41 LIMITED-FIELD AND LOW-DOSE RADIOTHERAPY + ABVD CHEMOTHERAPY FOR CHILDHOOD HODGKIN'S DISEASE.

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In 1979 a new therapeutic approach was designed for children presenting with stage I, II and III Hodgkin's disease admitted at INT, Milan. The aim was to reduce acute and late complications related to diagnostic surgical procedures, high-dose extended-field radiotherapy, and MOPP regimen. Staging procedures were carried out through foot lymphangiography, GA scan, bone marrow biopsies, and laparoscopy with liver and spleen biopsies. The initial treatment for all patients, regardless of age, stage and histologic subtype, consisted of 3 monthly cycles of ABVD (ADM 25 mg/m^2 + BLM 10 mg/m^2 + VLB 6 mg/m^2 + DTIC 375 mg/m^2 given on day 1 and 15). Fifty-five consecutive children (age: 3.1 to 15 yrs., median 12 yrs.) were treated so far. Stage distribution was as follows: IA 13, IIA 13, IIB 12, IIIA 1, IIIB 3, IIIS A+B 13. According to histology, patients were classified into the following subtypes: LP 4, MC 15, NS 34, LD 2. Following the three ABVD cycles, stage I and IIA achieved CR in 21 of 26 children (81%), and PR in 5 (19%). Stage IIB and III A+B attained CR in 13 of 29 (45%), and PR in 16 cases (55%). In no case disease progression occurred while on chemotherapy. Radiation therapy was then delivered according to the type of clinical response induced by ABVD: 30 and 35 Gy to involved area(s) to complete and partial responders, respectively; 25 Gy to the adjacent area(s). At the end of radiotherapy all patients achieved CR. Subsequently, 3 additional courses of ABVD were given only in stage III or when B symptoms were present. After a median follow-up of 43 mos. (range 18 - 82), 52 of 55 children remain alive in continuous CR. Three patients have relapsed following treatment completion: one stage IA showed nodal intradiaphragmatic relapse at 44 mos.; one stage IIE developed a single lung localization at 33 mos.; one stage IIIS B relapsed with visceral involvement at 13 mos. and died after 17 mos. due to progressive disease. The most important toxic effect of this treatment approach was represented by severe nausea and vomiting after ABVD. Myelosuppression was moderate and reversible. Partial hair loss occurred in each patient. No child showed either cardiac or respiratory abnormalities. It is too early to evaluate whether ABVD has a lower risk of second neoplasms in children as reported in adult series, and a longer follow-up is needed to establish the actual cure rate and treatment-related late effects.

42 UPDATE RESULTS OF THE PROTOCOLS LMB OF THE FRENCH PEDIATRIC ONCOLOGY SOCIETY (SFOP) FOR B-CELL ADVANCED STAGE NON-HODGKIN'S LYMPHOMA (NHL).

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In 1981, a new protocol called LMB 02.81 was designed for advanced stage (st) B-cell NHL and ALL (J Clin Oncol 4:1219-1222, 1986). This 9 drug intensive pulsed chemotherapy during 1 year was based on high dose (HD) Cyclophosphamide (CPM), HD Methotrexate (MTX) and Ara-C in continuous infusion. CNS prophylaxis was done by chemotherapy only. No radiotherapy was performed. 114 patients (pts) were treated in nineteen French and Dutch centers between November 1981 and March 1984. Results were : 1) 84 % achieved complete remission (CR). 3 pts with partial remission (PR) could be salvaged by HD polychemotherapy with autologous bone marrow transplantation. 2) 10 % died from toxicity. 3) 16 % relapsed : there was only one isolated relapse in CNS in the 93 pts without CNS involvement and most of the relapses were within the 6 first months. 4) Disease free survival (DFS) was 64 % for all the pts, 73 % for the 72 st III, 76 % for the 21 st IV CNS- and 19 % for the 21 st IV CNS+.

Based on these results, a new protocol, LMB84, was initiated in April 84 : after the same 3 first induction courses, pts without initial CNS involvement who achieved CR are randomised in a short arm (2 more courses) or a long arm (5 more courses) to a total of respectively 5 and 8 months of treatment. In November 1986, 168 pts were registered from 31 French, Dutch and Belgian centers. RC rate was 88 %. 2 pts with PR were salvaged by HD polychemotherapy. 9 toxic deaths occured during induction. 3 pts developped CNS disease before randomisation. 8 pts were not randomised because of various reasons : one of these because of infectious complications, but she died later on from pneumopathy. 120 pts were randomised. 8 relapses (1 in CNS) occured : 5 in short arm, 3 in long arm. 2 deaths occured late unrelated to tumor or treatment. DFS is 74 % for all the pts, 83 % for 8 huge nasopharyngeal st II, 74 % for 126 st III and 65 % for 34 st IV CNS-. DFS of the randomised pts is 86 %. This study is still going on with inclusion of pts until June 1986. So far, both arms seem equivalent.

For pts with initial CNS involvement, a protocol LMB86, with the adjunction of HD MTX 8 g/m2, HD ARA-C, multiple triple intrathecal and VP16, is going on with early encouraging results.

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B-TYPE NON-HODGKIN'S LYMPHOMAS AND LEUKEMIA: THE BFM STUDY GROUP EXPERIENCE. St. Müller-Weihrich[1], R. Ludwig[2], A. Reiter[3], J. Ritter[4], M. Schrappe[3], H. Riehm[3], Depts. of Pediatrics München (TU)[1], Heidelberg[2], Hannover[3], Münster[4], D-8000 München, FRG.

In trial NHL-BFM 75/81 a chemotherapeutic regimen, which proved to be very efficient in non-B-ALL and non-B-NHL, produced rather poor results in disseminated B-NHL. In trials NHL-BFM 81/83 and ALL-BFM 81, however, a treatment more specifically adapted to the B-type neoplasias, based on cyclophosphamide administered in fractions and supplemented with intermediate dose MTX, adriamycin, ARA-C, VM 26 and prednisone, improved prognosis substantially, though toxicity was considerable. In trial ALL/NHL-BFM 83/86, a slightly modified regimen was given: prednisone replaced by dexamethasone, intensified local chemotherapy in CNS disease at diagnosis (intraventricular injections of MTX and ARA-C via Ommaya-reservoir), reduced duration of therapy. At present (Dec 10, 1986), probability of event-free survival (EFS) for advanced B-NHL (stage II-NR (non-resected), III and IV) is 38% in trial NHL-BFM 75/81, 61% in trial NHL-BFM 81/83 and 82% in trial NHL-BFM 83/86 with 37, 38 and 78 pts on trial, respectively. Prognosis has been improved considerably in trial NHL-BFM 83/86, though only minor therapeutical changes were introduced. Short-term but intensive chemotherapy is justified because almost all relapses occurred within 6 months after diagnosis. In addition, no therapy-related deaths were encountered in this study.
The clinical staging and outcome of 137 pts with B-type neoplasia treated according to trials NHL-BFM 83/86 and ALL-BFM 83/86 (studies closed 10/86) are presented after 21 months (median duration of trials): stage I, 23 pts/22 pts in CCR; stage II-R, 12/10; stage II-NR, 22/20; stage III, 46/38; stage IV, 10/8; B-ALL, 24/14. The following table summarizes the results of all four NHL/ALL trials 81/86:

Stage	I	II-R	II-NR	III	IV	B-ALL
Pts	30	23	26	75	15	46
EFS	0.97	0.90	0.90	0.73	0.57	0.49

In the newly designed trial ALL/NHL-BFM 86 cyclophosphamide is partly substituted by ifosfamide and dosage of ARA-C and VM 26 is increased. Stage IV B-NHL and B-ALL are considered to be a biological entity and thus treated identically (high-dose MTX and triple-agent intrathecal therapy). Preventive and therapeutical brain irradiation will not be applied any longer in this protocol.

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A Decade of Progress in Childhood Non-Hodgkin's Lymphoma (NHL): The Childrens Cancer Study Group (CCSG) Experience. S. Siegel, R. Chilcote, P. Coccia, R.D.T. Jenkin, J. Kersey, A. Meadows, R. Sposto, G.D. Hammond. Childrens Cancer Study Group, Pasadena, CA, U.S.A.

Prior to the introduction of multiagent systemic chemotherapy, only 20-30% of children with NHL survived 2-3 years after diagnosis, and bone marrow/CNS metasteses were a common cause of therapeutic failure. The first CCSG Study in NHL, CCG-551, was opened in April of 1977 and compared the use of a modified 10-drug regimen (LSA_2-L_2) to a 4-drug program (COMP). Both regimens included CNS prophylaxis with intrathecal Methotrexate alone, and radiation to areas of bulk (>3 cm) disease. The results of this study were as follows: 1) Relapse free survival for all patients was 59% at 3 years; 2) The 3-year relapse-free survival rate for patients with localized versus disseminated disease was 84% and 50% respectively; 3) No difference in overall outcome between the 2 therapeutic regimens were noted for patients with localized or disseminated disease; 4) The LSA_2-L_2) regimen was superior to the COMP regimen for patients with lymphoblastic histology as determined by modified Rappaport criteria, while the reverse was true for patients with non-lymphoblastic histologies. In CCG-551 and its successor study 501, the use of 6 versus 18 months of COMP chemotherapy for localized non-lymphoblastic NHL was compared, and no difference in relapse-free survival was detected between the 2 regimens. Combined relapse-free survival for localized disease patients treated on both studies was 90% at 3 years. Currently, CCG-502 is comparing the use of LSA_2-L_2 to COMP plus Adriamycin for disseminated and localized lymphoblastic NHL. CCG-503 is comparing the use of COMP versus COMP plus Daunomycin in patients with disseminated non-lymphoblastic NHL. CCG-552 is a limited institution single-arm study assessing the toxicity and efficacy of an intensive chemotherapy regimen in non-lymphoblastic disseminated NHL. Children with NHL who relapse on initial therapy have an extremely poor prognosis regardless of their prior treatment regimen, histology, or extent of disease. Despite subsequent chemotherapy, less than 10% of relapsed patients remain alive 2 years after recurrence. New therapeutic agents as well as ablative therapy coupled with autologous or allogeneic bone marrow rescue are being explored as means of improving survival in relapsed NHL patients. Nevertheless, for the majority of childhood NHL patients, initial response is sustained, and long-term survival is achievable.

45 HIGH CURE RATE WITH REDUCTION IN TOXICITY FOR CHILDREN WITH LOCALIZED NON-HODGKIN'S LYMPHOMA: RESULTS OF A RANDOMIZED STUDY OF THE PEDIATRIC ONCOLOGY GROUP. Michael P. Link, Sarah S. Donaldson, Costan W. Berard, Jonathan J. Shuster, and Sharon B. Murphy. St. Louis, Missouri, USA.

Children with localized non-Hodgkin's lymphoma (NHL) in favorable sites have an excellent prognosis, and recent investigations have focused on reducing the acute and late toxicities of therapy. The standard treatment for localized NHL has included involved field radiotherapy (IFXRT) with systemic chemotherapy. The Pediatric Oncology Group has conducted a randomized controlled trial to address the contribution of IFXRT to local control and relapse-free survival for children with localized NHL in the context of a chemotherapy regimen of reduced intensity and duration. Children with stage I and II NHL were randomized to received chemotherapy plus IFXRT or chemotherapy alone. Induction and consolidation chemotherapy consisted of: vincristine 1.5 mg/M^2 weekly for 7 doses; adriamycin 40 mg/M^2 on days 1, 22 and 43; cyclophosphamide 750 mg/M^2 on days 1, 22 and 43; and prednisone 40 mg/M^2 daily for 28 days during induction and for 5 days with consolidation. IFXRT (27Gy in 150cGy fractions) was administered during induction to patients randomized to receive radiotherapy. After induction and consolidation, all patients received 24 weeks of continuation therapy with daily oral 6-mercaptopurine (50 mg/M^2/day) and weekly methotrexate (25 mg/M^2/week). Central nervous system prophylaxis with intrathecal methotrexate (12 mg/M^2) was administered 9 times during therapy only to patients with head and neck primaries. One hundred thirteen eligible patients were randomized, 57 to IFXRT plus chemotherapy and 56 to chemotherapy alone. There were 83 males and 30 females, ages 2 through 19. Primary sites included nasopharynx 14, tonsil 19, gastrointestinal tract 32, neck 27, peripheral nodes 7, scalp 5, and miscellaneous sites 9. Thirty-seven were stage I and 76 were stage II. Pathology has been reviewed for 93 cases and histologic classification was: Burkitt 28%, diffuse undifferentiated non-Burkitt 30%, large cell 24%, lymphoblastic 15%, and other 3%. One hundred five patients have completed induction and all have attained complete remission. Only 8 failures have occurred (3 after chemotherapy + IFXRT, and 5 after chemotherapy alone) including one death in remisson from toxicity and 7 relapses. Sites of relapse included meningeal 2, bone marrow 3, abdominal mass 1, and only 1 local recurrence was noted. All relapses occurred in patients with head and neck primaries. With a median follow-up of 534 days (range 1-1270 days), the projected two-year relapse-free survival is 95% (S.E. = 5%). No significant difference in outcome can be detected between the groups of patients receiving and not receiving involved field radiotherapy, although the toxicity experienced by patients receiving chemotherapy plus IFXRT was significantly greater than for those treated only with chemotherapy. We conclude that children with localized NHL can be treated successfully with a 6 month chemotherapy regimen of reduced intensity without radiotherapy.

46 HIGH DOSE METHOTREXATE (HD MTX) IN CHILDHOOD NON HODGKIN'S LYMPHOMA (NHL) : ITS EFFICACY FOR CNS PROPHYLAXIS. C. Patte, A. Bernard, C. Kalifa, O. Hartmann, F. Flamant, J. Lemerle, Pediatric Department, Institut Gustave-Roussy, Villejuif, France.

In a previous series of children with non Hodgkin's lymphoma treated in the Institut Gustave-Roussy between 1974 and 1980 by the same protocol COPAD (Vincristine, Cyclophosphamide, Adriamycine, Prednisone), CNS prophylaxis was made by cranial irradiation and intrathecal methotrexate (IT MTX). As in the following protocols, stage (st) I and abdominal st II did not receive CNS prophylaxis ; patients (pts) with initial CNS involvement or unstaged disease are not studied. Among 158 pts with non abdominal st II (21 pts), st III (97 pts) and st IV without CNS involvement (40 pts), 148 achieved complete remission (CR) and received this radiochemoprophylaxis. There were 82 relapses, 24 were isolated relapses in CNS, 13 were generalised including CNS. So the isolated CNS relapse rate was 15 % and isolated CNS relapse represented 29 % of all relapses.

A phase II study on HD MTX showed a 45 % response rate in refractory or relapsed patients and 60 % response rate on measurable CNS disease (Ped Hematol Oncol 3:11-18, 1986). After 1981, B and non B NHL received different chemotherapy regimens ; but in both cases, systemic chemotherapy was intensied and, based on these results, CNS prophylaxis was done without radiotherapy mainly by HD MTX : 3 g/m2 in 3 hours infusion followed by leucovorin rescue and IT MTX 24 hours after. 92 pts with B-cell NHL received the French protocols LMB (J Clin Oncol 4:1219-1226) ; 43 pts with non B cell NHL received the protocol LSA2L2 modified by the adjunction of HD MTX : 2 during induction, 3 during consolidation and 5 during maintenance. Among these 135 pts (17 st II, 97 st III, and 27 st IV without CNS involvement) treated between 1981 and December 1985 and thus with at least one year follow-up, 119 achieved CR. There were 11 relapses, only one was isolated in CNS (a st III pt treated by the LMB protocol) and 3 were generalised including CNS. So the isolated CNS relapse rate was < 1 % and isolated CNS relapses represented 9 % of all relapses. This rate was the same in the series treated by the LMB 02.81 protocol in all French centers. In the original LSA2L2 protocol, CNS relapse rate can be evaluated between 5 to 10 %, no CNS relapse rate was observed in our series treated by the modified LSA2L2 protocol.

We conclude that in childhood NHL, HD MTX associated to IT MTX and to a better systemic chemotherapy, including Ara-C and nitrosureas, has considerably diminished the frequency of CNS relapses without long term detected sequelae.

