2 d15, ifosfamide 1000 mg/m^2 d29-33, methotrexate 30 mg/m^2 d31, etoposide 100 mg/m^2 d29-31.
Feasibility: Comparing WHO grade 3/4 toxicity per cycle, emesis was less frequent (24% vs 9%) and leukocytopenia more frequent (31% vs 40%) in the COPP+ABV+IMEP scheme. In HD6 the median duration of chemotherapy was 237 days for COPP+ABVD and 195 days with COPP+ABV+IMEP. Similar for both regimens over 90% of projected total dose could be given, showing that rapid application was feasible.

Treatment results (12/92):	HD5		HD6	
	arm A	arm B	arm A	arm B
pts evaluable	202	227	155	156
CR-rate	93%	92%	76%	78%
FFTF-2yrs.	87%	86%	63%	67%
SV-2yrs.	96%	97%	85%	87%

To date no significant differences in treatment outcome are noticed in either studies. These data are preliminary, since many pts are still unter therapy and only ≤ 40% of the expected events have occured. Thus differences may still develop with longer follow-up.
Supported by the Federal Minister of Science and Technology (BMFT).

P 81

MINE REGIMEN FOR RELAPSED OR REFRACTORY HODGKIN'S DISEASE (HD). C. Fermé [1], J. Gabarre, G. Nedellec, F. Isnard-Grivaux, O. Reman, I. Plantier-Coucher, D. Assouline, J.P. Marolleau, O. Oberlin [2]. 1 for the GELA, Hôpital Saint-Louis 75475 - Paris cedex 10, 2 for the SFOP, IGR 94805 Villejuif, France.

Between 4/89 and 9/92, 88 patients (pts) with refractory or relapsed HD received MINE regimen: Methyl-gag 500 mg/m2 day 1+5, Ifosfamide 1500 mg/m2 day 1-5, Vinorelbine (Navelbine®) 15 mg/m2 day 1+5, Etoposide 150 mg/m2 day 1-3; q 4 weeks for 2-3 courses. Total number of courses was 213. Median age was 28.5 years (16 pts 6-17 yrs, 72 pts 18-59 yrs), M/F ratio 58/30. Prior to MINE, 85 pts had received anthracyclines therapy, 70 pts had 1-2 chemotherapy (CT) regimens, 17 pts had >2, 48 pts had previous radiotherapy (RT). For 59 pts the time from last treatment to salvage was ≤ 12 months. At salvage entry, pts had untreated relapse (45 pts), sensitive relapse (1 pt), resistant relapse (5 pts), primary resistant disease (37 pts). 44 pts had nodal disease only, 10 pts had extranodal disease only and 34 had both. 80 pts are evaluable for response. An objective response was achieved in 72.5% of the pts (CR 28 pts, PR≥ 75% 16 pts, PR ≥ 50% 14 pts) and 27.5% (22 pts) were unresponsive. CR or PR ≥ 50% was achieved in 90.2% (37/41 pts) of untreated relapse, 53.8% (21/39 pts) of pts with resistant relapse or primary resistant disease. The most frequent side effects were grade 4 neutropenia 85.7% of the courses (66/70 pts), grade ≥ 3 thrombopenia 55.7% of the courses (39/70 pts) and mucositis 47%. Neutropenic fever and infectious episodes (3 of which were fatal, with progressive disease in 2 pts) occured in 40% of the courses (51/81 pts). After MINE and additional treatment (high dose CT followed by autologous BMT or peripheral blood stem cells in 54 pts, allogenic BMT in 2 pts ; CT or RT in 14 pts), 42 pts were still in CR after 4 to 42 months. MINE regimen can provide an high response rate for relapsed or refractory HD pts.

P 82

CARDIAC FUNCTION FOLLOWING CHEMOTHERAPY FOR HODGKIN'S DISEASE (HD); A COMPARISON OF THE EFFECTS OF MVPP AND A DOXORUBICIN-CONTAINING REGIMEN. J. Barber[1], S. Owens[2], J.A. Radford[3], D.P.Deakin[1], R. James[1] and D. Crowther[3]. Departments of [1]Clinical Oncology (radiotherapy), [2]Radioisotopes and Nuclear Medicine and [3]CRC Department of Medical Oncology, Christie Hospital, Manchester, UK

Cardiac function has been assessed before and after chemotherapy (CT) in 48 patients with HD using the gated radionucleide left ventricular ejection fraction technique (LVEF). All patients studied were taking part in a randomised trial comparing MVPP and Hybrid CT in previously untreated, high risk stages IA-IIIA and stages IIIB-IVB HD. Sixteen patients received a median of 8 cycles (range 4-8) of MVPP (mustine 10mg i.v., vinblastine 10mg i.v., both on Days 1 and 8 with procarbazine 150mg daily and prednisolone 50mg daily on Days 1-14 of a 42 day cycle) and 32 patients a median of 8 cycles (range 6-8) of Hybrid CT (vinblastine 10mg i.v. on Day 1 with chlorambucil 10mg daily, procarbazine 150mg daily, prednisolone 50mg daily on Days 1-7 and etoposide 200mg/m^2 i.v., vincristine 2mg i.v., doxorubicin 50mg/m^2 i.v. on Day 8 of a 28 day cycle). The maximum cumulative dose of doxorubicin administered was 400mg/m^2 (in 27 patients). The post-CT measurement of LVEF was always performed before any radiotherapy was administered.

Presentation stage and presence of mediastinal bulk disease had no significant effect on baseline values of LVEF and, in the MVPP group, pre- and post-CT values of LVEF were not significantly different (medians, 49.2% and 46.2%, p>0.4). In the Hybrid group however, a significant fall between pre- and post-CT measurements was detected (medians, 51.4% and 46.6%, p=0.0001). Furthermore, of 15 patients who sustained a drop in LVEF >10% following treatment, 12 had received Hybrid CT. Despite these findings none of the patients in this study have so far developed clinical evidence of cardiac dysfunction.

Treatment of HD with Hybrid chemotherapy is associated with a significant fall in LVEF, presumably due to the known cardiotoxic effect of doxorubicin. Although clinically significant sequelae have not been identified in this small group, these results indicate that the incidence of cardiac morbidity/mortality in patients treated with doxorubicin containing combinations needs to be carefully monitored.

P 83

LONG-TERM FOLLOW-UP OF HODGKIN'S DISEASE STAGE III AT A SINGLE INSTITUTION. M. Wernli, R. Stupp, S. Watson, J.E. Ultmann. Section of Hematology/Oncology, The University of Chicago, Chicago, IL 60637, USA

In a 10 year period (1970-1979) 94 patients with Hodgkin's disease stage III were admitted to the University of Chicago. The stage was proven by laparotomy. Eighty-eight patients are evaluable for a retrospective analysis: 54 males and 34 females, age 6 to 67 (median 28). Twenty-nine patients were found to be in substage III_1A, 28 in III_2A, 11 in III_1B and 20 in III_2B. Nodular sclerosis was diagnosed in 52 patients, mixed cellularity in 27 and lymphocyte predominance in 6. Three patients had different histologies in different sites. The initial treatment was radiotherapy alone (RT) in 29 patients (extended mantle 5 and total nodal 24 patients), chemotherapy alone in 9 patients (cyclophosphamide, vincristine, procarbazine, prednisone) or combined modality treatment (CMT) in 48 patients. Two patients died before, 1 immediately after starting therapy; 11 had primary refractory disease. Seventy-four patients achieved a complete remission (84%). Twenty-seven patients relapsed within 5 to 163 months (median 33 – 2.8 years). Thirty-eight patients could be followed in 1st CR between 80 and 244 months (median 146 = 12.2 years). Seven patients died without evidence of Hodgkin's disease and 2 of unknown cause. Relapsed patients achieved a 2nd CR in 15 of 27 cases (56%) for a duration of 18 to 184 months (median 97 = 8.1 years). In 7 patients secondary malignancies were observed (large cell lymphoma 1; ANLL 1; sarcoma 1; bladder cancer 1; lung cancer 3).

The median disease-free survival (DFS) of patients with Hodgkin's disease of pathologic stage III in this study is not reached yet.

DFS ± 95% confidence interval

	all patients	# of patients at risk	stage III_1A	stage III_2A	stage III_1B	stage III_2B
5 years	70 ± 11	48	62 ± 19	87 ± 14	63 ± 34	58 ± 28
10 years	67 ± 11	33	58 ± 19	82 ± 16		58 ± 28
15 years	57 ± 14	14	58 ± 19			
18 years	52 ± 16	6				

In stage IIIA DFS at 10 years is significantly higher in patients treated with CMT (87% ± 14%) than in patients with RT alone (54% ± 19%).

P 84

GONADAL FUNCTION FOLLOWING CHEMOTHERAPY(CT) IN HODGKINS DISEASE(HD) - COMPARISON OF MVPP AND A NEW HYBRID REGIMEN. *S.T.Clark, #J.A.Radford, #D.Crowther, *S.M.Shalet. *Department of Endocrinology and CRC Department of #Medical Oncology, Christie Hospital, Manchester, U.K.

Gonadal function was assessed in 89 patients after treatment with MVPP (mustine, vinblastine, prednisolone, procarbazine) or a new Hybrid combination of chlorambucil, vinblastine, prednisolone, procarbazine, doxorubicin, vincristine and etoposide. Since 1984 these two regimens have been compared in a prospective randomised trial for the treatment of Hodgkins Disease. For these patients, many of whom are young adults, fertility is an important consideration.

50 men (MVPP=21,Hybrid=29) median age 26yrs (16-54), and 39 women (MVPP=16,Hybrid=23) median age 30yrs (15-47), were studied following CT. Patients were studied at a median of 30mths post treatment (4-83). Semen analysis showed azoospermia in 35/37 men and raised serum FSH levels in this group confirmed germinal epithelial damage. 6/49 men had serum testosterone measurements which were subnormal; leydig cell function was therefore not severely disturbed in the majority of men. There was no significant difference in results between MVPP and Hybrid treated patients.

In the female patients, 26 of 34 (76%) with a regular menstrual cycle before commencing CT became amenorrhoeic following treatment. Menses returned in 10, median age 25yrs (21-34), and there were two pregnancies in this group. In the other 16, median age 36yrs (27-47), amenorrhoea persisted, and premature ovarian failure was confirmed by raised serum gonadotrophins and reduced oestradiol concentrations. 15 women benefitted from HRT, (1 HRT contraindicated). There was no significant difference in results between MVPP and Hybrid treated patients.

It is clear that both regimens cause substantial gonadal damage in men, and in older women. These results are disappointing. Each cycle of Hybrid CT contains half the total dose of procarbazine, and less alkylating activity than each cycle of MVPP and it was hoped that gonadal toxicity would be correspondingly less. It is possible that some recovery may occur with longer follow-up, and further studies to assess this are required.

P 85 LATE MORTALITY IN YOUNG BNLI PATIENTS CURED OF HODGKIN'S DISEASE.

B. Vaughan Hudson, G. Vaughan Hudson, D. C. Linch, L. Anderson. Department of Oncology, University College London Medical School, Middlesex Hospital, London, W1, U.K.

Considerable attention has been paid in recent years to late treatment-related deaths in patients cured of Hodgkin's disease. To appreciate the overall significance of such late deaths we have analysed the outcome of young patients (aged 15-29) entered into British National Lymphoma Investigation trials and studies between 1970-1992 and cured of Hodgkin's disease either by first line therapy (n=774) or second line therapy (n=283). The median length of follow-up is 80 months with a range of 0-273 months.

The expected survival at 20 years for this age group in the general population is 98.5%. In patients cured by first line therapy the actuarial 20 year survival is 92.8%, the deaths being due to infection (8 patients), myocardial infarction (5 patients), accidental death or suicide (3 patients), second malignancy (4 patients), and other causes (3 patients). The actuarial 20 year survival of patients cured by second line therapy was lower at 84.1%, this being predominantly due to a higher incidence of second malignancies. There were 5 deaths due to infection, 1 to myocardial infarction, 9 to second malignancies, and 5 to other causes. Of the 13 infective deaths, 8 occurred in patients who had been splenectomised as part of a staging laparotomy, a procedure that is now rarely performed. A further death arose in a patient who died secondary to intestinal obstruction from post laparotomy adhesions. In young patients cured by first line therapy, the long-term survival should therefore in future be only just below the level expected in the general population.

For all patients with Hodgkin's disease under the age of 30 years (n=1607) the risk of dying from that disease within 20 years is 25% and compared to this, the risk of treatment related deaths are minor. The emphasis of future trials must therefore be to increase the efficacy of first line therapy rather than to reduce late mortality.

P 86 SPLENECTOMY AND THE INCREASING RISK OF SECONDARY ACUTE LEUKEMIA IN HODGKIN'S DISEASE (HD).

P. L. Zinzani, S. Tura, M. Fiacchini, E. Brusamolino, P. G. Gobbi. Institute of Hematology "L. e A. Seràgnoli", University of Bologna; Division of Hematology and Department of Medicine, University of Pavia.

Over a 15-year period (January, 1970 - December, 1984), 503 adult patients with previously untreated HD were treated by MOPP chemotherapy plus radiotherapy in our Institutions. The stage of the disease was established clinically in all patients and pathologically with laparotomy and splenectomy in 358 (71.2%), according to the Ann Arbor Staging System. All the patients were observed for 6.5 to 21.5 years and surviving 18 to 250 months from diagnosis (mean 115, median 116 months). During this observation period, 22 patients (4.37%), 15 males and 7 females, developed a therapy-related acute nonlymphocytic leukemia (ANLL) 34 to 184 months after treatment was initiated. None of these patients received any salvage treatment for HD. ANLL was observed only in 1 out of 145 (0.69%) patients not splenectomized and in 21 out of 358 (5.86%) splenectomized patients. We performed an univariate statistical analysis subdividing patients into two groups according to sex, symptoms, age, extent of radiotherapy, splenectomy and number of MOPP courses (more than 4 vs 4 or fewer): only splenectomy and number of courses of MOPP therapy proved to be prognostic factors. From this first analysis it is possible to observe that the relative risk of developing ANLL is 8.5-fold higher for splenectomized than for non-splenectomized patients. As a second step, to verify whether our results could be related to unequal distribution of covariates or, on the other hand, expressed an association with the event risk, we performed a Linear Logistic Model, confirming that patients undergoing splenectomy have a 10-fold risk of developing ANLL whether they received more or less than 4 cycles of MOPP. In particular, survival estimated by Kaplan-Meier and Cox models are quite similar for patients receiving up to four cycles of MOPP or more than four. Thus, we can assume a proportional hazard between splenectomized patients group vs not splenectomized group: accordingly, the former have a risk of ANLL per unit time 4.26-fold greater than the latter, independent of the number of MOPP courses. Our data confirm and strengthen other recent observations that the number of MOPP courses and the splenectomy procedure plays a statistically significant role on the risk of ANLL in HD patients.

P 87 SECOND MALIGNANT TUMORS AFTER TREATMENT FOR HODGKIN'S DISEASE

G.P. Biti*, E. Cellai*, S.M. Magrini**, M.G.Papi*, University(*) and Hospital (**) Departments of Radiotherapy, Florence, Italy

Second malignant tumors (ST) after treatment for Hodgkin's disease (HD) attracted the interest of many clinical investigators. In fact, a not negligible proportion of patients (pts) cured of HD will succumb to a ST. Therefore, the search for a possible link between the occurrence of ST and some clinical and therapeutic features of HD pts has not a purely academic relevance.

We analyzed in retrospect the large monoinstitutional series of 1121 pts with HD consecutively treated at the Florence Radiotherapy Department until 1988. To date, 72 of them presented a ST. Second solid tumors (SST) were registered in 62 cases (18/62 lung cancers, 14/62 breast cancers) , acute leukemia (AL) in 10. Forty-five SST and 5 AL occurred in patients who never relapsed or before the relapse. To better elucidate the possible link between ST occurrence and the characteristics of the treatment given for HD, we choose to study only the 50 ST that occurred during the relapse free period; therefore, to compare the incidence of ST in different clincal and therapeutic subsets of pts, we calculated the actuarial incidence of ST in each subset (Kaplan Meier), considering patients who experienced a relapse as censored at the date of relapse; comparisons were then performed with the Logrank Test and multivariate analysis (Cox model).

Cumulative incidence of ST, SST and AL at 20 yrs resulted to be respectively 20%,19% and 1.4%. While the cumulative incidence of AL seems to plateau after a few years, that of SST seems to rise constantly along with the increase of the period of observation. The mean latent period between the diagnosis of HD and that of a SST is of 11.7 yrs; the corresponding figure for AL is 6.5 yrs.

On the whole, the incidence of ST resulted to be higher in pts who had a diagnosis of HD at an older age (12.7% vs 15.3% vs 32.7% 20 yrs incidence respectively for age groups <27, 27-41,>41). The mean latent period between the diagnosis of HD and the occurrence of a ST was also shorter in the older age groups. Patients treated with chemotherapy (CT) or with chemo- and radiotherapy (RT) have an increased risk of developing a ST when compared to pts treated with RT only. Multivariate analysis showed that age at diagnosis ($p<0.001$) and treatment modality ($p=0.03$) are the only two parameters significantly linked with the occurence of ST (other factors entering multivariate analysis being sex, histology,general symptoms,laparosplenectomy, RT treated volumes, type and number of cycles of CT).

AL incidence was significantly higher (Logrank test) in pts treated with radiochemotherapy or CT than in those treated with RT (3%, 11%, 0.2% at 20 yrs, respectively); in those treated with MOPP as opposed to ABVD chemotherapy (5% vs 0% at 20 yrs); in those treated with 6 or more cycles of CT (9% vs 2% at 20 yrs).

When studied with multivariate analysis, the risk of developing a SST is significantly related with age at diagnosis of HD (being higher in older pts, $p<0.001$); it appears to rise also with the increase of the radiotherapy treated volumes (with marginal significance, $p=0.04$).).

P 88 HODGKIN'S DISEASE (HD) IN PATIENTS (PTS) WITH HIV INFECTION (HIV-HD) vs HD IN THE GENERAL POPULATION (HIV NEGATIVE-HD): COMPARISON OF CLINICO-PATHOLOGICAL FEATURES AND SURVIVAL

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

With the aim to compare the clinico-pathological features and survival of HIV-HD and HIV negative-HD, we analysed 176 pts with HD. 84 HIV negative-HD pts were seen at our institution since 1986, whereas 92 HIV-HD pts (group C) were seen within the Italian Cooperative Study Group on Aids and Tumors (GICAT) since 1985. Taking into consideration that age is the most important prognostic factor in HD, we divided the 84 HIV negative-HD pts into two groups with regard to age: in group A pts were less than 55 years of age and in group B pts were ≥55 years of age, in order to compare HIV-HD pts with the less favourable group of pts with HD in the general population, i.e. older pts. Treatments in all groups were chemotherapy with or without radiotherapy or radiotherapy alone. Anti-HIV therapy was concomitantly given in a small fraction of HIV-HD pts. The table shows the different clinico-pathological features at presentation and the outcome in the three groups:

	Group A	Group B	Group C	P value A vs B	P value A vs C	P value B vs C
N° PTS	52	32	92			
Median age	26(15-51)	64(55-76)	28(19-57)			
Sex: M/F	30/22	17/15	84/8	N.S.	<0.001	<0.001
Histology						
LP	4%	16%	1%	N.S.	N.S.	N.S.
NS	85%	31%	21%	<0.001	<0.001	N.S.
MC	10%	47%	52%	<0.001	<0.001	N.S.
LD	2%	6%	23%	N.S.	<0.001	0.06
Unclassificable	-	-	3%			
Stage						
I-II	60%	50%	20%	N.S.	<0.001	0.003
II-IV	40%	50%	80%	N.S.	<0.001	0.003
"B"symptoms	35%	34%	82%	N.S.	<0.001	<0.001
Only LN Involvement	73%	69%	37%	N.S.	<0.001	0.004
Response						
CR	92%	93%	51%	N.S.	<0.001	<0.001
PR	6%	3%	43%	N.S.	<0.001	<0.001
PD	2%	3%	6%	N.S.	N.S.	N.S.
Overall Survival at 4 years	100%	88%	33%	N.S.	<0.001	<0.001

NS is the predominant subtype in group A, while MC is the most frequent subtype both in the older pts with HIV negative-HD and in pts with HIV-HD. Peculiar features of HIV-HD are a higher rate of LD subtype, an increased prevalence of advanced stages, B symptoms and a lower CR rate, all at a significant level. Consequently the four-year-survival is significantly reduced in HIV-HD, obviously also due to the underlying HIV infection. In conclusion, while MC subtype is the commonest histological subtype either in HIV-HD and in older HIV negative-HD, HIV-HD has a worse prognosis than HIV negative-HD not only because of the underlying HIV infection, but for the more unfavourable clinico-pathological features at presentation.

Supported by grants of CNR '92 and AIRC '92.

P 89 CHEMOTHERAPY (CT) WITH AND WITHOUT ZIDOVUDINE (AZT) FOR HODGKIN'S DISEASE (HD) AND HIV INFECTION: A COMPARISON IN 49 PATIENTS (PTS)

D. Errante, U. Tirelli, E. Vaccher, D. Bernardi, M. Spina, L. Repetto, R. Foà, G. Rossi, R.Gastaldi, S. Monfardini for the Italian Cooperative Group on AIDS and Tumors (GICAT), Centro di Riferimento Oncologico, Aviano, Italy.

