32 CRITICAL REVIEW II - WHAT DO GROWTH FACTORS CONTRIBUTE TO DOSE INTENSITY AND OUTCOME IN THE TREATMENT OF NHL's

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The concept of dose intensity has been proposed as a significant factor affecting outcome in non-Hodgkin's lymphoma patients (NHL). As more intensive regimens have been used in NHL reduction in drug dose and alterations in the schedule of drug administration are often necessary to accommodate the toxicity encountered in individual patients. To evaluate the effects of chemotherapy dose intensity (DI) on outcome in patients with aggressive lymphoma, the received relative DI (received RDI) is usually calculated using Hryniuk's model. We applied this model to a selected patient subgroup included in the LNH87 protocol (LNH87-2 protocol), who has been treated with the ACVB induction regimen. A total of 87 patients out of the 311 included in the study (28 %) presented a RDI below 70 % of the theoretical DI. We demonstrated a decreased response rate (65 % vs 79 %, p = .01) and shorter overall 2-year survival (61 % vs 72 %, p : .02) in patients receiving a DI < 70 %. This difference remained significant when using multiparametric analysis (p = .004). To assess if glycosylated rHu-G-CSF could correct neutropenia and reduction on dose intensity a double-blind randomized trial was performed on 162 patients with NHL aggressive lymphoma. An interim analysis on 73 patients covering the four cycles of induction therapy showed a significant reduction of the median duration of neutropenia < 1 x 10^9/l. Only a marginal ratio of patients receiving Lenograstim (0-3 %) experienced chemotherapy delay because of neutropenia compared to placebo (55-65 %). The received dose intensity by placebo and Lenograstim groups was respectively 81 % and 93 % (p = .0001). There was no significant difference in complete remission rate 63 % vs 67 %. Longer follow-up and final analysis of the whole population will be necessary to evaluate the real impact on survival. If growth factors can contribute to the realization of high dose-intensive regimens, only randomized studies will allow to determine if these regimens are superior to conventional CHOP-like treatment.

33 INTENSIVE THERAPY WITH CYCLOPHOSPHAMIDE, BCNU, ETOPOSIDE ± CISPLATIN (CBV±P) AND AUTOLOGOUS BONE MARROW TRANSPLANTATION (AuBMT) FOR PATIENTS (PTS) WITH HODGKIN'S DISEASE (HD) IN FIRST RELAPSE (1 REL).

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Between 03/85-05/92, 100 pts with HD progressive after combination chemotherapy were treated with C ($7.2g/m^2$),B($0.5\text{-}0.6g/m^2$),V($2.4g/m^2$)±P($150mg/m^2$) and AuBMT. Overall event-free survival is 48% (95% [C.I.] 35 - 60%). Fifty-eight of these pts were entered onto AuBMT protocols in 1 REL. During this period only 12 pts referred in 1 REL received other treatments (allogeneic BMT in 1, radiotherapy [RT] in 7, conventional chemotherapy in 1 and refusal of all therapy in 3). Median age of AuBMT pts was 30 (range 13 - 51)yrs; 35 were male. All but 7 had received MOPP/ABV(D) - like regimens initially; prior RT had been given to 20. Sixteen had B symptoms and 21 had extranodal disease at 1 REL. Duration of initial complete remission (CR) was <1 year in 35. Before CBV±P 49 pts whose HD had recurred ≥3 mos after previous chemotherapy received a median of 2 cycles of MVPP (=nitrogen mustard, vinblastine, procarbazine and prednisone), 25 of whom also received local RT. Three received local RT only. MVPP and/or RT was not used as a test for disease responsiveness and all pts so treated subsequently proceeded to AuBMT. Conditioning included CBV in 14 and CBVP in 44 pts. One pt with active BM involvement was transplanted with peripheral blood stem cells while the remainder received AuBMT. Post-BMT growth factor support was used in 18. Three (5.2%) pts died of toxicity while 13 pts have had progression of HD at a median of 8 (range 1-42)mos post-BMT. Forty-two patients are alive continuously free of HD for an actuarial EFS of 64% (95% C.I. 46 - 78%) at a median follow-up of 28 (range 5-88) mos. The presence of B symptoms at relapse (p=<.001), initial CR duration <1 yr (p=.006), and extranodal disease (p=.029) were the significant independent predictors of unfavorable EFS in a multivariate analysis; pts with none of these features had an EFS of 100%, compared with 81% in those with 1 factor, 40% in those with 2 factors and 0% in those with all 3 factors. We conclude: 1) multimodality therapy involving conventional cytoreduction followed by CBV ± P and AuBMT is feasible in the vast majority of HD pts in first relapse; 2) mortality with this approach is low; 3) progressive HD remains the major problem; 4) future efforts will be directed towards methods of decreasing morbidity in good risk pts and the increasing antitumor effect in poorer risk pts.

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36 PERIPHERAL BLOOD PROGENITOR CELL (PBPC): THE SINGLE APHERESIS TRANSPLANT. R. Pettengell[1], G. Morgenstern[2], J. Chang[2], P. Woll[1], M. Rowlands[2], J. Radford[1], N.G. Testa[3] J.H. Scarffe[1] and D. Crowther[1], [1]Departments of Medical Oncology and [2]Haematology and [3]Department of Experimental Haematology, Paterson Institute for Cancer Research, Christie Hospital NHS Trust, Manchester, UK.

We have harvested PBPC with a single apheresis during routine outpatient chemotherapy in 34 high grade non Hodgkin's Lymphoma (NHL) and 10 relapsed Hodgkin's Disease (HD) patients. Following seven weeks of outpatient chemotherapy (VAPEC-B) subcutaneous rG-CSF (300μg/day) was administered and patients leukapheresed after 7-10 days. HD patients proceeded directly to ablative therapy. The NHL group first received three consolidation chemotherapy cycles (Ifosfamide 3gm/^{2}, Ara-C 800mg/m^2, infused intravenously at 3 weekly intervals). Following ablative therapy (in NHL Busulphan 4mg/kg and Cyclophosphamide 50mg/kg, each for four days; in HD Cyclophosphamide 50mg/kg for 4 days and BCNU 600mg/m^2), PBPC alone were reinfused and G-CSF (300μg sc daily) commenced.

An adequate yield of PBPC was obtained in both groups by processing approximately twice the patient's blood volume. For NHL and HD patients respectively; a median (range) of $3.2x10^8$ (0.22-9.7) and $1.7x10^8$ (1.3-2.8) MNC/kg; comprising $1.64x10^7$ (0.4-180), $0.5x10^7$ (1.9-2.8) CD34 positive cells/kg and $2.7x10^6$ (0.7-119), $5.2x10^6$ (1.3-184) GM-CFC/kg were harvested.

Post transplant recovery data is available in 20 NHL and 9 HD patients. For NHL and HD respectively, median days (range) to ANC $\geq 0.5x10^9$ were 9 (8-14) and 9 (8-18); ANC $\geq 1x10^9$/l, 11 (9-16) and 12 (10-17), platelets $\geq 20x10^9$/l, 9 (6-15) and 13 (8-68); platelets $\geq 50x10^9$/l, 15 (10-28) and 14 (12-80).

Compared with historical and contemporary controls receiving bone marrow transplantation with or without G-CSF support there was a significant reduction in RBC and platelet transfusions, antibiotic requirements and hospital days. There have been no graft failures to date. In both NHL and the heavily pretreated HD group, these findings indicate that a moderately myelosuppressive stimulus and G-CSF enable sufficient PBPC to be harvested at a single leukapheresis for haemopoietic reconstitution after ablative therapy. Re-infusion results in rapid haemopoietic engraftment and a reduction in supportive requirements. PBPC rescue is practicable and improves the therapeutic index of myeloablative therapy.

37 **Comparison of peripheral and bone marrow autologous transplantation for lymphoma patients: a case controlled analysis of the EBMT Registry data.**
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The effect of stem cell source on autograft was explored by a matched-pair anaalysis. 132 patients, 66 with peripheral blood stem cell tranplantation (PBSCT) and 66 with autologous bone marrow transplantation (ABMT) reported to the EBMT lymphoma registry were fully matched for the following characteristics: sex, histology, status at transplant, bone marrow involvement at transplant and conditioning regimen. The case-macthing was carried out following selection of the main prognostic factors for progression-free survival by multivariate analysis. In this analysis no differece statistically significant were observed in PFS (59% vs 56% at median follow-up time of 60 months) between the PBSCT vs ABMT. The transplanted-related mortality was 7,5 % for both groups. The neutrophil recovery occurred faster in PBSCT vs ABMT (13 vs 17, p=0.014). The platelets recovery (PLT>50.0) was not significantly (15 vs 26 days)(p= 0.149). A higher number of interstitial pneumonitis (1vs8) and fungus infection (Candida 2vs7, Aspergillus 0vs3) occurred in ABMT group than in PBSCT. In conclusion our results show that there is no difference in the progression free survival in this closely matched group of patients between PBSC and ABMT, for all histological categories of NHL and HD. However the patients autografted with PBSC have a rapid engraftment and a lower toxicity.