47 INTENSIVE SHORT-TERM CHEMOTHERAPY FOR ADVANCED CHILDHOOD BURKITT-TYPE NON-HODGKIN LYMPHOMA (B-NHL).

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An intensive chemotherapy program was utilized to treat 22 consecutive children with B-NHL. There were 19 males and 3 females, with an age ranging from 3 to 14 years. Stages according to the Ziegler's staging system were as follows: B 5, C 10, D 7, and according to the Murphy's one: II 1, III 13, IV 8. Treatment consisted for the first 5 weeks of the sequential weekly administration of VCR+CTX - MTX 100 mg/Kg + CF rescue - ADM - MTX 150 mg/Kg + CF_2 rescue - VCR. Following one-week rest, ARA C 6 g/m^2 and CDDP 80 mg/m^2 were given as a 96-hr continuous infusion. At the time of bone marrow recovery 3 additional courses of chemotherapy (VCR+CTX - VCR+MTX 200 mg/Kg + CF rescue - VCR+ADM) completed the treatment program. CNS prophylaxis consisted of i.t. MTX + ARA C for a total of 8 administrations. The entire treatment program was usually concluded within 4 months and required a prolonged hospital stay in the majority of patients. Two children died of sepsis during the first 6 weeks of therapy. CR was achieved in 19 of 20 patients within the first 4 weeks (in 6 of 19 the CR status was confirmed histologically on second-look laparotomy). At the time of this analysis, 14 children (64%) remain in CCR from 7 to 47 months of follow-up (median 24 months). Relapse occurred in 5 patients at 3,4,5,16,30 months from treatment start, respectively. The children who relapsed at 4 and 5 months had major protocol violations. Since the two patients who relapsed at 16 and 30 months were rendered disease-free with a second course of the same treatment program, 16 of 22 (72%) are currently alive and disease-free. Toxicity was always severe and life-threatening in the majority of cases, especially during the prolonged period of myelosuppression following the ARA C + CDDP course, when an intensive supportive therapy including total parenteral nutrition was necessary in all cases. This chemotherapeutic regimen designed on the basis of the characteristic cell-kinetic pattern of B-NHL proved to be highly effective in inducing a durable CR in two-third of patients. It is questionable whether a more prolonged treatment program could prevent late relapses that occurred in 2 of 16 (12%) children of this series.

48 ADVANCED B CELL LYMPHOMA IN CHILDREN. WHO REMAINS THE HIGH RISK PATIENTS ?

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. 50 children with advanced Murphy stage III and IV B Lymphoma were included in Lyon between 1981 and 1985 on a protocol comprising eigh drugs (SFOP protocol Patte, Philip et al J. Clin. Oncol 1986, 4, 1219). The overall complete response rate was 86 % (31/36 stage III and 12/14 stage IV). 4 treatment related deaths were observed. The overall disease free survival is 75 % with a median follow up of 44 months. There remains however two groups of patients in whom further intensification of therapy is indicated.

1) Those with initial CNS involvement especially in combination with marrow infiltration.

2) Those with extensive multiorgan involvement at presentation.

. We suggest to slighly modify the worldwilde accepted Murphy classification with two propositions :

1) to separate stage IV CNS and stage IV BM (patients with both should be included with CNS).

2) to separate stage III A (ie limited but unresectable disease often a very large tumor with ascite) and III B (ie extensive multiorgan involvement such as liver and kidney with disease often not confined to the abdomen but with normal CNS and BM).

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49 MALIGNANT LYMPHOMAS UNDER 20 YEARS OF AGE IN A JAPANEASE DISTRICT (KAGOSHIMA) WITH PREVALENT ADULT T-CELL LEUKEMIA/ LYMPHOMAS (ATLL).

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Malignant lymphomas (ML) under 20 years of age in Kagoshima district with prevalent ATLL (1) were reviewed and histologically analysed by using some antibodies. Hundred-four cases of MLs were recorded during the year from 1963 to 1985. The incidence rate was 1.0 per 100,000 population under 20 years of age, while the incidence rate of total MLs in Kagoshima was 7.0 with prevalent ATLL from 1981. Males were much more numerous than females (male/ female: 2.25) and diffuse non-Hodgkin malignant lymphomas (NHML) dominated (12 HD, 7 follicular NHML and 85 diffuse NHML). Lymphoma cells in 53 cases and atypical lymphocytes in 6 cases of skin infiltration (cutaneous type)(2) were examined, whether they possess the nature of T or B cells. The monoclonal antibody MT-1 (Bio-Science Products AG) was useful, as it reacts the surface of T cells even in paraffin sections. According to the Kiel classification and the followed T-cell lymphoma categorization (3), the lymphomas examined comprized 6 HD, 6 Burkitt type, 2 follicular and 2 diffuse centroblastic type, 16 T-lymphoblastic type of convoluted nuclei (convoluted type), 5 T-lymphoblastic type except convoluted type, 3 T-zone ML, 4 T-pleomorphic medium-sized cell type, 4 T-large cell type, 2 null large cell type and 3 true histiocytic lymphomas. Clinically, mediastinal tumor was observed in 5 cases of convoluted type and one case of T-lymphoblastic type except convoluted type and leukemia was noted in one case of Burkitt type, 2 cases of T-lymphoblastic type except convoluted type and one case of cutaneous involvement of convoluted type. One cutaneous type showed epidermotropism of atypical T cells and intraepidermal abscess formation, looking-like so-called cutaneous T-cell lymphoma, while the others involved only perivascular areas in the subepidermal dermis. These findings, especially the presence of MLs with T-pleomorphic medium-sized cell type and cutaneous type, are probably indicating that some MLs in younger generation are virus-related and thus, the smoldering ATL (4) is also present even in young people in this district with prevalent ATLL.

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50 BURKITT'S LYMPHOMA IN KUWAIT.

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Between 1975 and 1985 forty eight cases of Burkitt's Lymphoma were diagnosed, treated and followed up at the Kuwait Cancer Control Centre. Forty cases (83%) were 10 years old or younger. Only five cases were older than 15 years. The median age was 5 years. Males predominated with a male : female ratio of 1.8 : 1. None of the patients lived any time in endemic areas. The abdomen was the only site of involvement in 65% of cases. In another 15%, the abdominal involvement was accompanied with involved extra-abdominal sites. The facial bones as the only site of involvement occurred only in 6% of cases. Cases were staged according to the Ziegler staging, and 9 cases were in stages A&B, 25 in stage C, 6 in stage D, and 8 in stage AR. Thirty two cases were treated only by a combination of cyclophosphamide 1 Gm/m^2 i.v. day 1, oncovin 1.4 mg/m^2 day 1, methotrexate 15 mg./m^2, P.O. days 1 - 4, and continuous infusion of Ara-C 250 mg/m^2 days 15 - 17 (COMA). The courses were repeated every 4 weeks and a total of six courses were given. One patient did not receive any therapy, and the remaining 15 cases received CVP or CHOP combination in addition to abdominal irradiation. The actuarial two-year survival was 56%. Age and sex did not influence survival. Most deaths occurred in the first 6 month, and only one case relapsed after being in complete remission (CR) for one year. None of the cases in stages A&B died of their disease, and in cases in stage C the two-year survival was 40%, and those in stage AR was 85%. The cases treated by the COMA combination had a better survival than those treated by either CVP/CHOP with abdominal radiation (64% versus 38%). Twelve cases relapsed after achieving CR, only 4 in CNS and 1 in B.M. The study illustrates the pattern of Burkitt's Lymphoma in a middle eastern country which is completely different from that observed in endemic areas.

51 ABDOMINAL NON-HODGKIN'S LYMPHOMA IN CHILDHOOD: MIDDLE EAST TYPE.

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The survival of children with non-Hodgkin's lymphoma (NHL) has improved in the past decade. Surgical debulking of the tumor mass, combined with chemotherapy and, in a few cases, radiotherapy, have improved the prognosis of children with abdominal NHL. From 1978-1986 31 children (under 13 years of age) with NHL were treated at the Rambam Medical Center, Haifa, Israel. Of these, 21 patients (pts) presented with primary intra-abdominal disease. The age at diagnosis ranged from 2-13 years (median 4 years). In 12 children, abdominal masses were palpated on initial examination. All children, except one, underwent exploratory laparotomy. The terminal ileum, cecum and ascending colon were the organs most frequently involved with disease. In 16 pts, extensive resection was performed. Histologically, 17 children were found to have high grade malignancy (16-small non-cleaved cell, 1-large cell immunoblastic) and 4 had intermediate grade. Staging according to Ziegler classification revealed that 12 were in AR and 9 in C and D stages. Twenty pts were post-operatively treated with combination chemotherapy (19-COM; cyclophosphamide, vincristine and methotrexate, 1-LSA_2L_2). Three pts received additional radiotherapy. The overall survival is 85%, 17 are disease-free and only 1 has active disease, with a follow-up of 6 months to 8 years (median 50 months). The surgical and chemotherapy treatments of our pts did not substantially differ from those used in pediatric surgical centers outside the Middle East. Frequent presentation of childhood NHL in the abdomen, younger age (median - 4 years) of those with abdominal involvement and high survival rate (85%) are unique clinical features described in other studies from the Middle East. It is suggested that childhood abdominal NHL in the Middle East is of a different type.

52 LYMPHOPROLIFERATIVE DISORDERS ASSOCIATED WITH IMMUNODEFICIENCY (ID): TUMOR CHARACTERISTICS AND CYTOGENETIC ASSOCIATIONS.

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Four hundred ninety-one cases of malignancies that developed in persons with naturally-occuring (primary) immunodeficiencies worldwide have been collected in the ICR since 1973. These cases represent voluntary contributions from physicians as well as literature reports. The ICR contains a disproportionately high percentage of lymphoproliferative disorders, including NonHodgkin Lymphoma (NHL) (249 cases, 51%), Hodgkin disease (HD) (43 cases, 9%), and leukemias (62 cases, 13%). NHL are the predominant tumors reported in ID with T cell dysfunction: Wiskott-Aldrich syndrome (WAS): 75%, Ataxia Telangiectasia (AT): 46%, Common Variable ID: 47%, and Severe Combined ID (SCID): 74%. In contrast to NHL in nonimmunodeficient patients, NHLs reported to the ICR demonstrated the following characteristics: 1) they were frequently diagnosed at a very young age, 2) they had a proportional predominance of large cell, polymorphic, and/or so-called "histiocytic" morphologies, and 3) they frequently arose in the central nervous system or other extranodal sites, such as the intestine or lung. Cytogenetic analyses were not performed in many of the historical cases in the ICR. Among more recent cases "normal" karyotypes have been reported in a majority of cases submitted for routine cytogenetic analyses. A major exception to this observation is the frequent discovery of cytogenetic rearrangement in A-T cancers, and particularly T cell leukemias/lymphomas. Peripheral lymphocytes from A-T patients studied sequentially over time often reveal multiple clones with cytogenetic rearrangements involving chromosomes 7 and/or 14 principally. A number of T cell malignancies in A-T have appeared to arise from such populations of cells, and particularly from clones marked by a 14; 14 translocation: resultant malignant clones show a deletion of one chromosome 14, or the loss of 14q- ± other chromosomes. In contrast to the loss of chromosomal material in T cell tumors arising in patients with primary ID, multiple clones of B cells with more than 46 chromosomes have been observed in EBV-associated lymphomas in ID, especially in immunocompromised patients who have received T cell depleted bone marrow transplants. Prospective analysis of eight such cases at UMH demonstrated very rapid progression from polyclonal B cell hyperplasia to malignant lymphoma. Cμ heavy chain immunoglobulin gene rearrangements were demonstrated in 4/6 cases studied and cytogenetic abnormalities in tumor specimens from 2/5 patients.

53 ADULT T-CELL LEUKEMIA/LYMPHOMA (ATL)

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ATL is a unique T-cell malignancy first described by Takatsuki and colleagues in 1970s. We estimate that more than 200 patients a year have been detected in the endemic areas of Kyushu, Japan. The surface phenotypes of ATL cells characterized by monoclonal antibodies is T3+, T4+, T8-, T11+ and Tac+. In all cases the serum is positive for anti-HTLV-I antibodies and the ATL cells contain the proviral DNA of HTLV-I.

Variations in the clinical features of atypical ATL suggested a division of the spectrum of ATL into five types: acute; chronic; smoldering; crisis; and lymphoma. Typical ATL takes an acute course. The survival time is short, with 50% mortality within approximately 5 months. In general a poor prognosis is indicated by the elevation of serum lactate dehydrogenase, calcium, and bilirubin, as well as by high WBC. Smoldering ATL is characterized by the presence of a few abnormal cells (0.5%-3%) in the peripheral blood over a long period. Crisis in chronic or smoldering ATL means the progression of the disease to acute ATL. The lymphoma type of ATL is considered to be a form of T-cell-type non-Hodgkin's lymphoma in which malignant cells contain proviral DNA of HTLV-I.

Screening of the sera from healthy adults for presence of the anti-HTLV-I antibodies revealed that 3.6% of healthy individuals in Kumamoto Prefecture, which is located in the middle of Kyushu, were HTLV-I carriers. Family studies showed that the routes of natural infection of HTLV-I are from mother to child and also from husband to wife. The borderline between the healthy carrier state and smoldering ATL remains unclear. Smoldering ATL is frequently diagnosed in patients with fungus infection of the skin, chronic lymphadenopathy, interstitial pneumonitis, chronic renal failure and stronglyloidiasis.

Six patients with ATL refractory to conventional chemotherapeutic agents were treated with 2'-deoxy-coformycin (DCF), a potent inhibitor of adenosine deaminase. Three patients showed a good response, and three were resistant to DCF. In addition our experiences with a concurrence of lymphoma-type ATL in three sisters and spontaneous remissions in a patients with chronic ATL will be refered.

54 PROGNOSTIC VALUE OF BLOOD AND BONE MARROW T-COLONY-FORMI CELLS (T-CFC) IN PATIENTS WITH LYMPHADENOPATHY SYNDRO (LAS).

Y. Lunardi-Iskandar, V. Georgoulias, D. Vitteco W. Rozenbaum, P. Meyer and C. Jasmin. Unité d'Oncogénèse Appliqu (INSERM U 268), Hôp. Paul Brousse, B.P. 200, 94804 Villejuif Céde FRANCE ; Service de Santé Publique, Hôp. Pitié Salpétrière, B de l'Hôpital, 75013 PARIS Cédex and I.C.I.G., Hôp. Paul Brousse.

We have shown that patients with Acquired Immune Deficier Syndrome (AIDS) and with Persistent Lymphadenopathy Syndrome (LA present an impaired in vitro colony growth and differentiati capacity of peripheral blood T colony-forming cells (T-CFC) (1,2 In order to find whether the plating efficiency of peripher blood T-CFC could be of prognostic value, we studied the clinic evolution of 84 unselected LAS patients who were prospective followed over a period of up to 39 months. We report here th LAS patients (n=61) displaying a relatively conserved plat efficiency (more than 50 colonies/$5x10^4$ mononuclear cells) a better prognosis than patients (n=23) with a low plating efficie cy (less than 50 colonies/$5x10^4$ mononuclear cells) : indeed, the latter group, all 23 patients developed AIDS within 6-19 mon after the first detection of the low T-CFC number, whereas clinical status patients from the first group remained stab The difference between the 2 groups is highly signific ($p<0.00001$). The T-CFC assay appears thus to be of high prognos value in the follow up of LAS patients.

Ref (1) : Y. Lunardi Iskandar and al., Cl. Exp. Immunol. 19 60, 285.

Ref (2) : Y. Lunardi Iskandar and al., Blood, 1986, 67, 1063.

5 CLINICAL, MORPHOLOGIC, PHENOTYPIC, AND MOLECULAR GENETIC ANALYSIS OF AIDS/ARC-ASSOCIATED MALIGNANT LYMPHOID NEOPLASIA. DM Knowles, G Chamulak, M Subar, PG Pelicci, J Burke, R Schinella, R Dalla-Favera, B Raphael, New York University, New York, NY, and City of Hope, Duarte, CA, USA.

le identified malignant lymphoid neoplasms in 80 patients (pts.) lYU from 1981-1986 with AIDS 52, ARC 16 and at AIDS-risk 12. One was a 70-year-old woman with transfusion-related AIDS. The other ›ts. were males from 21 to 61, mean 38.7 years of age. Sixty-four (80%) were homosexual and 15 pts. (20%) were intravenous drug ;ers (IVDA). All 32 pts. tested had serum antibodies to the Human inodeficiency Virus. Opportunistic infections (OI) and Kaposi's :oma were present in 32.5% and 17.5% of the pts., respectively. :lassified the neoplasms as non-Hodgkin's lymphoma (NHL) 66, Hod-i's disease (HD) 12, and chronic lymphocytic leukemia (CLL) 2. We :lassified the NHLs as small non-cleaved 28, immunoblastic-plasma-›id 18, large non-cleaved 18, large cleaved 1, and unclassifiable \ll 21 NHLs examined expressed monotypic surface immunoglobulin /or B-cell antigens, suggesting a B cell origin. Antigen receptor e rearrangement analysis confirmed the B cell nature of all 14 s studied. Seven of these 14 B-NHLs contained multiple clonal B L populations and 10 of them contained a single B cell clone :ying c-myc gene rearrangements/translocations. The NHL pts. were ›ical stage(£) I(6), SII(3), SIII(8), and SIV(49). Forty pts. died 3 mos.), 17 pts. are alive (7.5 mos.), 6 pts. were diagnosed at ›psy and 3 pts. were lost to follow-up. We subclassified the 12 es of HD as nodular sclerosis 7, mixed cellularity 4, and lympho-e depleted 1. AIDS-associated HD was similar morphologically, notypically and genotypically to non-AIDS associated HD. These 13 . were clinical SII(1), SIII(3), and SIV(8). Six pts. died (14.3 .) and 6 pts. are alive (9.7 mos.). The 2 pts. with AIDS-associ-d CLL were IVDAs with lymphocytosis. The neoplastic cells were ll, mature appearing lymphocytes expressing the mature, peripheral pressor/cytotoxic ($T3^+T4^-T8^+$) phenotype and clonal T_B gene rear-gements. They lacked the morphologic and phenotypic features of ge granular lymphocyte/natural killer cell proliferations. One pt. d from OI (16 mos.); the other pt. is alive (11 mos.). These re-.ts demonstrate that 1) AIDS-associated malignant lymphoid neo-isms display marked clinical, morpholgic, and phenotypic diversity; AIDS-associated NHLs are diffuse aggressive B cell neoplasms dis-lying immunophenotypes similar to non-AIDS-associated B-NHLs of iparable morphology, are often multiclonal, similar to B-NHLs oc-ring in other immune deficiencies, and consistently display c-myc ie rearrangements/translocations, which may be important in their :hogenesis; 3) AIDS-associated HD is clinically aggressive but ierwise similar to HD occurring in the general population; and 4))S-associated T-CLL may represent a distinct clinicopathologic :ity.