Since 1985 HD has been described in 92 Italian pts with HIV infection, with a significant increase of mixed cellularity and lymphocyte depletion subtypes and advanced stages at presentation in comparison with the general population of Italian HD pts (Annals of Oncology 3, S69-S74, 1992).Taking into consideration that the median CD4+ cell count at diagnosis of HD of the overall group is 249/mmc, AZT is currently recommended in these pts. However, the combination of CT and AZT is difficult to be performed, especially because of the related bone marrow toxicity.The purpose of this study is to compare the outcome and, in particular, the occurrence of opportunistic infections (OI) in two consecutive groups of pts treated with CT with and without AZT. The first group of 32 pts was treated with CT (MOPP or MOPP/ ABVD) alone, the second group of 17 pts was treated with CT (EBV: epirubicin 70 mg/m2 i.v. day 1, bleomycin 10 mg/m2 i.v. day 1 and vinblastine 6 mg/m2 i.v. day 1) and AZT (500 mg/ day per os from the beginning of CT or after 3 cycles of CT).Only 13 pts of the latter group are evaluable for this study, in that 4 did not receive AZT therapy because of severe granulocytopenia at HD diagnosis (in 2 pts) and refusal in the other two pts. The table reports the treatment outcome in the two groups of pts:

	CT	CT+AZT	p value
N° of evaluable PTS	32	13	
- median CD4+ cell count/mmc (range)	275(29-842)	166(26-1100)	
- mean N. of CT cycles/pt	4.7(± 1.5)	5.4 (± 1.1)	0.08^
- complete remission rate	56%	61%	0.25*
- pts with grade 3 and 4 hematol. toxicity	52%	66%	0.21*
- pts with O.I.	57%	8%	0.003*
- median follow-up in months (range)	12 (1-64)	11 (3-36)	

While the median CD 4+ cell count and median follow-up in the 2 groups of pts are superimposable, only one OI occurred in the group of pts treated with CT + AZT in comparison with 16 OI observed in the 28 evaluable pts treated with CT without AZT (8% vs 57%, p = 0.003). The combined treatment seems also feasible and quite tolerable, with no toxic death and a high number of pts being able to receive the scheduled therapy. Therefore, our data demonstrate that the addition of AZT as antiretroviral therapy to CT decreases the occurrence of O.I. during CT or follow-up in pts with HD and HIV infection. ^Mann-Whitney Test; *Fisher Test Chi-Square.

Supported by grants of AIRC '91 and AIDS project, ISS '91

P 90 PRIMARY LYMPHOMA OF THE CENTRAL NERVOUS SYSTEM: 4-YEAR RESULTS ON 48 PATIENTS TREATED WITH THE POF LCP 88 TRIAL.

B. DESABLENS (Amiens), S. FRANCOIS (Angers), L. SENSEBE (Brest), P.-Y. LE PRISE (Rennes), Ph. COLOMBAT (Tours), J.-L, DUTEL (Compiègne), V. DELWAIL (Poitiers), C. ALLIOT (Amiens) - PARIS-OUEST-FRANCE Group.

In August 1988, we started the POF LCP 88 trial which combines 3 curses of MVBP (methotrexate 3 g/m^2 d1 & 15, teniposide 100 mg/m^2 d2 & 3, BCNU 100 mg/m^2 d4 and methyl-prednisolone 60 mg/m^2 d1 to d5) and a whole-brain irradiation (40 Gray), immediately started in case of failure after the 1st MVBP. All the 48 patients (pts) were HIV-seronegative. The sex-ratio was 1.29 (27 M/21 W) and the median age was 59 years (range, 22 to 73). Histological material showed a predominance of G and H types according to the WFC (35/38 classified pts) with a single case of low grade lymphoma. CSF was positive in 6/33 tested pts and an ocular involvement was certain in 2 pts and probable in 2 other pts. Mean values of seric LDH and β2microglobulin levels were respectively 0.94±0.36 x N/l and 1.7±0.8 mg/l. An initial clinical improvement under corticosteroids was seen in 17/23 pts.

The major toxicity of MVBP was infectious with 17 severe infections among 122 curses (13.9%), of which 4 were fatal but always associated with a poor performance status and/or progression of lymphoma. A renal toxicity was seen in 14/122 (11.5%) MVBP (9 grade 1 and 5 grade 2) and other toxicities were usual. According to the response after 1st MVBP, we noted 2 infectious deaths, 10 failures (5 progressions and 5 stabilisations) and 36 responses (75.0%) of which 15 were complete remission (CR). After the whole treatment, CR was observed in 34 pts (70.8%). On January 1st 1993, the median follow-up time is 28 months and we note:

- 4 relapses: 3 occurred within the 1st year (2 in situ and 1 abdominal and osseous) and were fatal whereas a nodal relapse at the 37th month of CR seems cured.
- 17 deaths due to 4 septic shocks, 10 failures and 3 relapses.
- 2 non-related deaths due to infection at the 6th and the 28th months of CR.
- 1 death at the 45th month of CR due to a cerebral radionecrosis.

For all the patients, the 4-year survival rate (SR) is 37.1 % (median: 45 months) but is 60.2% after excluding the 2 infectious non-related deaths. For the 34 pts in CR after the whole treatment, SR is 52.7% (all deaths) and 57.9% (without the 2 non-related deaths). A preliminary prognostic analysis showing that the major factor is the response to the 1st MVBP (SR 90.0% in case of CR against 0.0% - $p < 10^{-2}$), lead us to propose a new trial with hematopoietic growth factors and in hope to reduce the late consequences of treatment, a limitation of irradiation to 30-35 Gray.

P 91 TREATMENT MODALITIES IN PRIMARY NON HODGKIN LIMPHOMA OF BONE.

F. Perini, E. Barbieri, M. Silvano, A. Baldissera, G. Chiaulon, N. Teodorani, M. Del Duca, A. Veraldi, N. Sciascia, L. Babini. Institute of Radiotherapy University of Bologna.

From January 1980 to January 1992, 58 pts were referred to the Institute of Radiotherapy of the University of Bologna with biopsy proven diagnosis of non Hodgkin lymphoma of bone. All pts, after phisical examination, were submitted to the following staging procedures: chest film, lymphangiografy, bone marrow biopsy, abdominal ultrasound ecography with liver biopsy if indicated, 99 Tc scintigraphy, XRay, CT Scan and, in more recent years, MRI of primary lesion. Thirty eight pts out of 58 were in stage I and II and can be considered Primary Non Hodgkin Lymphoma of Bone (PNHLB) and are the material of our analysis. There were 28 males and 10 females with a median age of 40 years and with a median follow up of 71 months (12-150). Twenty two pts were in stage I and 16 in stage II. Primary sites were : femur 10, jaw 9, pelvis 4, tibia 4, humerus 4, spine 3, clavicle 1, scapula 1, rib 1, heel 1. We have treated with Radiotherapy (RT) alone 10 pts in stage I with non bulky lesion (< 5 cm) and with RT plus chemiotherapy (CT) 28 pts in stage I bulky and in stage II. RT was performed with megavoltage unit (60 Co or 6 Mv Xfoton) with convenctional fractionation and with doses of 40-44 Gy. Target volume included primary lesion with 5 cm margins in bone tissue and 2 cm in extraosseus soft tissue. The entire bone was irradiated in specific site. CT consisted in traditional association as CHOP, M-BACOD, N-CVP. All pts were induced in Complete Remission (CR), 29/38 (76.3%) are in persistent I CR. Nine of 38 pts (23.7%) relapsed at 1 to 3 years, 8 of them with distant and 1 with local relapse. Five of 10 pts treated with RT alone had distant relapse and 4 of them are now in II CR after CT treatment at 31, 53, 56, 69 months.None relapsed in primary site. Four of 28 pts treated with RT+CT relapsed in distant sites, one of them with associated local failure. Only 1 pt of these group re ached a II CR. The actuarial DFS at 11 years is 71.3% and the OS 80.3%. Our experience confirmed that, after an accured staging, 20/58 pts (35%) showed disseminated disease. The results analyzed vs therapy schow that RT offers an optimal local control in all pts but can be used alone only in stage I pts with non bulky lesion. The association with CT is necessary for all other pts. CT is usefule to induce II CR in pts treated as first line with RT alone..

P 92 PRIMARY OCULAR ADNEXAL NON-HODGKIN'S LYMPHOMA (NHL): A SINGLE CENTER STUDY OF 24 CASES.

A. Delmer, F. Bauduer, F. D'Hermies *, J.P. Marie, Y. Pouliquen * and R. Zittoun. Hematology Dpt and Ophtalmology Dpt (*), Hôtel-Dieu, 75181 Paris cedex 04, France.

From 1982 to 1992, we have studied 24 patients (pts) with NHL presenting primarily in the orbit. The F/M ratio was 13/11 and mean age at presentation was 54 years ± 20 (range 23 - 89). None was HIV-positive.

Twenty one pts had a low grade NHL according to the Kiel classification: diffuse lymphoplasmacytic 10 pts, diffuse centrocytic 10 pts, diffuse centrocytic centroblastic 1 pt. Histopathologic features of MALT-derived NHL were observed in 15 pts. The retro-orbital space was involved in 4 cases, the conjonctiva in 12 cases and the lacrymal gland in 5 cases. Three pts (lacrymal gland 1 pt, conjunctiva 1 pt and retroorbital presentation 1 pt) had bilateral involvement at presentation. A previous history of immune disorder (Sjogren's syndrome) was found in 2 pts. All pts but one had usual initial systemic work-up. Only one pt had peripheral lymphadenopathy and another one bone marrow involvement. A monoclonal gammapathy IgM kappa was disclosed in 2 pts. Radiation therapy alone (25 - 35 Gy) was proposed in 13 pts, resulting in all cases in a complete local response. Among the 4 pts who received chemotherapy (CVP and/or cyclophosphamide given orally) as primary treatment, only one achieved a complete local response. Two pts with totally excised conjunctival lesion did not receive additional treatment and 2 others refused any further treatment. With a median of follow-up of 6.5 years, 2 pts developped secondary systemic lesions (thyroid gland 1 pt, bone 1 pt), both with histologic progression to a high-grade lymphoma. Two pts with conjunctival NHL had local recurrence 12 and 24 months after radiation therapy (25 and 30 Gy respectively) and were therefore treated with surgical excision alone.

Three pts had localized high-grade B-cell NHL (centroblastic 2 pts, Burkitt-type 1 pt): retro-orbital mass 2 pts, conjunctiva 1 pt. Intensive systemic chemotherapy without adjuvant radiation therapy had resulted in persisting complete remission in 2 pts (follow-up 18 and 36 months), whereas the third pt aged 80 years received only radiation therapy and subsequently developped systemic disease.

We confirm the high predominance of low-grade NHL among localized primary orbital NHL. Their usual good prognosis after radiotherapy alone must be viewed in the context of their MALT origin.

P 93 Epidemiology of GI NHL in Lebanon and The Middle East

W. Rizk, N. Shamseddine, N.Taleb
St. Joseph University , Beirut - Lebanon

It is classical to separate gastro-intestinal (GI) non Hodgkin Lymphomas (NHL), into two epidemiological profiles:
1- An "occidental" type frequently encountered in West countries (Europe and USA)
2- An "oriental" type which is dominant in the Middle East regions, and is distinguished from the occidental type in the following features :
a) The younger age of patients
b) The rarity of gastric involvement (G-NHL) compared to the small intestinal involvement (SI-NHL)
c) The prevalence of Immuno Proliferative Small Intestine Disease (IPSID) within the SI-NHL

An epidemiological study was done on 100 Middle Eastern patients with GI-NHL seen in Lebanon between 1965 and 1991 The statistical analysis of our study leads to the following conclusions :

Period	1965-1975	1978-1991
Nb of Patients	43	57
Sex Ratio	1.86	0.9
Median Age (years)	35	55
G-NHL vs SI-NHL	1 vs 2.6	4.5 vs 1
%IPSID/GI-NHL	13.9	1.57
%IPSID/SI-NHL	20	10

Comparing the two periods of time, we find that :
-While the IPSID is disappearing in Lebanon during the last 25 years, the non-IPSID or localized SI-NHL was always the predominant category accounting for 80% and 90% in 1965-1975 and 1975-1991 periods respectively .
- The site of GI involvement is changing with time, the SI involvement becoming more rare and the G.involvement more frequent .
- The Median Age changed in parallel from 34 years to 55 years .

So during this 25 years period, there was an occidentalisation of the epidemiological profile .
We are studying environmental factors as a possible explanation of this varying pattern in the epidemiology of GI-NHL. We have already found a big change in the intestinal bacterial and parasitoligical infestation between the two periods of this study .

P 94 COMBINED MODALITY THERAPY FOR PRIMARY GASTRO-INTESTINAL NON-HODGKIN'S LYMPHOMA (GI-NHL): THE MILAN CANCER INSTITUTE EXPERIENCE.

C. Tondini, R. Giardini, P. Valagussa,A. Santoro, R. Bertulli, M. Balzarotti, A. Rocca and G. Bonadonna. Istituto Nazionale Tumori, Milano, Italy

The present study analyzes clinical features, treatment and outcome of all patients with primary GI-NHL referred during the past two decades to the Milan Cancer Institute. Clinical and histopathological data from 135 patients presenting with GI-NHL and disease localized into the abdomen were reviewed. Of these, 114 (84%) presented with limited disease (stage I and II), while 21 patients were found to have disease involvement of other abdominal organs (i.e., liver, pancreas, peritoneum) or more than one gastrointestinal site and were therefore classified as stage IV. Seventy-three percent had lymphoma of the stomach, 15% of the small intestine and 9% of the large bowel, while in 5 cases there were multiple localizations to the gastrointestinal tract. Median age was 50, with one fourth of patients older than 60. According to Kiel classification revised for GI-NHL, 61% of patients had pure high grade lymphoma, 9% had high grade NHL with evidence of residual low grade NHL, and 30% had low-grade NHL. Nine percent presented with bulky disease, 5% with elevated LDH and 21% with a Karnofsky performance $\leq$ 80. Laparotomy with radical (108 patients) or palliative (15 patients) intent was performed in all patients who did not have an elevated risk of complication from major surgery. Complete removal of all measurable tumor was possible in 101 patients (75%). Surgical morbidity and mortality were 11% and 2%, respectively. Overall, 83% of patients were treated with chemotherapy. Patients with limited disease were treated with 4 to 6 cycles of chemotherapy (CVP, BACOP or CHOP) followed by loco-regional radiotherapy. Patients with advanced disease were treated with systemic chemotherapy (single agent chlorambucil, CVP, CVP/ABP, ProMACE/MOPP, CHOP, ProMACE/CYTABOM or MACOP-B) untill CR plus two cycles of consolidation, with radiation therapy on sites of bulky disease. Twenty-two patients were managed with surgery alone (12 cases) or received only post-operative RT (10 cases) mainly because they had very superficial low grade lymphoma. Of patients with limited disease, 99% achived CR. After a median follow-up of 73 mos, 13 of 113 patients have relapsed, mostly outside the gastrointestinal tract (70%). Actuarial 10-yr FFP and OS were 84% and 86%, respectively. Aside from age, no other factor such as stage, PS, site of the primary nor bulky disease had a statistically significant impact on outcome. There was a trend in favor of low grade histology (FFP 97% vs 79%), that failed to reach statistical significance. Of patients with advanced abdominal disease, 48% achieved CR with chemotherapy with or without prior surgical debulking. Actuarial 10-yr FFP and OS are 44% and 42%, respectively. Tumor burden and LDH levels were the most important prognostic factors affecting outcome, while histologic subgroup did not show any significant impact on outcome. In conclusion, the present study show the good result obteined in a wide and unselected population of patients with limited stage primary GI-NHl using a combined approach that includes surgical debulking and systemic chemotherapy for most patients. Surgery alone can be considered adequate treatment for those patients with low-grade disease that does not infiltrate beyond the submucosa. A conservative approach is however feasable in those patients who are at higher risk of complications from abdominal surgery. Patients with advanced GI-NHL show a long term outcome similar to that of patients with advanced NHL arising outside the gastrointestinal tract and should therefore be treated the same way.

P 95 LYMPHOCYTE HOMING RECEPTOR (CD44) EXPRESSION AND PROGNOSIS IN GASTROINTESTINAL LYMPHOMA.

H. Joensuu, R. Ristamäki, P.J. Klemi, K-O. Söderström, S. Jalkanen. Departments of Oncology and Radiotherapy, and Pathology, Turku University Central Hospital, and National Public Health Institute, SF-20520 Turku, Finland

Lymphocyte homing receptor (CD44) is involved in lymphocyte adhesion to endothelial cells of high endothelial venules (HEVs) and lymphocyte exit from the blood circulation, and it may be involved also in hematogenous dissemination of malignant lymphoma. Prognostic significance of lymphocyte homing receptor expression defined by Hermes-3 antibody was studied from paraffin-embedded tissue among 27 gastrointestinal lymphomas followed up for 8 to 20 years after the diagnosis. Lymphomas with lacking or very weak homing receptor expression (N=14, 52%) were associated with 57% 10-year survival rate as compared with only 15% among lymphomas that expressed CD44 more strongly (p=0.02). We conclude that lack of lymphocyte homing receptor expression is common in gastrointestinal lymphoma, and that CD44 expression is associated with unfavourable prognosis.

P 96 GASTRIC LYMPHOMA: TREATMENT BY RADIOTHERAPY

J.M.V. Burgers, B. Taal, R. Somers, P. v. Heerde
L. Dewit, A.A.M. Hart / Netherlands Cancer Institute

Introduction: In 1978 a new treatment policy was introduced at the Netherlands Cancer Institute for gastric non-Hodgkin lymphoma (gNHL), with the aim of avoiding staging laparotomy and total or partial gastrectomy. This policy was based on our favourable experience in patients (pts) in stage (st.) I and limited st. II, who after gastrectomy received total abdominal irradiation (TAI) with a booster dose to the stomach (Radiotherapy and Oncology 1988 [11] 319-326).

Patients and methods: Staging procedures comprised endoscopy with biopsy, lymphography, abdominal CT-scan or sonography, and bone marrow biopsy. From 1978 - 1991, 52 patients (pts) with non-bulky stage I-II gNHL (mass < 5 cm on CT or primary tumour not infiltrating the entire stomach wall) (group I) received 20 Gy TAI, with partial shielding of the liver anteriorly and shielding of the right kidney posteriorly, followed by a boost to a total dose of 40 Gy to the area of the stomach including the para-aortic lymphnodes and the spleen, usually with parallel opposing fields. Twelve pts with bulky stage I-II (group II) were given induction chemotherapy (various schedules) followed by locoregional radiotherapy in case of CR, or TAI with a gastric boost when PR. Pt were carefully followed for local control and kidney function.

Results: In group I, CR was obtained in 49 of 52 cases. Three pts developed a local recurrence 12, 36 and 13 months after treatment, 2 developed liver hilar nodal disease and in 4 lymphoma recurred in lymphnodes outside the abdomen. Salvage treatment was successful in one of the PR, and 3 of the 6 pt with nodal recurrence. Of 3 pt with local recurrence, 1 pt is well 5 months later with additional chemotherapy, the other 2 pts have no significant endoscopic lesions with variable positive and negative biopsies and are subjectively well 21 and 8 months later without further treatment. Overall 5 and 10 years' survival in group I were 72 and 67%, respectively, whereas the respective disease specific survival rates were 86% and 86%. Serious late complications were 1 death through haemorrhage and one patient with a closed gastric perforation who survived. Severe unilateral renal functional impairment, down to 25-31%, was assessed in a small subgroup of pts.

Conclusions: TAI with a gastric boost is an effective treatment modality in non-bulky clinical stage I-II gastric non-Hodgkin lymphoma with an acceptable long term morbidity. The survival rates are similar to those obtained with gastrectomy and (neo)-adjuvant chemotherapy and/or locoregional irradiation.

P 97 PROSPECTIVE RANDOMIZED TRIAL FOR THE TREATMENT OF LOCALIZED GASTROINTESTINAL (GI) TRACT LYMPHOMAS (NHL) : PRELIMINARY REPORT OF A MULTICENTRIC STUDY.

D. Bron, U. Tirelli, H. Kluin-Nelemans, R. Holdrinet, R. Musella, F. Viseu, E. Vieira, P. Carde, M.Rauis, K. Roozendaal, W. Breed, B. Depauw, A. Efira, M. Fickers, P. Hupperets, J. Michel, A. Van Hoof, K. Peters and A. De Meuter. Institut Jules Bordet, Brussels, Belgium.

Although more than a thousand of GI-NHL have been reported, the literature does not indicate a clear therapeutic approach. This is primarily due to heterogeneous staging procedures and treatment strategies. Therefore, we initiated a prospective cooperative study with european centers using uniformed staging procedures, centralized pathological review and well defined therapeutical approaches. This prospective randomized trial is addressed to intermediate and immunoblastic NHL. It compares radiotherapy (40 GY) with 3 courses of chemotherapy (a CHOP-like regimen, CHVmP/BV according to the EORTC*) in pathological stage I GI-NHL. Patients (pts) with clinical or pathological stage II are treated with 6 courses of the same chemotherapy (CT) and if complete remission is achieved, they are randomized between iceberg radiotherapy or no further treatment. Between July 88 and August 92, 37 pts have been registered with a median age of 56 (26-69) years old. 66% were males, 82% (23/28) were localized in the stomach. 83% (20/24) were large cell lymphomas (WF : G). 35% (13/37) were stage I and among the 24 stage II pts, 7 (29%) had extended loco-regional disease. Among 13 pts with stage I, all are evaluable for response : 7 were treated by radiotherapy and 5 received three courses of CT. 12 pts (100%) are in complete response (CR) with a median follow-up of 25 (4-36) months. No relapse has been reported in this group. Among 24 pts with stage II disease, 18 are evaluable for response. 77% are in CR after CT with a median follow-up of 21 (2-36) months. 2 pts were excluded for pathological reasons (WF : C & melanoma). 2 pts went off study for excessive toxicity. 2 pts died early with progressive disease. No statistical analysis have been performed because of the low number of pts but these encouraging results deserve better enrolment in this unique multicentric prospective trial.

* Carde et al. Ann. Oncol. 2 : 431-435, 1991.

P 98 PATTERNS OF SURVIVAL WITH RECURRENT FOLLICULAR LYMPHOMA: A 20 YEAR STUDY FROM A SINGLE CENTRE

P.W.M. Johnson, J.S. Whelan, S. Love, J. Lim, A.Z.S. Rohatiner, T.A. Lister. I.C.R.F. Department of Medical Oncology, St Bartholomew's Hospital, London, England.