38 MYELOABLATIVE THERAPY WITH AUTOLOGOUS BONE MARROW TRANSPLANTATION AS CONSOLIDATION THERAPY FOR FOLLICULAR LYMPHOMA. Rohatiner AZS*, Freedman A^, Nadler L^, Lim J*, Lister TA*
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Since June 1985, 121 patients with follicular lymphoma (64: SBH, 57: DFCI, age range 24-61, median 43 years) have received Cyclophosphamide: 60mg/kg x 2 and total body irradiation: 200cGy x 6, supported by autologous bone marrow transplantation (CY + TBI + ABMT) as consolidation of second or subsequent remission. The marrow mononuclear cell fraction was treated in vitro with 3 cycles of the monoclonal antibody anti CD-20 and baby rabbit complement at SBH and with the addition of anti-CD10 and 'anti-B5' at the DFCI.

At the time of treatment, 50 patients were in complete remission (CR), 71 had residual disease present (BM infiltration <20% and/or lymph nodes <2cm in diameter at no more than 3 sites). The median time to engraftment was 26 days (range 10 to 59 days) for neutrophils >0.5 x 10^9/l and 30 days (range 12-73 days) for platelets >20 x 10^9/l respectively. One patient did not engraft and 7 have had delayed recovery of red cells and platelets (>3 months). Two other patients have subsequently developed acute myelogenous leukaemia and 5, evidence of myelodysplasia, presumably as a consequence of all the treatment for follicular lymphoma rather than of CY + TBI per se. Ninety eight patients are alive: 4 died as a consequence of the transplant procedure; 5 died in remission from unrelated causes and 14 have died of recurrent lymphoma.

Seventy two patients continue in remission between 3 months and 7 years with a median follow up of 21/2 years, 40 have developed recurrent lymphoma. Freedom from progression was the same, irrespective of whether patients received CY + TBI + ABMT whilst in a complete or partial remission and did not depend on the specific remission in which treatment was given (2nd: 90 patients vs >2nd: 31 patients).

Comparison with an age-matched, remission-matched historical control group who received 'conventional' therapy at SBH prior to 1985, shows a significant advantage in favour of treatment with CY + TBI + ABMT in terms of freedom from recurrence (p=0.001), with a projected 45% of patients remaining in remission at 5 years; currently, the survival curves have not diverged significantly. These results are preliminary but encouraging; it remains to be established whether further modifications to the treatment will improve outcome.

39 **HIGH DOSE THERAPY AND AUTOLOGOUS BONE MARROW TRANSPLANTATION (ABMT) IN FIRST COMPLETE REMISSION FOR ADULT PATIENTS WITH HIGH GRADE NON-HODGKIN'S LYMPHOMA: THE EBMT EXPERIENCE.** J.W. Sweetenham*, R. Pearce, G. Taghipour, A.H. Goldstone. For the EBMT Lymphoma Working Party, * c/o Medical Oncology Unit, University of Southampton, Southampton General Hospital, Southampton SO9 4XY, UK.

Long term survival for patients with high grade non Hodgkin's lymphoma (NHL) as defined in the Working Formulation (WF) is poor. Despite high response rates, most patients relapse rapidly, with less than 20% surviving for more than 2 years. ABMT has been used increasingly to consolidate 1st complete remission (CR) in these patients.
To date, 118 adult patients presenting with high grade (WF) NHL undergoing ABMT have been reported to the EBMT. Patients with lymphoblastic lymphoma are excluded, and have been reported separately. Patient characteristics at presentation: **Median age** -38yrs (range 16.5 - 58.5yrs). **Initial stage:** I-4%, II-23%, III-23%, IV-50%. **Symptom status:** A-58%, B-42%. **Bulk (>10cm) disease** -22%. **BM + -** 19%. **CNS + -** 3%. With a median follow up of 40 months, the 5 year actuarial overall and PFS for the entire group = 68%. Although most relapses have occured within 6 months from ABMT, some late relapses have been reported (latest at 52 months from ABMT). The presence of bone marrow and/or CNS disease at presentation did not influence overall or progression free survival after ABMT. In multivariate analysis, presenting stage was the only factor which predicted for PFS (p = 0.015), but not OS. Toxic deaths related to ABMT occured in 5 patients (4%).
ABMT has produced effective consolidation of 1st CR in this series of patients, even for those with poor risk features at presentation.

40 AUTOLOGOUS BONE MARROW TRANSPLANTATION (ABMT) VERSUS SEQUENTIAL CHEMOTHERAPY IN FIRST COMPLETE REMISSION AGGRESSIVE NON-HODGKIN'S LYMPHOMA (NHL): A STUDY ON 469 PATIENTS (LNH87 PROTOCOL).

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Intensive chemotherapy followed by ABMT seems to offer the best results in partial responder or sensitive-relapse patients with aggressive NHL. Numerous pre-treatment parameters have been recognized as prognostic variables leading to the identification of high-risk patients. A logical approach was to use ABMT earlier in the course of the disease in such high-risk patients. From October 1987 to December 1991, 881 adult patients were included in a multicentric randomized trial (LNH87-group2 protocol). Group 2 patients were younger than 55y and had at least one of the following adverse prognostic factors: performance status≥2 (27%), number of extranodal sites ≥ 2 (27%), tumoral mass ≥10cm (52%), bone marrow involvement (28%), CNS involvement (9%) and high grade histologic subtype (Burkitt and lymphoblastic)(11%). The induction treatment (4 cycles every two weeks) was that of the LNH84 protocol (J.C.O. 7:1018-1026,1989) with an open randomization on the anthracyclin (ACVBP with Doxorubicin 75 mg/m^2 versus NCVBP with Mitoxantrone 12 mg/m^2). No chemotherapy dose reduction was allowed, time between cycles being prolonged over 14 days if necessary. Response was assessed after 4 courses. Complete remission (CR) patients were further randomly assigned for consolidation between sequential chemotherapy (high dose methotrexate, ifosfamide plus etoposide, asparaginase and cytarabine) or ABMT after a CBV conditionning regimen (cyclophosphamide: 6g/m^2, carmustine: 300mg/m^2, VP16: 1g/m^2). At the time of analysis (January 1st, 1993), 811 patients were evaluable for response and survival (70 patients being ineligible, mainly for misclassification after histological review). There main characteristics were: large-cell subtype (68%), B-cell phenotype (69%), Ann Arbor stage III/IV (68%), LDH >1.N (60%). Sixty five percent of the patients achieved CR, 16% a partial response, 13% failed to respond and 6% died during induction. CR rate was 69% for ACVBP and 62% for NCVBP ($p<.05$). 469 CR-patients were evaluable for the consolidation phase (237 being randomized for sequential chemotherapy and 232 for ABMT). Two patients died from transplant-related complications. Overall 3-year disease free survival (DFS) was 56%, 78% of the relapses occurring within the first year. Overall 3-year survival was 57% with a median follow-up of 30 months. DFS and survival did not differ between the two consolidation arms ($p=0.62$); the same results were observed after stratification on the induction arm. We conclude that, on such a subset of patients in first remission, CBV regimen followed by ABMT as consolidation did not show any advantage over sequential consolidation chemotherapy.

41 ABMT vs DHAP IN RESIDUAL DISEASE FOLLOWING THIRD GENERATION REGIMENS FOR AGGRESSIVE NON-HODGKIN'S LYMPHOMAS.

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A multicentric randomized study on high-grade non-Hodgkin's lymphomas (HG-NHL) (categories G, J, H according to Working Formulation) was designed with two main objectives: 1- to compare two intensive chemotherapy regimens, F-MACHOP and MACOP-B, by a first randomization and 2- to evaluate by a second randomization the effect of DHAP, a cyclic combination chemotherapy, vs ABMT following very aggressive chemotherapy on early partial responders after the first therapeutic approach. We focus on the evaluation of the second randomization. DHAP regimen consisted of Dexamethasone (40 mg/m^2/day on days 1 to 4), Aracytin (2 g/m^2/12hrs on day 2) and Platinum (100 mg/m^2 in c.i. over 24hrs on day 1). The ABMT conditioning regimen consisted of BAVC scheme. 306 patients entered the first randomization and 51 the second one: 29 in the DHAP arm and 22 in the ABMT arm. Up to January 1993 all 51 patients were evaluable and the median follow-up is 30 months for DHAP group and 32 months for ABMT group, respectively. The previous therapy characteristics are comparable for both subsets: 13 and 9 F-MACHOP pretreatment respectively for DHAP salvage and ABMT, and 16 and 13 MACOP-B first-line respectively for DHAP and ABMT groups. Complete remission was achieved in 15 (52%) of the DHAP patients and 20 (91%) in the ABMT arm, a partial response was obtained in 3 patients (10%) following DHAP and 1 patient (4.5%) following ABMT, a resistance with progression of the disease was recorded in 11 patients (38%) of DHAP group and only 1 (4.5%) of the ABMT group. So far, we observed 9 never progressed patients (CR), 20 progressed patients (6 alive with active lymphoma and 14 dead for lymphoma) in the DHAP arm. On the other hand, we had 16 never progressed patients (CR) and 6 progressed patients (4 alive and 2 dead) in ABMT group. The progression-free survival curve shows at 48 months a probability of 73% and 31% for ABMT and DHAP, respectively. This study indicates that ABMT following aggressive treatment is superior than DHAP in reducing the risk of progression in HG-NHL patients with residual lymphoma following the first-line therapy in terms of CR rate and progression-free survival.