6 EXPRESSION OF THE DEOXYNUCLEOTIDYL TERMINAL TRANSFERASE IN PERIPHERAL BLOOD CELLS OF INDIVIDUALS WITH ANTI HTLV-III/LAV ANTIBODIES. G.A. Losa, Laboratory of Cellular Pathology, 6600 Locarno, Switzerland

·ipheral blood mononuclear cells(PBMN) were isolated by Ficoll .dient centrifugation from individuals with a positive level of :i-HTLV-III /LAV antibodies and belonging to groups at risk. ilyses of the immunologic phenotype and cell size were performed flow cytometry after staining of cells with fluorescent monoclo- and polyclonal antibodies directed against surface markers. The ichemical profile of PBMN was delineated by measuring the activity the ectoenzymes 5'-nucleotidase (5'-AMPase) and γ-glutamyltrans-itidase (γ-GT) and of the soluble deoxynucleotidyl terminal trans-·ase (TdT) in cytosol fractions following high speed centrifuga-›n of the total homogenate. In a main group including patients :h an helper/suppressor ratio (H/S) less than 1.0,but regardless the group at risk, the mean 5'-AMPase was highly impaired (4.4 $\pm$ 3 nmole/hr/10^6 cells) but not the mean γ-GT in comparison to the :ivity values established in control PBMN (20.3 $\pm$ 8.6 and 19.8 $\pm$ 5 U respectively). In a smaller group with $1.0 < H/S < 1.5$, both ecto :yme activities did not significantly change from normal values. :eworthy, in the first group, the TdT was measurable biochemically more than half of the cases with activity values ranging from 1.7 100 pmole/min/mg proteins, while this activity was almost absent the other group with $H/S > 1.0$. A variable frequency of young lym-›cytes was noticed in all the cases examined and in 20% of the ca-; also the presence of blasts. Blood samples with TdT positive lls had in addition an increased total cell count (+ 20%), an in-ease of cells with the suppressor phenotype (+ 40%), a lower γ-GT 1.9 $\pm$ 6.1 U) and an higher 5'-AMPase (6.2 $\pm$ 7.1 U) when compared samples which contained cells characterized by the absence of TdT t a larger scattering of membrane-bound enzyme activities (24.2 $\pm$ .7 and 3.8 $\pm$ 3.5 respectively). T helper cells were at a similar vel in both groups. While the presence of TdT positive cells may ggest that these individuals express the capability to renovate e immature T-cell pool subsequent to the viral onset, at present, e cannot evaluate wether or not they are better equipped for ghting the cytopatogenetic viral effect.

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MALIGNANT NON-HODKINS LYMPHOMA (NHL) IN PATIENTS WITH HIV INFECTION. GILL P., LEVINE A.M., RARICK M., MEYER P., PATTENGALE P., RASHEED S. University of Southern California School of Medicine, Los Angeles, California, USA.

Sixty-four patients with malignant lymphoma and Human Immunodeficiency virus (HIV) infection were seen between Aug. 1981 and Jan. 1987. Fifty-nine were homosexual men, four were men with H/O IV drug use while one was a female without known risk factor for AIDS. Ages ranged between 19 and 65 years (median 38). Thirteen patients had diagnosis of AIDS prior to the diagnosis of lymphoma. Extranodal sites of lymphoma were present at initial diagnosis in 54 pts (86%). Central Nervous System (CNS) was involved in 23, 14 of whom had disease only in this site. Gastrointestinal tract was involved in 15, bone marrow in 14, kidney in 5, lung and heart in 4 each, and bone in 2. Pathologically, the lymphomas were high grade B-cell small noncleaved or immunoblastic sarcoma in 55 of 63 cases, while others were intermediate or low grade. The B cell origin was proven in 37 of 40 patients studied, using phenotypic markers and while 9/9 cases studied by immunoglobulin rearrangement studies. Laboratory studies revealed absolute T4 lymphocytopenia ranging from 0-1923/dl (median 190). T4:T8 ratio ranged from 0-3.5 (median 0.3). HIV serology was performed in 58 and was positive in 40. In addition, periopheral lymphocytes were cultured for HIV in 9 seronegative cases and were positive for HIV in all 9 analyzed. 48 patients were treated, while 15 were either diagnosed at autopsy or died before a specific therapy could be instituted. Cranial radiation was administered to 9 patients with primary CNS lymphoma, 4 of whom achieved complete remission. 8/9 of these pts have subsequently died of AIDS related infections or recurrent NHL (5) while one remains alive in remission 3 years from diagnosis. Patients with systemic intermediate or high grade lymphoma were either treated with CHOP (6), BACOD (5) or M-BACOD (17). 13 of these 28 achieved CR, 9 of whom are alive with a follow up of 1-5 years. 9 additional patients were treated with a novel regimen which included high dose cytosine arabinoside, methotrexate and cyclophosphamide. 3 patients achieved CR, but died of opportunistic infections (OI). All partial and non responders died of the disease with or without OI, within 12 months of diagnosis.

Summary: 1) Malignant lymphomas in the setting of HIV infection are most often high grade and extranodal sites are frequently involved.
2) These neoplasms are of B cell origin
3) Decreased T4 lymphocyte count and reversed T4:T8 ratio are seen in the majority.
4) Complete remission can be achieved in nearly 50% of the high grade lymphomas, however the overall survival is short because of recurrent disease or intervening OI.

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MALIGNANT LYMPHOMAS (ML) IN PERSONS AT HIGH RISK FOR AIDS IN ITALY: A REPORT OF 46 CASES. S.Monfardini, U.Tirelli, E.Vaccher, A.Ambrosini, A.Andriani, I. Bianco Silvestroni, G.Broccia, T.Chisesi, S.Fassio, M.Gobbi, G.Lambertenghi Deliliers, F.Lanza, A.Lazzarin, F.Lombardi, G.Luzi, S.Parrinello, R.Proto, F. Puppo, G.Rezza, G.Rossi, F.Gavosto, Gruppo Italiano Cooperativo AIDS & Tumori (G.I.C. A.T.).

Since November 1985 a cooperative study group has been established in Aviano and Torino, Italy, looking at the incidence and type of ML in persons at high risk for AIDS in Italy. A questionnaire was sent to members of Italian societies of immunology and haematology, to selected members of Italian societies of medical oncology and to selected infectious diseases specialists. 142 of the 1853 questionnaires were received. 36 patients (pts) with non-Hodgkin's lymphoma (NHL) and 10 pts with Hodgkin's disease (HD), predominantly i.v. drug abusers (IVDA) (35 pts), have been diagnosed in 16 different Italian centers. The group of NHL has a median age of 26 yrs (range 16-64): 26 were IVDA, 3 politransfused, 3 IVDA+ homosexual men, 2 homosexual men and 2 without apparent risk for AIDS but carrying HIV antibodies. 81% of the evaluable pts had high grade NHL (32% Burkitt's type) according to the Working Formulation, 15% intermediate and 4% low-grade. Out of 23 pts with stage reported, 16 (70%) were stage IV, 2 (9%) stage III, 1 (4%) stage II and 4 (17%) stage I (CNS involvement). HIV infection was detected in 94% of the pts, with 81% of the pts being diagnosed as AIDS according to CDC definition. Persistent generalized lymphadenopathy (PGL) preceded the diagnosis of NHL in 10% of the pts. The group of HD has a median age of 25 yrs (range 20-40), 9 were IVDA and 1 IVDA+ homosexual. 4 pts had nodular sclerosis and 3 mixed subtypes out of the 7 pts with subtype reported. Stage III and IV were reported in 66% of the pts. 9 pts had HIV antibodies. The median survival is 4 months for NHL and 10 months for HD. The most common cause of death is opportunistic infection in 86% of the evaluable cases. In conclusion, these preliminary data reveal for the first time the presence in Italy of a consistent number of ML, in particular NHL with a peculiar clinico-pathological feature, among persons at high risk for AIDS. Treatment employed and toxicity observed are presently under evaluation.

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59 CURRENT DIRECTIONS IN THE THERAPY OF HUMAN IMMUNODEFICIENCY VIRUS INFECTION

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Recent advances in our understanding of the biology of HIV, the causative agent of AIDS, offer new possibilities for drug development. One drug, zidovudine (formerly called azidothymidine), has been shown to improve the clinical course of patients with advanced HIV infection. This drug reduces levels of circulating p24 antigen presumably by blocking viral replication through inhibition of reverse transcriptase and by causing DNA chain termination. Agents with similar postulated mechanisms of action include the nucleoside analogs dideoxycitidine and dideoxyadenosine. The first of these is more potent on a molar basis than zidovudine and has entered clinical trials. Other potential anti-HIV drugs have been designed to block viral attachment to or penetration of otherwise susceptible cells. Examples of such agents include the pentapeptide peptide T and the lipid mixture AL721. Still other drugs may function to prevent viral protein translation or viral assembly such as the alpha and beta interferons. While the individual role of the various drugs mentioned is unclear it is reasonable to hope that combinations may increase drug benefit. Clinical trials of anti-HIV agents will be critical to address three goals. These include the prevention of transmission to the uninfected, the maintenance of immune competence in the asymptomatic seropositive, and the restoration of immune status in the person with established AIDS or ARC. While clinical trials have been focused on the final goal our increasing evidence of high rates of progression in seropositives is leading to their inclusion in the next group of these studies.

60 HUMAN LYMPHOTROPIC VIRUSES (T & B CELL) AND THEIR ROLE IN MALIGNANCY, AIDS AND CENTRAL NERVOUS SYSTEM DISEASE.

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Human T-cell lymphotropic viruses (HTLV) are a group of related, but distinct retroviruses of man. HTLV-I, the prototype of this group of viruses, is the causative agent of adult T-cell leukemia/lymphoma (ATL). Over 200 HTLV-I isolates have been obtained since their discovery in sporadic cases of adult T-cell malignancies in the U.S. The vast majority of isolates are very closely related. HTLV-I is endemic in the Caribbean, South and Central America, southeast U.S., and especially Africa. Evidence indicates that HTLV-I is the direct cause of an aggressive form of adult T-cell leukemia and lymphoma (ATL). The mechanisms involved in the in vitro immortalization and in vivo malignancy appear to be by initiation of T-cell proliferation through a trans-acting activation of Il-2 and its receptors. Other genetic charges are probably necessary for conversion to the full malignant state, but apparently do not involve any visible consistent chromosomal change, consistent virus expression, or known onc gene. Recently, an involvement of HTLV-I in central nervous system disease has been established. A second class of human T-lymphotropic retroviruses (HTLV-II) shares many features with HTLV-I but has major genomic differences. This virus can also immortalize T4 cells. It has been isolated only from a few patients with hairycell leukemia. The role of HTLV-II in human disease is unknown. The third subgroup (HTLV-III) has been isolated from patients with AIDS and AIDS related complex (ARC). Over 300 isolates of HTLV-III have been obtained. This retrovirus is highly T4 tropic, but has only the cytopathic not immortalizing effects. Isolates of HTLV-III have come from patients with AIDS or people at high risk for this disease. Sera from over 90% of AIDS and ARC patients have antibodies specifically against this virus, whereas <1% of healthy heterosexuals are positive. These studies indicate that HTLV-III is the etiological agent of AIDS. We have demonstrated that HTLV-III is the cause of AIDS, developed a blood bank test and shown that there is genomic heterogeneity. The mechanism of how this virus causes disease, both neurological and immunological is under intensive study. Work is in progress to develp a vaccine and chemotherapeutic agents for control and treatment of this disease.

Recently, we have isolated a new herpes-like virus. We have called this virus HBLV for human B-cell lymphotropic virus. The potential role of this virus in human disease is currently under study.

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CURRENT STATUS OF NCI-TRIALS.
R.C. Young, Bethesda, USA

(not received)

62 NON-HODGKIN'S LYMPHOMAS: CURRENT TRIALS IN THE UNITED STATES.

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The Working Formulation classification divides the NHL into three broad categories for clinical trials: indolent or low-grade (L-NHL), intermediate, and aggressive or high-grade (H-NHL).

Advanced stage low-grade (L-NHL) are generally considered incurable with current therapies. This concept has often led to deferral of treatment until clinically indicated, as exemplified by the Stanford trials. While chemotherapy, single agent or combination, may result in high complete response (CR) rates, cures have not been observed. However, several caveats must be noted: 1) specific sub-types of L-NHL behave differently (follicular small-cleaved vs. mixed); 2) 20-40% of L-NHL transform over time to a more aggressive histology; 3) stage III may be potentially more curable than stage IV; 4) regimens more intensive than CHOP ± Bleo or M-BACOD have rarely been investigated. Newer approaches now in clinical trial include: chemotherapy regimens of maximum intensity; the use of biologicals, including the interferons, 2'-deoxycoformycin, monoclonal antibodies; and marrow-ablative treatment prior to transplantation. The goal of clinical trials in L-NHL should be to determine if cure is realistic with avaiable modalites.

Advanced stage intermediate and high-grade (H-NHL) are potentially curable with the chemotherapy regimens developed over the past decade. First generation regimens such as CHOP led to an improvement in the CR rate with a plateau in the survival curve indicating that 30% of all patients are cured after 13 years of follow-up. Second generation regimens, such as M-BACOD or ProMACE/MOPP, were followed by third generation combinations including MACOP-B, COP-BLAM III, ProMACE/CytaBOM. These newer regimens reported higher CR rates (70-86%), with both improved disease-free survival (50-76% at 3-5 years) as well as overall survival (50-69%). These impressive preliminary data from single institutions must be viewed with caution for the following reasons: 1) variability among known prognostic factors in various trials; 2) small numbers of patients entered; 3) short follow-up; 4) lack of confirmation to date in large-scale, multi-center, randomized trials. Current US randomized trials are investigating the relative efficacy of these newer regimens (CHOP vs. m-BACOD vs. MACOP-B vs. ProMACE/CytaBOM) with appropriate stratification for known prognostic factors. In addition, distinct clinicopathologic entities such as lymphoblastic lymphoma are being investigated separately with protocols similar to the treatment for acute lymphoblastic leukemia. The goal of front-line therapy for all stages of H-NHL remains cure.

63 CURRENT STATUS OF TRIAL IN EUROPE, ESPECIALLY UK.

T.A. Lister, Dep. of Medical Oncology, St. Bartholomew's Hospital, West Smithfield, London, EC1, England

Clinical trials of therapy for advanced non-Hodgkin's lymphoma (NHL) conducted during the 1970's and early 1980's demonstrated that relatively short term alkalating agent therapy was as effective as anything else in terms of survival for low grade NHL and that 'CHOP' or its varients yielded approximately 30% overall long term survival for high grade NHL.

Data from selected trials in progress in Europe, incorporating Interferon for low grade NHL, and very intensive chemotherapy with or without bone marrow transplantation for high grade NHL, will be presented to demonstrate the outstanding problem still to be addressed.

64 SURVIVAL OF GOOD PROGNOSIS DIFFUSE LARGE CELL LYMPHOMA PATIENTS TREATED WITH CHOP OR CHOP-VARIANTS.

JR Anderson, J Glick, S Ginsberg, A Gottlieb, D Harrington, M O'Connell for Cancer and Leukemia Group B (CALGB) and the Eastern Cooperative Oncology Group (ECOG), Brookline, MA 02146, USA.