Between 1968 and 1987, 179 of 212 patients who presented with newly-diagnosed follicular lymphoma responded to initial therapy. With a median follow up of 12 years, 116 patients developed recurrent disease, with a significant bias towards those with advanced (Stage III/IV) disease at presentation. 110 patients were re-treated, with 86 (78%) responses. 67 patients subsequently developed a second recurrence of whom 48(76%) were treated to third remission. Median survival following recurrence was 4.6 years, with a median failure-free survival of 1.7 years. The median duration of second remission was 13 months, compared to 31 months for the first. 80 patients died, 69 of lymphoma, 31 following transformation to higher grade histology. Only 8 patients died of causes unrelated to lymphoma or its treatment.

Multivariate analysis of prognostic factors showed only age at recurrence and previous responsiveness of the disease to treatment to predict subsequent survival. Only 13% of patients over 60 survived 10 years from recurrence, compared to 40% of those aged 60 or less ($p<0.001$). 5% of patients who required more than one course of treatment to reach first remission survived 10 years from recurrence, compared to 38% of those who required only one ($p<0.01$). None of the factors previously found to predict survival from presentation (B symptoms, hepatosplenomegaly, anaemia, liver blood tests) had significant influence upon survival after recurrence. The duration of second remission was related solely to the degree of response, with a median of 25 months for those reaching complete remission compared to 9 months for those in partial remission ($p<0.01$). 53% of patients reaching second complete remission remained alive 10 years later, as compared to 28% of those for whom the response was only partial ($p=0.02$).

This study confirms the long natural history of follicular lymphoma and its repeated responsiveness to therapy. The identification of those patients with recurrent disease for whom the prognosis is particularly poor will allow the study of new treatments to concentrate upon those for whom improvements are most urgently needed and in whom survival advantages will be most readily identified.

P 99 PERIPHERAL T-CELL LYMPHOMA OF LOW GRADE MALIGNANCY RESULTS OF STANDARDIZED TREATMENT REGIMEN

W.Siegert, C.Nerl, A.Agthe, M.Engelhard, G.Brittinger, K.Lennert

Peripheral T-cell lymphomas are rare lymphoproliferative disorders derived from post-thymic lymphocytes. Due to their rareness relatively little is known about their clinical presentation and optimum treatment, esp. of low grade PTL.

We conducted a multicenter, prospective nonrandomized trial to describe the response of **AILD-type T-cell lymphoma** to a standardized treatment regimen. Patients initially received prednisone and no further treatment if a CR was achieved. Relapsing or refractory patients received COPBLAM/IMVP16. Patients with lifethreatening tumor progression or tumor extension received COPBLAM/ IMVP16 initially. Sixty-two patients were registered, 39 were evaluable. Twenty-eight patients received primary prednisone, 18 received secondary chemotherapy and 11 received primary chemotherapy. CR rates were 29%, 56% and 64%, respectively. The probability of overall survival, EFS and relapse were 40%, 32% and 35%, respectively. Univariate analysis of 62 patients with AILD revealed that age, stage, presence of B-symptoms, LDH, hemoglobin and the number of clinical symptoms influenced the survival probability. At 5 years the actuarial survival was: Age 64 years < vs > - 39 %, 27% ($p = .04$); stage I+II vs III vs IV - 84%, 55%, 16% ($p = .035$); B-symptoms (-) vs (+) - 65%, 21% ($p.004$); LDH < vs > N - 63%,18% ($p = .0005$); hemoglobin 11.5 g/dl < vs > - 48% vs 22% ($p = .026$); number of clinical symptoms (B-sympt, rash/pruritus, edema, pleural effus, arthralgia, ascites) none vs 1 vs 2 vs 3 - 83%, 55%, 41%, 16% ($p = .004$).

Sixteen patients with **T-zone lymphoma, Lennert lymphma and pleomorphic small cell lymphoma** were uniformly treated with five cycles of COPBLAM. Their median age was 56 years (range, 20-75); stage I = none, stage II = 6, stage III = 5, stage IV = 5, B symptoms = 9. Treatment results in 15 evaluable patients were: 9 CR, 5 PR, 1 PD. CR-duration was 11 months median (range, 1+ - 59+). Continuous CRs lasted 1+, 18+, 31+, 32+ and 59+ months. The median survival was 26 months (range, 2 - 62+). Surviving patients are 2+, 3+, 21+, 27+, 33+, 38+, 38+, 44+ and 62+ months after diagnosis. We conclude that PTL of low malignancy are aggressive diseases. Intensive polychemotherapy can induce CRs in about half of the patients and long term event-free survival in approx. 30%.

P 100 INVOLVED REGION IRRADIATION; AN EFFECTIVE STRATEGY IN THE TREATMENT OF LOW STAGE LOW GRADE LYMPHOMA

By: Dr. N.J.S. Voss, Dr. R.N. Fairey, Dr. J.M. Connors, British Columbia Cancer Agency, Vancouver, British Columbia, Canada

Between 1/1/80 and 1/1/92, 78 consecutive patients with clinically staged, localized (Ann Arbor stage IA and IIA +/- extranodal disease), low grade malignant lymphoma [follicular small cleaved cell (FSC), follicular mixed (FM), small lymphocytic (SL) and small lymphocytic, plasmacytoid (SLP)] were treated with involved region irradiation at the BCCA. Of these, 46 patients were stage IA, 32 stage IIA and 28 had extranodal disease (E). The age range was 38 - 86 years (median 62 years), with 39 male and 39 female patients. Histological characteristics were 33 FSC, 25 FM, 15 SL and 5 SLP. Staging investigations for all patients included a blood count, liver function test, chest x-ray, abdominal computerized tomography and/or lymphogram and bone marrow biopsy. They were uniformally treated with irradiation to the involved region only, employing doses of 3500 cGy in 20 treatments over four weeks for large volumes and 3000 cGy in 10 treatments over two weeks for small volumes.

SURVIVAL ANALYSIS

	5 YEAR	10 YEAR
OVERALL	80%	80%
FAILURE FREE	68%	59%
DISEASE SPECIFIC	90%	90%

Ten patients have died, three of their lymphoma, two of treatment related causes (one of dementia following whole brain irradiation, the other of a fungal infection) and five from unrelated causes. Six patients are alive with lymphoma present, two are alive in second or subsequent remission. Three were lost to follow-up.

Involved region irradiation is an effective strategy for the treatment of low stage low grade malignant lymphoma.

P 101 TREATMENT OF ADVANCED STAGE LOW GRADE LYMPHOMA WITH BP-VACOP AND EXTENSIVE LYMPH NODE IRRADIATION (RT).

RJ Klasa, PJ Hoskins, SE O'Reilly, R Fairey, N Voss, R Gascoyne, JM Connors. British Columbia Cancer Agency and the University of British Columbia, Vancouver, BC, Canada

Between 8/87 and 5/91, 98 consecutive, newly diagnosed, previously untreated patients (pts) < 61 years (yrs) in age with advanced stage low grade lymphoma were offered a protocol utilizing dose intense weekly BP-VACOP (bleomycin, cisplatin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone) chemotherapy for 12 weeks (wks) followed by irradiation (2,500 cGy in 15 fractions) to all initial nodal sites of disease. The median age was 45 yrs among 56 males and 42 females. Histologic subtypes by the Working Formulation were: small lymphocytic (5), follicular small cleaved (47), follicular mixed (22), follicular large (1), diffuse small cleaved (19), low grade NOS (4). Seven pts had bulky (> 10 cm) stage IIA disease, 27 IIIA, 3 IIIB, 41 IVA, 20 IVB. Fifty-four pts had bone marrow involvement, 16 with additional sites of extranodal disease and 6 with circulating lymphoma cells on peripheral blood smear.

Chemotherapy was delivered in full dose (> 90%) on time (12-14 wks); 30% of pts had radiotherapy delays due to cytopenias with 10% unable to complete the planned course. There were no treatment related deaths. At follow-up (f-up) ranging from 8 to 65 months (mo) 28 pts have clinical evidence of disease: 3 had refused the protocol treatment, 1 achieved only a PR and 24 have relapsed. Nineteen of these 28 had stage IV disease; 7 had B symptoms and 3 circulating lymphoma cells. Eleven pts have died of lymphoma. Of 16 pts with stage IV disease and 2 or more extranodal sites of involvement 5 are alive with and 5 dead of disease. With a median f-up of 33 mo for surviving pts, the projected overall survival at 5 yrs is 79% and the failure (less than CR, relapse or death from any cause) - free survival is 66%. The 5 yr overall survival of a cohort of 131 similar pts matched for age, stage and histologic subtype seen at our institution between 1980 and 1985 is 64% (p = 0.08) (median survival 8.5 yrs). During this period watchful waiting (for asymptomatic pts) followed by single agent alkylators or CVP was the initial treatment strategy. BP-VACOP + RT at diagnosis appears to improve short term survival at modest toxicity. Further f-up will determine if a proportion of pts will remain free of disease long term.

P 102 INTENSIVE CONVENTIONAL DOSE CHEMOTHERAPY FOR STAGE IV LOW GRADE LYMPHOMA: HIGH REMISSION RATES, AND REVERSION TO NEGATIVE OF PERIPHERAL BLOOD BCL-2 REARRANGEMENT

P. McLaughlin, F.B. Hagemeister, F. Swan, F. Cabanillas, J. Romaguera, M.A. Rodriguez, M.S. Lee, O. Pate, A. Sarris, A. Younes. UT M.D. Anderson Cancer Center. Houston, TX.

We have previously observed that interferon (IFN) maintenance following CHOP-Bleo chemotherapy can lengthen remission duration in patients (pts) with low grade lymphoma (LGL) (McLaughlin et al, Ann Oncol 1993, in press). We have also observed that regimens such as ESHAP (Velasquez et al, Proc ASCO 8:256,1989) can produce high remission rates in pts with relapsing LGL. Starting in 1988, we explored the sequential use of non-cross-resistant regimens to try to achieve higher rates of durable remission. In some patients, we also assessed the quality of remission by monitoring peripheral blood for rearrangement of bcl-2 using the polymerase chain reaction (PCR).

Between 1988-92, 160 pts with stage IV LGL have been registered on a protocol utilizing an intensive regimen of 3 alternating combinations, based on cyclophosphamide-doxorubicin (CHOD-Bleo), VP16-araC-platinum (ESHAP), & mitoxantrone-procarbazine (NOPP), followed by maintenance IFN. Among the first 80 evaluable pts, with median follow up of 31 mos, results to date are as follows: complete remission (CR) 81%; partial (PR) 15%; survival 94% at 4 yrs; failure-free survival (FFS) 52% at 4 yrs. To date, there is no plateau in the FFS curve. Twelve of these 80 had serial PCR analyses of peripheral blood for rearrangement of bcl-2, and 10 CRs reverted to PCR negative status. There has been an excellent correlation between achievement of PCR negativity and durable CR (only 1 of 10 has relapsed to date), not previously seen with CHOP-Bleo (see Cabanillas et al, Proc ASCO 1993). Toxicity with this regimen has included platelets <50,000 in 18% of courses, granulocytes <500 in 44% of courses, infections in 10% of courses, and 3 toxic deaths. Careful monitoring and appropriate supportive care are necessary with this regimen. The high CR rate is encouraging, as is the finding that the achievement of PCR negativity appears to correlate with durable CR.

P 103 COMPARISON OF FRONT-LINE CHEMOTHERAPY FOR AGGRESSIVE NON-HODGKIN'S LYMPHOMA (NHL) USING CAP-BOP WITH ADRIAMYCIN (CB-A), ADRIAMYCIN AND INFUSIONAL BLEOMYCIN/VINCRISTINE (CB-AI), OR MITOXANTRONE (CB-M).

J. M. Vose, J. R. Anderson, P. J. Bierman, M. Bast*, D. Weisenburger, W. C. Chan, and J. O. Armitage - for the Nebraska Lymphoma Study Group. Omaha, Nebraska.

Between 9/82 and 1/92, 389 patients (pts) with diffuse mixed cell, diffuse large cell, or immunoblastic NHL were treated with cyclophosphamide, procarbazine, and prednisone with adriamycin and bolus bleomycin and vincristine (CB-A), adriamycin with infusional bleomycin and vincristine (CB-AI), or mitoxantrone with bolus bleomycin and vincristine (CB-M). The median age of all patients was 67 years (range 15-92). Results at 2 yrs were as follows:

			Age <60		Age >60	
Regimen	N	CR	OAS	FFS	OAS	FFS
CB-A	115	64%	70%	58%	42%	34%
CB-AI	138	66%	66%	54%	52%	39%
CB-M	136	65%	68%	62%	39%	30%

OAS = Overall survival, FFS = Failure-free survival

Good prognosis pts with age <60, stage I or II, Karnofsky score ≥ 80, normal LDH, and ≤ 1 extranodal site had a 2-yr survival of 100%, 82%, and 100% for CB-A, CB-AI, and CB-M, respectively. Pulmonary and cardiac toxicity were similar with each regimen, but neurologic toxicity was worse with CB-AI (22% vs. 10%, p = 0.01) and alopecia less with CB-M (38% vs. 100%, p< 0.01). In older pts, a slight advantage for the CB-AI group was evident in survival (P = 0.08) but not failure-free survival. Confirmation of any advantage for CB-AI will be necessary as its toxicity was higher. In younger pts, CB-M had comparable treatment outcome with less toxicity.

P 104 LONG TERM RESULTS OF A RANDOMIZED CONTROLLED TRIAL IN ADVANCED LOW GRADE NON HODGKIN'S LYMPHOMAS TESTING THE EFFICACY OF DOXORUBICINE: THE PCOP-PACOP STUDY.

C.Sebban,E.Lepage,Y.Bastion,B.Coiffier,M.Blanc,P.Y.Péaud, C.Gisselbrecht. Service d'hématologie. Hopital Edouard Herriot 69003 Lyon France

From 1981 to 1984, 113 patients less than 70, with low grade non Hodgkin's lymphomas (small follicular small cleaved cell: 70 cases, follicular mixed: 31 cases and lymphocytic small cell: 12 cases) and without cardiac contrindication to Doxorubicin were included in a randomized controlled trial. All of them were Ann Arbor bulky disease stages II, stages III or stages IV and were treated by an induction regimen including 6 monthly courses of Cyclophosphamide 400mg/m2 D1 and D8, Vincristine 1.4mg/m2 D1 and D8 and Procarbazine 80mg/m2 D1 to D14 (PCOP regimen: 56pts) randomly associated to Doxorubicin 20mg/m2 D1 and D8 (PACOP regimen: 57pts). Maintenance therapy consisted of 12 monthly courses of Chlorambucil (10mg/m2 for 5 days) or association of Cyclophosphamide 300mg/m2 D1 to D3, Vincristine 1.4 mg/m2 and prednisone 60mg/m2 D1 to D5. After induction regimen, 30 pts (27%) achieved CR with similar CR rates for the PACOP (28%) and PCOP (23%) allocation groups. 73% achieved PR and 10% had stable or progressive disease. After maintenance therapy, CR was documented in 21 previously PR patients and CR rate at 18 months was 45% (47% with PACOP vs 43% with PCOP). With a median follow-up of 80 months, median overall survival were not reached for the 2 groups and median FFR survival were respectively 104 months for PACOP regimen and 93 months for PCOP regimen. Documented histologic progression was observed in 9 cases in the PACOP arm and in 8 cases with the PCOP arm and median survival after progression was 14 months. Prognostic factors for response to therapy in a multivariate logistic regression were bone marrow involvement (p = 0.02) and involved nodal sites upper 5 (p = 0.001) . For overall survival, CR at the end of the therapy was significantly associated with a best survival (p < 0.0001) with a median survival not reached for the patients achieving CR and of 76 months for the patients achieving PR. Using a multivariate logistic regression, the pretherapeutic characterisics associated with a worst survival were age > 50 (p = 0.001), bone marrow involvement (p = 0.02) and involved nodal sites upper 5 (p = 0.05).

In conclusion, Doxorubicin did not improve long-term survival of patients with low grade NHL. Overall survival was significantly better for patients achieving CR.

P 105 MAINTENANCE THERAPY IN MULTIPLE MYELOMA; INTERFERON ALFA-2b (IFN) VS AN ALTERNATING IFN/CHEMOTHERAPY SCHEDULE.

A. Maniatis for the Greek Myeloma Study Group. Athens, Greece.

Remission, complete or partial is achieved in aproximately 75% of myeloma patients. Until recently remission maintenance could not be influenced by treatment; IFN as maintenance treatment has given encouraging results in some studies, either alone or in alternating cycles with chemotherapy. The aim of the present study was to compare the efficacy of IFN vs alternate monthly cycles of IFN and chemotherapy, in maintening remission in myeloma patients. One hundred forty eight myeloma patients were enrolled in a prospective multicenter study to evaluate the effect of remission duration of two maintenance schedules. Remission was induced by Melphalan - Prednisone (MP) in patients over 65y. and by VAD in those below 65y. of age. The response rate was 73% for the VAD group and 70% for the MP group. Patients entering remission were randomized to receive IFN 3X10 IU t.i.w. (group A) or the same dose of IFN alternating in monthly cycles with VAD (vincristine 0,4 mg/d d 1-4 continuous i.v. infusion (CIV) adriamycin 9mg/m/d d 1-4 CIV, dexamethasone 40mg/d d 1-4) mos 2 and 8 MP(melphalan 6mg/m/d d 1-5 p.o., prednisone 60mg/m/d d 1-5 p.o.) mos 4 and 10 and cyclophosphamide (1g/m IV bolus d 1) mos 6 and 12 (group B). The same sequence was followed during the 2nd maintenance year. Of 148 patients enrolled, 31 are still in the induction phase. Of the remaining 117, 85 (72%) have entered remission and were randomized, 45 in group A and 40 in group B. The two groups were similar in terms of age and sex distribution as well as disease stage (group A - stage I=3 II=7 III=35; group B, II=5 III=35). In group A, 10 of 45 and in group B, 13/40 had at least one poor prognostic factor (anemia, thromtocytopenia, serum albumin <3g). The paraprotein in group A was IgG=24 IgA=13, BJ=7 NS=1 and in group B IgG=18 IgA=15 BJ=7. In group A 21 patients have relapsed for a median remission duration of 9 mos (1-23,5) and in group B 16 with a median remission duration of 6 mos (2-17). The overall remission duration for both groups todate is 6 mos - whereas for patients who had entered CR 8,5 mos (1+24+). From these preliminary results it appears that the addition of chemotherapy to IFN for maintenance does not prolong relapse-free survival. Results for overall survival are pending.

1. Mandelli F et al N. Engl J Med 1990, 322: 1430-1434
2. Oken MM et al Proc. Am Soc Clin Oncol 1988, 7, 225

P 106 ALPHA IFN TREATMENT IN MACROGLOBULINEMIA: A MULTICENTRIC TRIAL.

B.Rotoli, A.De Renzo, F.Frigeri, S.Buffardi, R.Marcenò, A.M.Cavallaro, P.Ruggeri, V.Liso, P.Musto, A.Andriani, V.Callea, M.Pizzuti, E.Iannitto, R.Cimino, S.Molica, P.Citarrella, C.Musolino, S.Guarino, G.Lucarelli, A.Espinosa, L.Del Vecchio.

Italian Study Group on Immunoproliferative Disorders
Division of Hematology, Federico II University of Medical School, Naples, Italy

Waldenstrom's macroglobulinemia (WM) is an incurable disorder of B cells with a number of biological similiarities with hairy cell leukemia (HCL). In view of the effectiveness of interferon (IFN) treatment in HCL, we have tested this agent in a relatively large group (n=88) of patients with IgM monoclonal component (MC) greater than 10 g/l. Thirty eight patients had a MC >30 g/l and were operationally classified as WM, while fifty had a MC level between 10 and 30 g/l and were classified as IgM-MGUS. IFN (INTRON-A, Schering Plough) schedule was the same for all patients, consisting of 3 MU/day for one month and then 3 times/week for at least 6 months. Response criterium was MC reduction assessed in 2 consecutive determinations (>50%: major response; 25-50%: minor response). In some patients bone marrow lymphoplasmacytosis and bone marrow T/B cell ratio was assessed by flow cytometry. Of 36 evaluable WM patients, 12 had a major and 6 a minor response; of 41 evaluable IgM-MGUS patients, 2 had a major and 6 a minor response. Response rate and entity were unrelated to time from diagnosis and previous treatment. In 2 WM patients who had a major response, a reverted bone marrow T/B cell ratio was observed after treatment. Responder patients with symptoms at the start of treatment showed marked clinical improvement. Tolerance was excellent in a majority of patients; only 15% left the study for side effects, although median age was 67 y. Our results suggest that IFN treatment does not help patients with a low IgM monoclonal component, while it causes MC reduction in 50% of the patients with IgM > 30 g/l.

P 107 INTERIM CLINICAL RESULTS OF PHASE 1/EARLY PHASE 2 CAMPATH®-1H STUDIES IN NHL/CLL (December 1992).

A.B.W. Nethersell†, J.C. Fussell†, D.J. Daly†, N. Clendeninn§, M. Collier§, J.E. Scott†. †Wellcome Research Labs., Beckenham, Kent, UK and §Burroughs Wellcome Co., North Carolina, USA.

(® CAMPATH is a trademark of the Wellcome Foundation Ltd)

CP-1H, a humanised monoclonal antibody effects lysis of lymphoid cells by complement and ADCC mechanisms following binding to CDw52 surface antigen. European and US studies in 34 centres commenced early in 1992 enrolling NHL/CLL patients (all grades) who had failed conventional chemotherapy. Three dosing schedules were examined (x1, x3 and x5 doses/week); dose escalations were made in successive patient cohorts.