42 MYELODYSPLASTIC SYNDROME (MDS)/ACUTE MYELOGENOUS LEUKEMIA (AML) FOLLOWING HIGH-DOSE CHEMOTHERAPY AND AUTOLOGOUS STEM CELL TRANSPLANTATION FOR LYMPHOID MALIGNANCY: CHARACTERIZATION AND RELATIVE RISK.

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The use of high-dose chemotherapy and autologous stem cell rescue for the treatment of lymphoid malignancies has expanded and more patients are surviving for extended periods of time following this therapy. Long-term toxicities such as MDS/AML are now being recognized with increasing frequency. Between 4/83 and 12/91, 509 patients received high-dose chemotherapy and autologous bone marrow transplantation (ABMT) or peripheral stem cell transplantation (PSCT) for Hodgkin's disease (N=249) or non-Hodgkin's lymphoma (N=260) at UNMC. Nine cases of MDS (N=7) or AML (N=2) have been diagnosed to date following high-dose chemotherapy and ABMT or PSCT. The FAB classification includes: refractory anemia (N=2), MDS-unclassifiable (N=1), refractory anemia - ringed sideroblasts (N=1), refractory anemia with excess blasts (N=2), refractory anemia with excess blasts in transformation (RAEBT) (N=1), AML-M_4 (N=1), AML-M_7 (N=1). The MDS/AML was diagnosed a median of 43 months following high-dose chemotherapy and ABMT/PSCT (range 13 to 78 months). These patients had received a median of 2 chemotherapy regimens prior to ABMT/PSCT (range 1 to 3). Radiation had been given to 7 of the 9 patients either as involved field (N=5) prior to or after ABMT/PSCT, or total body irradiation (TBI) (N=4) as a part of the regimen for BMT. Two of the patients received both TBI and involved field radiation. Six of the nine patients had chromosomal analysis of the bone marrow at the time of MDS/AML diagnosis. All six had either a chromosome 5 or 7 abnormality. The overall five year estimated rate of MDS/AML was 2% for patients undergoing high-dose chemotherapy and ABMT/PSCT for either HD or NHL during this time frame. At this time, only one of the 9 patients survives, but with RAEBT. As more patients are successfully treated with high-dose chemotherapy and ABMT/PSCT for lymphoid malignancies, the proportion developing MDS/AML may increase.

43 TRISOMY 12 IN B-CELL CHRONIC LYMPHOCYTIC LEUKEMIA DETECTED BY IN SITU HYBRIDIZATION: CORRELATION WITH ADVANCED STAGE DISEASE AND WITH REFRACTORINESS TO TREATMENT

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Trisomy 12 is known as a common chromosomal aberration in B-cell chronic lymphocytic leukemia (B-CLL). Its impact on therapy free survival and on overall survival has been discussed controversily. However, a proliferative advantage of trisomy 12 positive B-cells over trisomy 12 negative ones has been suspected. Therefore, in situ hybridization was performed to study incidence and clinical significance of trisomy 12 in 50 patients (pts) with B-CLL at various stages of disease. Trisomy 12 was detected in 12%-65% (median 53%) of the circulating neoplastic cells of seven out of 20 pts at Binet stage C, whereas 22 pts at Binet stage A and another eight pts at Binet stage B were found to be trisomy 12 negative ($p<0.005$). Moreover, trisomy 12 was associated with the presence of B-symptoms ($p<0.01$) and hepatosplenomegaly ($p<0.05$), thus further reflecting the correlation with advanced stage disease. No correlation with a lymphocyte doubling time of <12 months nor with a marked lymphadenopathy nor with prior treatment became apparent. Within the group of Binet stage C pts, those with trisomy 12 displayed higher serum levels of CD25 than pts without trisomy 12 ($p<0.05$), whereas no differences were detected in serum levels of CD8 and CD23. Interestingly, median survival as determined from first diagnosis was shorter in trisomic than in non-trisomic pts at Binet stage C (32 months , two out of seven pts still alive; versus 60 months, eleven out of thirteen pts still alive). This could be caused by refractoriness to treatment evident frequently in trisomy 12 positive pts ($p<0.05$). In conclusion, trisomy 12 in B-CLL appears to occur predominantly in advanced and symptomatic disease. It indicates a high risk for treatment failure and seems therefore to serve as marker of poor prognosis.

44 A GENE ENCODING AN HOMOLOGUE OF A DROSOPHILA ZINC FINGER PROTEIN IS DISRUPTED BY THE TRANSLOCATIONS INVOLVING BAND 3q27 IN NON - HODGKIN'S LYMPHOMAS.

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We have recently reported that translocations involving band 3q27 and immunoglobulin genes regions were the third most common specific translocations in non-Hodgkin's lymphoma. To clone the breakpoint, an EMBL3 library prepared from the cells of a patient (LAR) carrying a t(3;14)(q27;q32) and showing two rearranged bands upon southern analysis using a JH probe was screen with the same probe, allowing the identification of two kinds of rearranged clones. The first one corresponded to a somatic VDJ rearrangement of immunoglobulin genes (V4-D2-J6 junction) whereas the second one corresponded to a complex JH3-inverted VH3-3q27 translocation. Southern analysis of the DNAs obtained from 17 patients with 3q27 rearrangements using probes derived from the involved chromosome 3 region allowed us to identify a breakpoint cluster region at 3q27, since 13 of these patients had a breakpoint located in a unique 10 kb BamH1-Xba1 fragment. We found that a genomic DNA probe spaning a 7kb segment 13 Kb telomeric from the 3;14 junction identifies a 3.8 kb muscular transcript when used to probe a multi tissue northern blot. Sequence analysis of a cDNA clone isolated from a skeletic muscle library shows an open reading frame encoding a putative protein of 706 amino acid (AA), the carboxy terminus of which contains six zinc finger of the C2-H2 type. The N terminus, from AA 12 to AA 118 shares homologies with several transcription factors: these included the Tramtrak and Broad-complex proteins which are zinc finger containing transcription factors involved in *DROSOPHILA* development, and human protein KUP which is also a zinc finger DNA-binding protein implicated in transcription regulation. This sequence also shares homologies with a number of proteins of the poxviruses, and could correspond to a conserved binding domain for ligands other than DNA. We termed this gene LAZ-3 for Lymphoma Associated Zinc finger protein. As the first exon of this transcriptional unit is located centromeric to the breakpoint, the gene is disrupted in patients with 3q27 rearragements. Thus the LAZ-3 gene could be fused to and governed by ectopic promoter and enhancer sequences in these lymphomas.

45 A RELIABLE APPROACH FOR SEQUENCING CLONE-SPECIFIC CDR-III REGIONS IN B LYMPHOMA.

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The CDR-III regions are part of the rearranged immunoglobulin heavy chain genes in B cells. In B cell-derived lymphoid malignancies, the CDR-III region of the malignant clone represents a unique marker by which very low numbers of malignant cells in the blood, bone marrow or other tissues can be detected using PCR. For the generation of clone-specific primers, the CDR-III regions of the NHL or ALL must be sequenced. Direct sequencing of respective PCR fragments amplified with universal primers frequently results in a suboptimal quality of the autoradiogram, due to co-amplification of a variable background of normal B cells, which all carry individual CDR-III regions. On the other hand the subcloning of PCR fragments usually requires an enzymatic modification of the fragment ends, which often results in a reduced efficiency of subcloning.