Improved survival for patients with diffuse large cell lymphoma (DLCL) has been reported for regimens like m-BACOD & MACOP-B as compared with CHOP. Other reports have identified pretreatment patient characteristics predictive of treatment outcome. Performance status and symptomatic stage (A vs B) are important predictors of survival. To assess how survival might differ among different patient sub-groups, we compared the survival of 323 stage III/IV patients on recent studies by CALGB [C7851, Proc ASCO 4:202, 1985] or ECOG [E5477, Proc ASCO 3:214, 1984] treated with CHOP or CHOP-variants by performance status and symptomatic stage:

		Estimated 5-Year Survival				
#pts	PS0, A	PS1, A	PS2+, A	PS0, B	PS1, B	PS2+, B
CALGB(168)	57%(39)	32%(33)	31%(13)	23%(20)	34%(36)	32%(27)
ECOG (155)	56%(37)	33%(32)	29%(13)	39%(15)	22%(35)	26%(23)
TOTAL(323)	56%(76)	33%(65)	30%(26)	30%(35)	27%(71)	30%(50)

After adjustment for performance status and symptomatic stage, neither clinical stage, age nor gender was prognostic for survival. Stage II patients treated on E5477 had survival that exceeded that for the PS0, A patients (62% at 4 years). In this analysis, five-year survival for most subgroups of patients with DLCL treated with CHOP or CHOP-variants is about 30%. However, there exists a subset of good prognosis patients (defined as Stage II or stage III/IV with PS 0 and asymptomatic) for whom CHOP or CHOP variants produces long-term survival in excess of 55%. Recent single institution trials for DLCL may have treated a majority of good prognosis patients. If so, the improved survival of these patients may only reflect the better prognosis of the patients being treated. Prospective randomized controlled trials are required before second and third generation regimens may be accepted as being superior to CHOP.

65 CHOP IS CURATIVE IN THIRTY PERCENT OF PATIENTS WITH DIFFUSE LARGE CELL LYMPHOMA: A TWELVE YEAR SOUTHWEST ONCOLOGY GROUP FOLLOW UP.

C.A. Coltman, Jr., S. Dahlberg, S.E. Jones, T.P. Miller, B.W. Dana, E.M. McKelvey, R.J. Hartsock, and D.O. Dixon. For the Southwest Oncology Group, 5430 Fredericksburg Road, Suite 618, San Antonio, TX 78229-3533.

Between 1972 and 1983, the Southwest Oncology Group has conducted three studies (SWOG 7204, 7426, and 7713) using CHOP (cyclophosphamide, hydroxyldaunorubicin, vincristine, and prednisone) alone, and in combination with bleomycin, BCG and levamisol, involving 1873 patients with non-Hodgkin's lymphoma. None of these CHOP combinations have substantially changed the treatment outcomes of patients with non-Hodgkin's lymphoma, when compared to CHOP alone. A subset analysis of 418 patients with diffuse large cell lymphoma treated with CHOP, and its variants, on these three studies reveals a complete response rate of 53% (SWOG 7204, 37/67-55%; SWOG 7426, 75/134-55%; and, SWOG 7713, 110/217-50%. The relapse free and overall survival curves show that patients continue to relapse and die through seven years of follow up. At seven years the curves plateau at 49% for relapse free survival and 30% for overall survival. Maximum follow up is twelve years. The relapse free and overall survival in the two more recent CHOP studies (SWOG 7426 and 7713) were significantly superior to the initial study (SWOG 7204)(P=0.005 and 0.008, respectively). The differences may be due to the fact that patients in SWOG 7204 received four to seven cycles of CHOP, compared to eight to eleven cycles in the latter two studies. Considering the two latter studies only (SWOG 7426 and 7713), the relapse free survival of the diffuse large cell lymphoma patients plateaus at 52% and overall survival at 32%. The complete response rate, among the 360 diffuse large cell lymphoma patients, in the two recent comparable studies (SWOG 7426 and 7713) decreases significantly with increasing age (≤55 yrs, 82/130-60%; 55 to 64 yrs, 66/130-51%; 65 or greater, 37/92-40%). Relapse free and overall survival similarly decrease with increasing age (P=0.04 and 0.0002 respectively). Among those less than 55, the relapse free survival plateaus at 63% with four years of follow up and the overall survival at 47% with 4 2/3 years of follow up. These data are compatible with the hypotheses that CHOP is curative in 30% to 32% of patients with diffuse large cell lymphoma, and that age is one of the important pretreatment prognostic factors.

The Southwest Oncology Group is now involved in a large intergroup Phase III clinical trial in which CHOP is being compared to m-BACOD, ProMACE-CytaBOM, and MACOP-B in intermediate and high grade lymphoma. This trial will answer, in a definitive way, which of these regimens will provide the optimum result in the various stages, age groups and histologies of aggressive lymphoma.

66 CHOP-B ALTERNATED WITH CMED IN THE TREATMENT OF AGGRESSIVE LYMPHOMAS.

W.S. Velasquez, S. Batizy, F. Cabanillas, P. McLaughlin, F.B. Hagemeister, F. Swan, B. Barlogie. U.T. M.D. Anderson Hospital and Tumor Institute, Houston, Texas, U.S.A.

Based on the Goldie-Coleman hypothesis we have used 2 alternating non-cross-resistant regimens (CHOP-Bleo and CMED) to treat 102 patients with Intermediate and High Grade Lymphoma with exception of lymphoblastic and undifferentiated types. Two cycles of CHOP-Bleo were alternated with two cycles of CMED: Cytoxan (500 mg/m^2 d1), MTX (1.0g/m^2 d3) with leukovorin rescue, VP-16 (100 mg/m^2 daily on d1-3) and Decadron 40 mg daily d1-4. A total of 12 courses were given, with XRT administered to stage II and III patients achieving PR or CR. Median age was 56 (range 17 to 82). There were 80 patients with Diffuse Large Cell or Immunoblastic Sarcoma and 19 patients with other aggressive lymphoma histologies. Responses are given below:

Stage	PTS	CR(%)	Relapses(Pts)	PR(%)	NR(%)
II	30	26 (87)	2	2 (7)	2 (6)
III	26	20 (77)	1	5 (19)	1 (4)
IV	46	30 (65)	2	12 (26)	4 (9)
	102	76 (75)	5	19 (18)	7 (7)

No significant differences in response were noted for age, sex, constitutional symptoms and histopathology. However, LDH value and tumor burden (stage III-IV) were significantly related to achievement of CR. Twenty-three patients (52%) among 44 with LDH >300 mg achieved CR, while 43 (77%) of the remaining 56 patients achieved CR. Also, CR was higher for patients with low tumor burden (75%) than for high tumor burden patients (62%), defined as having 2 or more areas of extensive nodal or extranodal involvement or its combination. With a median follow-up of 14 months, a projected 2 year relapse rate was of 12%. The treatment has been well tolerated with the expected myelosuppression and rarely, mucositis. No septic deaths have been seen. These preliminary data demonstrate the efficacy of this treatment associated with fewer complications than other chemotherapy regimens.

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MACOP-B, 12 Weekly Treatments for Aggressive Lymphomas: 6 Years of Experience. P.Klimo, J.M.Connors, Cancer Control Agency of British Columbia, Vancouver B.C., Canada, V5Z 4E6.

125 new patients (pts) with advanced aggressive(large cell) lymphomas were treated with MACOP-B chemotherapy (methotrexate with folinic acid rescue,doxorubicin (Adriamycin), cyclophosphamide, vincristine (oncovin), prednisone and bleomycin). This novel program emphasizes the frequency of treatments (weekly), alternation of potentially non-cross-resistant agents (Goldie-Coldman somatic mutation hypothesis), strict dose reduction guidelines, brevity (3 m), daily administration of steroids and anti-infectious prophylaxis (cotrimoxazole and ketoconazole).

105 pts (84%) achieved complete remission (CR), 18 pts (14.4%) had only partial response (PR) and 2 pts (<2%) were primary failures. 6 pts (4.8%)died of treatment related toxicity. 10% pts had to be hospitalized for either proven or suspected non fatal systemic infections. The most frequent toxicity was methotrexate related mucositis(>50%). 107 pts (86%) received the full complement of 12 treatments and 117 pts (94%) took at least 10 doses of chemotherapy.

All but 3 of the PRs died from lymphoma within 18 m from the diagnosis. 24 pts relapsed; all relapses of aggressive lymphoma (22) took place within the first 12 m of follow up. The majority of relapses failed to enter a 2nd remission and died.

The actuarial survival of all 125 pts at 66 m of follow up is 68% (median follow ups of all and living pts only are 22 m and 36 m respectively). The actuarial relapse free survival of the 105 CRs at 63 m of follow up is 75% (median follow up of all CRs is 21 m).

MACOP-B results are at least equal to the best reported in the literature to date. They have been achieved with an acceptable degree of treatment related toxicity, over a shorter period of time and with much diminished socioeconomic impact on the treated patients.

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Aggressive lymphomas treated by intensive chemotherapy: updated results of LNH-80 protocol with a median follow-up of 52 months. B Coiffier, C Sebban, M Ffrench, PA Bryon, F Berger, JP Magaud, JJ Viala. Hematology Hematology Service. Hopital Edouard-Herriot, Lyon France.

From 1980 to 1984, we have treated 100 patients (pts) with the LNH-80 protocol (J Clin Oncol 1986;4:147): intensive 3 courses induction, sequential consolidation, and terminal intensification. Working Formulation histologic grade was intermediate in 47 pts and high in 53 pts. Immunological phenotype was B in 24 pts, peripheral T in 23 pts, and unknown in 63 pts. 23 pts had stage I-II, 11 stage III, and 66 stage IV. B symptoms were present in 48 pts. PS was >= 2 in 46 pts. A large tumoral mass was present in 65 pts, and more than 1 extranodal site was involved in 59 pts.

Results of induction were: CR in 84 pts, PR in 8 pts, failure in 3 pts, and death in 5 pts. 23 pts have relapsed (27 %), 3 after 2 years. Median survival and median FFR survival were not reached with a median follow-up of 52 months. Currently 64 pts are alive, 3 with disease and 2 in stable 2nd CR (during more than 3 years). 4 pts had died in CR. Survival of not-CR pts is very poor with only 2 pts alive at 2 years. With the logrank test, variables negatively associated with CR are: marrow involvement, LDH > 2.5 times normal level, peripheral T phenotype, PS >= 2, hepatic involvement, Hb < 100 g/l, and more than 1 extranodal site. With multivariate analysis, variables negatively associated with response are: marrow involvement, PS >=2, age, and more than 1 extranodal site. Variables associated with death before 4 years are: age, high grade histological type, PS >=2, marrow involvement, LDH level, large tumoral mass, and dose-intensity of induction therapy (logistic regression and Cox model analysis). The strongest prognostic variables are marrow involvement, PS and age. Immunological phenotype was not included in the multivariate analysis due to the small number of pts analysed but was equally very strong in univariate analysis. The index defined by MA Shipp with M/m-BACOD therapy (Ann Int Med 1986;104:757), containing PS, tumoral mass, and number of extranodal site, keep some prognostic signification ($p<0.05$) but less than in its description and it disappears in multivariate analysis.

This intensive chemotherapy is currently being tested in a randomized multicentric study (protocol LNH-84). More than 580 pts have been enrolled in 28 months. Preliminary results are identical to those describe for LNH-80, and will be presented after the completion of the study (750 pts).

69 TREATMENT OF LYMPHOBLASTIC LYMPHOMA IN ADULTS. J. Colgan, J. Andersen, J. Glick, M. O'Connell, J. Earle. Mayo Clinic, Rochester, MN 55905, University of Pennsylvania, Philadelphia, PA 19104, and Eastern Cooperative Oncology Group (ECOG), Madison, WI 53706.

Between 1980 and 1985, 38 patients with lymphoblastic lymphoma (LL) were treated with an aggressive multidrug induction regimen, early central nervous system (CNS) prophylaxis, and maintenance (M). Patients ranged in age from 18 to 62. Those with CNS involvement at presentation or >5000 circulating lymphoblasts were ineligible. Induction: Cytoxan 750 mg/m^2 IV day 1, 22; Adriamycin 50 mg/m^2 day 1, 22; Vincristine 1.2 mg/m^2 day 1, 8, 15, 22, 29; and Prednisone 40 mg/m^2 p.o. day 1-40; and L-Asparaginase 6000 U/m^2 (max 10,000) for five doses q.o.d. beginning day 24. CNS treatment: 2400 cGy to whole brain in 12 fractions day 35-49; intrathecal Methotrexate day 1, 22, 35, 38, 42, 45. M: CHOP alternating with Ara-C, 50 mg/m^2 weekly and 6-Thioguanine 75 mg/m^2 four days a week. To date, 31/38 patients have achieved CR (82%). Eleven have relapsed, and all relapsed patients have died. There were three CNS relapses. Median follow-up is 2.2 years, and 20 patients continue in CR, with a median duration of relapse free survival (RFS) of 24 months (6-60 months). For all patients, actuarial survival at 36 months is 49%. Performance status 0, 1, 2, female sex, and pathological Stage I, II, III were favorable prognostic indications. 13/16 patients with negative bone marrow are alive as opposed to 11/22 with positive bone marrow, but survival differences are not yet significant. There were two toxic deaths and life-threatening cytopenia in 70% of patients. This regimen is highly effective in inducing CR in LL and can produce long RFS in some patients. Longer follow-up will be needed to assess the role of M.

70 SOUTHWEST ONCOLOGY GROUP CLINICAL TRIALS FOR INTERMEDIATE AND HIGH GRADE NON-HODGKIN'S LYMPHOMAS. T.P. Miller, B.W. Dana, J.K. Weick, S.E. Jones, C.A. Coltman, S. Dahlberg, R.I. Fisher. Tucson, Arizona. For the Southwest Oncology Group.

The Southwest Oncology Group (SWOG) began testing adriamycin-containing combination chemotherapy in 1972 using the CHOP regimen (cyclophosphamide, hydroxyldaunorubicin, vincristine and prednisone). CHOP has been shown to be curative in 32% of advanced stage diffuse large cell lymphomas including 350 patients followed for up to 13.3 years. The CR rate varied depending on age (68% for patients younger than 40, and 37% for those older than 65). Recent unconfirmed single institution pilot studies suggest that several new aggressive regimens including m-BACOD, ProMACE-CytaBOM and MACOP-B may be better than CHOP as gauged by CR rates (the CR rates for these regimens vary from 73% - 84%). Consequently, the SWOG developed a strategy to directly compare these 3 regimens to standard CHOP. In 1984 the SWOG began testing these regimens in sequential Group-wide phase II trials to confirm therapeutic activity, establish feasibility with regard to toxicity in a cooperative group setting, and gain experience using the complex schedules and dose modification schemes. Those phase II studies have been completed and preliminary results follow.

Regimen	No. Patients	No. Response evaluable	CR %	Toxicity %LT	Toxicity %fatal
m-BACOD	84	84	65	31	6
ProMACE-CytaBOM	97	83	58	20	5
MACOP-B	131	TE	TE	28	2

TE=too early, LT=life threatening.

We conclude that these three "third generation" drug regimens can be safely administered in a cooperative group setting, and have subsequently activated a phase III comparative trial using CHOP as the standard treatment arm.

71 PATTERNS OF RELAPSE IN LARGE CELL LYMPHOMA PATIENTS WITH MASSIVE BULKY DISEASE.

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In large cell lymphoma (LCL) patients treated with combination chemotherapy, the presence of massive bulky disease (MBD) has consistently been associated with poorer response rate and shortened survival. The optimal therapy for LCL patients with MBD will depend on whether treatment failures result from inadequate sterilization of bulk sites or from distant dissemination. To address this issue, we have evaluated patterns of relapse in LCL patients with MBD treated with M- or m-BACOD from 1976 to 1985. Fifty-eight of the 169 LCL patients had disease which was greater than 10 cm in largest dimension (MBD); 50 of these patients achieved either a complete or partial response to therapy. Twenty-one MBD patients had only local disease (Stage II), whereas 29 patients had additional distant involvement (Stage III/IV). Among the Stage II MBD patients, there were 18 complete responders (CR) and 3 partial responders (PR). Four of these Stage II patients subsequently relapsed, each in the site of prior bulk disease. Among the Stage III/IV MBD patients, there were 16 CR and 13 PR. Although 22 of the 29 Stage III/IV MBD patients eventually relapsed, only two patients relapsed solely in the site of prior bulk disease. The remainder recurred in either a new site (4), a new and an old site (11), an old non-bulk site (3), or both old non-bulk and bulk sites (2). These results suggest that while certain stage II MBD patients may benefit from additional directed local radiation therapy, Stage III/IV patients are unlikely to do so.

72 FACTORS ASSOCIATED WITH RESPONSE, SURVIVAL (SURV) AND TRANSFORMATION (TRANSF) IN RECURRENT LOW GRADE FOLLICULAR LYMPHOMAS (LGFL).