Unit dose in mg and numbers (n) receiving protocolled dose for ≥ 4 weeks

Weekly		7.5 (13)	24 (17)	75 (4)	240 (3)
x3/week		2.5 (12)	8 (12)	25 (12)	80 (3)
x5/week	0.5 (5)		5 (24)		

Following initial 2 hour infusions fever, rigors and hypotension were common (premedication not routinely given), decreasing particularly on x3- and x5-weekly schedules. Other side effects included nausea, vomiting, diarrhoea, cough, dyspnoea, bronchospasm, headache, somatic pain (various sites including tumour), and rash (frequently urticarial) which responded to antihistamines. In addition to anticipated reduction in circulating lymphocytes, acute and chronic suppression of neutrophils and platelets occurred (sustained neutropenia/thrombocytopenia in ~10% of all patients). Infections encountered were caused by bacteria, CMV, candida, PCP as well as reactivation of H.simplex and zoster.

Within-patient dose escalations were introduced (protocol amendment) for doses above 25mg in order to induce tolerance at lower doses. Although an MTD as such was not defined, successful escalation to doses of 75mg and higher was achieved in only a small proportion of patients.

Although principally a Phase 1 study, disease assessments occurred at 4 weekly intervals. There were no responses at 0.5mg x5/week and few below 25mg x3/week. Thrice weekly dosing produced more responses than weekly dosing. Disease regression was greatest for circulating neoplastic cells, intermediate for bone marrow and spleen and least for bulky lymphadenopathy. Low grade disease (including CLL) appeared more responsive than high. Assessments based upon % reduction of all measurable disease (e.g. bidimensional lesions, marrow infiltration, total count) showed:

	Patients responding
No evidence of disease:	B-CLL (159mg), T-PLL (865mg)
>75% reduction:	B-CLL (600mg), Diff.small cleaved (300mg), M.Fungoides (75mg), Small non-cleaved (144mg)
>50% reduction:	Small lymphocytic (600mg), Lymphoplasmacytoid (134mg), Small lymphocytic (100mg)
Limited improvement:	29 patients (some significantly improved in blood/bone marrow)

P 108 FLUDARABINE THERAPY IN LOW-GRADE NON-HODGKIN'S LYMPHOMA (LG-NHL): RESULTS OF THE LYON-SUD EXPERIENCE.

C. Dumontet, Y. Bastion, M. Bazin, G. Salles, P. Felman, P.A. Bryon, B. Coiffier. Service d'Hématologie, Centre Hospitalier Lyon-Sud, 69310 Pierre-Bénite, France.

Fifty patients (pts) with LG-NHL were treated with intravenous fludarabine in a phase II trial. There were 36 male and 14 female pts with a diagnosis of follicular (n=18), diffuse small cleaved cell (n=16), lymphoplasmacytic/Waldenström's disease (n=12) or miscellaneous (n=4) NHL. Thirty-eight patients (76%) had stage IV disease. Twenty-nine pts (58%) had received prior chemotherapy (average number of protocols: 2, range: 1-5) and 21 pts received fludarabine as primary treatment. All patients received fludarabine at 25 mg/m² five days/week every 4 weeks. The median number of courses delivered was 4 (range: 1-12). Immediate toxicity was mild with grade 1-2 nausea or diarrhoea in 4 pts (8%). Twenty one pts (42%) had grade 3-4 neutropenia, 10 pts (20%) were readmitted for febrile aplasia, and two of them died. High grade thrombocytopenia was observed in 7 pts (14%). One patient developed lethal post-transfusion graft-versus-host disease. One patient developed incipient tumor lysis syndrome and two pts developed CNS symptoms during fludarabine treatment, with a lethal outcome in one case. The overall toxic death rate was 8%. Dose reductions were performed in 7 pts (14%). Forty-eight pts were evaluable for response. Four complete responses (8%) and 26 partial responses (52%) were observed for an overall response rate of 60%. There were 11 responses (52%) in the pts receiving fludarabine as first-line chemotherapy and 19 responses (66%) in the pretreated pts (not statistically significant). The 2-year overall survival (OS) was 59% with a median freedom-from-progression survival of 11 months. Fludarabine administered as a single agent appears to be an interesting treatment for pts with low-grade lymphoma, with significant hematological toxicity.

P 109 2-CHLORODEOXYADENOSINE (2-CDA) FOR THE TREATMENT OF NON HODGKIN'S LYMPHOMA AND CHRONIC LYMPHOCYTIC LEUKAEMIA.

D. C. Betticher, M. F. Fey, H. Jenzer, K. W. Brunner, T. Cerny for the SAKK Lymphoma Group. Institute of Medical Oncology, Inselspital, University of Berne, 3010 Berne, Switzerland

The purine analogue 2-CDA has shown significant activity in various haematological neoplasms. We treated 39 heavily pretreated patients (31 ♂, 8 ♀, median age: 55, 30-76) with Non Hodgkin's lymphoma (NHL, n=26), mycosis fungoides (MF, n=2) and chronic lymphocytic leukaemia (CLL, n=11) with 2-CDA in order to study response and toxicity. 13/26 NHL and 9/11 CLL had progressive disease under standard therapy and 13/26 NHL had a relapse. Patients received a total of 70 cycles of 2-CDA at 0.1 mg/kg/day as a continuous iv. infusion over 7 days, q28d. The last chemotherapy prior to 2-CDA dated back to ≥3 weeks. They had no kidney or liver dysfunction and their performance status was ≤2. All patients received full doses except one (50% dose reduction due to compromised bone marrow after previous chemotherapy). There was no GI toxicity, alopecia, neuro-, nephro- or hepatotoxicity. Haematological toxicities were granulocytopenia (0.5-1x10⁹/l) in 9 (two agranulocytoses) and thrombocytopenia (<100x10⁹/l) in 9 patients which was severe only (<20x10⁹/l) if the bone marrow was infiltrated at the beginning of 2-CDA treatment. In patients with a normal lymphocyte count at start of 2-CDA a >50% lymphocyte decrease was observed as of day 7 and was more marked after the 2nd or 3rd 2-CDA cycle. In 12 patients with NHL (20 cycles) the lymphocytes were <0.5x10⁹/l for more than 4 weeks. There were 13 mainly opportunistic infections (1 CMV, 4 Herpes, 1 candida stomatitis, 1 E. coli sepsis, 1 Aspergillus- and 4 bacterial pneumonia, 1 acute cholecystitis). The response rate was 54% for NHL/MF and 73% for CLL. There were no differences in response between refractory and relapsed malignancies. Response duration can not be assessed due to limited follow up.

Diagnosis		Pat. n	years since diagn.(n)*	pretreatments(n)*	2-CDA cycles(n)*	Response CR	PR	NC	P
NHL	IWF								
-low grade	(A-C)	12	4(1-16)	3(1-5)	2(1-3)	1	8	2	1
-int. grade	(D-G)	9	3(2-5)	3(1-3)	2(1-6)	-	4	3	2
-high grade	(H-J)	5	3(2-10)	3(2-5)	1(1-2)	-	-	-	5
CLL		11	6(2-13)	3(1-7)	1(1-2)	-	8	2	1
MF		2	2(2-3)	1(1-2)	2(2-3)	1	1	-	-

CR + PR: Complete + partial remission, NC: no change, P: Progression. * Median and range.

These preliminary results show that 2-CDA exerts virtually no toxicity other than myelosuppression. Interestingly, infections in our cases were more frequent than reported in the literature. 2-CDA has significant activity even in heavily pretreated and refractory low grade lymphoproliferative disorders. In the future regimes combining 2-CDA and other active drugs with different toxicity profiles should be studied, and clinical trials with different applications of 2-CDA (for example, sc. or po.) should be undertaken.

P 110 COMBINED MODALITY THERAPY VERSUS RADIOTHERAPY ALONE IN LARGE CELL NON HODGKIN'S LYMPHOMA STAGE I-II OF THE WALDEYER'S RING

E. Gallo, P. Gavarotti, C. Tarella, D. Caracciolo, D. Ferrero, F. Zallio, A. Urgesi, G. Rossi, A. Pileri. Divisione Universitaria di Ematologia, Ist. Radioterapia; Ospedale Molinette, Torino, Italy.

Between October 1972 and July 1992, 36 adult patients with diffuse large cell lymphoma of the Waldeyer's ring (stage I - II) received radiotherapy (RT) alone or combined MACOP-B treatment followed by RT (34-40 Gy). Seventeen patients were given RT alone and 19 patients received MACOP-B + RT. The first 13 patients received chemotherapy for 12 weeks, while in the last 6 patients chemotherapy included only 8 infusions. Clinical stage and histology (grade G and H, according to WF) were equally distributed in the two groups. Altogether there were 24 grade G and 12 grade H; 17 had stage I and 19 stage II. In both arms no difference was observed for different stages or histology groups. Overall survival (OS) and disease free survival (DFS) were significantly longer in patients treated with the combined modality. All 36 patients reached complete remission. Ten out of 17 patients in the RT group relapsed, compared to only one patient receiving MACOP-B + RT. In the RT group DFS is 38% projected at 140 mos, whereas it is 88% projected at 72 mos in the group receiving MACOP-B + RT ($p < 0.001$). Median age in the combined modality group was lower compared to the RT group (55 years vs. 68). However, if we consider only patients younger than 65 years, DSF is 100% in the chemoradiotherapy group, and 32% ($p<0,001$) for patients receiving RT only. All relapses occurred within 42 mos and a plateau phase is observed thereafter. OS is 54% projected at 140 mos in the RT group and 86% projected at 84 mos in the combined modality group respectively ($p<0.01$). In the latter group only one patient died for miocardial infarction at 56 mos while still in CR. No differences in OS and DFS were observed in patients treated for 8 or 12 weeks. In conclusion MACOP-B + RT seems superior to RT alone. A milder chemotherapy schedule has to be tested in older patients.

P 111 LOCALIZED LOW-BULK AGGRESSIVE LYMPHOMAS TREATED WITH CHEMOTHERAPY ALONE IN THE LNH-87 PROTOCOL GROUP 1. A GELA STUDY.

H. Tilly, B. Coiffier, P. Brice, C. Sebban, A. Bosly, P. Lederlin, P. Biron, B. Dupriez, D. Bordessoule, E. Lepage, MF d'Agay, F. Reyes, C. Gisselbrecht. Centre Henri Becquerel, 76038 Rouen, France.

Standard management of localized lymphomas of aggressive histology usually includes the use of radiation therapy. However, it has been shown that combination chemotherapy, used alone or followed by radiotherapy, could significantly improve the prognosis in patients (pts) with stage I or II disease.

The **group 1 of the LNH-87 protocol** included pts with a good prognosis lymphoma of aggressive histology. Inclusion criteria in this group were: intermediate or high-grade lymphoma except lymphoblastic or Burkitt's histology, age under 70 and none of the following prognostic factors: ECOG performance status > 2, number of extranodal sites > 2, tumoral mass > 10 cm, bone marrow or CNS involvement. In an attempt to reduce toxicity of the treatment, the LNH-84 protocol (3 induction courses of ACVBP: Doxorubicin 75 mg/m² day 1, Cyclophosphamide 1200 mg/m² d 1, Vindesine 2 mg/m² d 1&5, Bleomycin 10 mg d 1&5, Methylprednisolone 60 mg/m² d 1 to 5, at a two-week interval followed by consolidation with Methotrexate, Ifosfamide, VP16, Asparaginase and Cytarabine) was compared to the m-BACOD regimen (8 courses of: Doxorubicin 45 mg/m² d 1, Cyclophosphamide 600 mg/m² d 1, Vincristine 1 mg/m² d 1, Bleomycin 10 mg/m² d 1, Methotrexate 200 mg/m² d 8&15 at a three-week interval). At the time of first interim analysis 594 patients were included, no difference appeared in response to treatment, disease free survival and overall survival between the two treatment modalities.

We focused the present study on the 389 patients from group 1 (65%) with stage I and II disease. Sixty patients (15%) had a stage I, 88 (23%) a stage IE, 135 (35%) a stage II and 106 (27%) a stage IIE. 56% of the patients had a diffuse large cell lymphoma, 27% were older than 60, 14% had systemic symptoms, 41% a tumor-mass >5 cm, 22% LDH >1N, 4% serum albumin <30 g/l, 9% beta2-microglobulin >3 mg/l. 341 pts were evaluable for response and survival. Complete remission was obtained in 87% of the pts, stage I: 92%, stage II: 84%. Toxic death occurred in 12 pts (3%), LNH-84: 8, m-BACOD: 4. Three-year overall survival was 83% (±4%). Survival did not differ between the two treatment arms. Several adverse prognostic factors were identified: age above 60 ($p<0.002$), stage (I vs II, $p<0.02$), tumor-mass > 5cm ($p<0.003$), performance status (0 vs 1, $p<0.003$), albumin level < 30 g/l ($p<0.0001$), LDH > 1N ($p<0.0001$). In the subgroup of 291 patients with LDH < 1N, only age >60 yrs had a significant influence on survival ($p<0.02$).

In conclusion, well-known prognostic factors continue to influence survival of localized low-bulk aggressive lymphomas. Chemotherapy alone appears to be an alternative to more classical approaches in this selected group of patients.

P 112 LONG TERM RESULTS ACHIEVED WITH 12 WEEKS OF MULTI-AGENT CHEMOTHERAPY FOR ADVANCED STAGE DIFFUSE LARGE CELL LYMPHOMAS: THE VANCOUVER EXPERIENCE

PJ Hoskins, JM Connors, SE O'Reilly, R Klasa, P Klimo. British Columbia Cancer Agency, Vancouver, Canada.

288 pts with previously untreated diffuse large cell malignant lymphoma, large cleaved (n=50), non-cleaved (n=81), mixed (n=31), immunoblastic (n=84) or large, not otherwise specified (n=42) with advanced stage disease (stage III or IV or II with either B symptoms or a mass > 10cm) were treated between April 1981 and Oct 1990 on the consecutive regimens of MACOP-B, VACOP-B. The basic structure, as exemplified by MACOP-B, of the regimens is intravenous treatment at weekly intervals alternating between myelosuppressive (doxorubicin/cyclophosphamide) and non-myelosuppressive agents (vincristine, bleomycin, methotrexate). VACOP-B differs from MACOP-B: methotrexate is omitted and etoposide is substituted for one-half of the cyclophosphamide doses and prednisone is given on alternate days. Follow-up is 2-12 yrs (median = 6 yrs). The addition of cisplatin to VACOP-B for 72 pts did not alter 5 yrs OS (64% vs 67%). Prognostic subgroups (0,1 factors vs 2 or 3 factors present) can be defined using the following: B symptoms, age over 60 and 2 or more sites of stage IV extra nodal disease. Within these subgroups both regimens are equally effective.

	MACOP-B	VACOP-B*
n	126	162
Age median (range)	52 (20-70)	53 (17-70)
Male %:	63	66
% B symptoms	49	44
% Stage III	26	23
% Stage IV	37	39
LDH median (range)	225 (64-2820)	219 (50-2937)
% LDH > 2 times normal	22	20
% 5 year overall survival (OS)	63	65
% 10 year OS	54	-
% 5 year disease specific survival (DSS)	67	68
% 10 year DSS	62	
% lethal toxicity	5	2
% severe mucositis	50	5
% 5 year OS 0,1 factors	72 (n=93)	73 (n=124)
% 5 year OS 2,3 factors	36 (n=33)	36(n=38)

In conclusion (1) we achieved consistent results throughout our study period with 64% 5 yr overall survival (2) the change from MACOP-B to VACOP-B did not alter efficacy either when analyzed for all patients or by prognostic subgroups but did reduce lethal toxicity and mucositis.

P 113 SEQUENTIAL CHOEP VS ALTERNATING HCHOP/IVEP: A MULTICENTER RANDOMIZED TRIAL FOR HIGH GRADE NON-HODGKIN'S LYMPHOMAS.

H. Köppler, J. Birkmann, W. Zeller, U.E. Steinhauer, C. Gropp, S. Oehl, H. Kuhn, P. Drings, H.H. Gossmann, M. Khoury, R. Schubotz, K. Havemann. Dept. Internal Medicine, Baldingerstr., D-3550 Marburg, Germany

185 patients with high grade non-Hodgkin's lymphoma stages II-IV were randomized to receive four cycles of CHOEP (cyclophosphamide 750 mg/m^2 i.v. d 1, doxorubicin 50 mg/m^2 i.v. d 1, vincristine 2 mg i.v. d 1, etoposide 100 mg/m^2 i.v. d 3-5, prednisolone 100 mg p.o. d 1-5) (treatment arm A), or four cycles of chemotherapy with hCHOP (cyclophosphamide 1,200 mg/m^2 i.v. d 1, doxorubicin 40 mg/m^2 i.v. d 1+2, vincristine 2 mg i.v. d 1, prednisolone 100 mg p.o. d 1-5) alternating with IVEP (ifosfamide 1,500 mg/m^2 i.v. d 1-5, vindesine 3 mg/m^2 i.v. d 1, etoposide 120 mg/m^2 i.v. d 3-5, prednisolone 100 mg p.o. d 1-5) in treatment arm B. After four cycles of chemotherapy an involved field irradiation with 35 Gy was given to all patients in complete or partial remission. 173 patients were evaluable for response and survival. A complete response (CR) was seen in 148/173 patients (85%) with 86% CR in arm A vs 84% CR in arm B. With a median follow-up of 35 months (range 17-61) the overall projected survival at 48 months is 61% vs 65% for arm A and B, respectively. Event-free survival is projected to be 57% in arm A and 47% in arm B at 48 months. So far, the differences in CR, survival and disease-free survival are statistically not significant. Factors associated with poor survival were advanced stage (III, IV) and an LDH > 250 U/l. When the score system of the International Prognostic Factors Project was applied the survival rates at 2 years were 81% for low risk, 64% for low intermediate risk, 50% for high intermediate risk and 43% for high risk patients. Toxicity was acceptable. Main side effects were mild nausea/vomiting, leukopenia and fever/infection associated with leukopenia. Two treatment related deaths accounted for the toxic death rate of 2%. In conclusion, both treatment modalities produced high complete remission rates and survival data indicate that the majority of patients will be longterm survivors.

P 114 MULTICENTRIC RANDOMIZED TRIAL OF MACOP-B VS F-MACHOP IN HIGH GRADE NON-HODGKIN'S LYMPHOMA.

P. Mazza, P. L. Zinzani, S. Amadori, G. Papa, M. F. Martelli, F. Calabresi, F. Dammacco, G. Lucarelli, S. Pileri, M. Martelli, M. Antimi, S. Coluzzi, C. Guglielmi, V. M. Lauta, L. Moretti, E. M. Ruggeri, B. Falini, F. Gherlinzoni, M. Bocchia, S. Tura, F. Mandelli. Italian Cooperative Study Group on High Grade Malignant Lymphoma (Bologna, Roma, Perugia, Pesaro, Bari).

In a multicentric randomized trial we are evaluating the role of two different third generation regimens in high grade non-Hodgkin's lymphomas (categories G, J, H, according to Working Formulation). The study was finalized to compare F-MACHOP, a cyclic monthly heavy combination therapy over six months duration, versus MACOP-B, a sequential weekly combination chemotherapy over three months duration. The study included patients younger than 65 years, with stage II-IV, performance status <3, HIV negative, and with normal hepatic, renal and cardiac functions. From September 1988 to August 1991, 306 patients were randomized and 286 are evaluable: 140 patients were randomized to receive MACOP-B and 146 F-MACHOP, respectively. The mean age was 39 years. The distribution of sex, stage, symptoms, bulky and different histologies are almost equally distributed among groups. 86 of 140 (61%) patients treated by MACOP-B achieved complete response (CR) instead of 98 (67%) treated by F-MACHOP achieved CR. 51 patients (21 F-MACHOP and 30 MACOP-B) achieved partial response after 2/3 of planned therapy and were randomized for intensification program (29 DHAP regimen and 22 ABMT). The probability of survival at 50 months is 68% for F-MACHOP group and 66% for MACOP-B group with a median follow-up of 30 months, respectively. The probability of relapse-free survival is 75% for F-MACHOP patients and 74% for MACOP-B patients at 44 months, respectively. In conclusion, this study suggests that F-MACHOP and MACOP-B regimens give same results in terms of CR rate and relapse-free survival in high-grade non-Hodgkin's lymphoma, but an ongoing analysis of survival among different histologies shows that patients with immunoblastic and Burkitt type lymphoma are better benefited by F-MACHOP than MACOP-B regimen. Moreover, the reevaluation after two third of first line treatment has an important role to identify, as soon as possible, the subset of patients who needs a modification of the chemotherapeutic approach.

P 115 EORTC STUDY NON-HODGKIN LYMPHOMA. Phase III study comparing CHVmP/VCR-Bleo vs ProMACE-MOPP in patients with stage II, III and IV intermediate and high grade lymphomas.

R. Somers, M. v. Glabbeke, U. Tirelli, J. Thomas, P. Garde. The Netherlands Cancer Institute, Plesmanlaan 21, 1066 CX, Amsterdam, The Netherlands.

In the EORTC lymphoma cooperative group a phase III study was performed for stage II, III, IV intermediate and high grade lymphomas (International Working Formulation categories D, E, F, G, H).
Treatment 1, 8 cycles of CHVmP-VB (Cyclophosphamide 600 mg/m^2, Adriamycine 50 mg/m^2, VM26 60 mg/m^2 d.1, Prednisone 60 mg/m^2 d. 1-5, Oncovin 2 mg d. 15, Bleomycine 10 mg/m^2 d 15), was compared with 8 courses of ProMACE-MOPP (treatment 2), consisting of Adriamycine 25 mg/m^2, Cyclophosphamide 600 mg/m^2, VP16 120 mg/m^2 d. 1, nitrogen mustard 6 mg/m^2, Oncovin 14 mg/m^2 d. 8, Prednisone 60 mg/m^2 d. 1-15, Procarbazine 100 mg/m^2 d. 8-15.
Response was evaluated after 8 courses, additional radiotherapy was given to initial lesions >5 cm or residual masses after 4 courses.
Of 430 patients entered, 51 (12%) are ineligible mainly for pathology reasons, 31 patients are to early, 348 are evaluable for reponse. Stage II 35%, stage III 30.5%, stage IV 33%. Mean age: 52 y, 32% is older than 60 y.
Liver involvement 14%, bone marrow involvement in 18%. There are no statistical differences between the two arms regarding the patient population.
Results:

treat.1: nr. 188	CR 115 (61%),	PR 21%,	NC/PD 13%,	Tox/Refus. 7%	p= 0.001
treat.2: nr. 160	CR 76 (48%),	19%,	20%	14%	

5y FFP (44% vs 42%) RFS (47% vs 51%) and S (57 vs 47%) were not significantly different comparing treatment 1 with treatment 2. WHO grade III, IV toxicity for WBC (60 vs 71%), platelets (4% vs 20%, p.0064) occurred more frequently in the ProMACE-MOPP arm leading to more treatment interruptions and refusals.
CHVmP-VB is a safe outpatient regime, with equal results and less toxicity than other third generation regimens.