We chose to subclone the CDR-III PCR fragments from NHL or ALL samples, amplified by the use of universal primers, directly into a special vector (TA Cloning System, Invitrogen). This cloning system takes advantage of the activity of Taq Polymerase to add single deoxyadenosines to the 3'-ends of the PCR products. The TA vector provides the complementary deoxythymidines for subcloning. Purification of the PCR fragments was not required and an aliquot of the PCR reaction put directly into the ligation reaction enabled an efficient subcloning. Recombinant clones can be identified by the white appearance of the bacterial colonies. Restriction analysis of miniprep DNA showed that 90% of these closes carried a PCR fragment integrated into the vector. After purification of plasmid DNA with PEG, the different cloned CDR-III regions were sequenced by cycle sequencing. For this, about 20ng of plasmid DNA was required, representing only a small fraction of the miniprep DNA. Between 6 and 10 different clones from each ligation were sequenced and all yielded high quality autoradiograms. From this sequence data, clone-specific primers were prepared and used for the detection of occult lymphoma cells in patients with high grade NHL. Sequential peripheral blood samples from 15 patients included in a clinical trial in which G-CSF was given to prevent dose-limiting neutropenia are under investigation by PCR. In addition five series of peripheral blood samples from patients in which G-CSF was used to mobilise peripheral stem cells are also being studied. The latter study is ongoing and will recruit more patients for molecular analysis. The aim of our molecular study is to see what effect G-CSF has on the level and/or persistence of minimal residual disease and to which extent, if any, peripheral stem cell harvests are contaminated with lymphoma cells. PCR data from our patients will be presented.

46 PRAD1/CYCLIN D1 OVEREXPRESSION IN NON-HODGKIN'S LYMPHOMA WITH CHROMOSOME 11 BCL-1 REARRANGEMENT.

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The t(11;14)(q13;q32) chromosomal translocation and associated rearrangements at the bcl-1 MTC and p94ps breakpoint loci are strongly associated with centrocytic (mantle cell) lymphomas (CL) (Path Annual, in press). Recently the PRAD1/cyclin D1 gene, which lies approximately 110 kb centromeric of the bcl-1 MTC locus, has been identified as a candidate bcl-1 oncogene. Translocation breakpoints also have been identified within 1-15 kb upstream of the first PRAD1 exon in CL (Ca Res 52:5541s, 1992; Leukemia, in press). In order to determine PRAD1 expression in NHL with bcl-1 rearrangement, total RNA was isolated from peripheral blood cells of 3 B cell lineage NHL patients in leukemic phase using a PRAD1 cDNA probe (provided by A. Arnold). Each showed clefted and/or prolymphocytoid cells on smear; node biopsy of one patient showed the blastic variant of CL. Northern blot in each case showed high levels of PRAD1 expression, whereas no expression was detected in RNA from samples of CLL, T cell prolymphocytic leukemia or NHL which lacked bcl-1 or PRAD1 rearrangements. Thus, overexpression of PRAD1/cyclin D1, a G1 cyclin implicated in cell cycle regulation, may play a critical role in the pathogenesis of t(11;14)-positive lymphomas. Whether this gene has a direct transforming capability or requires interaction with other growth regulatory genes or oncogenes is unknown, but is currently being tested utilizing PRAD1/cyclin D1 expression vectors.

47 INVESTIGATION OF THE ACTIVATION STATE OF THE X-CHROMOSOMES IN NON-HODGKIN'S LYMPHOMAS.

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We have recently reported the presence of additional X-chromosomes in over 30% of biopsy samples from patients with non-Hodgkin's lymphoma (NHL) [Hammond et al., 1992, Cancer Genet Cytogenet, 61, 31-38]. This was observed in both male and female patients, and in both low and high grade disease. As sex-chromosome syndrome individuals (eg. Klinefelter males) contain additional X-chromosomes in their cells, but do not show increased incidence of NHL, it might be concluded that additional X-chromosomes would not contribute to the malignant transformation of cells. However, the X-chromosome can exist in both an active and an inactive state, and in the sex-chromosome syndrome individuals, the additional X-chromosomes are always present in the inactive state. We were therefore interested to determine the activation state of the additional X-chromosomes in NHL cells. As Barr bodies are difficult to detect in lymphoid cells we adopted a fluorescence in-situ hybridization strategy to study the X-chromosomes. Hybridization of a centromere probe to interphase nuclei revealed an elongated or a discrete hybridization signal for activated or inactive X-chromosomes respectively. Initial studies indicated that unlike sex-chromosome syndrome individuals 4/11 NHL samples contained additional X-chromosomes that were present in the active state. There were problems, however, in quantifying the degree of elongation which varied during the cell cycle, and so we investigated the methylation status of the X-chromosomes by probing Southern blots with the M27β probe. So far this has revealed evidence of activation of some of the additional X-chromosomes in 2/8 NHL samples. We are currently investigating loss of heterozygosity of the X-chromosome in these samples, to determine whether the additional activated X-chromosomes arise by duplication of the original active X-chromosome, or whether the original inactive X-chromosome had become activated during malignant transformation of the cells. These data indicate that, at least in some cases of NHL, the additional copies of the X-chromosome may be present in the activated state and that the X-chromosome might therefore contain a NHL-associated oncogene. We have recently analysed 280 NHL cases for structural abnormalities of this chromosome and have identified Xp22 and Xq28 as being the most likely locations for such an oncogene [Goyns et al., 1993, Leukemia, In press].
This work was supported by the Yorkshire Cancer Research Campaign.

48 **ALTERED EXPRESSION OF THE RETINOBLASTOMA GENE PRODUCT IN HUMAN HIGH GRADE NON-HODGKIN'S LYMPHOMAS.** R. Weide[1], M. Tiemann[2], K.-H. Pflüger[1], H. Köppler[1], B. Parviz[1], H.-H. Wacker[2], H.-H. Kreipe[2], K. Havemann[1], M.R. Parwaresch[2]. [1]Department of Haematology/Oncology, Philipps-University Marburg, Baldingerstr., 3550 Marburg, Germany, [2]Department of Haematopathology, University Kiel, Niemannsweg 11, 2300 Kiel, Germany

Background: The retinoblastoma gene (RB) is a growth suppressor gene on the human chromosome 13q14. It encodes a 105 kDa phosphoprotein (p105) with DNA-binding capacity. P105 is thought to be involved in cell cycle control. Inactivation of RB is responsible for the development of retinoblastomas and occurs frequently in osteosarcomas and small cell lung cancer. In this study we looked at the RB-structure and expression in cell lines and primary lymphoma samples from patients with high grade (aggressive type) non-Hodgkin's lymphoma (NHL).

Methods: 45 primary high grade (aggressive type) NHL, the B-lymphoblastoid cell line IM-9 and the NHL cell line WSU-NHL were studied for RB structure by Southern blotting and for RB-expression by Northern blotting, Western blotting and immunocytochemistry. In all experiments freshly cryopreserved material was used. Southern and Northern experiments were performed with the 0.9kb and 3.8kb RB-cDNA probe. For the detection of p105 two different anti-p105-monoclonal antibodies were used in immunocytochemistry and Western blotting experiments.

Results: No RB mRNA and no p105 could be found in IM-9 cells. 26 aggressive type NHL samples (58%) showed no p105 expression. In the subgroup of centroblastic lymphomas (large cell) 16 out of 21 and in Burkitt's lymphomas 5 out of 8 showed no p105-expression.

Conclusions: P105 expression is absent in 58% of aggressive type NHL, particularly in centroblastic (large cell) and Burkitt's lymphomas, suggesting that inactivation of RB may play a crucial role in the pathogenesis of high grade NHL.

49 Antibody-mediated effector mechanisms with CAMPATH-1 antibodies.

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The advent of humanised antibodies into serotherapy requires that we understand which of the available isotypes is best capable of harnessing the effector mechanisms which might result in cell destruction, and to find ways of improving the recruitment of those effector mechanisms. As it is impossible to test every engineered immunoglobulin construct in the clinic, it is desirable to have a suitable pre-clinical models. We have recently observed that human immunoglobulins can exploit murine effector systems to bring about in-vivo cell depletion. This then provides a model for establishing the key immunoglobulin motifs that influence therapeutic behaviour, and selecting engineered improvements. In vitro studies have also established a critical role for the C-terminal half of the CH2 domain both in ADCC and in complement lysis, and have indicated the existence of a polymorphism in ADCC between individuals.