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Patients (pts) with LGFL have an indolent clinical course, but the factors associated with response and surv once they relapse are not known. In an ongoing study, we have analyzed 60 pts with relapsed or primary resistant (5 pts) LGFL treated under 4 salvage protocols (salv prot). Median number of relapses at entry into salv prot=2 (0-6). Forty-eight had follicular small cleaved cell and 12 follicular mixed cell lymphoma. Median surv from diagnosis (dx) was 117 months (mos) and from salv prot 44 mos. Analysis of 10 factors at time of dx showed that none was of prognostic value for response or surv from entry into salv prot. Five of 14 factors analyzed at entry into salv prot were significant for response and/or surv:

Characteristic	No.	CR(%)	P	CR+PR (%)	P	Median Surv(mos)	P
B Symptoms:							
Yes	13	0(0)	.009	3(23)	.005	9	.002
No	46	16(35)		31(67)		46	
Bulky	25	4(16)	.06	9(36)	.007	18	.011
Non Bulky	34	12(35)		24(71)		46	
No. Relapses:							
>2	37	3(8)	<.001	17(46)	.03	18	.024
≤2	22	13(59)		16(73)		46	
LDH: <400	15	1(7)	.03	8(53)	.23	10	.002
>400	44	15(34)		25(57)		46	
Stage IV	30	6(29)	.11	13(43)	.017	26	.186
<IV	29	10(34)		21(72)		48	

Median surv from first relapse was 71 mos, from second relapse 45 mos, from third 31 mos, and from fourth 12 mos. Transf to an intermediate grade lymphoma occurred in 23 cases (38%) at a median time of 6 yrs (2-17). Their median surv after transf was 14 mos (1-64). Since transf was a late event, it appears that factors associated with a favorable surv (from dx) were the only ones predictive of transf. Only 2 factors at dx were significantly associated with transf: non bulky presentation (19/38=50% transformed) vs bulky (4/22=18%) and <2 extranodal sites (20/44=45%) vs ≥2 extranodal sites (3/16=19%). Relapsed pts with either B symptoms, LDH ≥400, ≥2 relapses or bulky tumors have a poor surv; they should be considered for innovative or intensive therapy. Transf is associated with poor surv once it occurs, but is seen mostly in pts with long standing disease, and consequently it does not affect surv from original dx.

73 INCIDENCE OF TRULY INDOLENT LYMPHOMA AND THE IMPACT OF A "NO TREATMENT" POLICY.

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The selected series of patients attending the Stanford lymphoma clinics have provided the best data in recent years on the natural history of low grade non-Hodgkin's lymphoma (LGNHL). What is not known is the frequency of truly indolent lymphoma and whether physicians have a better than random ability to select patients who may never require treatment. At two major UK centres, the population of patients with lymphoma is less selected than at most US research institutions and patients are predominantly managed in the hospital out-patient clinics.

We have obtained data on 182 patients with LGNHL from these clinics and their records were analysed to study the natural history of the disease, median follow-up 62 months, range 12-192 months. 71 patients had been allocated treatment according to the presence or absence of B symptoms (stage I excluded) in a randomised trial. The remaining 111 were managed with a "watch and wait" policy in the absence of systemic symptoms or rapidly progressive disease (stage II 19; III 44; IV 93). 51 patients received no treatment at the time of diagnosis. Of these 22 were allocated the no treatment arm of a "no treatment vs. chlorambucil" randomisation (B symptoms excluded). The other 29 received no treatment by the choice of the attending physician. 11/22 (50%) and 13/29 (44.8%) have not required systemic treatment with a median follow-up of 59 m (12-182 m). This group of "never treated" patients had no special characteristics in terms of their age, sex, clinical stage, pathology or sites of involvement and did not differ from the 27 patients who have eventually required treatment. Median time until treatment required for this latter group was 10 m (2-68 m) in trial and non-trial patients.

From this we conclude that there are no established prognostic variables which will characterise patients with LGNHL who will never require treatment (random allocation 50% have not yet been treated, by selection 44.8% have not yet been treated) but by allocating a policy of no initial treatment in this group at least 13% (24/182) may never require treatment.

74 LONG-TERM OUTCOME WITH OR WITHOUT TUMOR PROGRESSION IN FOLLICULAR LOW GRADE NON-HODGKIN´S LYMPHOMA.

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93 patients with follicular small cleaved cell (F-SC) and 34 patients with mixed small cleaved and large cell (F-M) lymphomas were followed for a minimum of 6.5 yrs (6.5-16.3 yrs for pts alive at cut-off). 99 pts were treated with low toxicity regimens (extended field irradiation, single agent chemotherapy or CVP), 22 were treated with CHOP, 6 had no initial treatment. Response and relapse rates were unaffected by the regimen used. 75/127 (59%) relapsed or had PD. Tumor progression was defined as 1)change in histology to diffuse growth pattern and/or large cell cytology and/or 2) change in disease topography from typical (T) sites of involvement (lymph nodes, Waldeyer´s ring, spleen liver, bone marrow, peripheral blood) to atypical sites (all other extranodal sites) (AT). 28/49 (57%) with repeat biopsy had histologic tumor progression, and the actuarial risk of histologic conversion among relapsing pts was 30% at 5 years and 54% at 9 years. The ratio T:AT was 120:7 at diagnosis decreasing to 39:36 during follow-up in relapsing patients. Overall 42/75 had either topographic or histologic tumor progression, and this change in disease behaviour did not seem to be a late event, since the overall survival for pts with tumor progression was 52 mos compared to 102.5 mos for pts with relapse not associated with tumor progression (P =.00005). The only covariates that significantly increased the risk of tumor progression were no achievement of initial CR (P = .0001), and CSIV (P =.025). No effect on tumor progression could be demonstrated for age, sex, symptoms, abdominal bulky tumor or type of treatment. F-M histology did not increase the risk of tumor progression.

84/127 pts (66%) died during the follow-up period, and 50% of long-term survivors (at 8- and 10-years) had had active disease. The only subset of pts that seemed to be cured had CSI at presentation. In a Cox multivariate analysis, high age was shown to be the most important negative prognostic factor, but examining the causes of death we found that 45% of pts older than 60 years died of causes unrelated to lymphoma or therapy, whereas younger pts died of lymphoma (69%), and secondary malignancies (11%). Follicular low grade lymphomas are incurable with low toxicity therapy and CHOP,and with a long follow-up 50-60% of the pts will develop signs of tumor progression implying a poor prognosis. Except for the few patients with atypical topography at presentation, we were unable to identify subsets of pts with a particular high risk of tumor progression. A search for more reliable and refined methods for factors defining pts at high risk for tumor progression is needed. In selected younger patients with symptomatic disease very intensive experimental treatment seems justified if the dismal long term prognosis should be improved.

75 DOSE INTENSITY ANALYSIS FOR CHOP CHEMOTHERAPY IN UNFAVORABLE LYMPHOMA. R. Epelbaum, Y. Ron, N. Haim M. Ben-Shahar, Y. Cohen. Northern Israel Oncology Center, Rambam Medical Center and Faculty of Medicine, Technion-Israel Institute of Technology, Haifa 35254, Israel.

Ninety newly diagnosed patients (pts) with diffuse histiocytic (71 pts) and diffuse mixed (19 pts) lymphoma were treated primarily with CHOP chemotherapy (Cyclophosphamide-C, Adriamycin-H (A), Oncovin-O, Prednisone-P) at our center between April 1977 and December 1984. There were 45 men and 45 women with a median age of 60 years (range 16-79). Forty pts had stage I-II and 50 pts stage III-IV. Sixty-four pts (71%) achieved complete remission (CR) with 5-year relapse-free survival of 70%. Overall actuarial 5-year survival was 51%. Seventy-eight pts had complete data available for analyzing the relationship between dose intensity (DI) and outcome. The reference regimen used was the full dose CHOP in a cycle of 21 days (after McKelvey, Cancer, 1976), with projected C DI=35.7 mg/m^2/day, A DI=2.4 mg/m^2/day and O DI= 0.07 mg/m^2/day. The median relative DI (RDI), i.e., the fractions of the DI actually received (after reduction for toxicity and delays) were 0.72 (0.24-1.10) for C, 0.70 (0.24-1.07) for A, and 0.69 (0.19-1.04) for O. The average RDI, i.e., the arithmetic means for the RDI of the 3 drugs in each pt ranged from 0.22 to 0.98, with a median of 0.69. In order to correlate the probability of attaining CR with RDI we calculated, in each pt, the DI parameters for the initial cycles needed to achieve maximum response (median-4). A significantly greater proportion of complete responders received >0.8 average RDI, C RDI and A RDI, as compared to non-complete responders: 52% vs. 23%, 62% vs. 34% and 61% vs. 29%, respectively (x^2, $p<0.05$). The analysis of survival was performed in 61 pts who achieved CR. Among DI parameters, calculated for all cycles, the RDI of C was best and significantly correlated with survival: pts receiving >0.7 had 81% actuarial 5-year survival as opposed to only 54% actuarial 5-year survival of those receiving <0.7 ($p<0.05$). This relationship was valid in pts with stage I-II as well as in pts with advanced stage III-IV. These data indicate that there is a clear dose rate effect of CHOP therapy on the therapeutic outcome. Particularly, we have been able to isolate the DI effect of C on response and survival. High dose rate of C may be necessary to achieve improved results, while the role of high DI of A and especially O is questionable.

76 AUTOLOGOUS BONE MARROW TRANSPLANTATION IN HODGKIN'S DISEASE. J. O. Armitage, Department of Internal Medicine, University of Nebraska Medical Center, 42nd and Dewey Avenue, Omaha, Nebraska USA.

The majority of patients who develop Hodgkin's disease are currently able to be cured with conventional therapies. However, patients who have failed a frontline chemotherapy regimen for Hodgkin's disease do not have a good outlook. The most frequently utilized regimen has been ABVD, utilized primarily in patients who have failed a MOPP-like regimen. Long-term, disease-free survival has ranged from 0 to 40% (i.e. being 22% in the largest series). Patients who relapse after 2 chemotherapy regimens for Hodgkin's disease are rarely cured with further chemotherapy. Because of this poor outlook with further conventional therapy, high dose therapy and autologous bone marrow transplantation has been tested in these patients. In 7 large series utilizing high dose therapy and autologous bone marrow transplantation in Hodgkin's disease including 173 patients, 96 patients (55%) achieved complete remission. Toxicity of this approach was significant with early death in 20 patients (12%). The largest series reported to date has found a 70% complete remission durability at 2 years. Both the number of preceding therapies (i.e. favoring less therapy) and tumor bulk (i.e. favoring less bulk) appear to be important prognostic factors. A proportion of patients with Hodgkin's disease who would otherwise be good candidates for this treatment approach are ineligible because of bone marrow involvement or previous radiotherapy making bone marrow collection impossible. We have recently treated 5 such patients utilizing peripheral blood stem cells collected by cytopheresis. These patients underwent eight 4-hour phereses. The pheresis products were cryopreserved and reinfused after high dose therapy. The number of mononuclear cells x 10^8/kilogram patient weight collected varied from 8 to 49. These patients recovered marrow function slightly more rapidly than patients receiving bone marrow (e.g. median time to 0.5 x 10^9/L granulocytes was 19 days) and the engraftments have been durable for as long as 340 days. Thus, almost all patients can be eligible for high dose therapy. In conclusion, this treatment approach offers a new treatment option in Hodgkin's disease. The optimal timing for high dose therapy and autologous bone marrow transplantation in Hodgkin's disease is not clear, but treatment of poor prognosis patients early in the course of the disease at a time of minimal tumor burden when the neoplasm is still responsive to therapy will likely offer the best therapeutic ratio.

77 AUTOLOGOUS BONE MARROW TRANSPLANTATION FOR NON HODGKIN LYMPHOMAS : PRESENT STATUS : RESULTS OF THE PARIS-SAINT ANTOINE TRANSPLANT TEAM AND 1987 SURVEY OF THE EBMTG.

N.C Gorin, M.P. Lemonnier, J.P. Laporte, A. Najman (Paris-Saint-Antoine), T. Goldstone, A. Marmont, T. Philip, O. Hartman, J. Goldman et al (EBMTG)

Autologous bone marrow transplantation (ABMT) has considerably improved the prognosis of poor risk non Hodgkin lymphomas (NHL). In our Institution, from February 1978 to October 1986, 28 patients (median age : 29, range 17-55, M/F : 20/8) have received 30 ABMT (2 double ABMT) following high dose chemotherapy and/or total body irradiation (TACC : 13, TACC + TBI or TAI : 3, BEAM : 12, TBI : 2). The median follow up is 48 months (4-106). The NWF classification was : low grade : 2, intermediate grade : 13, high grade : 12, histiocytic lymphoma : 1. At time of initial diagnosis, 71% (20/28) had bulky disease including 9 patients with abdominal masses $>$ 10 cm. ABMT was done at initial diagnosis in 3 patients (2 bulk), as consolidation in first CR (9), in first PR (7 with 4 residual bulk), in refractory lymphomas (3 bulks), in untreated relapse (2), sensitive relapse (1) and in second CR (3). 17 patients received non purged marrow and 11 received marrow purged by Mafosfamide at a dosage adjusted to the CFUGM LD 95 (Blood 1986, 67, 1367-1376). The kinetics of engraftment were the same in the 2 groups (WBC $>10^9/l$: d 18, retic $>0.1\%$: d 15, plts $>50.10^9/l$: d 22). 57% of the patients (16/28) are actually disease free, with no relapse observed after 24 months. Results are better in patients autografted in CR1 (7/9 disease free 13+, 88+ months). Bulk at initial diagnosis had no impact on outcome while the presence of bulky disease at time of ABMT was unfavourable (33% DFS vs 72%, $p<0.1$). The toxicity of the BEAM regimen was negligible as compared to the TACC.
Results of the 1987 EBMTG survey on 309 NHL from 42 centers confirm previous data on smaller numbers : patients autografted in CR1, CR2 + responding relapse, and in resistant relapse, have an event free survival of respectively 60%, 50% and 15% at 62 mo. Multivariate analysis indicate 2 variables to be significant for overall survival: status as mentionned above ($p = 0.00001$) and age with younger patients ($<$ 16 y) doing worse ($p = 0.03$). Results in patients with lymphoblastic NHL were similar to non lymphoblastic NHL.
We conclude from these data that it is now opportune to commence a prospective randomized trial in relapsed NHL, comparing ABMT to the best conventionnal salvage therapy, and that there may be some indications for ABMT in selected groups of NHL in CR1.

78 MARROW TRANSPLANTATION AS TREATMENT FOR MALIGNANT LYMPHOMA.

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Between July 1970 and January 1985, 100 patients with recurrent malignant lymphoma were treated with high-dose chemoradiotherapy and bone marrow transplantation. Twenty-eight of the 100 are alive and the actuarial probability of disease-free survival five years from transplant is 22%. The most common reason for treatment failure was disease recurrence, the actuarial probability of which was 60%. A proportional hazards regression analysis showed that neither disease histology (Hodgkin's disease, high grade lymphoma, or intermediate grade lymphoma) nor source of marrow (syngeneic, allogeneic or autologous) significantly influenced either disease-free survival or probability of relapse. However, the likelihood of disease-free survival was less in patients transplanted in resistant relapse and in those previously treated with chest radiotherapy. These results point towards the need for earlier transplantation and the development of better preparative regimens.

With regard to earlier transplantation, we have now carried marrow transplantation in 37 patients with malignant lymphoma either in early first relapse or in second remission. Disease-free survival at 3 years is 42% with a 40% probability of disease recurrence, demonstrating that earlier transplantation yields superior results, but even in this setting disease recurrence remains a significant problem.

Our efforts to develop better preparative regimens have included the use of I-131-labeled anti-tumor antibodies. The initial patient entered on this study had recurrent nodular poorly differentiated lymphocytic lymphoma and received trace labeled anti-idiotype antibody at 50, 250 and 1000 mg doses. With higher doses of antibody, decreased uptake in normal organs and greater uptake in tumor was seen. Treatment with 1000 mg anti-idiotype antibody labeled with 232 mCi I-131 delivered an estimated 615 cGy to tumor, 429 cGy to liver and less than 262 cGy to all other organs. Toxicity was limited to marrow suppression which was reversed with autologous marrow transplantation. The patient achieved a complete remission (CR) and remains alive in CR 6 months from therapy.

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EBMT RESULTS OF AUTOLOGOUS BONE MARROW TRANSPLANTATION IN HODGKIN'S DISEASE. A.H. Goldstone, Department of Haematology, University College Hospital, London. On behalf of the EBMTG.

117 patients have been autografted in European centres for Hodgkin's disease as reported to 31.12.86. There were 111 adults and 6 children, median age of 27 years. The histological patterns of those grafted were as follows:- nodular sclerosing 67%, lymphocyte predominant 5%, lymphocyte depleted 2.5%, mixed cellularity 26%. The patients were assessed for disease status at ABMT and the status patterns were as follows:- patients in first CR 3.4%, patients in later CR 6.9%, patients who never achieved CR 10.3%, patients grafted in first partial response 4.3%, patients grafted in responding relapse 20.7%, patients grafted in resistant relapse 46.6%, patients grafted at diagnosis 0.9%.