P 116 INTERMEDIATE-HIGH GRADE NON-HODGKIN'S LYMPHOMA (NHL) IN ELDERLY PATIENTS TREATED WITH A NOVEL WEEKLY CHEMOTHERAPY REGIMEN (PVEBEC) WITH OR WITHOUT rG-CSF.

M.Bertini, U.Vitolo, L.Orsucci, A.Levis, R.Freilone, P.Viero, V.Meneghini, M.Pini, E.Gallo, M.Pizzuti, L.Marchi, F.Salvi, V.Secondo, C.Volta for the MRSGNHL. Division of Hematology, Ospedale Molinette, Torino, Italy.

Approximately 25-35% of NHL cases occurs in patients older than 65 years. Elderly Pts are generally excluded from therapeutic protocols and very few are specifically devised for these pts. From November '91 to December '92 62 pts with advanced stage NHL over 65 years were treated with P-VEBEC regimen. P-VEBEC consisted in: Epirubicine 50 mg/m2 + Cyclophosphamide 300 mg/m2 and Etoposide 100 mg/m2 on weeks 1,3,5,7; Vinblastin 5 mg/m2 and Bleomycin 5mg/m2 on weeks 2,4,6,8; Prednisone 50 mg/day p.os in the first 2 weeks and thereafter every other day. 26 pts received rG-CSF 5 ug/kg/die throughout the treatment starting on day 2 of every week for 4 consecutive days. The median age was 71 years (65-80) with 28 male and 34 female. Histology according WF was: D 6, E 17, F 15, G 17, H 7. 27% had B symptoms, 32% bulky disease, 37% LDH level > normal and 46% had PS=2. 13% were stage II, 43% stage III and 44% stage IV of whom 17 (27%) had Bone Marrow (BM) involvement. Sixty percent of patients achieved a CR, 26% a PR and 8% a NR. CR was adversely affected by LDH above normal value, advanced stage and BM involvement. Severe toxicity (grade WHO 3 or 4) was never recorded neither toxic deaths. With a median follow-up of 12 months the overall survival and disease free survival were 70% and 56% respectively. The method of Hryniuk and Bush was used to calculate the relative dose intensity (RDI) of each drug. T8 was defined as the days to complete the planned cycle (theorical 56 d.). Blood counts were checked every week. Median age, PS,LDH, stage, bulky, CR were not significantly different between patients receiving or not rG-CSF. Patients who received rG-CSF had a significantly ($p<0.01$) shorter T8 (60 d. vs 70 d), a higher median RDI (94% vs 78%) and a lower myelotoxicity (neutrophil nadir <500 23% vs 61%) compared with the patients who were not given rG-CSF. P-VEBEC is a feasible cycle in elderly patients, in an outpatient setting. The use of rG-CSF improve RDI, but not the rate of CR. A large number of pts and a longer F.U. is needed to state if a high RDI may correlate with a better outcome.

P 117 A COMPARATIVE STUDY OF WEEKLY CHEMOTHERAPY (CAPOMEt) VERSUS CYCLICAL CHEMOTHERAPY (CHOP-Mtx) IN THE TREATMENT OF HIGH GRADE NON-HODGKIN'S LYMPHOMA (HG-NHL)

J A Child, N Bailey, J Fletcher, M H Cullen, E Bessell and A V Simmons. For the Central Lymphoma Group (data centre: CRC Trials Unit, Birmingham, U.K.)

274 patients with HG-NHL (Kiel classification) were randomised in a study comparing weekly (CAPOMEt, regimen A) with cyclical chemotherapy (CHOP-Mtx regimen B). A comprises cyclophosphamide 400mg/m^2, doxorubicin 50mg/m^2, both i.v. day 1, vincristine 2mg i.v. day 8, prednisolone 60mg/m^2 p.o. days 8-12; methotrexate 250mg/m^2, etoposide 100mg/m^2 both i.v. day 15, etoposide 50mg t.d.s. p.o. days 16 and 17; vincristine and prednisolone repeated days 22-26 as for days 8-12. Treatment is given to 13 weeks minimum with at least one module being given post CR. B comprises cyclophosphamide 750mg/m^2, doxorubicin 50mgs/m^2, vincristine 2mg, all i.v. day 1, prednisolone 40mg/m^2 p.o. days 1-7, methotrexate 250mg/m^2 i.v. day 14. The regimen is repeated in a 3 week cycle to CR plus 3 cycles (minimum 5).

142 patients (median age 60) received A and 132 patients (median age 57) received B. The percentage of patients given A and B respectively were, according to stage: I=11,14; II=30,28; III= 20,21; IV=39,36; B symptoms = 50,55. Distribution by sex and blood biochemical parameters (including albumin and LDH) showed no significant differences between the treatment arms. Grade 3/4 neutropenia was recorded in 48% pf patients given A compared with 60% of patients given B. Neuropathy of any grade was more frequent during A (42%) than during B (27%). The overall CR rate was 55% with A, 60% with B; 95% confidence limits (CI) of difference -7% to 17%; survival at 2 years (95%CI) was 50% (41-58%) and 54% (46-63%) respectively. The results of this study do not support the hypothesis that weekly chemotherapy is more effective than a standard cyclical chemotherapy regimen. Comparisons between these and similar regimens need to take account of differences in total dose as well as dose intensity in relation to the individual drugs. Further studies, of "accelerated" chemotherapy (with G-CSF) are being carried out by the Group.

P 118 MEDIASTINAL LARGE CELL LYMPHOMA WITH SCLEROSIS - RESULTS OF TREATMENT AT A SINGLE CENTRE.

Rohatiner AZS[1], Norton AJ[2], Whelan JS[1], Arnott SJA[3], Ganjoo R[1], Wilson A[1], Lister TA[1]. [1]ICRF Dept of Medical Oncology and Depts of [2]Histopathology and [3]Radiotherapy, St Bartholomew's Hospital, London, UK

In a retrospective analysis, 23 patients (age range 19-71, median 30 years) were identified as having mediastinal large cell lymphoma with sclerosis on the basis of clinical and pathological features. The latter group represents 6% of a total of 399 patients with high grade lymphoma (Kiel Classification) treated during the same 14 year period (1978-1992). At presentation, 15/23 had 'bulky' disease and 11/23 had evidence of superior vena-caval obstruction. Thirteen patients had stage II disease (6:II, 7:IIE), 10 presented with stage IV disease. Extra nodal involvement in the latter 17 patients comprised pericardium 9, lung 8, pleural effusions 5, chest wall 4, liver 2 and 1 patient with each of the following: bone, adrenal, pancreas and bone marrow.

Complete remission (CR) was achieved in only 4/23 patients with the initial Adriamycin containing regimen. 'Good partial remission' (GPR = no clinical evidence of disease, minimal abnormalities of uncertain significance on radiological investigation) was achieved in a futher 7 patients and 'poor partial remission' (PPR = a reduction in measurable disease >50%) in 5, giving an overall response rate of 16/23 (67%). One patient died within 48 hours of arrival at the hospital, 17 of the 18 remaining patients in whom anything less than CR was achieved subsequently received additional, alternative treatment (2: chemotherapy, 6: mediastinal radiotherapy, 9: both treatment modalities) but in only 2/17 did this result in any further degree of response. With a median follow up of 5 years, 11/23 patients remain well without recurrence between 3 months and 14 years (5/6 in whom CR was eventually achieved and 6/12 in whom only a partial remission was ever documented). The 7 patients in whom the initial treatment demonstrably failed have all died.

These results suggest that a proportion of patients with this rare sub-type of high grade B cell lymphoma may be cured by chemotherapy alone and that the presence of a residual mediastinal mass after treatment does not necessarily imply treatment failure. However, patients in whom the initial chemotherapy fails have a very grave prognosis

P 119 AGGRESSIVE NON HODGKIN'S LYMPHOMA (NHL) IN THE ELDERLY : RESULT OF THE MEMID PROTOCOL WITH OR WITHOUT rh GM-CSF.

A.CREISSON [1], M. FABBRO [2], J.OTTO [1], M.H.GASPARD [1], JF. ROSSI [2], A.THYSS [1].
1 - Centre Antoine-Lacassagne - Nice Cedex France
2 - Centre Paul Lamarque - Montpellier - France.

Age is a major prognostic factor in NHL. About 1/3 of patient are over 65 yrs at diagnosis and their prognosis remains poor specially because of poor hematological tolerance of chemotherapy. Despite this, response rate is quite similar to younger patient when the full doses of treatment are used, and long survivals can be obtained. In our 2 institutions we treated from july 90 to september 92 , 60 patients with aggressive NHL (group E,F,G,H of the W.F.) age over 65 (mean age 73, 66-86).
The first 26 patients have received 3-6 cycles of the MEMID protocol with Mitoxantrone 10 mg/m2 D1, Etoposide 100 mg/m2 D1-3, Methylglioxal 100 mg/m2 D3, Ifosfamide 1000 mg/m2 D1-3. For 23 evaluable patients, response rate was encouraging with 48 % of CR and 22 % PR (response rate : 70 %). Since april 91, 34 other patients have been treated with 4 courses of the same protocol plus rh GM-CSF (Schering-Plough) in order to optimize the dose- intensity effect.
rh GM-CSF 5 µg/kg was given D4-D11 sub-cutaneously after cycles 1-3-4. Cycle 2 was done without rh GM-CSF to allow an intra-patient comparison. Responding patients received 2 more cycles. In this second group of 34 patients (21 men, 13 women, mean age 73 yrs), 30 patients are still to be evaluated . The responses were CR 50 %, PR 27 %, (response rate 77 %). Hematological toxicity was assessed by blood samples twice a week between courses of treatment. Grade 3 or 4 occurred after 78 % of 103 cycles with no significant difference of nadir between cycles with or without rh GM-CSF, but a significant reduction of the median time interval between courses (21D versus 32 D).
Infection grade 3 or 4 occurred in 22 % of cycles including 3 septicemia and 19 FUO. 3 toxic deaths (10 %) occurred. In september 92 , 62 % of patients were alive with a median follow up of 8 months (1-17). The survival probability at 12 months is 52 % and probability of survival in CR is 35 %.
In conclusion use of rh GM-CSF allowed an increase of dose-intensity treatment for NHL in the elderly and significantly shortened the time interval between courses of treatment.

P 120 ALTERNATING REGIMEN (VIMMM/ACVBP) IS NOT SUPERIOR TO ACVBP IN PATIENTS BETWEEN 55 AND 70 YEARS WITH A POOR PROGNOSIS AGGRESSIVE LYMPHOMA. LNH87 PROTOCOL GROUP 3 : A GELA STUDY.

A. Bosly, E. Lepage, M.F. d'Agay, B. Coiffier, J.L. Michaux, P. Brice, B. Dupriez, R. Herbrecht, M. Divine, C. Nouvel, P. Biron, H. Tilly, D. Bordessoule, C. Sebban, C. Gisselbrecht. Catholic University of Louvain, Mont-Godinne University Hospital, 5530 Yvoir, Belgium

Therapeutic improvement in elderly non Hodgkin lymphoma with adverse prognostic factors remains a great challenge. Indeed, intensive therapy followed by stem cells transplantation is not applicable because of age. Another approach, as in Hodgkin's disease, may be the use of non-cross resistant alternating therapy. In the group 3 of the LNH87 protocol, we tested the benefit of alternating chemotherapy in comparison with LNH84 protocol (JCO 1989; 7 : 1018). Group 3 patients were between 55 and 70 years and had at least one of the following adverse prognostic factors : high grade histology subtype (lymphoblastic or Burkitt) (4.6 % of the cases), ECOG ≥ 2 (32.7 %), number of extranodal sites ≥ 2 (27.1 %), tumoral mass ≥ 10 cm (56.4 %), bone marrow (36 %) or CNS (11.7 %) involvement.
Patients were randomized in two arms :
Arm A : LNH84 protocol with 4 courses of induction : ACVBP : Adriamycin 75 mg/m^2 day 1, Cyclophosphamide 1200 mg/m^2 d 1, Vindesine 2 mg/m^2 d 1, 5, Bleomycin 10 mg d 1, 5 and Methylprednisolone 60 mg/m^2 d 1-5 every 3 weeks followed by consolidation with Methotrexate, Ifosfamide, VP16, L. Asparaginase, Cytarabine).
Arm B : induction : 4 courses every 3 weeks, comprising 1 cycle of VIMMM : VM16 100 mg/m^2 d 1, 5, Ifosfamide 1000 mg/m^2 d 1-5, Mitoxantrone 10 mg/m^2 d 1, Methyl-GAG 300 mg/m^2 d 1, 5, Methotrexate 1500 mg/m^2 d 3, Methylprednisolone 60 mg/m^2 d 1-5, 1 cycle of ACVBP and 2 cycles VIMMM/ACVBP, followed by a consolidation with Mitoxantrone, VP16, Ifosfamide, Adriamycin, Cyclophosphamide, Vindesine, Methotrexate.
At the time of analysis, 576 patients were studied. Histologic distribution showed a large majority of large cells (81.7 %). LDH > 1.N was present in 52.5 % of the patients, β_2 microglobulin ≥ 3 in 51.1 % and advanced stage (III-IV) in 79.2 %.
Sixty-three percent of patients treated by arm A achieved a complete response (CR), 11% a partial response (PR), 10% a failure (F) and 16% died during induction (D); against CR 51%, PR 19%, F 6% and D 24% for the arm B (p=0.004). Median relapse free survival (RFS) and median overall survival (OS) were respectively 32 and 28 months, without any difference according to the two arms (p = 0.15 for RFS and p = 0.78 for OS). In multivariate analysis, independent adverse prognostic factors for survival were ECOG ≥ 2 (relative risk [RR] = 2.4), LDH > 1.N (RR = 1.71) and stage III-IV (RR = 1.47).
Stratified analysis on the new international index did not show any difference in the RFS or OS according to the two arms.
In conclusion, in this subgroup of high-risk patients, this study did not permit to demonstrate any advantage in survival and RFS of alternating regimen in comparison with LNH84 regimen. Moreover, response rate is significantly higher with ACVBP than with VIMMM/ACVBP.

P 121 COMPARABLE PROGNOSTIC FACTORS AND SURVIVAL IN ELDERLY PATIENTS WITH AGGRESSIVE NON-HODGKIN'S LYMPHOMA (NHL) TREATED WITH STANDARD DOSE ADRIAMYCIN BASED REGIMENS.

L.Grogan, D.Devaney, N.Corbally, PA. Dervan, DN. Carney. Depts. of Medical Oncology and Pathology, Mater Misericordiae Hospital & Dept. Pathology, University College Dublin, Dublin, Ireland.

We retrospectively analysed the prognostic factors at diagnosis, clinical response and survival in 192 patients with newly diagnosed aggressive NHL treated in a single institution between 1985 and 1991. Overall 37.5% (72/192) of patients were 65 years or older (average 71yrs, range 65-85yrs) and 62.5% (120/192) were under 65 years (average age 45, range 16-64yrs). All patients were completely staged and had intermediate or high grade NHL. 141 patients were treated on similar regimens with the same chemotherapy dose intensity regardless of age. Standard dose M.B.A.C.O.D. (methotrexate, bleomycin, adriamycin, cyclophosphamide, vincristine and dexamethasone) or C.H.O.P. (cyclophosphamide, adriamycin, vincristine, prednisone) was used to treat 66/72 (92%) of elderly patients and 69/120 (56%) of patients less than 65 years. There was no significant differences between the groups with regard to stage, histological grade, cell type, elevated LDH, number of extranodal sites, presence of B symptoms or bulky disease.Elderly patients had a significantly ($p<0.05$) poorer performance status (P.S.), with 43% (31/72) having a P.S. of 2 or greater, compared to 29% (20/69) in the under 65 age group. Elderly patients had an inferior complete response rate, 60% versus 73%, however overall response rates of 92% and 91% were similar. The disease free survival at 3 years for complete responders was not significantly different, 72% in patients over 65 compared to 70% in those under 65, with comparable 3 year overall survivals of 54% and 57% respectively. These results suggest that elderly patients do just as well as younger patients when treated with standard dose adriamycin regimens and in general, despite poorer performance status, can still be treated with curative intent.

Supported by Cancer Research Advancement Board, Irish Cancer Society.

P 122 HUMAN IMMUNODEFICIENCY VIRUS-RELATED LYMPHOMA TREATMENT WITH LNH84 CHEMOTHERAPY.

C. Gisselbrecht, U. Tirelli, E.Oksenhendler, E. Lepage, J. Gabarre, J.P. Farcet, R. Gastaldi, B. Coiffier, A. Thyss M. Rapahel, S. Monfardini.
For the French-Italian Cooperative Group. Saint Louis Hospital, Paris, France.

An increased risk of high grade non-Hodgkin's lymphoma (NHL) is observed in patients who are seropositive for human immunodeficiency virus (HIV). Treatment of such patients is complicated by their underlying acquired immunodeficiency syndrome (AIDS). Patients without severe AIDS may derive significant benefits from intensive therapy. In a prospective study, treatment outcomes were assessed in 141 cases of HIV-seropositive lymphomas. Methods : Adult lymphoma patients with a performance status < 3 and no active opportunistic infection were consecutively treated with 3 cycles of doxorubicin 75 mg/m^2, cyclophosphamide 1 200 mg/m^2, vindesine 2 mg/m^2, X 2, bleomycin 10 mg X 2 and prednisolone 60 mg/m^2 X 5 (ACVB). This treatment was followed by a consolidation phase of high dose methotrexate plus leucovorin, ifosfamide, etoposide, asparaginase and cytarabine (LNH84). CNS prophylaxis with intrathecal methotrexate was routinely used. Zidovudine maintenance was started after chemotherapy. 93 pts had high grade lymphomas (59 Burkitt), 48 had intermediate grade. Stage III-IV was present in 86 pts, meningeal involvement in 29, and bone marrow infiltration in 30; 62 pts had more than 2 extranodal localizations. LDH were above the normal value in 95 cases. The median CD4-positive lymphocyte count was 227 X 10^6/l. Results : 89 pts (63 %) achieved complete remission (CR) and 19 (13 %) partial remission, while 13 failed to respond and 20 (14 %) died during the course of ACVB, 8 of them from progressive disease. With a median follow-up of 28 months, median survival and disease free survival were 9 and 16 months, respectively. Median survival for non responders was 5 months; 23 pts died of opportunistic infections while in persistent CR. In multivariate analysis, four factors were strongly associated with shorter survival : (1) CD4 < 100 X10^6/l. (2) performance status > 1, (3) immunoblastic lymphoma ; and (4) prior AIDS. In the absence of all risk factors, the probability of survival at 2 years was 50 %. Conclusion : In a selected group of HIV-related lymphomas, intensive chemotherapy with LNH84 is feasible and yields a high complete remission rate. Survival is short due to death from HIV-related infections. However, in a subgroup of patients without adverse prognostic factors, long term remission was observed. (Supported by ANRS, GICAT, GELA).

P 123 VAPEC-B CHEMOTHERAPY (CT) FOR HIGH GRADE NON-HODGKIN'S LYMPHOMA (NHL) AND HODGKIN'S DISEASE (HD) DOES NOT CAUSE MALE STERILITY.

J.A.Radford[1], S.Clark[2], S.M.Shalet[2], D.Crowther[1]. [1]CRC Dept of Medical Oncology and [2]Dept of Endocrinology, Christie Hospital, Manchester, M20 9BX.

The VAPEC-B combination (doxorubicin 35mg/m^2 wks 1,3,5,7,11; cyclophosphamide 350mg/m^2 wks 1, 5, 9; etoposide 100mg/m^2 po daily x 5 days, wks 3,7,11; vincristine 1.4mg/m^2 wks 2,4,6,8,10; bleomycin 10mg/m^2 wks 2,6,10; prednisolone 50mg daily wks 1-5, 25mg daily wks 6-11) has been used at this institute for remission induction in high grade NHL since 1987. Having also demonstrated activity in relapsed HD (Annals of Oncology 2, 505-509, 1991) the first 4 weeks of the VAPEC-B schedule in combination with radiotherapy (RT) is currently being compared with RT alone in previously untreated clinical stage IA/IIA HD. For these latter cases, most of whom are young, fertility issues are of particular importance.

Twenty seven men have received VAPEC-B (±RT but no other CT) for HD or NHL; 3 had undergone vasectomy, 8 declined to take part in the study and 2 were unsuitable for inclusion by reason of advanced age or psychiatric illness. Fourteen men (median age 29.5 years, range 16-45) consented to providing a semen sample. Seven pts had received 11 weeks of VAPEC-B for NHL and 7 pts, 4 weeks of VAPEC-B for HD. Median time lapse since completion of CT was 13.5 months (5-30) and 13 pts had also received RT which in 2 cases incorporated a pelvic field. Semen contained motile spermatozoa in 12/14 pts and in 9 cases the count was >20x10^6/ml. One patient (4 weeks VAPEC-B plus pelvic RT) was azoospermic and another (11 weeks VAPEC-B plus RT to the head and neck) had a count of 21x10^6/ml but sperm were non-motile, possibly due to a delay in analysis.

These results suggest that VAPEC-B does not cause permanent damage to the male germinal epithelium. More detailed assessment of gonadal function in both sexes receiving the 11 week schedule for advanced HD is currently in progress.

P 124 LATE RELAPSE FROM INTERMEDIATE GRADE LYMPHOMA.