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Lymphokine Receptors: A Target for Immunotherapy of Lymphomas. TA Waldmann MD, National Cancer Institute, NIH, Bethesda, MD 20892

Many lymphomas express lymphokine receptors not expressed by normal resting cells. Such receptors provide rational targets for immunotherapy. Specifically the leukemic cells of patients with human T-cell leukemia virus I (HTLV-I)-associated ATL express the IL-2 receptor α, β and γ subunits. In contrast, normal resting cells do not express the IL-2 receptor α-subunit identified by the anti-Tac monoclonal antibody. Patients with ATL were treated with different forms of IL-2 receptor-directed therapy to exploit the difference in IL-2 receptor expression between normal and malignant cells. Using the unmodified anti-Tac monoclonal antibody, seven of the 19 patients with ATL treated have undergone a remission, in two cases complete, There was no toxicity observed. However, unmodified murine monoclonal antibodies are limited by their immunogenicity and their poor effector functions. To address these issues we used genetic engineering to produce humanized anti-Tac that contains the complementarity-determining regions from the mouse antibody with the remainder of the antibody derived from human IgG1-κ . This antibody is dramatically less immunogenic than the murine version, has improved pharmacokinetics and, in contrast to the parent antibody, manifests antibody-dependent cellular cytotoxicity with human mononuclear cells. To enhance its effector function anti-Tac was armed with toxins or with α- or β-emitting radionuclides. In a clinical trial with ^{90}Y-anti-Tac at the doses used (5, 10 and 15 mCi), 11 of the 17 patients with ATL treated underwent a partial of sustained complete remission. Thus, the clinical application of IL-2 receptor-directed therapy represents a new perspective for the treatment of certain lymphomas including HTLV-I-associated ATL.

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LYMPHOMAS ARISING IN STATES OF ABNORMAL IMMUNITY. AM Levine,MD. University Southern California School Med, Los Angeles,CA 90033.

Lymphomas are seen with increased frequency in various states of abnormal immunity including (1) congenital immune deficiency diseases, such as Wiskott Aldridge syndrome, ataxia telengectasia, and the X-linked lymhoproliferative syndrome (XLP); (2) acquired auto-immune disorders, such as Hashimotos thyroiditis, rheumatoid arthritis and others; (3) organ transplantation with iatrogenic immunosuppression; and (4) underlying infection by the Human Immunodeficiency Virus (HIV). The lymphomas which arise in all of these settings share certain features in common, including (1) predominance of high-grade pathologic types, predominantly large cell or immunoblastic lymphomas, or small non-cleaved lymphoma; (2) restriction to B-cell origin; (3) presence of widely disseminated disease at presentation; (4) poor prognosis, when compared to patients with "usual" lymphomas. Despite these similarities, however, certain very basic differences exist, including (1) clonality of the lymphoproliferative process; (2) association with Epstein-Barr Virus (EBV); (3) specific sites of extra-nodal involvement; and (4) optimal strategies for therapeutic intervention. While the biologic aspects of these lymphomas are only partially understood, significant heterogeneity has already been demonstrated within the lymphomas comprising each particular type of underlying immune dysregulation. The simultaneous and prospective study of lymphomas arising in the various states of abnormal immunity may serve to clarify the pathogenesis of these tumors, which are expected to increase in incidence over time. In the model of AIDS-related lymphoma, approximately 3-5% of patients develop lymphoma as the first AIDSdefining condition, while the expected incidence of lymphoma arising three years after a previous diagnosis of AIDS is approximately 19% (Pluda et al, 1992).

52 TRANSFORMATION IN FOLLICULAR LYMPHOMA: FREQUENT P53 AND BCL-2 ONCOPROTEIN OVEREXPRESSION, CELL PROLIFERATION AND APOPTOSIS.
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Transformation in follicular lymphoma represents an abrupt transition in clinical behavior and tumor biology. Mutations of p53 oncogene may play a role in transformation. Wild-type p53 produces a tetrameric DNA-binding protein which acts as a checkpoint for cells in late G1 phase of the cell cycle, particularly after noxious stimuli, and may also induce apoptosis. The mutant protein has altered conformation, oligomerization, and DNA binding; is more stable; and achieves higher intranuclear levels than wild-type p53. Cytoplasmic bcl-2 oncoprotein is overexpressed in most follicular lymphomas and impairs apoptosis (programmed cell death). We studied 11 transformed lymphomas (TLs) which were all large cell type (3 biopsies, 8 fine needle aspirates (FNAs)) and 7 follicular lymphomas (FLs) prior to transformation (6 biopsies, 1 FNA) made up of small cleaved (FSCL) (4), mixed cell (FMCL) (2), and large cell (FLCL) (1) types. In 6/7 FLs the patient's subsequent TL was available. We compared these with two control groups of lymphomas recently diagnosed by FNA and with no evidence of subsequent or previous transformation. These contained 9 small cleaved cell lymphomas (SCLs), and 10 large cell lymphomas (LCLs) with histologic confirmation of diffuse (7) or follicular (3) LCL. Two reactive lymphoid hyperplasias (both FNAs) were also studied. All lymphoma specimens had proven immunoglobulin light chain restriction. The following criteria were assessed: immunostaining for p53 (PAb1801 and PAbDO-1) and bcl-2 (bcl-2, 124) in tumor cells, high proliferation index (PI) (Ki-67 or PCNA (lateG1,S,G2M) immunostaining ≥25% of tumor nuclei or S+G2M ≥15% by flow cytometry), and the presence of numerous apoptotic bodies (ABs) by light microscopy. In cytospin preparations from FNAs the proportion of benign T-cells was assessed by immunostaining for CD-3.

	p53 ≥10%	p53 ≥50%	bcl-2 ≥50%	High PI	Numerous ABs
TL	11/11	6/11	7/11	6/11	7/11
FL	4/7	2/7	7/7	4/5	0/7
SCL control	0/9	0/9	9/9	0/9	0/9
LCL control	2/10	0/10	5/10	5/10	5/10
RH	0/2	0/2	0/2	0/2	0/2

p53 immunostaining was typically in the nuclei of large cells. In TLs there was no correlation between p53 overexpression (≥50%) and high PI or numerous ABs. bcl-2 expression <50% was associated with numerous ABs in 4/4 TLs and 4/5 LCLs. One FMCL and one FLCL had overexpression of p53. The 2 LCLs with p53 expression both had diffuse histology. In 6 patients, p53 expression increased to ≥50% in 3/6 and bcl-2 expression decreased to <50% in 2/6 after transformation. We conclude that 1) p53 expression is frequent in TL, is higher in TL than in de novo LCL, and may represent more frequent mutations in this group; 2) low levels of p53 expression may develop in FL prior to transformation; 3) p53 expression may be greater in FMCL and FLCL than in FSCL; 4) p53 overexpression does not specifically correlate with high PI, apoptosis, or bcl-2 overexpression; and 5) reduced bcl-2 expression in TL and LCL is associated with increased apoptosis.

53 INCIDENCE, PREDICTIVE FACTORS AND PROGNOSIS OF HISTOLOGIC TRANSFORMATION (HT) IN FOLLICULAR LYMPHOMA.
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Incidence and parameters affecting the occurrence of HT and freedom-from-transformation (FFT) were analyzed in 220 follicular lymphoma (FL) patients (pts) treated from 1975 to 1991. Median follow-up was 8 years. Initial slides were reviewed and patients were classified according to the Working Formulation. 92 pts had FSC; 75 pts FM; and 53 pts FLC. 157 pts had stage III or IV and 106 bone marrow involvement. Estimated median survival is 10.8 years. HT occurred in 56 pts (25%), mostly during the 6 years following diagnosis, with a clear trend for a plateau: after 6 years, only 7 HT occurred with 85 pts remaining at risk. Among the 220 pts, 85 pts died, and 41 (48%) of these pts had HT. Other causes of death included: progression of FL without evidence of HT, 23 pts (27%); non-lymphoma related cause (in CR), 13 pts (15.5%); treatment-related death, 5 pts; unknown origin, 3 pts. The only parameters affecting FFT were BM involvement, β2-microglobulin ≥3 mg/l, and response to initial therapy. HT was proven 51 pts (38 histology and 13 cytology)and 5 pts were considered to have HT because of very aggressive course (rapidly growing bulky disease with B symptoms and high LDH level). Among the whole group, 34 pts were treated with CHOP-like regimens, 20 without anthracyclin, and 2 were not treated. 26 pts had a response (46%, 20 CR and 6 PR) and 30 pts (54%) failed to respond. 9 pts who responded were secondarily treated with ABMT, but 6 of them relapsed. Median survival after HT was 8 months. 15 pts are still alive with 8 remaining in CR after 10 to 60 months. Factors affecting overall survival after HT were previous CR ($p=0.04$), HT treatment with an anthracyclin-containing regimen ($p<0.001$), response to HT treatment ($p<0.001$). Time to transformation (< or > 3 years after diagnosis of FL), age at HT, initial histology did not influence outcome. We conclude that HT occurs early in the course of FL in pts with adverse prognostic factors. HT is responsible of 50% of the deaths of FL pts. We confirm the poor prognosis of HT in FL, even in pts who can be treated with intensive chemotherapy regimens.