Response Rates. The overall response rate was 84% with 50% achieving a clinical CR and 27% a clinical PR. Of those who achieved a CR, the percentage of relapses was 33% and of those who relapsed the median time to relapse from ABMT was 170 days. The median time to follow up of all patients is 406 days. By univariant analysis the overall survival of Hodgkin's patients was around 40% and there was no significant difference between patients of different statuses. In an analysis restricted to those patients who had been followed up for a minimum of two years, the disease-free and event-free survival was also around 40% (30 patients) with a plateau at that level. The attainment of CR or not post-ABMT was clearly related to the patients's overall survival. Those achieving a complete response following the graft (66) had an overall survival of around 60% whilst those who did not achieve a CR following a graft (49) showed an overall survival of less than 20% at 2 years. p value between these two was highly significant, p= .0000.

Overall survival of HD in relation to previous therapy. There were 43 Hodgkin's patients who were on third line therapy, ie had failed at least 2 separate regimens of chemotherapy before ABMT. The survival curve of these patients shows a plateau of 40% with 10 patients at or beyond 1.5 years.

Multivariant analysis for HD. In a multivariant analysis of 117 patients for status at ABMT, age, purging, histology and number of courses of first and second line therapy, the only significant variable for overall survival was status, p= 0.035. The disease-free survival by multivariant analysis showed no one single factor was significant.

Conclusions. (1) Response rates for high dose therapy with bone marrow rescue in HD are very high. (2) Failure to achieve CR following high dose therapy is associated with bad prognosis reflecting probably the poor prognostic significance of bulk refractory disease at the time of transplant. (3) Multivariant analysis shows that status at transplant is important for overall survival but still as yet no factor is significant for disease-free survival.

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SEQUENTIAL HIGH-DOSE CHEMO-RADIOTHERAPY FOLLOWED BY AUTOLOGOUS BONE MARROW TRANSPLANTATION (ABMT) IN REFRACTORY OR RELAPSED HODGKIN'S DISEASE. A.M. Gianni, M. Bregni, S. Siena, L. Gandola, A. Lattuada, G.A. Sciorelli, G. Pellegris and G. Bonadonna. Istituto Nazionale Tumori, 20133 Milano, Italy.

Twelve patients with refractory or relapsed Hodgkin's disease were treated between 3/85 and 1/86 with a three-course high-dose sequential regimen, followed by ABMT. The standard regimen consisted of cyclophosphamide (6-7 g/m2) followed about 17 days later by vincristine (1.4 mg/m2), methotrexate (8 g/m2 with leucovorin rescue), and cysplatin (90-120 mg/m2). After 17 additional days total body irradiation (11 Gy over 3 days) plus melphalan was administered (180 mg/m2) with bone marrow reinfusion. Immediately after marrow recovery, eligible patients were given local involved field irradiation to the site(s) of initial tumor bulk up to 25 Gy. Bone marrow was preserved when histologically normal, either prior to chemotherapy or after the first/second drug course. In 4 patients not eligible because of prior mediastinal irradiation, BCNU (300 mg/m2) was substituted for TBI. The rationale of this high dose intermittent (kinetically oriented) drug schedule was to deliver non cross-resistant drugs alone or in combination, at nearly full individual doses, while keeping morbidity and mortality within the range of current high dose regimens.

Two patients were treated at the time of first relapse occurring within 12 months from initial chemotherapy (MOPP alternated with ABVD), and the remaining 10 patients at time of refractory, progressive end-stage disease. Seven patients had received prior radiation therapy. The median age was 25 years (range 13-39). Overall, 10 patients achieved a complete response, 1 patient a partial response and 1 patient died of septicemia on day 20 post-ABMT while in complete clinical remission (not evaluable). As of 1/1987, all 10 complete responders are alive and disease-free with a median relapse free survival of 33 weeks (range 11-89) post-ABMT. Toxicity was moderate to absent after the first two drug courses, but it was considerable after the final course. It consisted of delayed engraftment (1 patient), documented infections (4 episodes, 1 death), severe mucositis (universal) and severe liver damage (1 episode). All patients had neutropenia < 500/μl lasting for a median of 7 days following cyclophosphamide, moderate to mild myelosuppression after the second drug course, and severe neutropenia and thrombocytopenia requiring supportive therapy after the final drug course (median 10 days; range 5 to 34). These preliminary very high response rates and the overall acceptable toxicity in heavily pretreated, refractory patients with Hodgkin's disease, are encouraging. They strongly suggest that high-dose sequential chemo-radiotherapy appears as a new promising treatment modality.

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81 ALLOGENEIC BONE MARROW TRANSPLANTATION FOR MALIGNANT NON HODGKIN'S LYMPHOMAS.

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Fifty-eight patients received an allogeneic marrow graft for NHL. In 56 cases the donor was a HLA identical sibling whereas two patients received a partially HLA matched graft from a related donor. There were 43 male - and 15 female patients, age 3-43 years (med: 29). Forty-nine patients had stage IV at diagnosis and 37 of the patients had lymphoblastic lymphoma, 8: high grade, 4: intermediate grade and 9: Burkitt's lymphoma. Thirty-one of the patients had marrow involvement. Twenty-four patients had received 2' line, 11: 3' line and 3: 4' line therapy. Time from DX to BMT was 2-50 months (med: 8). Twenty-six of the patients were transplanted in 1' CR, 12 in 2' CR, 5 in subsequent CR, whereas 5 and 8 were transplanted in responding and resistant relapse, respectively. The majority of patients received total body irradiation and cyclophosphamide (41), only two patients were conditioned without TBI.
Results: All patients except one achieved engraftment. For patients transplanted in 1' CR: 19/26 are alive with NED 1+ m - 54+ (med: 14 m), 2' CR: 6/12 (5+ - 43+ m), 3-5' CR: 2/5 (7+, 13+ m). All patients transplanted in relapse have died, median 3 m after BMT, although 8 patients achieved CR. 9/50 patients at risk developed severe acute GVHD.
Cause of death were relapse: 17, GVHD: 4, interstitial pneumonia: 5, VOD: 1, infection: 2, and graft failure: 1.

82 SELECTION CRITERIA IMPROVE DISEASE-FREE SURVIVAL (DFS) IN PATIENTS WITH POOR PROGNOSIS NON-HODGKIN'S LYMPHOMA (NHL) FOLLOWING AUTOLOGOUS BONE MARROW TRANSPLANTATION (ABMT).

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Although ABMT has been employed as curative therapy for > 2000 patients with NHL, long-term DFS is only approximately 20%. In an attempt to determine which subgroups of patients would most benefit from ABMT, we undertook a study of patients with relapsed NHL utilizing strict selection criteria. Patients were selected: 1) who could achieve through conventional cytoreductive techniques a minimal disease status which was defined as nodal disease < 2cm in greatest diameter and bone marrow (BM) involvement histologically less than 5%; and 2) whose tumor cells expressed the B1 antigen. Patients were excluded if significant co-morbid disease was evident or Karnofsky status was less than 80%. The 48 patients who met these criteria (median age 43 years; range 25-61 years) exhibited poor prognostic features to their disease including multiple relapses (41 patients); short prior disease-free intervals (median 4 months); histologic conversion (19 patients); a high incidence of BM involvement (33 patients, including 16 at BM harvest); and extra-nodal involvement at extra-medullary sites (24 patients). Seven patients with poor prognostic features to their illness were treated with ABMT as consolidation of their initial therapy. Histology included high, intermediate, and low grade lymphoma in 27, 15 and 6 patients respectively. Ablative therapy consisted of cyclophosphamide and total body irradiation followed by infusion of autologous bone marrow treated in vitro with anti-B1 monoclonal antibody and complement. Following ABMT, all patients achieved hematologic and immunologic engraftment, although normal B cell reconstitution was delayed 6 to 12 months. Acute toxicity of significance included hemorrhagic cystitis (1 patient) and veno-occlusive disease of the liver (1 patient) resulting in the only treatment-related death. We observed no radiation or CMV pneumonitis; dermatomal H. zoster was seen in 8 patients. As of January 1987, 36 patients remain in an unmaintained disease-free remission from 1+ to 49+ months (median follow-up 12+ months) with a projected survival of 65% at 47+ months. This order of DFS is similar to that seen in patients with advanced high grade NHL receiving first-line combination chemotherapy. This study demonstrates minimal toxicity and high efficacy of ABMT in that subset of patients who are otherwise incurable but still responsive to cytoreductive therapy. This suggests a role for ABMT as consolidative treatment for selected patients with newly diagnosed NHL who have poor prognostic features to their illness for cure following conventional dose combination chemotherapy.

ABSTRACTS - Third International Conference on Malignant Lymphoma, Lugano

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ABMT IN BURKITT'S LYMPHOMA (50 CASES IN THE LYON PROTOCOL). T. Philip, P. Biron, I. Philip, D. Frappaz, G. Souillet, JL Bernard, JP Laporte, F. Demeocq, JF Dufillot, F. Bonetti, M Favrot, M Brunat-Mentigny Centre Leon Berard 28 rue Laennec Lyon France

A total of 52 courses are reviewed. All patients were children, except 5 who were adults, included in a pediatric protocol at initial presentation. 23 were stage III, 21 stage IV (12 CNS +/- BM and 9 BM alone) and 5 were initially stage I or II. They all had received adriamycin containing regimens prior to Autologous BMT. The median interval between diagnosis and ABMT was 6 months (range 1-11). At time of ABMT **24 patients (26 courses) were in relapse but still responding to rescue protocol** (sensitive relapse). **9 patients were in resistant relapse** (6 pt) or **progressive disease** (3 pt). **3 were in partial remission** after first induction therapy and **14 in 1st CR** (6 long delay to CR and 7 initial CNS disease and 1 L3 Burkitt leukemia). All relapses were relapses **on** therapy. Monoclonal antibody and complement purging procedures were used in 29 patients. Indications for and practical aspect of such procedures have been previously reported (Philip et al Europ. J Clin. Oncol. 1986, 8, 1015). The massive regimens used in this study are the Appelbaum BACT protocol used in 3 courses, the Institut Gustave Roussy modified BACT (IGR BACT) in 15 courses and the BEAM protocol in 22 courses. 1 patient received cyclophosphamide (CPM) alone (60 mg/kg x 5). Details of the drug infusion protocol have been previously published (Philip et al 1986). Only 9 patients were in resistant relapse or progressive disease at time of massive therapy. We observed only 2 PR and all 9 patients died before day 54 post ABMT. In sensitive relapses as expected results were good with an overall survival NED of 58 % despite 3 therapy related deaths in CR in this group. Median observation time for the survivors is 565 days post ABMT. All disease related deaths were observed before day 90. Only 3 patients were submitted to massive therapy when in PR after initial induction therapy. All 3 are alive NED 960 +, 1235 +, 1955 + post ABMT. 14 patients were grafted in 1st CR either for long delay to CR or consolidation for those with initial CNS involvement or L3 Leukaemia. Of those 8 are alive NED (54 %) including 5/6 with a long delay to CR and only 2/7 with initial CNS disease. The L3 leukaemia relapsed day 35 and died day 73 post ABMT.

28 patients were grafted either for isolated CNS relapses (19 cases) or after initial CNS involvement who achieved only PR or CR (9 cases). No clear difference is observed in the results between CNS relapse and initial CNS involvement (47 % versus 55 % NED survivors). This group of patients with initial CNS involvement does very badly with conventional therapy. 5/9 are alive NED 1235 +, 960 +, 767 +, 353 + and 270 + post ABMT. No major difference was observed between patients grafted with a marrow harvested in 1st CR and the others. During the 52 courses of intensive therapy morbidity was observed in 13 (25 %), 6 patients died of therapy related complications in CR : 1 myocardiopathy, 1 acute pulmonary oedema, 2 candida sepsis, 1 VOD and 1 unexplained brain complication, producing a 12 % mortality rate for theses 52 courses of massive therapy in 50 patients. The overall survival NED for the 50 patients is 50 %. The median observation time post ABMT is 27 months. If patients transplanted in 1st CR are excluded the overall survival is 47 % i.e. 17 out of 36 patients. It is well known, that in such a group (24 relapses on therapy, 9 progressive disease, 3 PR) survival is very unlikely with conventional chemotherapy regimen. Comparison between the purged (n = 29) and unpurged (n = 21) group is difficult because of the predominance of initial CNS in the purged group. However, if the analysis is limited to the patients in SR at time of ABMT, the overall survival NED for the 2 groups are comparable (61,5 % versus 54,5%).

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CYTOXAN (CTX)+TOTAL BODY IRRADIATION (TBI) WITH AUTOLOGOUS BONE MARROW TRANSPLANTATION (ABMT) IN ADULT LYMPHOBLASTIC LYMPHOMA (LbIL) IN FIRST COMPLETE REMISSION (CR). A REPORT OF THE ITALIAN LYMPHOMA STUDY GROUP. G.Santini (Genova)*;P.Coser (Bolzano); V.Rizzoli (Parma);T.Chisesi (Vicenza);R.Sertoli (Genova);A.Porcellini (Pesaro);A.Contu (Sassari);M.Congiu,E.Rossi,D.Scarpati,M.R.Raffo,A.Maiolino,A.Mammont (Genova).*Dept.Hematology,Osp.S.Martino,Genova,Italy.

Prognosis of LbIL was recently improved by sequential chemotherapy (CT). The aim of this study is to improve long term survival of LbIL patients (pts.) in CR by intensification with high-dose CT and TBI followed by ABMT. A modified LSA_2-L_2 was used as induction regimen (VCR 1.4mg/mq d. 1,8,15,22,29; ADM 30mg/mq d. 8,15,22; CTX 750mg/mq d.15,22,29; L-ASE 10.000U/mq d.8-14; PDN 40mg/mq d.1-29; intrathecal MTX 10mg/mq d.3,10,17,24; DNR 50mg/mq d. 43,46,50; ARA-C 200mg/mq continuous inf. d.43-49; MTX 400mg/mq d.64 with Leucovorin rescue). If CR was attained 1000-1400cc. of BM were criopreserved at recovery. 5pts. whose BM at diagnosis were infiltrated were purged with ASTA-Z (70-100µg/ml). At the median time of 2.5 months from CR pts. underwent CTX (60mg/Kg)d. 1,2 followed by TBI (10Gy single dose) d.4 and BM reinfusion d.5 or 6. Twenty pts. entered the protocol and eighteen are presently evaluable: 10 males and 8 females with a median age of 23ys. (range 15-49), in stage II and III one pt. each, in stage IV sixteen. Fourteen presented with mediastinal and twelve with BM involvement.

Sixteen out 18 achieved CR (88%), one PR with hypoplastic BM underwent radiotherapy and one NR died. Of sixteen CR, 3 refused ABMT (two are alive in CR on CT, one died in relapse), 3 are scheduled to and 10 underwent ABMT. Presently nine out 10 post-ABMT pts. are in CR, off therapy, 2 to 20mo. (median 12mo.); one relapsed and died 2mo. after ABMT. Except one pt. who showed a relevant but transient liver and kidney toxicity all others tolerated well the procedure. The haemopoietic recovery was prompt after ABMT, except in five purged cases rising a platelet count over 20 X 10^9/L in median day 35 (range 25-65).

In conclusion a possible role of ABMT in LbIL is suggested althoug more data are required. However the short duration of treatment, the acceptable toxicity and the good post-ABMT quality of life encourage further pts. recruitment.

85 MALIGNANT HISTIOCYTOSIS: PHENOTYPIC AND GENOTYPIC HETEROGENEITY.

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We selected 12 cases of malignant histiocytosis (MH) on the basis of the usual histopathological features. 9 superficial nodes, two skin and one breast lesion were analyzed from 7 female and 5 male patients, aged 4 to 64 years. All cases were tested with a large panel of leukocyte differentiation antigen-specific antibodies on frozen sections and on paraffin embedded material. The cases were HLA-DR+ (12/12), CD30+ (Ki-1)(12/12), CD25+ (Tac)(11/12), CD4+ (10/12) and CD2, 3, 6, 7, 8, 10,19, 20, 22, 23 negative (11/12). Analysis of DNA for TCR ß chain status and immunophenotypic staining with monoclonal antibodies(MAbs) CD5, UCHL1, CD45R (F.8.11.13), Ki-M6 revealed 4 groups of MH: -'true' histiocytic (TCR ß germline, CD5-, UCHL1+, CD45R-, Ki-M6+): 2 patients with typical clinical symptoms. The neoplastic cells showed intrasinusoidal growth and erythrophagocytosis . - T cell derived (TCR ß rearranged, CD5±, UCHL1±, CD45R-, Ki-M6-): 5 patients with mild symptoms. The neoplastic cells revealed a diffuse growth and marked atypia. -B cell derived (CD4-, CD5-, UCHL1-, CD45R+, Ki-M6-): one patient. -unclassified (TCR ß germline, CD5+, UCHL1-, CD45R-, Ki-M6-): 4 patients, clinically heterogeneous. The neoplastic cells showed a carcinoma-like type of growth with high anaplasia. This last group of MH showed phenotypic and genotipic heterogeneity with unusual coexpression of T-cell, B-cell, and histiocytic markers .
The clinicopathological correlations are presented and the diagnostic implications are discussed.