P.P.B. James, G.M. Mead, J.W. Sweetenham, J.M.A. Whitehouse. CRC Wessex Medical Oncology Unit, Southampton General Hospital, Southampton SO9 4XY, UK.

A proportion of the intermediate grade lymphomas are curable with modern therapy, but successful salvage from systemic relapse is uncommon. Recurrence usually occurs in the first 2 years and follows an aggressive course. The clinical features of later relapse are less well characterized. We have reviewed our experience over 14 years of the treatment of intermediate grade non-Hodgkin's lymphoma, with reference to relapse occurring 2+ years after completing first-line therapy. A total of 547 patients (pts) were treated over this period, including pts with follicular large cell and diffuse large cell lymphoma (FLC, DLC), diffuse mixed cell (DM) and immunoblastic lymphoma (IMM).

	Total	*Relapses*	*Relapses at 2+ Yrs*
DLC	408	144	10
DM	101	44	3
FLC	23	13	2
IMM	15	4	1
	547	*205*	*16*

16 pts (11 male, 5 female; median age 60 yrs, range 34 - 75 yrs) relapsed 24 - 96 mths after completing their primary therapy (median 45 mths), which comprised involved-field irradiation (RT) in 4 pts, doxorubicin-based chemotherapy (CT) in 10, combined modality in 1, and surgery only in 1. Eleven pts had stage I-II disease, 5 stage III-IV disease. Three had B symptoms. Five pts (31%) initially had extranodal presentation of lymphoma (as did 186 [34%] of all 547 pts at diagnosis). The outcome of these pts was surprisingly good. Five pts are free of disease at 21 - 69 mths after relapse -- 3 (all IA) had relapsed from 1° RT or surgery and were successfully salvaged with combination CT, and 2 required further doxorubicin-based CT. Two pts currently have indolent, slowly progressive disease behaving not unlike a low-grade lymphoma (both had intermediate grade lymphoma on rebiopsy), 40 and 99 mths from relapse. Four pts are receiving salvage chemotherapy, 36 - 68 mths after initial diagnosis. Five pts (3 male) died of progressive lymphoma 6 - 43 mths after first relapse. (Four pts died within 10 mths, the fifth had an indolent course).

Late relapse in the intermediate grade lymphomas is not common (16/205 = 7.8%), but prolonged survival in such patients may be seen, and durable CR is possible. Other pts display an indolent, relapsing disease course more in keeping with the clinical behaviour of the low-grade lymphomas.

P 125 Autologous bone marrow transplantation for Hodgkin's disease in first complete remission: results from the EBMT lymphoma registry.

S.J.Bradley1 , A.M.Carella2 , R.Pearce1 , G.Taghipour1 , A.H.Goldstone1.
1Department of Haematology, University College Hospital, London,
2Division of Haematology, Ospedale San Martino, Genoa.

There has recently been some interest in the use of autologous bone marrow transplantation (ABMT) in first complete remission as consolidation therapy for those patients perceived as having poor - risk Hodgkin's disease (HD). We have looked at the 42 patients on the EBMT registry in this group.

Median age at diagnosis was 28 years (range 16-50). 74% of patients were male. Most patients had advanced disease at diagnosis: 21% were stage III, and 76% stage IV. 86% had B symptoms. We looked for the presence of previously defined poor prognostic factors at presentation, namely bulky mediastinal disease (76%), lung or pleural involvement (57%), marrow involvement (17%) and disease at 2 or more extranodal sites (55%). Additional factors examined were haemoglobin, lymphocyte count and serum lactate dehydrogenase at presentation.

86% of patients received some form of alternating regime. 66% remitted on first line therapy. Median time from diagnosis to first CR was 5.5 months (range 2-19), and from first CR to ABMT was 4 months (range 1-13).

Progression free survival post ABMT was 79.1% with a median follow up of 27.8 months. There were 2 toxic deaths (5%). 5 patients (12%) have relapsed post ABMT - 3 are dead, 1 is in second CR post radiotherapy, and 1 is alive in relapse.

Since, by attaining CR, such patients already have a better outlook, it remains to be seen whether ABMT confers any additional benefit. Randomised controlled trials are now required, however due weight must be given to prognostic factors in case selection to reduce the likelihood of autografting patients who are already 'cured'.

P 126 THE ROLE OF HIGH DOSE CHEMOTHERAPY AND AUTOLOGOUS BONE MARROW TRANSPLANTATION (ABMT) IN PRIMARY REFRACTORY HODGKIN'S DISEASE .

R. Chopra, DC. Linch, AM. Carella, R. Pearce, D. Cunningham, D. Winfield, F. Mandelli, G. Meloni, AH. Goldstone on behalf of the European Bone Marrow Transplant Group (EBMTG).

Although the majority of patients with Hodgkin's Disease can be cured by radiotherapy or conventional dosage chemotherapy, some patients will fail to achieve a remission (Primary refractory) or will subsequently relapse. Primary refractory patients carry a particularly poor prognosis even when treated with further conventional dose salvage chemotherapy. In order to ascertain the role of high dose chemotherapy and ABMT we have analysed 162 primary refractory patients out of 867 patients reported to the EBMTG Lymphoma registry. There were 85 males and 77 females. The proportion of females with primary refractory disease compared to the rest of the group was significantly higher (77/162 vs 361/705; $\chi 2 = 6.3$; p=0.01). The patients had received the following chemotherapy regimens prior to ABMT : MOPP type therapy followed by second line chemo/radiotherapy (66 pts), MOPP/ABVD type therapy alone (46 pts), MOPP/ABVD type followed by second line chemo/radiotherapy (50 pts). The actuarial progression free survival was 29% at 5 years with a median follow up of 37 months. Multivariate analysis for PFS, shows that length from diagnosis to ABMT, patient sex and type of initial therapy prior to ABMT were significant for predicting for PFS (length from diagnosis to ABMT >12mths 34% vs <12 mths 21% p=0.015; males 35% vs females 23% p=0.02; initial MOPP type therapy 27% vs initial MOPP/ABVD type therapy 32% p=0.04). This study suggests that in patients with poor prognosis Hodgkin's disease, there is a preponderance of females with primary refractory disease who respond poorly to any therapy. A proportion of primary refractory patients will show long term response to high dose chemotherapy and ABMT. Refractory patients who receive initial alternating MOPP/ABVD type of therapy show a better subsequent response to high dose chemotherapy and ABMT.

P 127 Autologous Bone Marrow Transplantation Using Cyclophosphamide, Carboplatin, and Etoposide with Post-transplant α Interferon for Patients with Hodgkin's and Non-Hodgkin's Lymphoma

D. P. Schenkein, P. Dixon, J. L. Ascensao*, E. Berkman, J. Desforges, J. Erban, and K.B. Miller.
Division of Hematology/Oncology and the Bone Marrow Transplant Unit, New England Medical Center, Tufts University School of Medicine, Boston, MA, USA, and University of Nevada, Reno, NV, USA*.

Autologous transplantation is effective in achieving long term remissions in many patients with relapsed Hodgkin's disease (HD) and Non-Hodgkin's Lymphoma (NHL). Using standard preparative regimens such as CBV or Cy/TBI approximately 50% of these patients achieve a durable remission. In an attempt to improve on these results we tested a novel preparative regimen combined with post transplant treatment with the biological response modifier α Interferon. Thirty two (32) patients with HD (11 patients) and NHL (21 patients) received high dose chemotherapy with Cyclophosphamide 1800mg/m^2 days -6,-5,-4,-3 (total dose 7.2 gm/m^2), Carboplatin 400 mg/m^2 days -6,-5,-4,-3 (total dose 1600mg/m^2), and Etoposide 400 mg/m^2 days -5,-4,-3,-2(total dose 1600mg/m^2). On day 0 patients received either autologous unpurged bone marrow (18 patients) or peripheral blood stem cells (14 patients). Patients with a history of bone marrow involvement received peripheral blood stem cells. The majority of patients did not receive growth factors following marrow or stem cell infusion. The chemotherapy was well tolerated with mucositis as the major side effect (77% of patients Grade 4). No infection related deaths occurred. Transient renal dysfunction (creatinine >2) was noted in 26% patients with no cases of long term renal dysfunction. Prior treatment with cisplatin or carboplatin increased the risk of transient renal dysfunction during transplantation (57% vs 16%, p= .005). Mild elevations in liver function tests were noted in 12 % of patients with no cases of fatal VOD. Two cardiac deaths were observed. Immediate transplant related mortality was 6% with 59% overall survival and 50% disease free survival at 18 months median follow-up. Prompt engraftment occurred in all patients. The interferon was administered S.Q. T.I.W. @ 1 x 10^6 U/m^2 x 1 month, 2 x 10^6 U/m^2 x 1 month, 3 x 10^6 U/m^2 to six months. IFN was well tolerated with neutropenia as the major side effect.
This intensive regimen appears to be highly effective and well tolerated in patients with HD and NHL with acceptable transplant related complications. Interferon was safe and well tolerated in the post transplant setting. Further investigation of this treatment plan and comparison to other potentially more toxic preparative regimens is warranted.

P 128 ACCELERATED HYPERFRACTIONATED TOTAL LYMPHOID IRRADIATION, HIGH-DOSE CHEMOTHERAPY AND AUTOLOGOUS BONE MARROW TRANSPLANTATION FOR REFRACTORY AND RELAPSING PATIENTS WITH HODGKIN'S DISEASE.

J. Yahalom, S. Gulati, and Z. Fuks, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Forty-seven patients with Hodgkin's disease (HD) who either relapsed after chemotherapy (19 patients), or failed to respond (28 patients) to at least 2 regimens of combination chemotherapy were studied. No patient received prior radiation. Patients were prepared for bone marrow transplantation with a sequential radiation-chemotherapy protocol. Treatment started with reinduction with standard-dose chemotherapy and involved-field irradiation to areas of relapsed or persistent disease (1500 cGy).This was followed with total lymphoid irradiation (TLI) (2004 cGy given at 167 cGy t.i.d. fractions within 4 days). Subsequently the patients received etoposide (250 mg/m^2/day i.v. x 3 days) and high-dose cyclophosphamide (60 mg/kg/day i.v. x 2 days). Infusion of cryopreserved, unpurged autologous bone marrow was given 48 hours after completion of chemotherapy. All surviving patients had a minimum follow-up of one year. The median follow-up for survivors was 44+ months and the maximal follow-up was 84+ months.

Of the 47 treated patients, 8 (17%) died of toxicity at the peri-transplant period. Twenty nine of the remaining 39 evaluable patients (74%) attained a complete response (CR), while 10 remained with residual disease and showed evidence of early progression after AuBMT. Four of the CR patients (14%) relapsed at 11, 23, 32 and 39 months after autologous bone marrow transplantation (AuBMT) and 25 patients remained alive and free of disease. The actuarial disease-free survival (DFS) for the whole group at 7 years was 50%. Patients who received the protocol for relapsing HD had a significantly better DFS (79%) compared to patients treated for continuous refractory disease (DFS of 33%; P<0.03).

Previously unirradiated patients with failing HD who have exhausted conventional chemotherapy may still respond to an aggressive therapeutic approach consisting of accelerated hyperfractionated TLI, high-dose chemotherapy and AuBMT rescue. This program offers a potential for long-term DFS to approximately one half of the patients who would otherwise have a dismal prognosis with standard-dose salvage therapy.

P 129 AUTOLOGOUS BONE MARROW TRANSPLANTATION (ABMT) FOR LOW GRADE NON-HODGKIN'S LYMPHOMA (NHL): THE EUROPEAN BONE MARROW TRANSPLANT GROUP (EBMT) EXPERIENCE.

H.C. Schouten, Ph. Colombat, L.F. Verdonck, N.C. Gorin, B. Björkstrand, A.H. Goldstone on behalf of the EBMT working party for lymphoma. University Hospital Maastricht, the Netherlands.

The EBMT collects data on ABMT for malignant lymphoma. In this registry 92 patients (pts) [male (n=56), female (n=36), median age 39 years (19.9-59.2)] could be identified who had been treated with high-dose therapy followed by ABMT for low grade NHL. The status at BMT was complete remission (CR) (n=35), very good partial response (VGPR) (n=29), responsive relapse (RR)(n=17) and refractory disease or untreated relapse (RD/UR) (n=8). Eight pts had transformed NHL at BMT. In 51 pts marrow involvement was present at diagnosis and in 19 at BMT. The median duration from diagnosis to BMT was 24 months. Pretransplant conditioning included TBI in 37 pts. Marrows were purged in 27 pts. With a median follow-up of 19 months overall survival is 65%. Progression free survival is 52%. Three toxic deaths occurred. Duration between diagnosis and BMT was not of influence on outcome. There was an overall survival difference for status at BMT between CR (72%), VGPR (80%), RR (48%) and RD/UR pts (0%) ($p<.001$). Survival after chemotherapy only conditioning was comparable with chemotherapy/TBI pretransplant conditioning (65 vs 60%, $p=.4$). Survival for pts with purged BMTs was 75% compared to 58% for unpurged grafts ($p=.3$). Because of the natural behavior of this disease longer follow-up is necessary. However, we conclude that the data are very promising and warrant a randomized study comparing purged vs. unpurged BMT with chemotherapy. This study will be activated April, 1993.

P 130 HIGH-DOSE THERAPY (HDT) FOLLOWED BY AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION (AHSCT) FOR FOLLICULAR LOW GRADE AND TRANSFORMED LYMPHOMA.

A. Molina, A. Nademanee, G.M. Schmidt, M.R. O'Donnell, D.S. Snyder, P. Parker, A.S. Stein, E.P. Smith, D.E. Stepan, J. Taguchi, K.A. Margolin, G. Somlo, J. Raschko and S.J. Forman. Department of Hematology and Bone Marrow Transplantation, City of Hope National Medical Center, Duarte, California, U.S.A.

Patients (pts) with advanced stage low grade follicular lymphoma (FLGL) are generally not curable with standard chemotherapy or combined modality approaches. The curative potential of HDT followed by AHSCT in the treatment of FLGL and transformed lymphoma (TF-NHL) remains to be established. Between 1989 and 1992 we undertook a pilot study of HDT followed by AHSCT in 35 pts with FLGL and TF-NHL. Eligibility required: 1) physiologic age 60 yrs or less; 2) KPS > 70%; 3) advanced stage disease in 1st CR or PR with minimal residual disease (MRD) and 2nd or subsequent CR or PR with MRD. Median age was 43 (range 32-57). Histologic subtype: follicular small cleaved - 18 pts; follicular mixed 8 pts; transformed lymphoma - 9 pts. Disease status at the time of AHSCT: 1st CR/PR - 10 pts; 2nd CR/PR - 12 pts; 3rd CR/PR - 7 pts; 4th or subsequent CR/PR - 6 pts. The median time from diagnosis to time of AHSCT was 35 mos (6.5-146). Conditioning regimen prior to transplant: etoposide 60 mg/kg, cyclophosphamide 100 mg/kg and either fractionated total body irradiation (24 pts) or BCNU 450 mg/m^2 in 11 pts who received radiation (XRT) as part of their initial therapy. Three pts received involved field XRT as part of their conditioning regimen and 1 pt in 1st PR/MRD received XRT after AHSCT to site of initial bulky disease. Source of hematopoietic stem cells: peripheral blood stem cells (PBSC) - 6 pts; G-CSF primed PBSC (GCSF-PBSC) - 23 pts; bone marrow (BM) - 1 pt; BM and PBSC - 2 pts; BM and GCSF-PBSC - 1 pt; monoclonal antibody purged BM - 2 pts. 27 pts received post-transplant G-CSF. Graft failure (2 pts) and poor graft function (1 pt) were seen in pts who received PBSC alone but two of these pts achieved sustained engraftment with the use of GM-CSF; the other pt remains dependent on platelet transfusions. There were no toxic deaths. 27 pts are alive and 23 are in remission (1-46 mos after AHSCT). All deaths were from relapsed disease. The 10 pts transplanted in 1st CR/PR are alive and 8 remain in remission. Among the 16 pts in 2nd and subsequent CR/PR, 12 are alive and free of tumor progression; 4 have died from relapsed disease. Among the 9 pts with TF-NHL, 3 are alive in remission; 6 have relapsed and 4 of these have died from uncontrolled disease, suggesting a need for the early use of AHSCT prior to histologic transformation. The use of GCSF-PBSC with post-transplant G-CSF reduced the time to hematopoietic recovery and reduced the incidence of graft failure (Nademanee et al. Proc Am Soc Clin Oncol 317, 1992). This approach may be an alternative to the use of purged BM. Because of the long natural history of this disease longer follow-up is necessary to determine if HDT followed by AHSCT prolongs survival.

P 131 AUTOLOGOUS BONE MARROW TRANSPLANTATION (ABMT) AS CONSOLIDATION THERAPY MAY PROLONG REMISSIONS IN NEWLY DIAGNOSED HIGH-RISK FOLLICULAR LYMPHOMA: A PILOT STUDY OF 34 CASES.

Morel P, Laporte JP, Fouillard L, Noel MP, Lesage S, Detourmignies L, Jouet JP, Najman A, Bauters F, Gorin NC. Service des Maladies du Sang, CHRU Lille, Hôpital Saint Antoine, Paris, and CH Lens. France

Immunologic purging removed detectable lymphoma cells from bone marrow rescue in some FL patients (pts). Those pts who received autologous marrow containing detectable lymphoma cells had an increased incidence of relapse after ABMT. We present the results of a pilot study of early ABMT with mafosfamide-purged marrow rescue as consolidation therapy for high-risk-FL pts achieving minimal disease (MD). Criteria for MD were either complete remission (CR) or good partial remission (GPR) >75% with stable residual mass. Conditioning regimen was BEAM (BCNU 300 mg/m2 on day 1, cytosine arabinoside and etoposide each 100 mg/m2 q 12 h from d 2 to 5 and high dose melphalan 140 mg/m2 on d 6 followed by reinfusion of purged marrow rescue). Localized radiotherapy followed ABMT in pts with GPR. From November 1986 to April 1992, 34 untreated FL pts (median age 38 years, range 25 to 52, sex ratio M/F=1,26) fulfilled at least 1 of the following high-risk criteria: involvement of 3 or more lymph node sites, each with a diameter >3cm (30 pts), tumor size>7cm (26 pts), effusion or involvement with a risk of local complication (10 pts), massive spleen enlargement (8 pts), B symptoms (7 pts), plt<100x109/L (1 pt). Histology was B in 30 pts, C in 2 pts, mantle zone in 2 pts. Ann Arbor stage was: II in 2 pts, III in 7 pts, IV in 25 pts. 21 pts had bone marrow involvement, 14 presented with 2 or more extranodal sites of disease. Increased β2 microglobulin and LDH levels were found respectively in 48% of 23 pts and 36% of 28 pts. The 8 first patients received as induction regimen 6 weekly courses of CVP (cyclophosphamide 600 mg/m2 d 1, vincristine 2 mg d1, prednisone 40 mg/m2 d1-7). The remaining 26 patients received 3 to 4 courses of ACVB: doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone (LNH-84, JCO, 1989, 7, 1018). Responding pts received a maintenance with COP (cyclophosphamide, vincristine, prednisone) before ABMT. Twenty-one of the 34 pts (62%) achieved a MD (including 5 GPR). The 2 last pts did not underwent ABMT yet. One of the 21 pt relapsed and received ABMT in partial response. Seventeen pts with MD received ABMT 2 to 12 months after CR (median 4 months). One pt received a syngeneic BMT. 4 pts relapsed at 4 (histological transformation: HT), 21, 29 and 51 months after ABMT. Two of the grafted pts died (1 toxic death, 1 pt with HT). Actuarial DFI, was estimated 71% at 48 months. Thirteen of the 34 pts failed to achieve a MD. 3 pts with partial response were grafted without salvage therapy, they are alive in CR. 3 other pts were grafted after salvage therapy, 2 toxic deaths occurred. Estimated time to treatment failure (TTF) and overall survival were 43% and 80% at 48 months with a median follow-up of 36 months. Comparisons were made with an historical series of 14 pts (median age 44, range 22-59) with the same high-risk criteria, who received the LNH-84 regimen. 9 pts achieved a MD, 6 relapsed 5 to 42 months after CR, including 3 HT. 3 pts remained in CR, 2 of them after 8 years. 6 pts died. Actuarial DFI, TTF and survival at 36 months were 40%, 26%, 75% respectively. The comparison was restricted to ACVB pts of our pilot study. Initial characteristics did not differ significantly between the 2 groups. Difference was significant for DFI ($p=0.04$), but not for TTF and survival ($p=0.09$). Although this is a historical comparison and follow-up of our pilot study is still limited, our results suggest that ABMT with mafosfamide purged marrow rescue may prolong response in some pts with high-risk FL. Further studies are needed to assess the effectiveness of our marrow purging procedure for removal of detectable lymphoma cells.

P 132 ALLOGENEIC BONE MARROW TRANSPLANTATION IN CHRONIC LYMPHOCYTIC LEUKEMIA: 55 CASES. Report of European Bone Marrow Transplantation and International Bone Marrow Transplantation Registry.