54 MOLECULAR PATHOGENESIS OF NON-HODGKIN'S LYMPHOMA.

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The pathogenesis of B cell non-Hodgkin lymphoma (B-NHL) is associated with genetic lesions involving the activation of dominantly acting oncogenes as well as the loss or inactivation of tumor suppressor genes. The frequency and type of these lesions varies in different B-NHL cases allowing for the identification of pathogenetic subtypes which partially overlap with known clinico-pathologic subtypes (ref.1): i) in low grade, small lymphocytic (grade A, Working Formulation), no recurrent genetic lesion has been identified; a related subtype, mantle-cell lymphoma, displays activation of the oncogene bcl-1/cyclin D1 by chromosomal translocation in 50% of cases; ii) low- and intermediate-grade follicular-type NHL (grades B-D) are characterized by the activation of the bcl-2 oncogene by chromosomal translocation in 70-90% of cases; ii) intermediate- and high-grade NHL (grade E-J) are characterized by variable frequency of activation of the c-myc oncogene (20% in diffuse-type NHL, grades E-G; 100% in small non-cleaved Burkitt-type NHL, grade J), and inactivation of the tumor suppressor gene p53 (40% in grade J).

Clinical and/or histologic progression from low/intermediate to intermediate/high-grade tumors is accompanied by the accumulation of specific lesions which only occasionally involve c-myc activation, while frequently p53 inactivation (30%) (2). At least in some B-NHL subtypes, multiple genetic lesions can accumulate during a relatively short period of time, as shown by studies in AIDS-associated NHL where as many as 4 distinct lesions including activation of c-myc and N-ras and inactivation of p53 in addition to infection by EBV have been found in tumors developing in 4-6 years since AIDS diagnosis (3).

A number of other recurrent chromosomal abnormalities which are likely to contribute to NHL pathogenesis are currwently under investigation. These abnormalities include chromosomal translocation or deletion breakpoints at 10q24, which involve the NFKB-2/lyt-10 proto-oncogene (4); translocations involving 3q27, which involve the newly identified gene bcl-6 (5); and deletions of 6q, which involve at least two putative tumor suppressor genes within 6q21-23 and 6q27 (6).

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55 HODGKIN`S DISEASE IN CHILDREN: COMBINED MODALITIY TREATMENT FOR STAGE IA/B AND IIA. RESULTS IN 356 PATIENTS OF THE GERMAN PEDIATRIC STUDY GROUP

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Therapy of Hodgkin's disease (HD) has to guarantee not only the possible high cure rates but also to minimize the late effects of therapy. Unfortunately, there is no international agreement about a preferred treatment modality (radiotherapy alone vs. combined modality treatment) and about the type and extent of chemotherapy for the early stages. With combined modality treatment (CMT) dosage and fields of radiotherapy (RT) can be considerably reduced in comparison to the high-dose extended-field-(EF)-irradiation which has to be used if radiotherapy alone is given. Regarding the late effects of chemotherapy (ChT) the specific toxicities as well as the cumulative total doses of the different drugs have to be considered. As salvage therapy increases the risk for long term sequealae, treatment strategies with relatively high relapse rates cannot be considered acceptable even if high survival rates can be achieved.
Since 1978 CMT has been applied for all stages of Hodgkin's disease in 5 consecutive German multicenter studies in order to develop, step by step, a strategy using chemotherapy of low long-term toxicity together with low dose involved-field irradiation. A total of 356 children below 16 yrs of age with CS/PS IA, IB and IIA were enrolled in the studies HD-78, HD-82, HD-85, HD-87 and OEPA-pilot-87 between June 1978 and Sept 1990. 2 courses of ChT plus RT were given to these pats. In HD-78 and HD-82 the MOPP-derived drug combination OPPA (ADR instead of MUST) was applied. EF-RT was still given in study HD-78 using 36-40 Gy to IF and 36-40 Gy vs 18-20 Gy to EF. In HD-82 only IF-RT was applied using 35 Gy. When gonadotoxic effects of procarbazine (PC) in boys had been detected in follow-up examinations, this drug was eliminated in studies HD-85 and HD-87 arriving at 2 courses of OPA. Dosages of IF-RT were 35 Gy in HD-85 and 30 Gy in HD-87. Simultaneously to HD-87 a pilot study was initiated to test the new combination OEPA (E= etoposide) together with 25 Gy IF-RT.
Results (June 1992): Rates for event-free survival (survival) are: HD-78 (73 pats): 0.90 (0.97) at 13 yrs; HD-82 (100 pats): 0.98 (1.0) at 10 yrs; HD-85 (53 pats): 0.85 (0.98) at 7 yrs; HD-87 (104 pats): 0.85 (0,99) at 5 yrs; OEPA-pilot (26 pats): 0.96 (0.96) at 4 yrs. - No secondary leukemias, MDS and tumors have been observed during the 14 yrs. After 2 OPPA, elevated FSH levels indicating impaired spermatogenesis were found in 29% of male pats. In contrast, after 2 OPA (without PC) only normal FSH levels were observed. In female patients no gonadal dysfunction was found. Subclinical hypothyroidism was seen only after RT doses of › 30 Gy. Cardiomyopathies were not observed. - Conclusions: 2 OPPA plus IF-RT using ‹30 Gy can presently be considered optimal therapy for girls with localized HD. 2 OEPA plus 25 Gy IF-RT are being evaluated for boys in a phase-III study (HD-90). In summary, there are good reasons for a CMT in the early stages of HD in children, i.e. a highly effective ChT of short duration and low long-term toxicity plus low-dose IFI.

56 PRELIMINARY RESULTS OF AN EORTC-GPMC CONTROLLED CLINICAL TRIAL IN EARLY STAGE HODGKIN'S DISEASE.

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From November 1988 to November 1992, 701 clinical stage (CS) I-II Hodgkin's disease patients from 47 centres in 8 european countries were enrolled in a phase III trial (EORTC protocol # 20881). No staging laparotomy was done. Patients were grouped according to ab initio prognostic characteristics. The very favourable (VF) group included CS I females <40 years, with good histologic type and without bulky mediastinal involvement. The unfavourable (U) group included patients aged 50 years or more, or with 4 or 5 involved nodal sites, or with elevated ESR and/or B symptoms, or with bulky mediastinal involvement. All other patients composed the favourable (F) group.
Patients of the VF group were treated with mantle field irradiation (RT) alone. Those of the F group were randomised between subtotal nodal irradiation (STNI, 40 Gy to involved areas, 36 Gy to uninvolved areas, including splenic RT), and 6 cycles of EBVP (epirubicin, bleomycin, vinblastine, prednisone), followed by involved field irradiation (IF-RT). Patients of the U group were randomised between 6 cycles of EBVP plus IF-RT, and 6 cycles of MOPP/ABV hybrid plus IF-RT. Failure-free survival (FFS), including progressions, relapses, and early deaths as events, and overall survival (OS) are considered the end-points in the present report which only includes the **531** (76%) patients who completed their initial therapy.
Of the 31 VF patients, none have progressed under RT and two patients have relapsed, leading to a 3-year FFS rate of 84% and a 3-year OS rate of 100%.
Of the 235 F patients, 117 were treated with STNI and 118 with EBVP + IF-RT. At 3 years, FFS rates were 81% (1 progression, 11 relapses) and 83% (5 progressions, 5 relapses), respectively. Only one patient died after relapse in the STNI arm.
Overall, 281 patients were unfavourable; 138 were treated with EBVP + IF-RT and 143 with MOPP/ABV hybrid + IF-RT. At 3 years, FFS rates were 89% (7 progressions, 5 relapses) in the MOPP/ABV arm and 71% (16 progressions, 19 relapses) in the EBVP arm ($p<0.001$). Although no statistical difference was observed in OS rates between the two arms (3-year rates 91% and 90%, respectively), the trial was stopped on the basis of these preliminary results.
It is concluded that 1) treatment strategy based on prognostic factors allows the use of less aggressive treatment in patients with favourable prognosis, and 2) in patients with poor prognosis or bulky disease, EBVP is less efficacious than MOPP/ABV, inducing less initial complete remissions and, probably, less long-lasting complete remissions.