86 THE CLINICAL AND PROGNOSTIC RELEVANCE OF A MODIFIED 'RYE' HISTOLOGICAL CLASSIFICATION OF HODGKIN'S DISEASE.

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The apparent lack of correlation between the Rye classification and prognosis has prompted a critical review of the diagnostic histological sections of all cases entered into the BNLI Hodgkin's disease studies between 1970 and 1980. 1500 evaluable patients were accepted as HD.

The full Lukes & Butler classification criteria were applied strictly to derive the 'Rye' category. LP nodes with more than occasional classical RS cell were reclassified MC. If histiocytes predominated with few RS like cells, NHL of Lennert type was diagnosed and the case excluded. NS was subdivided into grades I and II: in NSII more than 25% of the nodules showed obvious lymphocyte depletion or numerous pleomorphic lacunar cells. Nodes with lacunar cells but no birefringent sclerosis were classified MC as also were nodes with both MC and LD areas. In MC no significant survival difference was found whether the node also had areas of LP, LD, or had lacunar cells but no sclerosis (so called "cellular phase NS"). LD was only diagnosed if the whole node showed lymphocyte depletion. Some nodes originally classified LD showed areas with nodule formation, lacunar cells and birefringent collagen and were reclassified NSII.

The results of histological review of this large series of uniformly managed patients with HD show that critical application of the criteria proposed by Lukes & Butler plus subdivision of NS into two grades demonstrate significant differences in clinical features and prognosis between subtypes which are not obliterated by modern therapy and may be clinically helpful in assessing the need for aggressive initial therapy.

	% Cases	% Stage I & II	%'B' Symptoms	%CR	% Actuarial Survival 5yr rel.free	10 yrs
LP	5	85	8	92	80	82
NSI	55	51	27	85	55	72
NSII	22	48	50	68	32	47
MC	16.5	42	37	81	41	51
LD	1.5	5	86	32	18	22

87 SINUSOIDAL B-CELL LYMPHOMA IS THE MALIGNANT LYMPHOMA OF SO-CALLED IMMATURE SINUS HISTIOCYTOSIS.

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"Immature sinus histiocytes" (ISH-cells) or "monocytoid cells" of the lymph node have been recognized as a unique B cell population developing in a variety of infectious and autoimmune diseases. We present 6 cases of low-grade B cell lymphoma in which the neoplastic infiltrate is based in lymph node sinuses and the predominant cell population exhibits specific morphological and immunophenotypic features of ISH-cells. The neoplastic nature was proven in all cases by demonstration of monotypic immunoglobulin light chain. Two cases showed a clonal rearrangement pattern for immunoglobulin heavy and light chain genes. We apply the term of sinusoidal B-cell lymphoma to this entity.

Subcortical, intermediate and medullary sinuses were equally involved. Two types may be distinguished. The first variant exhibited plasmacytic differentiation with monoclonal plasma cells surrounding sinuses and infiltrating germinal centres. The second type lacked complete plasmacytic differentiation, but moderate formalin-resistant immunoglobulin expression was observed in most of the tumor cells.

Additional histological features are 1) capsular sclerosis, 2) delicate sclerosis of the sinus reticulin framework, 3) proliferation of capillaries and venules, 4) reactive follicular hyperplasia. Immunophenotypically, the lymphoma cells showed, analogous to ISH-cells, expression of IgM or IgG but not IgD. CD19, CD20 and CD22 antigens as well as B-cell associated antigen Ki-B3 were constantly found. On the other hand, CD5, CD9, CD10, CD21 and CD23 were negative. Such a phenotypic pattern is unique and allows distinction from other malignant lymphomas of low grade malignancy.

Clinical course is hallmarked by frequent gastrointestinal involvement and a favourable prognosis, similar to other low-grade B-cell lymphomas (small lymphocytic).

88 CLONALITY, PHENOTYPIC DIVERSITY AND SURVIVAL IN 26 CASES OF ANGIOIMMUNOBLASTIC LYMPHADENOPATHY.

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Angioimmunoblastic lymphadenopathy (AILD) is still a poorly understood process. In the past it was predominantly interpreted as a premalignant disease leading to immunodeficiency or to development of malignant lymphoma.

We investigated 26 cases of AILD and two cases of hyperimmune reaction by immunohistochemistry and DNA rearrangement studies for beta and gamma chain genes of the T-cell antigen receptor and for heavy and light immunoglobulin chain genes. Clinical follow-up data of the cases were obtained.

Immunohistochemistry showed a distribution of follicular dendritic cells with large irregular foci extending into T-cell areas, a pattern never seen in any other malignant lymphoma or reactive lymph node lesion. The overall predominating T-cells showed proliferation rates (Ki67) from 5-80% with a mean of 40%. CD4 phenotype predominated in proliferating T-cells in all but one case. 7 cases had elevated numbers of proliferating CD8+ cells ranging from 15 to 24%.

Southern blot analysis exhibited clonal rearrangement for gamma and beta chain genes in all the cases of AILD, but not in those that had been classified as hyperimmune reactions. Additionally 7 cases of AILD had clonal rearrangement for heavy chain joining region genes.

Survival data showed that about 70% of the patients died within 30 months irrespective of treatment.

From these data it could be concluded: 1. AILD is a clonal T-cell process in all cases investigated so far. 2. Hyperimmune reaction is primarily a polyclonal T-cell proliferation which may turn into a monoclonal T-cell process. 3. Some cases showed spontaneous remission although monoclonal T-cell proliferation had been detected. From these data we can conclude that AILD is a multistep clonal process with the potential for evolving into overt malignant lymphoma but which may also follow a self-limiting course. The available data are correlated with the diverse clinical evolution.

89 THE CYTOLOGICAL APPEARANCES OF FOLLICULAR LYMPHOMA SMALL CELL TYPE AND THEIR RELATIONSHIP TO NATURAL HISTORY AND PROGNOSIS

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Follicular lymphomas are widely accepted as neoplasms of germinal centre B cells and contain a variable percentage of cleaved and non-cleaved follicle centre cells (centrocytes and centroblasts). Many classifications subdivide follicular lymphoma into predominantly small, mixed and predominantly large cell subtypes on the basis of the relative numbers of large non-cleaved cells present within the neoplastic follicles. The commonest subtype of follicular lymphoma entered into BNLI randomised trials has proved to be follicular lymphoma small (FL small). Within this apparently histological homogeneous group nearly 30% of patients pursue an aggressive clinical course as defined by vital organ involvement, rapidly progressive disease and the presence of systemic (B) symptoms and these patients have been shown to have a poor survival.

In an attempt to histologically predict an aggressive natural history in FL small, we have reviewed the diagnostic lymph node biopsies of 192 patients with stage III or IV FL small. A quantitative assessment of the percentage of non-cleaved cells and the number of mitoses within the neoplastic follicles has been carried out. 19% of cases contained an excess of non-cleaved cells (>15%), a high mitotic rate (>8 mitoses per follicle) or both of these features. These patients had a significantly decreased survival ($P<0.01$), worse response to initial and subsequent therapy and a higher relative frequency of clinically aggressive disease as defined above.

90 THE IMMUNO-PHENOTYPE OF NON-HODGKIN'S LYMPHOMA DOES NOT CORRELATE WITH CELL MORPHOLOGY.

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We determined the immunologic phenotype in a series of 160 non-Hodgkin's lymphoma (NHL) cases. Amongst others, reagents in the "Clusters of Differentiation" (CD) established during workshops on leukocyte differentiation antigens (1982,1984,1986) were applied. B-cell markers were found in 130 cases (117 with monotypic immunoglobulin expression), and 30 cases were of T-lymphocyte origin. In the B-NHL group, there was no significant correlation between histopathologic diagnosis (Kiel classification) and either the immunoglobulin isotype or the expression of CD-antigens CD9, CD10, CD19-24, CD37 and CD38. Conversely, the cases were grouped according to the phenotypes (CD or immunoglobulin) which occur in distinct stages of (physiologic) B-cell differentiation. This "fitting" was possible in 86 of the 130 cases, and also did not yield a significant relation between phenotypic expression and histologic classification. Most B-NHL had the phenotype compatible with intermediate stage of B-cell differentiation/maturation.

In the group of T-NHL most cases exhibited the phenotype (CD1-8, terminal transferase, and peanut agglutinin binding capacity) compatible with a mature stage in T-cell maturation. The exceptions were lymphoblastic convoluted lymphoma, which exhibited an immature phenotype.

We conclude that NHL in distinct histopathologic categories are heterogenous in immunologic phenotypes associated with distinct stages in physiologic cell differentiation/maturation.

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PRIMARY CUTANEOUS B CELL LYMPHOMAS: A MOLECULAR STUDY. D. Delia, D. Biassoni, M.G. Borrello, E. Berti*, R. Caputo*, M.A. Pierotti, G. Della Porta. Istituto Nazionale Tumori, Milano and *I Clinica Dermatologica, Università di Milano, Milano, Italy.

B cell lymphomas of cutaneous origin are quite rare as compared to the better known cutaneous T cell lymphomas. Unlike the nodal counterparts, they show a better prognosis, and the treatment usually does not require systemic chemotherapy but only radiotherapy. Only recently their B cell derivation has been certified by immunohistological phenotyping with monoclonal antibodies and in a few cases by Ig gene rearrangement studies (Berti et al., J. Am. Ac. Dermatol., in press, 1987). The morphological and histological similarities of the majority of cutaneous B cell lymphomas with the nodal centroblastic/centrocytic follicular and/or diffuse lymphomas suggests a common germinal centre derivation. This led us to investigate the BCL2 locus normally involved in the t(14;18) translocation of Cb/Ccf lymphomas in order to ascertain at the molecular level whether the two diseases are induced by a similar genetic abnormality. In addition the J region of the Ig heavy chain gene was studied. 11 cases were tested (all adults, age 26-85 years) all phenotypically B (CD19+, CD20+, CD21+, CD22+, CD2-, CD5-, HLA-DR+) with 4 cases unequivocally showing serological Ig light chain monoclonality; histologically 8 cases were Cb/Cc follicular + diffuse or diffuse and 3 cases centroblastic. Southern blot analysis of DNAs from biopsies of the 11 cases digested with the restriction enzymes Hind III and Pst I and hybridized with pFL1 probe, were negative for the BCL2 rearrangement. So far 2/2 cases tested for JH showed rearrangement. Though these results are preliminary and further molecular and cytogenetic analysis is in progress, the lack of BCL2 involvement in cutaneous B cell lymphomas suggests that the neoplastic event differs from that of nodal Cb/Cc follicular lymphomas. However, since the BCL2 probe pFL1 does not cover the whole break region as it has been recently reported (Cleary et al., J. Exp. Med., 164: 315-320, 1986) the t(14;18) translocation cannot be excluded. Alternatively this feature could indicate a common similarity with the nodal Cb/Cc diffuse lymphomas which are BCL2-.

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A NON PREVIOUSLY DESCRIBED, DIFFUSE, NON BLASTIC, NON BLASTOID B-MEDIUM CELL NON-HODGKIN'S LYMPHOMAS (NHL). Georges Mathé and M. Gil-Delgado, Service des Maladies Sanguines et Tumorales & ICIG (CNRS), Hôpital Paul-Brousse, 94804 Villejuif, France.

We have observed 13 cases of chronic lymphomas the cells of which are of homogenous medium size, the nucleus chromatin non blastic and intermediate between that of blasts and that of small lymphocytes, the cytoplasm non blastoid (not hyperbasophilic, non ribosome rich, not vacuolized). The immunologic cell phenotype is SIgM+ or G+ and EBNA-, and the serology HIV-. The histologic pattern is never nodular but always diffuse.

This B-medium cell lymphoma mainly affects adults (contrary to endemic Burkitt's tumor which affects young children and non endemic Burkittoid NHL which most often affects young adults and HIV+ subjects. It predominates at the age of 40-50 years. It is most often rapidly converted into a leukemic NHL, the cells of which nearly resemble the so-called Galton's "prolymphocytic" leukemia, which is not prolymphocytic as its cells are SIgG+.

The NIH meeting gave a bimodal age curve of what it called "small cell non cleaved NHL": we think that the presently described B-NHL type corresponds to its adult's small cell non cleaved type, which is a non homogenous group.

93 PERIPHERAL T-CELL LYMPHOMAS (PTCL): THERAPEUTIC ANALYSIS AND PROGNOSTIC FACTORS IN 54 PATIENTS (pts).

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54 pts (38 males) with non-lymphoblastic non-epidermotropic PTCL were treated in our institution between January 1982 and June 1986. Morphologically PTCL do not easily fit in the Working Formulation: diffuse small cells 5 pts, diffuse mixed 31 pts (with pleomorphic and 10 IBL-like PTCL), diffuse large cells immunoblastic 17 pts, unclassified with anaplastic large cells 2 pts. Histologic progression toward large cells has been observed in 10 pts. Immunologic phenotype was T4 in 16 pts, T8 in 9 pts, T4 and T8 in 20 pts, and immature T (panT+, T4-, T8-) in 9 pts. The median age was 58 y (19-87). Clinical presentation was severe: 12 pts stage I-II with B symptoms in 7 and visceral localization in 5, 7 pts stage III (2 with B symptoms), and 35 pts stage IV (28 with B symptoms). Performance status was >= 2 in 26 pts. An extranodal localization was present in 42 pts with 21 of them with more than 1 site. Results of treatment are presented in the table.

	n	CR	PR	relapse	death
radiotherapy	2	2	-	1	0
monochemotherapy	6	0	3	-	3
CHOP chemotherapies	16	5	6	3	11
LNH-80/LNH-84	30	21	2	7	14

LNH 80 & LNH 84 are intensive and sequential combination chemotherapies (J Clin Oncol 1986,4:147). The median survival is 26 months, 33 months for CR pts. 16 pts died before 12 months. Only 3 pts without CR are alive at 12 months. 14 pts are alive at 2 years, 10 without disease. Compared to B NHL or not-typed NHL, PTCL have a worse prognosis in LNH80/84 protocols. Classic prognostic factors like PS, large mass, number of visceral localisations, B symptoms keep prognostic value but with borderline statistical significance. Large cell or immature phenotype have the worst survival among PTCL, again with borderline statistical significance.

PTCL are a heterogeneous group of NHL, with aggressive presentation (stage IV B, large tumoral mass and several visceral localisations). Without CR, death is rapid. Intensive chemotherapy should be used, but is often difficult to manage due to the severity of the disease.

94 PERIPHERAL T-CELL LYMPHOMA: A CLINICOPATHOLOGIC STUDY OF 74 CASES.

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This study presents a clinicopathologic analysis of 74 peripheral T-cell lymphomas (PTCL). Diagnosis was made on paraffin embedded sections and the post-thymic T-cell origin of the tumors was confirmed by immunologic phenotyping on fresh frozen tissue in 55 cases employing a broad panel of monoclonal antibodies directed against various differentiation antigens and Ki-1. In the remaining 19 cases paraffin embedded material was tested using a monoclonal T-cell(MT1) and a monoclonal B-cell(KiB3) antibody. Referring to a recommendation of the European Lymphoma Study Group the 74 PTCL were classified as T-CLL(3),cutaneous T-cell lymphomas(9),Lennert's lymphomas(3), T-zone lymphomas(7),LGR-X/AILD-type lymphomas(19),pleomorphic lymphomas (19), immunoblastic lymphoma(1) and large cell, anaplastic,Ki-1 positive lymphomas(13). Cutaneous T-cell lymphomas (6 cases of mycosis fungoides 3 cases of Sezary's syndrome) represent a distinct category of PTCL morphologically and the median survival time (MST) of 38mths differs singnificantly from the MST of noncutaneous PTCL(14mths). Among the group of non-cutaneous PTCL the average age was 51yrs with no sex prevalence. Large cell,anaplastic,Ki-1 positiv lymphomas occurred in patients with a median age of 38yrs seven of them younger than 25yrs. Striking sex prevalences within the subgroups are only found in T-zone lymphomas (7 females,no male) and pleomorphic PTCL(12 females, 7 males). Primary extranodal involvement of soft tissues occured in 11 cases and was predominantly found in the pleomorphic PTCL-type (9/19). Clinical staging of 62PTCL at presentation (T-CLL and cutaneous lymphomas excluded) was as follows:
stage I in 9,stage II in 5,stage III in 25 and stage IV in 23 patients
No correlations between clinical stage and survival were obvious. The MST was 14mths for both LGR-X/AILD and large cell anaplastic Ki-1 positiv lymphomas but only 11mths for patients with pleomorphic PTCL. More than 12mths survuval was found in 61% of large cell anaplastic, Ki-1 positiv cases, in 52% of LGR-X/AILD cases and in 42% of the patients with pleomorphic PTCL.Response to therapy was worst in the pleomorphic PTCL group(NR:9,CR:4) compared wirh the data of LGR-X/AILD patients (NR:4,CR:5) and the large cell, anaplastic, Ki-1 positiv cases (NR:4,CR:4). In our series of PTCL the pleomorphic lymphoma type turned out to be the most aggressive disease with poor prognosis.