M. Michallet.Sce d'Hématologie Hôpital Edouard Herriot 69003 Lyon France

The study of allogeneic Bone Marrow Transplantation (BMT) in Chronic Lymphocytic Leukemia (CLL) concerned 55 patients, 41 males and 14 females, who were reported to the European Bone Marrow Transplantation and to the International Bone Marrow Registries. The median age was 42 years. There were 49 BMT from an HLA identical sibling donor, 3 from a mismatch HLA related donor and 3 from identical twin. The immunological type was reported only for 49 patients = 47 BCLL and 2 TCLL. Among evaluable 50 patients for conventionnal therapy only three patients did not receive any treatment before BMT , 31 patients were splectomized. The median time from diagnosis to BMT was 40 months. At the start of conditionning 54 patients were evaluated : 4 stage 0, 9 stage I, 8 stage II, 8 stage III and 25 stage IV. The conditionning regimen was TBI CYCLOPHOSPHAMIDE (CY) in 32 patients, TBI CY and VEPESIDE in 11 patients, TBI, CY and other drugs in 10 patients. 2 patients received only chemotherapy (BUSULFAN and CY). For GVHD prevention 3 patients (syngeneic BMT) did not receive any prevention and the others received variable treatment : the majority METHOTREXATE and CICLOSPORINE.
6 patients died during the first month post BMT (5 before engraftment) and 2 patients had a graft failure.Of 49 patients who could be evaluated 42 were in CR after BMT. 47 patients who could be evaluated for acute GVHD. It was absent in 9 patients and present in 36 patients. Of 27 evaluable patients for cGVHD : 16 presented a cGVHD (11 limitted and 5 extensive). At the time of the most recent follow up (80 months) 31 patients died and 24 patients (23 in CR, 1 in relapse) were alive. The most common cause of death was GVHD (acute and chronic). The acturial rate of long term survival was 46 % at 60 months and 38 % at 80 months. There were no difference according to age, Raiclassification at diagnosis, splenectomy and conditionning regimen. Although there was a high statiscally significant difference between conventional therapy responders and non reponders before BMT ($p = 0.001$).In addition patients who had grade I acute GVHD do significantly better than patients with grade II, III and IV and there was a trend toward improved survival among patients who received METHOTREXATE and CICLOSPORINE. There was also a high statiscally significant difference in survival between patients with limitted cGVHD and patients with an extensive cGVHD ($p < 0.0001$).The acturial rate of DFS was 44 % at 80 months and 6 patients were still in CR 50 to 80 months after BMT. 6 patients relapsed, 5 died and 1 was alive, among them, one was a syngeneic BMT and 3 patients received a Tdepleted marrow.

P 133 IDENTIFICATION OF PATIENTS WITH LARGE-CELL LYMPHOMA IN REMISSION CANDIDATES TO "CONSOLIDATION" STRATEGIES

E. Montserrat, A. López-Guillermo, J.C. Reverter, F. Cervantes, L. Escoda, D. Tassies, J. Bladé, P. Marín, J. Sierra, E. Campo, F. Bosch, M.J. Terol, C. Rozman. Postgraduate School of Hematology "Farreras-Valentí". Hospital Clínic, University of Barcelona, Spain.

To improve the outcome of patients with poor-risk lymphoma, different approaches are being investigated. One strategy is to give some form of "consolidation" treatment (e.g., high-dose chemoradiotherapy followed by ABMT) to patients in remission but likely to relapse. Because of this, to identify patients prone to relapse after conventional treatment is important.

In 133 patients (median age, 53 yrs; range, 17-82) with large-cell lymphoma treated at a single institution with doxorubicin containing regimens, prognostic factors for survival were analyzed by multivariate analysis. Four different groups were considered: (1) all patients at diagnosis; (2) patients in stages II-IV at diagnosis; (3) patients achieving CR; (4) patients in CR and ≤ 60 yr-old. Results are summarized in the table.

Parameter	All (n=133)	II-IV (n=111)	CR (n=91)	CR ≤60 (n=54)
Ann Arbor stage	<.001	NS	NS	NS
Immunoblastic type	.021	.021	NS	NS
PS	.018	.001	NS	NS
Bulky-disease	.004	NS	NS	NS
Bone marrow (+)	NS	.009	NS	NS
LDH	NS	<.001	.008	.016

In this analysis only LDH retained its prognostic value in CR patients. Most prognostic studies in lymphoma do not take into consideration that predictive factors may change once a remission is achieved. This study emphasizes the need for a careful selection of patients to be included in experimental treatments, particularly when a CR has already been achieved.

P 134 AUTOLOGOUS BONE MARROW TRANSPLANTATION (ABMT) FOR ADULT DISSEMINATED HISTOLOGICALLY AGRESSIVE NON HODGKIN'S LYMPHOMAS (NHL) IN FIRST PARTIAL RESPONSE (PR).

N. Milpied, P. Moreau, T. Lamy, B. Desablens, V. Delwail, C. Gandhour, J.M. Tourani, M. Gardembas, P. Colombat, P. Cassasus, J.L. Harousseau, (For The POF Group). Department of Hematology - C.H.R.U. 44035 NANTES - FRANCE

Response to initial chemotherapy is a major prognostic factor in NHL. High dose therapy plus ABMT in sensitive relapse can yield a high long term disease free survival for patients with disseminated high grade NHL. Thus in Ann Arbor stage III/IV histologically agressive NHL (Type F-G-H in the working formulation) we initiated a protocol in which the type of consolidation therapy depends on the response achieved after the first 2 courses : CTX 1.2 G/m² D2, VDS 3 mg/m² D1 and D5, 4 epi ADR 100 mg/m² D1 to D5 and Methyl PDN 80 mg/m² D1 to D5. Patients in complete response (CR) or very good partial response (VGPR) (> 80 % reduction of measurable lesions) received a consolidation with 2 courses of VP16 100 mg/m² D1 to D5 and Cisplatinum 20 mg/m² D1 to D5 followed with 2 courses of MTX 3 g/m² D1 plus Cytarabine 100 mg/m² D1 to D5. Patients in PR (< 80 % reduction of measurable lesions) had an unpurged ABMT. Conditioning regimen was TBI plus CBV (CTX 1.5 g/m² D-9 to D-6, BCNU 300 mg/m² D-9 and VP16 200 mg/m² D-8 to D-6). Since 09/88 22 Pts underwent an ABMT in 1st PR. Their median age was 38 y.o. (19 to 57 y.o.). One hundred and seven pts achieved a CR or VGPR after 2 induction courses. There was no difference between these two groups of pts regarding disease bulk performance status and number of extranodal sites of di-sease. The actuarial 3 years probability of survival and event free survival for patients who underwent ABMT is 82 % (+/- 5% SE) and, actuarial probability of relapse is 15 % (+/- 10% SE). One patient died on D12 with infection. The actuarial 3 years probability of survival and even free survival for patients who received chemotherapy only 74% (+/- 5% SE) and 55% (+/- 6% SE) respectively the actuarial probability of relapse is 40% (+/- 5% SE). ABMT can salvage pts with poor initial response to chemotherapy and the results achieved are at least comparable to those achieved with chemotherapy for patients in CR.

P 135 AUTOLOGOUS BONE MARROW TRANSPLANTATION IN SLOW RESPONDING, CHOP INTERVENED BY HIGH OR LOW DOSE MTX TREATED, PATIENTS WITH NHL UNFAVOURABLE HISTOLOGY.

Free University Hospital, Department of Haematology, Amsterdam, The Netherlands. G.J.Ossenkoppele, P.C.Huijgens, A.R.Jonkhoff, K.v.d.Hem and M.M.A.C.Langenhuijsen.

Intensive chemotherapy is curative for patients with NHL of unfavourable histology. The addition of intervening cycles of non myelosuppressive agents to antilymphoma chemotherapy programs may improve prognosis. We compared high dose MTX (1 g/m²) with low dose MTX (400mg/m²) allowing outpatient adminstration. Chemotherapy was delivered every 10 days starting with CHOP intervened either by high dose MTX (group A) in the first 26 pts. or low dose MTX (group B) in the following 45 pts. Four of these cycles were administered followed by response evaluation. Patients in CR received another 2 cycles.If no CR was reached patients were considered to be slow responders and subsequently entered in a bone marrow transplant program consisting of two courses IMVP followed bij AuBMT with BEAM as conditioning regimen.

RESULTS

CLINICAL CHARACTERISTICS		GROUP A MTX(1 g/m²)	GROUP B MTX(400mg/m²)	p-value
AGE	< 40	11	12	0.16
	40-60	6	17	
	> 60	9	17	
STAGE	II	5	18	0.10
	III-IV	21	28	
EXTRANODAL LOCALISATION	YES	21	31	0.11
	NO	5	15	
BULKY DISEASE	YES	9	15	0.82
	NO	17	31	
LDH > 1.5xN	YES	7	22	0.46
	NO	19	24	

RESPONSE

	Group A	Group B
Evaluable patients	26	45
Follow up (months)	55-82	11-49
CR after 4 cycles	20(77%)	29(64%)
Relapse	4(20%)	6(20%)
AuBMT in PR	3	8
Disease free after AuBMT	2	9
Overall Survival	19(73%)	33(73%)

The two patient groups are comparable with regard to prognostic factors except for LDH level. The toxicity of both regimens was low,no drug dose reduction was necessary. Although the CR rate was different between the two groups significance was not reached. This treatment program consisting of CHOP-MTX, response evaluation after 4 cycles selecting partial responders for an AuBMT program (IMVP +BEAM) is an very effective approach. Taken together the two patient groups 52 of 71 patients(73%) are in a longstanding continuous complete remission(median follow up 45 months).

P 136 AUTOLOGOUS BONE MARROW TRANSPLANTATION FOR NON-HODGKIN'S LYMPHOMA. REPORT OF 104 PATIENTS FROM THE SPANISH COOPERATIVE GROUP GEL/TAMO.

E. Conde, J. Sierra, A. Iriondo, I. Romón, A. Domingo-Albós, J. García-Laraña, J. Marín, D. Caballero, F. Martinez, A. León, J. García-Conde, F. Hernandez, D. Carrera, R. Mataix, J. Zuazu, B. Cuesta, J. Díaz Mediavilla, JJ. Lahuerta, C. Richard, J. Baro, E. Montserrat. Servicio de Hematología. Hospital "M. Valdecilla". Facultad de Medicina. 39008 Santander. Spain.

One hundred and four patients with non-Hodgkin´s lymphoma received high dose chemotherapy or chemoradiotherapy followed by infusion of autologous bone marrow. Patients were classified according to the Working Formulation as low-grade (9 patients), intermediate grade (31 patients) and high-grade (64 patients). Disease status at transplant was: first complete remission (CR) in 46 patients, second CR in 14 patients, third CR in 7 patients, chemosensitive disease in 16 patients and chemoresistant disease in 21 patients.

Estimated 5-year disease-free survival (DFS) for all 104 patients was 49% (95% CI, 36-63%) with a median follow-up of 24 months. Five-year relapse-free survival (RFS) for 80 evaluables patients was 74% (95% CI, 56-86%). The 8-year DFS and RFS for the 46 patients transplanted in first CR were 75% (95% CI, 63-82%) and 85% (95% CI, 67-93%) respectively, with a median follow-up of 27 months (range, 13 to 104) and a median time to relapse of 5 months (range, 4 to 20).

In the univariate analysis, variables correlated with DFS were disease status at ABMT (p<0.0001), performance status at ABMT (p<0.0001), LDH level at ABMT (p=0.0005), failure to achieve CR at diagnosis (p=0.0015) and front-line chemotherapy (1 vs 2 or more regimens) (p=0.0088). After multivariate analysis, performance status was the only variable retained as an independent predictor of DFS. Variables correlated with RFS were: disease status at ABMT (p=0.0419), preparative regimen (p=0.0445) and Coiffier's index at diagnosis (p=0.0463). Multivariate analysis showed that disease status at ABMT was the best relapse predictory variable. In patients transplanted in first CR, variables correlated with DFS were stage at diagnosis (p=0.0328) and performance status at ABMT (p=0.0483). LDH level at diagnosis was the only variable correlated with relapse in patients transplated in first CR (p=0.0426).

The overall mortality was 45% (47/104). Twenty-eight patients (27%) died because of lymphoma and the remaining 19 (18%) as a result of toxicity. Among patients in the first CR, 5 (10.8%) died in relapse and the other 5 because of toxicity. This series confirms that the outcome of ABMT is better when performed early in the course of the disease. It is also noteworthy that well-known prognostic parameters at diagnosis wich identify patients not probably to be cured with conventional chemotherapy (namely, stage and LDH level) are also associated with a poor outcome after transplant in patients in first CR.

P 137 AUTOLOGOUS BONE MARROW TRANSPLANTATION (ABMT) FOR ADULT ADVANCED STAGE LYMPHOBLASTIC LYMPHOMA (LBL) IN FIRST CR. AN UPDATE OF THE NON-HODGKIN LYMPHOMA COOPERATIVE STUDY GROUP.

G. Santini*, P. Coser, V. Rizzoli, T. Chisesi, M. Vespignani, A. Contu, A. Porcellini, M.R. Sertoli, O. Vinante, A.M. Congiu, D. Pierluigi and E. Damasio.*Department of Hematology I, Ospedale S.Martino, 16100 Genova, Italy.

Sequential multi-agent chemotherapy has improved prognosis of advanced-stage adult LBL patients (pts.) However the 3-years probability of survival and DFS in stage III-IV patients (pts), is 10 to 20% in spite of attaining CR because of the high number of relapses. In order to increase long-term survival and DFS a trial of ABMT-supported megatherapy consolidation was started in 1984. 45 pts were treated with a short LSA2-L2 type induction-consolidation regimen lasting 64 days. 30 pts entered CR (70%) and 26 (median age 25 yrs, 2 in stage III and 24 in stage IV, 11 with a BM involvement at diagnosis) received Cytoxan (60 mgs/Kg for 2 days) plus TBI (10 Gy in single dose) followed by ABMT. Three pts refused and 1 received allogenic BMT. At this time 16 out of 26 pts, (62%) are alive and well 2-88 mos. post-ABMT procedure (median follow-up 71 mos.) with an actuarial 7-yrs. probability of survival and DFS of 62% and 60% respectively. While these results look extremely encouraging, if we analyze the overall population of 45 pts it turns out that only 30% of the pts. with initial bone marrow involvement are now in CR and this in spite of the fact that 60% of these pts. reach CR. This means that 50% of the BM pts. in CR relapse. On the contrary 71% of the pts in stage IV plus LDH > 150% of normal value, and 50% of the pts. in other condition (stage III, stage IV with LDH level < 150%) are in CR. Therefore, a large randomized study is requested to draw a definitive conclusion on the superiority of this approch over conventional chemotherapy, and to define the role of added negative prognostic factors at diagnosis.

P 138 G-CSF ACCELERATES GRANULOCYTIC RECOVERY FASTER THAN GM-CSF IN NON-HODGKIN'S LYMPHOMA PATIENTS SUBMITTED TO AUTOLOGOUS BONE MARROW TRANSPLANTATION (ABMT).

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

We analyzed the hematologic recovery of 31 consecutive, non-randomized, patients (pts) undergoing ABMT for resistant/relapsed NHL. All the pts were conditioned with the same regimen (BAVC - BCNU 200 mg/sm on day -4, ARA-C 150 mg/sm every 12 h on days -5 to -2, VP-16 150 mg/sm every 12 h on days -5 to -2, Cyclo 45 mg/kg on days -5 to -2). Ten pts received no GFs after marrow reinfusion; 10 pts received GM-CSF (10 mg/kg) and 11 received G-CSF (5 mg/kg). GFs were administered from day +1 until the achievement of > 0.5 x 10^9/l neutrophils for 3 consecutive days.

Results G-CSF-treated pts showed the median fastest neutrophil recovery: absolute neutrophil count (ANC) of 0.2 x 10^9/l on day 11.3 vs 13.7 for GM-CSF pts vs 13.4 for no GFs pts; ANC of 0.5 x 10^9/l on day 13.1 vs 16 vs 19.6, respectively ($p < 0.05$). G-CSF-pts had a median of 3.1 days with > 38° fever (GM-CSF-pts 6.7, no GFs-pts 6.4) ($p < 0.05$); they received parenteral antibiotics for 7.9 days (GM-CSF-pts 14, no GFs pts 15.9) ($p < 0.05$), and were discharged by a median of 18.3 days following marrow reinfusion (GM-CSF-pts 21.6, no GFs-pts 31.3) ($p < 0.05$). Platelet recovery was not accelerated by GFs. No side effects correlated with G-CSF administration were recorded.

Conclusions These data suggest that G-CSF is more effective than GM-CSF in enhancing granulocytic recovery after ABMT for NHL. Moreover, G-CSF is devoid of any side effect.

P 139 FROZEN VS. NON-FROZEN BONE MARROW FOR AUTOLOGOUS TRANSPLANTATION IN LYMPHOMAS: A COMPARATIVE STUDY FROM THE SPANISH GEL/TAMO COOPERATIVE GROUP.

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

To investigate the impact of frozen and non-frozen marrow on engraftment kinetics and disease outcome, the Spanish (GEL/TAMO) Group for Bone Marrow Transplantation in Lymphomas compared 94 patients with non-Hodgkin's lymphoma (NHL) autografted with frozen marrow (F group) versus 38 who received marrow stored at 4°C or 10°C (NF group). The major end-points of this study were: 1) time to hematopoietic recovery, 2) disease response, 3) toxic deaths, 4) survival, 5) disease-free survival (DFS), and 6) relapse rate. Both groups were comparable in terms of main initial and pretransplant characteristics. Conditioning regimens included cyclophosphamide and total body irradiation in half of the patients in the F group and in 79% of the NF group cases. In the later group marrow was reinfused between 24 and 72 hours after harvesting.

Upon comparison of the NF and F groups, no significant differences were found in either the period of time required to achieve a granulocyte count higher than 0.5x10^9/L (20 and 22 days, respectively, p= 0.47) or a platelet count higher than 20x10^9/L (28 and 27 days, respectively, p= 0.54). Moreover, both groups behaved similarly in respect to response rate (complete remission 78% in both groups), toxic deaths (NF group 13%, F group 22%, p= 0.36), and long-term survival (NF group 48%, F group 56%, p= 0.91), DFS (NF group 48%, F group 49%, p= 0.66) and relapse rate (NF group 30%, F group 19%, p= 0.37).

This study shows that the lack of bone marrow freezing facilities should not be regarded as a limiting factor for autologous bone marrow transplantation (ABMT) in NHL. In addition, ABMT with non-frozen bone marrow may contribute to reduce the burden of cryopreservation laboratories and to avoid treatment delays.

P 140 Peripheral Blood Stem Cells (PBSC) for Autotransplantation in Non-Hodgkin's Lymphoma (NHL) can be Efficiently Collected following Cytokine-supported Chemotherapy.

R. Ehrhardt, H. Goldschmidt, R. Haas.
Dept. of Internal Medicine V, University of Heidelberg, Germany

Patients with relapsed high-grade NHL can be rarely cured by conventional chemotherapy. With hematopoietic growth factors a higher dose intensity can be administered, however, whether this results in an improved anti-tumor efficacy remains questionable. Substantial dose escalation is possible by using bone marrow or blood-derived hematopoietic progenitor cells which are capable of circumventing the deleterious effects of high-dose radiochemotherapy. In a group of 16 pts. with high-risk NHL (10 relapsed high-grade NHL / 6 advanced-stage low-grade NHL), we administered IL-3/GM-CSF (Sandoz AG) sequentially or G-CSF (Amgen) after high-dose ara-C/mitoxantrone to enhance the rebound of hematopoietic progenitor cells during marrow recovery. Responding patients were then eligible for high-dose conditioning therapy with PBSC support. Both cytokine regimens proofed to be equally efficient in mobilizing hematopoietic progenitor cells post-chemotherapy. However, dependent on the amount of previous chemotherapy, the quantitiy of CD34+ cells varied interindividually with an up to 48-fold difference. Analyzing the CD34+ subpopulations, the distribution and percentage of coexpression was not different whether IL-3/GM-CSF or G-CSF were administered. Even the percentage of CD34+/HLA-DR- or CD34+/CD38- cells, which represent noncommitted hematopoietic stem cells was equally low in both groups, ranging from 0% to 6.3%. In contrast, a significantly higher number of activated T cells was found in the IL-3/GM-CSF-exposed autografts (19.1% ± 3.3% compared with 8.4% ± 2.4% in the G-CSF autografts). In the context of B-lymphoid malignancies another relevant feature was the extremly low content of CD19+ B cells with less than 0.2% of the total nucleated cells, on average. This finding was independent of the growth factor regimen used.

Following high-dose pretransplant conditioning therapy (TBI/cylophosphamide or BEAM), 11 pts.were autografted using the cytokine-exposed blood stem cells. No additional bone marrow support or hematopoietic growth factor was given post-transplantation. Rapid neutrophil (median of 12.5 days to > 0.5 x 10^9/l) and platelet recovery (median of 12.5 days to 20.0 x 10^9/l) was observed with the exception of one patient who suffered from early relapse. The kinetics of hematological recovery were closely related to the number of CD34+ cells infused and no major transplantation-related toxicity was observed. The chemotherapy-induced mobilization pattern of hematopoietic progenitor cells appears to be less dependent on the cytokine regimen used than on the individual hematopoietic reserve which is related to disease status and previous chemotherapy.

P 141 PREDICTION OF MAXIMAL PERIPHERAL BLOOD PROGENITOR RELEASE FOLLOWING CHEMOTHERAPY ALONE OR WITH rG-CSF.

R. Pettengell[1], D. Crowther[1], T.M. Dexter[2] and N.G. Testa[2]. Departments of [1]Medical Oncology and [2]Experimental Haematology, Paterson Institute for Cancer Research, Christie Hospital NHS Trust, Manchester, UK.

Efficient peripheral blood (PB) progenitor cell collection requires a practical method of predicting the time of maximal release in individual patients. We compared the release of haemopoietic progenitors in the PB in high grade Non Hodgkin Lymphoma patients following chemotherapy alone (doxorubicin 35mg/m^2, cyclophosphamide 350mg/m^2, AC), (doxorubicin 35mg/m^2, etoposide 100mg/m^2 p.o. x five days, AE) in 13 patients or with G-CSF (37 patients). Chemotherapy alone increased median progenitor numbers 7 fold (AC) and 40 fold (AE) over baseline. Chemotherapy with G-CSF increased progenitor numbers 56 fold (AC) and 100-120 fold (AE) over baseline.