57 EARLY-STAGE HODGKIN'S DISEASE: LONG-TERM RESULTS WITH RADIOTHERAPY ALONE OR COMBINED RADIO-CHEMOTHERAPY.

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Purpose: To evaluate the role of radiotherapy (RT) alone or combined radio-chemotherapy (CT) in the treatment of patients with early-stage Hodgkin's disease (HD) and analyze long-term toxicity and late relapses.
Patients and Methods: This study included 161 patients with stage I-IIA HD diagnosed from Oct 77 to Dec 88; the diagnostic procedures and therapy were based upon presenting features and their attendant prognostic significance. The RT alone group included 85 patients; all underwent staging laparotomy with splenectomy, 54% were in stage I, 75% with "favorable histologies", without bulky disease, E lesions or polmonary hilus involvement. The combined modality group included 76 patients; laparotomy was done in 38% of them; altogether, 18% were in stage I, 72% had "favorable histologies", 18% had bulky disease and 21% polmonary hilus involvement. In the RT group, 85% of patients received STNI or extended mantle including para-aortic lymph nodes (40-44 Gy); 7 cases with infradiaphragmatic disease were given TNI. In the combined modality group, RT consisted of mantle (49%), extended mantle (37%), and extended field irradiation (14%); CT consisted of 6 cycles of MOPP in 37 patients before 1984 or 3 cycles of ABVD in 39 patients diagnosed thereafter.
Results: Complete remission was achieved in 80 (94%) and 75 (99%) patients in the RT and combined therapy groups, respectively. The 5 and 10-year actuarial RFS in the RT alone cohort was 69% and 60%; the duration of remission was significantly ($p=.04$) influenced by the stage (10-year RFS of stage I and II were 68% and 51%). Relapses occurred in nodal sites in 65 % (11/19 in irradiated areas) and extranodal relapses occurred in 20% of total events. The RFS in the combined therapy group at same intervals was 90% and was not influenced by stage, mediastinal involvement and/or presence of bulky disease. All relapses occurred in nodal sites.and no differences were observed between the patients given the 6 MOPP or 3 ABVD regimens. The 10-year OS of RT and combined therapy groups was 84% and 81%; the freedom from tumor mortality was 89% and 90%, respectively. A multivariate analysis of all cases indicated the type of therapy as the only significant factor for RFS ($R^2=0.96$). Six patients (21%) relapsed beyond the 4th year of remission; 5 had been treated with RT alone. The causes of death (15 cases) were HD progression in 6, solid tumors in 5, acute leukemia in 2, unrelated to HD in 2 patients. RT-related complications occurred in 13 cases: mediastinal fibrosis in 8, myelitis in 3, hypothyroidism in 2; other events included two cases of acute leukemia in patients treated with RT and MOPP, and two cases of non-Hodgkin's lymphoma.
Conclusions: In stage I-IIA HD, combined CT and RT proved significantly better to minimize the risk of relapse compared to RT alone; 3 cycles of ABVD followed by RT proved to be as effective as RT plus 6 cycles of MOPP with lesser toxicity. Long-term toxicity of RT alone was not neglegible and relapses could occur late.

58 ChlVPP (chlorambucil [Chl], vinblastine [V], procarbazine [PCB], prednisolone or prednisone [P]) Therapy for Hodgkin's Disease: Experience of 960 Patients. The International ChlVPP Treatment Group (Nebraska Lymphoma Study Group, Omaha, NE, USA; Royal Marsden Hospital, Sutton, Surrey, UK; CRC Wessex Medical Oncology Unit, Southhampton, UK; Scotland and Newcastle Lymphoma Group, UK).

We analyzed the experience of 4 research groups which use ChlVPP as standard therapy for Hodgkin's disease. Drug doses were standard (Days 1-14: Chl: 6 mg/m^2/day, PCB: 100 mg/m^2/day, P: 40 mg/day; Days 1, 8: V: 6 mg/m^2/day. The use of radiotherapy varied across research groups, with some (but not all) patients receiving radiotherapy.

Data on 960 patients (pts) were analyzed. 60% were male, 25% were aged 50+, 59% had nodular sclerosis histology. Distribution by stage, complete response (CR) rates, failure-free survival (FFS) and survival at 5 years was as follows:

Stage	N of pts	CR rate	FFS @ 5 years	Survival @ 5 years
IA	63	84%	78%	82%
IIA	168	89%	73%	85%
I/IIB	152	77%	62%	69%
IIIA	180	89%	67%	78%
IIIB/IV	397	72%	51%	63%

Adverse prognostic factors for all pts included age 50+ and 'B' symptoms. Patients aged 50+ of all stages did especially poorly on ChlVPP therapy. The 34 stage IIIB/IV pts with lymphocyte depleted histology also did poorly.

These results compare favorably with other reported series, including data reported by the International Workshop and Symposium on Hodgkin's disease. ChlVPP therapy is frequently an appropriate alternative to other treatment approaches for Hodgkin's disease often with a substantially reduced toxicity profile. Other chemotherapy may be preferred in patients greater than 50 years of age.

59 A RANDOMIZED PHASE III TRIAL OF MOPP/ABV HYBRID VS. SEQUENTIAL MOPP-ABVD IN ADVANCED HODGKIN'S DISEASE: RESULTS OF THE INTERGROUP TRIAL. J. Glick, A. Tsiatis, R. Schilsky, T. Beck, M. Oken, B. Peterson, R. Fisher, Philadelphia, PA, Boston MA, Chicago IL, Minneapolis, MN.

Between 1/87 and 6/89, 737 patients (pts) with previously untreated HD, stages III$_1$A (>5 splenic nodules), III$_2$A, IIIB, IVA, IVB, and patients relapsing after radiotherapy, were treated on an Intergroup trial that randomized patients to either: 1) MOPP/ABV hybrid X 8 cycles (Klimo, J Clin Oncol 3:1174, 1985), or 2) Sequential MOPP--ABVD (6-8 cycles MOPP followed by 3 cycles of ABVD). Radiotherapy was not administered. This trial tested the relative merits of the Goldie-Coldman vs. the Norton-Simon hypothesis. Known prognostic factors are evenly balanced on the two arms. With a median followup of 3.0 years, the 3-year results are:

	MOPP/ABV Hybrid %	Sequential MOPP-ABVD%	P Value
CR Rate	82	73	<0.02
CR Duration	79	72	0.03
Failure-Free Survival (FFS)	77	65	0.0006
Overall Survival (OS)	89	82	<0.02

Failure-free survival is defined as time from randomization to progression, relapse after response, or death from any cause for all patients entered on study. Significant prognostic factors that predicted for improved FFS included no B symptoms (p<0.02) and nodular sclerosis histology (p<0.03). For overall survival, ambulatory performance status (p=0.02) and age ≤40 (p<0.0001) were significant prognostic factors. After adjusting for significant independent prognostic factors using Cox regression analysis, treatment with MOPP/ABV hybrid was still significantly related to improved CR rate, FFS, and OS. There were 4 toxic deaths during chemotherapy on MOPP/ABV Hybrid compared to 1 toxic death on sequential MOPP-ABV.

The preliminary Intergroup MOPP/ABV hybrid data confirm the results reported by Klimo and Connors, with significantly improved failure-free survival and overall survival for this regimen compared to sequential MOPP--ABVD. Updated 5-year data will be presented.

60 HYBRID LOPP/EVA IS NOT BETTER THAN LOPP ALTERNATING WITH EVAP, A PREMATURELY TERMINATED BRITISH NATIONAL LYMPHOMA INVESTIGATION (BNLI) RANDOMISED TRIAL.

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Previous BNLI studies in advanced Hodgkin's disease have shown: (1) MOPP is more effective than MOP (prednisolone omitted), (2) addition of bleomycin to MOPP is of no benefit, (3) maintenance with CCNU (lomustine), vinblastine and bleomycin is of no benefit (4) LOPP (Leukeran substituted for mustine) is as effective yet much less toxic than MOPP and (5) LOPP alternating with EVAP (etoposide, vinblastine, adriamycin, prednisolone) is superior to LOPP alone as initial treatment. Between 1990 and 1991 we undertook a randomised multi-centre study of LOPP/EVAP versus a hybrid of this (LOPP/EVA) given in the same total doses. This trial was closed 'prematurely' when preliminary analysis of the response data on the first 169 patients entered showed a much lower complete response (CR) rate in the hybrid arm (40%) than with the alternating arm (64%); it was clear that it was most unlikely that there could ever be an advantage to the LOPP/EVA regimen. There was no significant difference in relapse rates of CR patients in the 2 arms, the CR relapse free survivals being 86% in the LOPP/EVAP arm and 83% in the LOPP/EVA arm, but the low CR rate in the LOPP/EVA arm resulted in a low overall disease free survival (33%) compared to that in the LOPP/EVAP arm (55%). Toxicity was less with LOPP/EVA than with LOPP/EVAP; severe (WHO grade III/IV) haematological problems were seen in 8% of patients on LOPP/EVA compared with 27% on LOPP/EVAP; the figures for infection were 4% and 10% respectively. Recruitment into this trial was terminated 18 months into the study. We are continuing to acquire longer term follow up data on all patients.