95 PROGNOSTIC FACTORS IN STAGE III AND IV NON HODGKINS' LYMPHOMA (NHL).

M. Van Glabbeke, N. Duez, M. Burgers, J. Meerwaldt, P. Carde, R. Somers and C. De Wolf-Peeters for the EORTC Lymphoma Cooperative Group (LCG). EORTC Data Center, Boulevard de Waterloo 125, B1000, Brussels, Belgium.

Between 1975 and 1986, the LCG has conducted 3 controlled clinical trials in stages III/IV NHL. Induction chemotherapy was a CHOP-like regimen in all trials. Prognostic factors of survival and response were studied on the 589 patients for whom histology had been reviewed by a panel. Histological cell type and pattern (Kiel and Rappaport classifications, and International Working Formulation-IWF-), age, sex, systemic symptoms, and localisation of the disease were investigated both by univariate (Kaplan-Meyer estimate, logrank and chi-square tests) and multivariate techniques (Cox and logistic stepdown regression models). Survival hazard rates were analyzed by the Gehan method.

None of the histological classification significantly influenced complete response rates. For survival, univariate analysis demonstrated that all histological classifications were of significant prognostic value. Multivariate analysis showed that cell type (Kiel) and cell pattern (Rappaport) had independent prognostic values, but not IWF. Hazard rate remained constant over time for low grade histology, but decreased for high grade histology, leading to similar long term survival rates.

Liver involvement significantly decreased the complete response rate and the survival, but not the total response rate. Mediastinal and/or hilar nodes involvement significantly decreased the total response rate and the survival, but not the complete response rate. Bone marrow involvement did not affect response or survival.

Age adversely influenced survival for patients with low grade histology, and for patients with mediastinal or hilar nodes involvement, but not for other subgroups of patients.

The presence of systemic symptoms was often associated to high grade histology, and severe involvement of the disease. However, the multivariate analyses demonstrated an independent prognostic value of this factor for survival, response, and complete response rates.

This analysis confirms the influence of both histological cell pattern and cell type on the survival of patients with NHL, but not on the response to CHOP-like regimen. The level of disease involvement affects the reponse rates and the survival, but the Ann Arbor classification, grading patients with bone marrow involvement as "stage IV" does not seem appropriate for this disease. The presence of systemic symptoms adversely affects response and survival, independently of all other prognostic factors. Age only influences survival in subgroups of patients. Further studies by the Group will demonstrate the evolution of those prognostic factors with more aggressive induction therapies in high grade disease.

96 AN ANALYSIS OF PROGNOSTIC FACTORS IN HIGH AND INTERMEDIATE GRADE NON-HODGKIN'S LYMPHOMA

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Over an 11 year period the Manchester Lymphoma Group have treated 260 patients with high and intermediate grade non-Hodgkin's lymphoma in protocols incorporating uniform induction chemotherapy with VAP (Vincristine, Adriamycin and Prednisolone). In all cases the histology has been reviewed by one of the authors (MH) and classified as high grade histology in Rappaport and Kiel: patients with diffuse centroblastic/centrocytic and diffuse centrocytic lymphoma have also been included in this analysis. The median follow up of the group is 72 months.

Over 30 clinical, radiological and laboratory parameters have been studied for their influence on disease outcome. The variables were analysed using a logrank test on Kaplan Meier survival curves and Cox's proportional hazards model. In a Cox multivariate analysis attainment of complete remission (CR) was the most important predictor of overall survival, $p = <0.000001$, a low serum LDH was also associated with a favourable prognosis, $p = 0.000002$, as was limited stage disease, $p = 0.01$, and a high serum albumen, $p = 0.047$. A repeat of the analysis after excluding remission status, revealed clinical stage to be the most significant prognostic indicator, $p = <0.000001$, followed by serum albumen, $p = 0.00009$, patient age, $p = 0.029$, gamma GT, $p = 0.032$, B symptoms, $p = 0.024$ and histology by Kiel classification: the centroblastic lymphomas having a more favourable outlook than the other histological categories, $p = 0.013$. Bone marrow involvement was the only factor to independently influence the relapse-free survival and clinical stage alone predicted for survival of the complete remitters. Dividing the patients into localised (stage I & II) and widespread disease (Stage III & IV) both serum LDH and albumen proved significant predictors of survival.

We conclude that, as in other studies, CR is the single most important prognostic factor. Further, although our data has confirmed the prognostic validity of Ann Arbor staging, we propose that serum LDH and albumen represent biochemical markers of tumour burden which carry prognostic influence within each Ann Arbor stage and thus may usefully be incorporated into a modified staging system in the future.

97 TREATMENT OF LYMPHOMA IN JAPAN.

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Characteristics of malignant lymphomas in Japan, comparing with those in Europe and USA are as follows: (1)incidence of Hodgkin's disease and follicular lymphoma is low, (2)incidence of T-cell lymphoma is high, (3)among T-cell lymphomas, there are lymphomas associated to retrovirus, HTLV-I (ATL; adult T-cell lymphoma and leukemia) in the southern part of Japan.

Treatment of adult NHL in Japan is reviewed. Patients (pts) with localized disease are treated with combined modality of irradiation and chemotherapy. In some institutions, chemotherapy has been used in the beginning to them. Pts with more advanced disease receive combination chemotherapy, such as CHOP (AVCP, VEPA).

In our institution, trial with alternating non-cross resistant combination regimens [AVCP/EMLP (VP-16•MTX•L-asp•PDN)] was conducted for advanced NHL. Thirty three pts were evaluated for response and survival time. CR was obtained in 18 pts (55%) and PR in 10 pts (30%). Median duration of CR was more than 14 months (3-31+). The actuarial relapse free survival of complete responders was 83% at 2 years.

Cooperative lymphoma study group (LSG) in Japan evaluated VEPA in 100 previously untreated advanced NHL pts in 5 institutions. Overall CR rate was 52%. By immunological phenotypes, pts with T-cell lymphoma had a CR rate of 36%. B (non-T)-cell lymphoma 60%, and lineage undetermined lymphoma 70%. Among T-cell lymphomas, pts with ATL had a CR rate of 17%. Median duration of CR, and survival period of all pts and CR pts were different by cell types; T-cell lymphoma 4, 6, 8 months, B (non-T)-cell lymphoma 16, 13, 37 months, and lineage undetermined lymphoma, more than 36 months in each.

The next study of LSG was a randomized trial of VEPA vs VEPA-M (VEPA+MTX). One hundred sixty three pts was evaluated. CR rate was 57%; VEPA 52% and VEPA-M 62%. CR rate and survival curves were better in pts with VEPA-M than with VEPA, but these were not statistically significant. Among 81 pts with T-cell lymphoma, there were 54 pts with ATL. Number of CR of ATL pts was 15 (28%) in each with both regimens. Early relapses were frequently seen in pts with CR. In an attempt to improve therapeutic results, especially for pts with T-cell lymphoma and ATL, better treatment modalities are urgently needed.

98 A PHASE I STUDY OF THE FEASIBILITY OF USING AUTOLOGOUS LYMPHOCYTES AS VECTORS TO TARGET RADIO-ACTIVE MATERIAL TO SITES OF DISEASE IN NON-HODGKIN'S LYMPHOMA.

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It has been shown that after the intravenous administration of autologous lymphocytes labelled with the Beta-emitting radio-nuclide Indium 114m, the cells migrate normally for up to 12 hours before succumbing to the toxic effects of the radiation they carry. The radio-active material is then released from the cell and taken up by the neighbouring radio-resistant macrophages, thereby localising a radio-active field to the site of lymphocyte death. Using this technique lymphocytopenia has been produced in rats and an anti-tumour effect was seen in an animal leukaemia model.

As a phase I study we have measured whole body distribution and excretion of activity in eight patients receiving escalating doses of Indium 114m-labelled lymphocytes up to 22 MBq. All patients had active non-Hodgkin's lymphoma involving the liver and spleen which had proved resistant to conventional chemotherapy and radiotherapy. Following intravenous administsration, the labelled cells clear rapidly from the vasculature with only 20% remaining in the peripheral blood by 30 minutes. The activity continues to fall over the next 48 hours to approximately 2% of the injected dose and thereafter it remains constant for up to 90 days. There is almost immediate uptake of radio-activity by the liver and spleen reaching approximately 75% of the injected dose by 48 hours. Between 2 and 7% of activity is localised to the bone marrow and this figure remains constant for up to 12 weeks. The distribution of radio-activity within the body stabilises by 48 hours and thereafter the whole body activity falls by approximately 1% per day and is excreted equally by the urine and faeces. The doses administered thus far have been too low to expect any lymphocytopenia or any anti-tumour effect but certainly no toxicity was experienced by the patients.

In conclusion, we have shown that the labelling of autologous lymphocytes with Indium 114m represents a feasible technique for the targetting of radiation to sites of disease in lymphoid malignancies.

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DEOXYCOFORMYCIN: AN ACTIVE NEW DRUG IN LYMPHOID MALIGNANCIES. O'DWYER PJ; KING SA; HOTH DF; LEYLAND-JONES B. INVESTIGATIONAL DRUG BRANCH, CANCER THERAPY EVALUATION PROGRAM, NATIONAL CANCER INSTITUTE; BETHESDA, MD; FOX CHASE CANCER CENTER; PHILADELPHIA, PA.

2'-Deoxycoformycin (dCF, Pentostatin) is a tight-binding inhibitor of adenosine deaminase (ADA) which has been evaluated extensively in the clinic. Inhibition of ADA results in intracellular accumulation of adenine deoxynucleotides; dATP levels correlate in vivo with toxicity and in vitro with cytotoxicity. The mechanism of cytotoxicity has not been determined and may differ between cell types. Inhibition of ribonucleotide reductase, depletion of ATP and of NAD, inhibition of cellular methylation reactions, and DNA incorporation of dCF have all been associated with dCF toxicity. Inhibition of ADA is especially toxic to lymphocytes, and the majority of dCF studies have been conducted in lymphoid malignancies. In Phase I studies in adults, doses up to 5 mg/M^2/dx3 were tolerable; however less frequent administration (e.g. 4 mg/M^2 every other week) seems as effective and is less toxic. Associated biochemical pharmacology studies support the less aggressive schedule in that recovery of lymphocyte ADA activity may be delayed for a week following a single dose. In addition to lymphocytes the major organs affected by dCF are bone marrow, CNS, and kidney. Enhanced susceptibility to infection is also described. Severe toxicity may be avoided by careful patient selection, limiting eligibility to those with PS 0,1 and normal renal function. Ongoing studies will define suitable dose modifications for less able patients and those with renal impairment. Results in Phase II trials have been especially promising in hairy cell leukemia. Of 67 patients treated to date, there have been 44 complete and 15 partial remissions (88%). The total response rate is comparable to, and the CR rate superior to results with α-interferon. In addition several interferon-resistant patients have responded to dCF. Most patients require less than 6 months treatment for maximal response, and remissions are unmaintained. Maturation of survival data will be required to demonstrate if dCF is superior. A randomized comparison of dCF and α-IFN in hairy-cell leukemia is underway in the U.S. Responses in heavily pretreated patients with CLL (15/36, 24%) and mycosis fungoides (15/38, 39%) demonstrate that dCF may also have a role in those diseases; studies to combine dCF with standard approaches are underway. Early results with small numbers of patients in other neoplasms of lymphoid origin promise a broad role for this novel antimetabolite.

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COMBINATION OF CISPLATIN, HIGH DOSE ARA-C AND DECADRON (DHAP) IN RELAPSING LYMPHOMA. W.Velasquez, F.Cabanillas, P. McLaughlin, M.Fridrik, F.Hagemeister, F.Swan, B.Barlogie, Univ Texas M.D. Anderson Hospital, 1515 Holcombe Blvd., Houston, Texas 77030 USA.

Based on the synergism between Cisplatin and Ara-C observed in colonic and lymphoma cell lines, 90 patients (pts) with relapsing and refractory lymphoma received Decadron 20-40 mg IV daily for 4 days, Cisplatin 100 mg x m2 by continuous infusion on day 1 followed by Ara-C 2 g x m2 given every 12 hours for 2 doses. Intense hydration with saline and mannitol (50 g in each liter to run at 250 cc/hr) was administered before and during Cisplatin administration. Treatment was repeated every 3-4 weeks. All pts had received adriamycin and cyclophosphamide previously, many had been treated with other chemotherapy combinations, including VP-16, Methotrexate, Cisplatin, and Interferon. The majority of pts had elevated serum lactic dehydrogenase (LDH), "B" symptoms, and had not obtained complete remission (CR) previously. Thirty-two pts had high tumor burden. Intermediate grade lymphoma was the most frequent histopathologic group (72 pts), followed by low grade lymphoma. Seven pts died in the first 2 weeks after treatment (early deaths). Of the remaining 83 pts, 28 (34%) obtained CR; another 22 (26.5%) pts achieved partial remission. No differences in CR rate were seen among the different pathological diagnoses, including transformed large cell lymphoma. LDH and tumor burden were the more important prognostic features related to the achievement of CR. Of the 19 pts with normal LDH values, 58% obtained CR, while this rate decreased to 18% for pts with LDH over 300 mU/ml. Pts have high tumor burden, defined as having more than one area of extensive nodal involvement or more than 2 sites of extranodal involvement, obtained only 4% CR rate, while the 58 pts with low tumor burden obtained a 47% CR rate. With the median follow-up of 14 months, the projected 2-year survival is 28% for the entire population and 62% for those pts who achieved CR. The main serious toxicity was myelosuppression, and the expected febrile complications in 28 pts. Ten of these pts died with sepsis, including 2 early deaths. Another 18 pts had creatinine elevations to twice the baseline value, which was reversible in 14 pts. Five pts developed acute tumor lysis syndrome which caused 4 deaths. DHAP was reasonably well tolerated and proved to be an efficacious non-cross resistant combination in the treatment of relapsing and refractory lymphoma.

101 REPORT FROM THE CONFERENCE IN LYGON ARMS (November 1986).

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The Ann Arbor staging classification for description of the distribution of Hodgkin's disease was introduced in 1971. Since that time, new techniques have been developed for the demonstration of lymphadenopathy, and others, previously utilized have become irrelevant. In addition, it has been shown that the prognosis of Hodgkin's disease, with radiation, chemotherapy or both, may correlate with other presentation features (for example, bulk of disease) which are not taken into account in the Ann Arbor classification. Proposals for a modification of the classification will be presented.

102 FUTURE DIRECTIONS OF RESEARCH IN LYMPHOMA - CLOSING REMARKS.

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The concepts of meticulous staging and combination chemotherapy for advanced disease were established for Hodgkin's disease (HD) in the 1960s and then applied to non-Hodgkin's, or lymphocytic lymphomas (LL). Recently a revolution in the biological sciences has begun to change our concept of neoplastic disease. Advances in immunology have shown that specific subclasses of lymphoma have similar immunophenotypes to specific stages of lymphocyte differentiation. This will allow more precise and possibly more relevant classification of the LL, and possibly more rational therapeutic decisions. The Goldie-Coldman hypothesis predicts that regimens incorporating multiple chemotherapeutic agents, all used within the first few weeks of treatment, will be more successful in preventing the development of chemotherapeutic drug resistance than regimens using sequential cycles of chemotherapy. This has led to a change in the design of new regimens, typified by the successful MACOP-B regimen for large cell lymphoma. Recently, high dose alkylator therapy with autologous bone marrow rescue has been employed to overcome drug resistance in refractory or relapsed LL and HD. Developments in the field of molecular biology have demonstrated that B-cells are characterized by rearrangements of the immunoglobulin (Ig) genes, and T-cells by rearrangements of the T-cell receptor (TCR) genes, which generate gene arrangements unique to each lymphocyte. This allows identification of clonal expansions of B- or T-cells. Specific cytogenetic abnormalities are beginning to be identified in the LL, many of which involve the Ig or TCR gene loci at the breakpoints, and/or inappropriate expression of oncogenes. This underlines the probable importance of specific cytogenetic abnormalities and their consequences in the pathogenesis of specific LL. The advances in these various fields are beginning to come together in a complementary fashion, increasing understanding of the pathobiology of LL. This new understanding will allow more specific tailoring of therapy for specific types of lymphoma. Innovative techniques now being developed in the LL will also be applicable eventually to HD. Just as understanding and treatment of LL benefitted from early advances on HD, so eventually ideas being formulated for LL will benefit patients with HD.