Despite variability between patients, both the magnitude and timing of progenitor release are reproducible following an identical stimulus in individual patients unless infection supervenes, where progenitor cell release was delayed until resolution of the infection. In all patients the rise in circulating WBC following myelosuppressive chemotherapy with or without G-CSF parallels the release of progenitor cells but lags 24 hours behind it. In patients receiving VAPEC-B and G-CSF the nadir for progenitor cells following AE fell on median day 7 (range 6-9) and the WBC nadir on median day 9 (range 4-11). The progenitor peak occurs on median day 11 (range 9-15) and the WBC peak on median day 15 (range 7-18). The WBC declined precipitately after discontinuation of G-CSF so that the last day of G-CSF administration was always the day of peak WBC. In 19 of the 30 G-CSF treated patients, the colony peak was achieved before the WBC peak, implying that circulating colony numbers were stable or decreasing despite G-CSF treatment and a rising WBC. No patients achieved a WBC peak before the colony peak. In all patients peak progenitor release coincided with the exponential rise in the WBC following the chemotherapy induced nadir. In patients receiving chemotherapy and G-CSF this occurred when the WBC was 5-10x10^9/l.

In any individual the WBC was as useful for predicting the day of peak progenitor release as were the CFU-GM numbers. An exponentially rising WBC predicts haemopoietic progenitor release following a chemotherapy induced nadir, enabling optimal harvesting and a reduction in the number of apheresis procedures.

P 142 INTENSIVE CHEMOTHERAPY WITH PERIPHERAL BLOOD STEM CELL (PBSC) TRANSPLANTATION IN HEAVILY PRETREATED NON-HODGKIN LYMPHOMA PATIENTS. PRELIMINARY RESULTS IN 27 PATIENTS.

Y. Bastion, A. Sonnet, C. Dumontet, D. Espinouse, L. Campos, G. Salles, B. Coiffier. Service d'hématologie, Centre Hospitalier Lyon-Sud, 69310 Pierre-Bénite, France

Since June 1990, 27 patients (pts) with advanced NHL were included in a phase II trial of intensive chemotherapy plus total body irradiation (TBI) followed by PBSC transplantation. 20 pts had persistent bone marrow (BM) involvement at the time of procedure. The histological type was follicular low-grade in 17 pts (7 with histologic progression); diffuse large cell in 8 pts; and chronic lymphocytic leukemia in 2 pts. Median age was 48 y (23-58). At time of PBSC collection, 7 pts were in first CR or PR (respectively 2 and 5 pts), 15 pts in 2nd progression, and 5 pts in subsequent relapse. The number of previous chemotherapy regimens was 1 in 3 pts, 2 in 8 pts, 3 in 11 pts, >=4 in 5 pts. Only 3 pts were in CR at time of intensification. Median time from diagnosis to PBSC collection was 26 months (6-168). PBSC were harvested after MIV chemotherapy (mitoxantrone, 10 mg/m^2 day 1, ifosfamide 1.5 g/m^2/d day 1-3, etoposide 150 mg/m^2/d day 1-3) in 5 pts or cyclophosphamide 3 to 6 g/m^2 in 22 pts, both followed by 5 μg/kg/day GM-CSF (Schering-Plough/Sandoz). A mean of 3.4 cytaphereses (2-6) was performed. The median numbers of cells collected for each pt was 2.69 x 10^8/kg MNC (.85-6.16), 4.9 x 10^4/kg CFU-GM (.4-40.1), 31.7 x 10^6/kg CD34+ cells (.89-413), and 6.86 x 10^6/kg CD34+CD33- cells (.02-350). Intensification was done after a median time of 51 days (33-140) with BEAM in 10 pts or cyclophosphamide (60 mg/m^2/d x 2 days) plus etoposide (300 mg/m^2/day x 3 days) and TBI in 17 pts. Median time to reach granulocyte $\geq$500/mm^3 and platelet $\geq$20,000/mm^3 was 14.5 (7-53) days and 22 (10-548+) days respectively. Response was evaluated at 3 months in 21 pts (BM evaluation has not yet been performed in 6 pts): 14 pts (67%) were in CR, 2 pts had rapid progression within 3 months, 5 pts had early death (2 sepsis during 1st month, 3 delayed hematopoietic recovery). With a 18 months median follow-up (1-30 m), 19 pts are alive and 17 are free from progression. We conclude that treatment intensification with PBSC as support is feasible therapy in heavily pretreated pts and in pts with persistent BM involvement. Despite the short follow-up, specially for follicular lymphoma pts, these results are encouraging in these poor prognosis pts.

P 143 OUTCOME OF PATIENTS WHO PROGRESS AFTER AUTOLOGOUS BONE MARROW TRANSPLANTATION (ABMT) FOR NON HODGKIN LYMPHOMA (NHL)

R. Bouabdallah, P. Brice*, J.P. Marolleau*, D. Blaise, H. Dombret*, C. Gisselbrecht*, J.A. Gastaut, D. Maraninchi. Institut J. Paoli - I. Calmettes, Marseille, France* Hopital Saint-Louis, Paris, France

Between march 1983 and december 1992, 205 patients received high dose therapy and ABMT for advanced aggressive NHL in our 2 institutions.

Objectives : to asses the outcome of the patients who failed after this procedure.

Patients and Methods : initial pathological diagnosis was high grade (lymphoblastic and Burkitt, n = 60 pts) or intermediate grade (n = 145 pts). The mean age was at 36 years and extranodal disease was present in 54 % of all cases. Before high dose therapy, 97 pts were in first complete remission (CR1), 45 pts in second CR (CR2) and 63 in refractory disease (RD). The conditioning regimen included TBI in 51 pts.

Results : the median follow up is 33 months ; 115/205 (56 %) are alive and well in continuous CR ; 74/205 (36 %) relapsed or failed to achieve a response after ABMT at a median time of 7 months (range 1 to 74 months) : 29 pts were considered as primary failure without CR, and 45 pts were relapsing after at least 3 months of CR following ABMT.

For these 74 failures of therapy, the ABMT was performed from 3 to 75 months after diagnosis (median 9 months). Histological characteristics showed : High grade NHL : 20 pts, intermediate grade : 54 pts ; Status : CR1 : 17 pts ; CR2 :12 pts ; RD : 45 pts. 58 pts died from NHL, 1 to 34 months after ABMT (median 6 months) and 16 patients are remaining alive 9 to 84 months post ABMT (median 34 months). All the surving patients were treated again with chemotherapy and/or radiotherapy and/or immunotherapy. Two patients received a second BMT (allogenic : 1 pt ; autologous : 1 pt). The overall survival curves will be presented.

Conclusion : in this serie of 205 pts, 74 progressed after high dose therapy in which 58 died from progressive disease. 16 pts are remaining alive in CR or PR. Relapse after ABMT in agressive NHL has a poor prognosis, but some of progressive patients efficiently respond to new treatment.

P 144 Dose escalation of etoposide in the Dexa-BEAM regimen using GM-CSF support: Results of a randomized placebo-controlled double-blind multicenter trial of the German Hodgkin's Lymphoma Study Group for refractory HD.

B. Lathan, M. Pfreundschuh, U. Rueffer, D. Hasenclever, M. Loeffler, P. Koch, G. Ehninger, H. Kirchner, N. Schmitz, V. Diehl (chairman) for the German Hodgkin's Lymphoma Study Group (GHSG), Cologne, Germany.

To test whether CSFs allow for dose escalation beyond that achievable without CSF, the GHSG started a dose escalation study of etoposide in the Dexa-BEAM regimen. Sixty-one patients with HD relapsing after or refractory to COPP+ABVD $\pm$ RT or COPP+ABV+IMEP $\pm$ RT received 4 cycles of Dexa-BEAM (dexamethasone 8 mg q8h p.o. days 1 to 10, BCNU 60 mg/m^2 i.v. day 2, melphalane 20 mg/m^2 day 3, etoposide 75 mg/m^2 i.v. days 4-7, cytosine arabinoside 100 mg/m^2 i.v. q12h days 4-7) or 2 cycles followed by HDC/ABMT. GM-CSF 250 μg/m^2 (31 pts.) or placebo (30 pts.) was given from day 8 until leukocytes reached > 2500/mm^3. Dose limiting events (DLE) were: leukocyte recovery (> 2500/mm^3) later than day 24, platelet recovery (> 100 000/mm^3) later than day 32 or any other toxicity of WHO grade 4 (exept alopecia, nausea). The maximum tolerated dose level (MTDL) was defined as the dose level where 1/3 of the pts. are expected to have a DLE. Etoposide dose levels were: 1=75, 2=100, 3=150, 4=200, 5=250, 6=300, 7=400 and 8=500 mg/m^2 . Based on first cycles only, MTDL for pts. with placebo was 5.8 (80% confidence interval: 4.4 - 7.2) or 1160 mg/m^2 etoposide per cycle, MTDL for GM-CSF was 7.5 (80% CI: 6.4-8.7) or 1800 mg/m^2 per cycle. This difference is significant (p = 0.045) when considered as a one-sided question. We conclude that considerable dose escalation of etoposide is possible with and without CSFs and that GM-CSF allows for somewhat higher doses than placebo. Whether this gain will translate into higher response and/or survival rates remains to be shown. Supported by a BMFT Grant 01ZP550/A/O and by Essex/Schering-Plough.

P 145 THE INFLUENCE OF DOSE INTENSITY (DI) ON THE OUTCOME OF DIFFUSE LARGE CELL LYMPHOMA (DLCL) TREATED WITH MACOPB.

U Vitolo, M Bertini, G Todeschini, E Brusamolino, R Freilone, A Gallamini, AM Gatti, A Levis, G Luxi, L Orsucci, D Rota-Scalabrini, F Salvi, C Tarella, P Viero for the MRSGNHL. Division of Hematology, Ospedale Molinette, Torino, Italy.

Between June 1986 and December 1990, 225 pts with advanced stage DLCL were treated with MACOPB. The median age was 47 yrs (range 15-68). 43% were advanced stage II, 21% stage III and 36% stage IV. 11% had bone marrow (BM) involvement. CR was achieved in 70%, 12% had a PR, 13% a NR while toxic deaths occured in 5%. With a median follow-up of 54 months, 5-yr survival was 58% and 5-yr disease-free survival (DFS) for the 158 CRs was 67%. Failure-free survival (FFS) was 47% at 5 years. Actual dose intensity (ADI) and relative dose intensity (RDI) were calculated with the method of Hryniuk and Bush. ADI and RDI were evaluated for each drug after the first 8 weeks of therapy and at the end of MACOPB. ADI and RDI of Vincristine, Bleomycin and Prednisone did not correlate with the outcome. ADI and RDI of Methotrexate (M), Adriamycin (A) and Cyclophosphamide (C) greater than 75% significantly predict higher FFS rates. A stronger correlation was observed for the data assessed early after the first 8 weeks of therapy compared with the data collected at the end of treatment. This supports the importance of giving chemotherapy on schedule mainly in the first part of the treatment.

RDI 8th week <75% vs >75%

	CR	DFS	FFS
M	56% vs 79% *	56% vs 69%	30% vs 55% *
A	69% vs 76%	55% vs 70% *	37% vs 53% *
C	61% vs 77% *	54% vs 69% *	35% vs 53% *

* p<0.05

Patients with a higher mean RDI of M+A+C at the 8th week did significantly better with 5 yr FFS rate of 55% vs 29% (p<0.01). A low RDI of M+A+C was more frequently observed in patients with age over 60 and poor performance status (PS). However in a multivariate regression analysis with FFS as endpoint including age, PS, LDH, bulk, stage, BM involvement and the mean RDI of M+A+C, only BM involvement, LDH, stage and RDI retained a prognostic significance. Thus RDI appeared to be independent from age and PS. These data suggest that in advanced stage DLCL, a low DI predict a worse outcome. It seems particularly important to preserve a high DI in the first part of the treatment.

P 146 DOSE INTENSIFICATION OF CYCLOPHOSPHAMIDE (CTX) AND DOXORUBICIN (DOX) WITH ADJUNCTIVE FILGRASTIM (rG-CSF) IN INTERMEDIATE GRADE LYMPHOMA.

D.W.Blayney, S. Horning, N. Bartlett, S. Williams, J. Mortimer, W. Robinson, D. Tomita, L. Bean, E. Malta. Los Angeles Oncologic Institute, Los Angeles, CA Stanford, CA; University of Chicago, Chicago, IL; Washington University, St. Louis, MO; University of Colorado, Denver, CO; and Amgen, Inc., Thousand Oaks, CA, U.S.A.

Filgrastim ameliorates neutropenia during cytotoxic chemotherapy for lymphoma and for solid tumors. Dose intensification of active cytotoxic agents may increase the cure rate, but is limited by myelosuppressive toxicity. A phase II dose escalation study was conducted to establish the safety of a dose intensified cyclophosphamide (CTX), Doxorubicin (DOX), Vincristine (VCR), and prednisone (P) combination regimen (CHOP). Successive cohorts of patients with intermediate or immunoblastic Non-Hodgkins Lymphoma, Stage II-IV were treated with standard dose CHOP every 21 days without (Cohort 1) or with (Cohort 2A) Filgrastim support. Filgrastim was given subcutaneously at 5ug/kg/day starting on day 2 of each cycle and continuing until the post nadir absolute neutrophil count (ANC) was ≥ 10,000 mm^3 on 2 consecutive days. ANC counts were obtained thrice weekly. Standard dose CHOP with Filgrastim support was also administered in Cohort 2B but on a 14 day cycle. In the absence of dose limiting toxicities subsequent cohorts (3-5) received escalated doses of CTX and DOX with Filgrastim support administered on a 14 day cycle. Projected dose intensity (PDI) was calculated for CTX and DOX and for the total regimen according to the method of Longo et al (*J Clin Onc.* 1991;9:2042-2051).

COHORT (N)	CTX/(PDI*) mg/m^2	DOX (PDI*) mg/m^2	TOTAL PDI*	F†	Cyc Length (Days)	# Cyc	MEDIAN ANC Nadir	MEDIAN DAYS <500/mm^3
1 (5)	750 (1.0)	50 (1.0)	1.0	0	21	26	808	0
2A (10)	750 (1.0)	50 (1.0)	1.0	5	21	51	1917	0
2B (10)	750 (1.5)	50 (1.5)	1.5	5	14	45	480	1
3 (3)	1200 (2.4)	50 (1.5)	1.73	5	14	14	72	1.5
4 (4)	1200 (2.4)	65 (1.95)	1.84	5	14	19	39	2
5 (5)	1600 (3.2)	65 (1.95)	2.04	5	14	17	72	1

* = Projected Dose Intensity

† = Filgrastim (μg/kg/day)

Dose intensification of this entire CHOP regimen due to both the increased doses of the CTX and DOX and to the compression of the cycle length is possible with Filgrastim support. This regimen built around the standard CHOP regimen is suitable for evaluation in Phase 3 studies.

P 147 LENOGRASTIM (GLYCOSYLATED RECOMBINANT HUMAN G-CSF) SUPPORTED CHEMOTHERAPY OPTIMISATION IN AGGRESSIVE NON-HODGKIN'S LYMPHOMA (NHL).

F. Reyes, B. Coiffier, E. Lepage, H. Tilly, A. Bosly, B. Dupriez, J. Reiffers, J.Y. Cahn, C. Haioun, A. Yver, C. Gisselbrecht GELA study - Hopital Henri Mondor, 94010 Creteil, France. Chugai-Rhone Poulenc - Antony - France (*).

Between 05/92 and 07/90, 162 patients with an intermediate and high grade NHL included in the group 2-LNH87 protocol (age 16-55), at least one poor prognostic factor) were entered in a double-blind randomized placebo-controlled phase III trial. The objectives were: 1) to assess the efficacy of Lenograstim in the correction of neutropenia and the effect on infection-related parameters 2) to evaluate the effect of neutropenia reduction on dose intensity of chemotherapy. Patients were randomly assigned to receive subcutaneous Lenograstim or vehicle: 5 μg/kg/day from day 6 to day 13 of each chemotherapy cycle. No prophylactic antibiotics were given for the duration of treatment. The induction treatment (4 cycles every two weeks) was that of the LNH 84 protocol (J.C.O. 7, 1018-1026, 1989) with an open-label randomization on the anthracyclin (Doxorubicin versus Mitoxantrone). No chemotherapy dose reduction was allowed, time between cycles being prolonged over 14 days if necessary. An interim analysis covering the first two cycles was performed on the frist 73 patients. 58 patients were evaluable for calculation of neutropenia duration (ANC < 1.10^9/l) at cycle 1. The median duration of ANC < 1.0 X 10^9/l and < 0.5 10^9/l was respectively 7 and 5,5 days in the vehicle group compared to 3 and 2 days in the Lenograstim group (p < 0,001). These results have been observed in the evaluable population but also in the total population. The incidence of patients ghaving recovered ANC > 1 X 10^9 at day 15 (and therefore eligible for the next cycle) was also affected by the Lenograstim administration: vehicle 24 % versus Lenograstim 94 % (p < 0,001). The overall incidence of infection during neutropenia (ANC < 1 X 10^9/l) did not differ between the treatment groups (65 %). The analysis of the effect of neutropenia reduction on dose intensity of chemotherapy over the four cycles and its outcome on tumor response in the 162 enrolled patients is being performed and will be presented.

P 148 PHASE I DOSE ESCALATION OF PROMACE-Cyta-BOM WITH GM-CSF SUPPORT IN PATIENTS WITH DIFFUSE AGGRESSIVE LYMPHOMAS: ANALYSIS OF NORMALIZED DOSE INTENSITY (NDI) AND TOXICITY (TOX).

LI. Gordon, J. Andersen, T. Habermann, J. Winter, D. Hogan, J. Glick, P. Cassileth. Northwestern Univ., Dana- Farber Cancer Center, Univ of Pennsylvania, Mayo Clinic for ECOG. Chicago, Ill. USA.

Previously untreated patients (pts) with diffuse mixed or diffuse large cell lymphoma (LYM) were entered onto a Phase I trial designed to determine the maximum tolerated dose of chemotherapy with GM-CSF (10ug/kg/d) support. Pts were treated with Promace-Cyta-BOM, with escalating doses of cyclophosphamide (CTX), doxorubicin (ADR), VP-16 (E) and cytosine arabinoside (ARA). GM-CSF was given from days 9-19. Doses were escalated according to a modified Fibinnachi scheme, and cohorts of patients were analyzed separately on the basis whether bone marrow (BM) was positive (+) or negative (-) for LYM. Hematologic toxicity was defined as the number of days of absolute neutrophil count (ANC) < 500/mm^3, and ANC was measured every other day. NDI was defined as the ratio of the actual dose intensity (DI=mg drug/sqm/week) to 100% Promace-Cyta-BOM. Thus far, 35 patients have been entered. Twenty-four had Stage IV disease, 4 had Stage III, and 7 had bulky Stage II. Thirty three are eligible for analysis. The median age was 44. The overall median average NDI over 6 cycles for each drug at each dose level was calculated. Since there appeared to be no differences when the BM + and BM - groups were analyzed, the data are expressed for both groups in aggregate in the following table below on the left, where n= number of pts in each cohort. We examined toxicity within each cohort, and calculated the median number of days of ANC < 500 for each cycle (C1, C2 etc). These data are shown in the table below on the right.

	CTX	ADR	E	ARA	n		C1	C2	C3	C4	C5	C6
100%	1.0	1.0	1.0	1.0	(8)		0	0	0	0	0	0
133%	1.24	1.23	1.25	1.11	(7)		1	1	1	0	1	1
160%	1.56	1.56	1.52	1.52	(8)		1	1	0	1	1	1
175%	1.7	1.69	1.64	1.19	(6)		1	1	5	5	3	2
200%	1.92	1.88	1.89	1.17	(4)		1	3	2.5	3.5	5	1

The NDI for CTX, ADR and E appears to be close to the designed dose for each cohort, but the NDI for ARA is reduced in the 133%, 175% and 200% cohorts. The CR rate for the 33 evaluable pts was 53%, which is similar to what we observed in pts <60 yrs in the recently completed CHOP vs m-BACOD trial (NEJM 1992; 327:1342). We conclude that CTX, ADR, and ARA can be escalated in this regimen to as high as 200% with GM-CSF support, but some dose reductions occur. Although this results in higher actual DI than in "standard" (100%) Promace-Cyta-BOM, no correlation between DI and response can be made. An approved Phase II trial at 200% Promace-Cyta-BOM will define tox and response. The relationship between DI and outcome remains to be established in Phase III trails.

P 149 THE FOLLICULAR NON HODGKIN'S LYMPHOMAS - 1: THE POSSIBILITY OF CURE

J W Denham, G Vaughan-Hudson, B Vaughan-Hudson, M H Bennett, A M Jelliffe, W R Pratt, and E E Denham, for the British National Lymphoma Investigation

The records of 398 patients with Follicular Non Hodgkin's Lymphoma followed for a minimum of 12 years, who were entered into the British National Lymphoma Investigation Trials between 1974 and 1980, have been reviewed to determine whether any of these patients may now be considered cured and if so at what stage in the dissemination of the disease process cure becomes unlikely.

Long term relapse free survival has been observed in 58.3 ± 14.1% (95% C.I.) of patients at 10 years with Ann Arbor Stage I disease (54.8 ± 14.9% at 15 years), and 29.2 ± 13.6% in patients at 10 years with Ann Arbor Stage II disease (29.2 ± 13.6% at 15 years) that were entered into the Limited Disease Trial that addressed the value of adding six months oral chlorambucil to radiotherapy.

Long term disease free survival was also observed in patients with Ann Arbor Stage III and IV disease who were treated in the Disseminated Disease trials that compared two years of oral chlorambucil with a minimum of six cycles of COP (intravenous cyclophosphamide and vincristine and oral prednisone). The proportions were lower (20.9 ± 6.7% and 18.1 ± 6.6% at 10 and 15 years respectively in Ann Arbor Stage III disease, and 13.0 ± 5.9% at 10 and 15 years in Stage IV disease) but nevertheless significant.

Relapse data from both sets of trials conform to lognormal distributions as predicted in the statistical "cure prediction model" of Boag. Application of this model suggests that 30-40% of patients with Ann Arbor Stage I and II disease are unlikely ever to relapse and therefore may be considered cured. The figure for patients with Ann Arbor Stage III and IV disease is under 10% but the possibility of cure is **not** ruled out in some of these patients.