61 MVPP VERSUS A SEVEN DRUG HYBRID REGIMEN IN HODGKIN'S DISEASE (HD); RESULTS OF A RANDOMISED TRIAL.

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Since 1984, 423 patients (pts) have been recruited to a randomised trial comparing MVPP with a seven drug hybrid regimen for the treatment of high risk stages IA-IIIA and stages IIIB-IVB HD. Six pts remain on treatment, 2 refused CT after randomisation, 1 was randomised in error (high grade NHL, not HD) and 1 was withdrawn after the first cycle of CT for treatment of a glioma. The remaining 413 pts form the basis of this analysis.

Median age at presentation was 29 yrs (range 15-68) and 251 were male and 162 female. Ten (2.4%) pts had stage IA; 5 (1.2%) IB; 68 (16.5%) IIA; 91 (22%) IIB; 40 (9.7%) IIIA; 63 (15.3%) IIIB; 35 (8.5%) IVA; 101 (24.4%) IVB. Bulk disease (nodal mass ≥ 10cm or, in the mediastinum, transverse mediastinal diameter: internal thoracic diameter at D5/6 ≥0.33) was present in 217 (52.5%) cases. Age, sex, histological type, stage and bulk were evenly distributed between the two arms of the trial.

204 pts received a median of 6 (range 1-8) cycles MVPP (mustine 10mg iv, vinblastine 10mg iv on Days 1 and 8 with procarbazine 150mg daily and prednisolone 50mg daily on Days 1-14 of a 42 day cycle) and 209 pts a median of 8 (range 1-8) cycles Hybrid (vinblastine 10mg iv on Day 1 with chlorambucil 10mg daily, procarbazine 150mg daily, prednisolone 50mg daily on Days 1-7 and etoposide 200mg/m^2 iv, vincristine 2mg iv, doxorubicin 50mg/m^2 iv on Day 8 of a 28 day cycle). Following CT, 106 pts in the MVPP arm and 132 pts in the Hybrid arm received RT to sites of previous bulk or to areas of residual radiographic abnormality.

On completion of MVPP, 114 of 204 pts (55.8%) had achieved CR/CR(u), 52 (25.5%) PR and 38 (18.7%) had failed to respond, progressed or died. In the Hybrid arm, 140 of 209 pts (67%) were in CR/CR(u), 59 (28.2%) in PR and 10 (4.8%) had failed to respond, progressed or died.

With a median follow up of 48 months (range 4-90), relapse-free survival for 254 pts achieving CR/CR(u) is not significantly different (Hybrid, 86%; MVPP, 80%, both at 5 years) but progression-free survival (time to first relapse or progression for all 413 pts) is significantly better in the Hybrid arm (80% vs 66%, both at 5 years, p=0.0035). These differences are not translated into a survival advantage for the whole group (Hybrid 80%, MVPP 72%; p=0.3) but for 214 pts with stages IA-IIIA, actuarial survival at 5 years is 92% in the Hybrid arm and 78% for those treated with MVPP (p=0.015).

These results indicate a significantly better progression-free survival following Hybrid chemotherapy and, in pts with high risk stages IA-IIIA disease, a survival advantage has also been identified.

62 LEUKEMIA RISK FOLLOWING HODGKIN'S DISEASE: RELATION TO TREATMENT FACTORS AND TREATMENT-RELATED BONE MARROW DAMAGE.

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Purpose: The development of leukemia is one of the most serious long-term complications of modern treatment for Hodgkin's disease. This study was undertaken to examine the relation between risk of leukemia and various treatment factors (including cumulative dose of cytostatic drugs, interaction with radiotherapy (RT), and splenectomy), while also assessing the effect of other factors, such as stage of Hodgkin's disease and treatment-induced bone marrow toxicity.

Methods: We conducted a case-control study in a cohort of 1939 patients treated for Hodgkin's disease between 1966 and 1986 in two large treatment centers in the Netherlands. Forty-four cases of leukemia were identified, and 124 controls were selected, matching for age, gender, year of Hodgkin's disease diagnosis, and survival time. Detailed information was collected on characteristics of Hodgkin's disease, treatment, and indicators of bone marrow toxicity (platelet and white blood cell counts during and after treatment).

Results: The cumulative dose of mechlorethamine was the most important factor in determining leukemia risk. As compared to patients who received RT alone, patients treated with six or less cycles of combinations including nitrogen mustard and procarbazine had eightfold increased risk of leukemia ($p=0.08$), while patients who received more than six of such cycles had over fortyfold excess risk ($p<0.001$). Treatment with lomustine or a combination of teniposide and cyclophosphamide, also significantly increased the risk of leukemia. The number of episodes of chemotherapy (CT) was a strong determinant of leukemia risk: patients who had received CT during two or more time periods, had nearly fortyfold increased risk of leukemia as compared to patients treated only once (adjusted for cumulative doses of cytostatic agents). The extent of RT did not further increase leukemia risk among patients who also received CT. Patients who underwent a splenectomy had a 2.3 fold increased risk of leukemia; splenal RT did not affect risk of leukemia. After adjustment for all CT variables, stage was not an independent risk factor for the development of leukemia. Significantly increased risk of leukemia was found among patients with low platelet counts, both in response to initial therapy and during follow-up. Patients who experienced two or more half-year periods with platelet counts below 75 x 10^6 per ml had about fivefold risk of leukemia, and a similar risk increase was found for patients who responded to initial treatment with a fall of their platelet of 70% or more (as compared to patients showing a drop of 50% or less; adjusted for all CT received.

Conclusion: Present treatment strategies for Hodgkin's disease are already focussing on the selection of chemotherapy regimens with a lower leukemogenic potential. However, such therapies should continue to have high cure rates, since the number of chemotherapy episodes is a also strong determinant of leukemia risk. Further studies are warranted to investigate whether patients at high risk for developing leukemia, may be identified from the response of their thrombocytes to initial therapy for Hodgkin's disease.

63 HIGH SURVIVAL RATE OF CHILDHOOD B-CELL LYMPHOMA AND LEUKEMIA (ALL) AS RESULT OF THE LMB 89 PROTOCOL OF THE SFOP (French Pediatric Oncology Society).

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In July 1989, the SFOP initiated a new study called LMB 89 for all B-cell malignancies (small non cleaved-cell, "lymphoblastic" SIg+, and B-large cell). Treatment intensity was adapted to 3 risk groups: in group A (resected stages (st) I and abdominal (abd) st II) patients (pts) receive only 2 polychemotherapy courses without any CNS prophylaxis. In group B (other st I and II, st III, st IV and ALL with bone marrow (BM) involvement less than 70 %), pts receive a 5 course regimen during 4 months similar to the short arm of protocol LMB 84 (J CLin Oncol, 1991 9, 123-132) based upon high dose (HD) methotrexate (MTX) (3 g/m²), cyclophosphamide and continuous infusion of Ara-C. In group C (pts with more than 70 % blasts in BM and/or with CNS involvement), treatment last 7 months, consolidation is with HD Ara C and VP 16 and CNS treatment is done by HD MTX (8 g/m²), HD Ara-C, triple intrathecal injections; 24 Gy cranial irradiation is performed in case of CNS involvement.

At January 15th 1993, 225 pts are evaluable from 37 French, 1 Belgian and 1 Dutch centers. Ages range from 1 to 17 years (median 8) and sex ratio is 3/1. The majority are classified as small non cleaved-cell lymphoma. There are 13 st I, 31 st II, 105 st III, 22 st IV and 54 B-ALL. 31 have initial CNS involvement, 25 associated to BM involvement. Among the pts with detectable primary, the sites are: abdomen in 136, head and neck in 33, nodes in 17, elsewhere in 17. LDH level (known in 201 pts) is normal in 20 % of the pts, more than twice the normal level in 54 % and more than four times the normal level in 26 %.

18 pts are treated in group A, 149 in group B, 58 in group C. Failures are : 4 toxic deaths, 4 initial tumor failures, and 14 relapses 3 to 15 months (median : 5) after the beginning of treatment. With a median follow-up of 24 months, 203 pts are alive in 1st CR, 4 in 2nd CR. EFS is 89 % $\pm$ 2 for all pts, 100 % in group A, 90 % $\pm$ 2 in group B, 84 % $\pm$ 8 in group C, 100 % for st I and II pts, 87 % $\pm$ 5 in st III, 85 % $\pm$ 16 in st IV and 87 % $\pm$ 8 in ALL.

In conclusion, risk adapted therapy with a short intensive polychemotherapy regimen results in a high cure rate in childhood B-cell malignancies even in pts with known bad pronostic factors as high LDH level or CNS involvement (supported by the "Association pour la Recherche contre le Cancer", Villejuif, France).