64 INVOLVED FIELD RADIOTHERAPY IN CLINICAL STAGE I-II LOW GRADE LYMPHOMA.

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The curative role of radiation therapy in localized Non-Hodgkin's lymphoma is well established. However, in low grade lymphoma the frequency of generalized presentations, prolonged natural course of the disease and excellent long term survival of untreated disease cast doubt on the value of involved XRT as a curative approach.

The results of treatment of 285 patients with clinical stage I and II low grade Non-Hodgkin's lymphoma treated with involved field radiotherapy between 1967 - 1986 were analyzed for survival, risk of relapse and local control. The male to female ratio was 1.02 (144:141). The median age was 57 years (range 18-89). Two hundred and six patients had nodal and 79 extranodal presentations. One hundred and sixty nine patients presented in supradiaphragmatic sites and 116 in infradiaphragmatic sites. Histology was initially classified according to the Rappaport classification and translated into the Working Formulation classification. Small lymphocytic histology was present in 54 patients, follicular small cell in 145 patients and follicular mixed in 86 patients. The majority presented with stage IA (188 patients) disease and only 3% (9pts) had B symptoms at presentation. The median XRT dose was 33 Gy in 18 fractions in 4 weeks (range 10-47.5 Gy).

The overall actuarial survival was 65% at 10 years and 57% at 15 years; the cause specific survival was 77% and 71% respectively. The complete response rate was 98.9%. No dose response relationship could therefore be demonstrated. The local relapse free rate was 94% at 10 and 15 years. The overall relapse free rate was 52% at 10 years and 48% at 15 years. The majority of relapses occurred within the 5 years from the initial treatment (73%) and in areas distant to the presenting site. In univariate analysis, the following were identified as prognostic factors for relapse (reflecting the risk of occult distant disease) tumour bulk, histology, stage and gender. Cox regression analysis confirmed independent prognostic significance of age (0.0001), tumour bulk (0.003), histology (0.005), and stage (0.004).

Treatment with involved field radiotherapy produces excellent local control in patients with localized low grade lymphoma. Patients with large tumour bulk, follicular mixed histology, and stage II with >2 areas of involvement are at high risk of distant relapse. These variables therefore predict for presence of occult disseminated disease.

65 CHLORAMBUCIL/PREDNISON (ChP) VERSUS CHOP IN SYMPTOMATIC LOW GRADE LYMPHOMAS.

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Aim : To compare the effect of intensive chemotherapy (CHOP) with that of palliative low dose chlorambucil/prednison (ChP) in patients with symptomatic low grade non-Hodgkin lymphomas (NHL).
Patients and methods : 259 untreated patients with low grade NHL stage III and IV with symptomatic disease were randomized (April 1982 to February 1988) to CHOP (Cyclophosphamide 750mg/m^2, Doxorubicin 50mg/m^2,Vincristine 2mg day 1 and Prednison 50mg/m^2 day1-5, every fourth week) or ChP (Chlorambucil 0.4mg/kg day 1 p.o. and Prednison 75mg day1-3, every 2nd week). The therapeutic strategy was to achieve an asymptomatic state in the ChP group, while in patients allocated to CHOP, the intention was complete remission (CR).
The patients were stratified according to histological subgroup (the Kiel classification; CLL:84, immunocytic:48, centrocytic:16, follicular CB/CC:46, follicular& diffuse CB/CC:31 and 34 low grade lymphoma NUD). Half of the patients (53%) were leukemic (lymphocyte count >5.0x10^9/l) with the highest frequency (82%) in CLL and the lowest (10%) in follicular & diffuse CB/CC. Time from diagnosis to randomization (time with asymptomatic disease) was longer than one year in half of the patients; mean time 8 months in patients with foll.CB/CC and 20 months in the CLL group.
Results : As expected, a higher remission rate (CR+PR) and a shorter remission indction time was seen in the CHOP-group. However, most patients showed a relapse during follow up and no significant difference was noted in total survival between the two regimens. Three- and 5-year actuarial survival from randomization was 59 and 41% (ChP) and 64 and 44% (CHOP), respectively. No survival advantage was seen with CHOP in any of the histological subgroups. Nor did leukemic and non-leukemic patients differ regarding response rate or survival. Toxicity was lower with the ChP regimen.
Conclusion: The results do not support the use of aggressive chemotherapy as first line therapy in symptomatic low grade NHL.

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66 ON THE INFLUENCE OF HUMAN RECOMBINANT ALPHA-2 INTERFERON (ROFERON-A) ON REMISSION DURATION IN PATIENTS WITH STAGES III AND IV LOW GRADE MALIGNANT NON-HODGKIN'S LYMPHOMA. RESULTS FROM A PROSPECTIVE, RANDOMISED PHASE III CLINICAL TRIAL IN 346 PATIENTS.

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Phase II studies have indicated that alpha-2 interferon (IFN) has significant efficacy in non-Hodgkin's lymphoma (NHL) of low grade malignancy. Therefore, a prospective, randomised phase III study was initiated 6½ years ago in the EORTC Lymphoma Cooperative Group. The objective of the study was to investigate whether prolonged IFN administration in the phase of "minimal residual disease" will increase relapse-free survival or postpone progression of disease. Previously untreated patients older than 15 years with NHL (Working Formulation class B,C) were eligible. All patients received 8 courses of combination chemotherapy (Cyclophosphamide 300 mg/m^2 per os, days 1-5; Vincristine 1.4 mg/m^2 i.v. day 1, and Prednisone 40 mg/m^2 per os, days 1-5). After CVP all patients were evaluated and submitted to iceberg radiotherapy. Thereafter, responding and stable disease patients were randomised to either recombinant alpha-2 interferon (Roferon-A) 3x10^6 IU s.c. three times per week for a period of 12 months or to "no further treatment". As of November 1992, 346 patients were registered of which 262 are now evaluable for response to CVP with a total response rate of 85%, i.e. 125/262 (48%) complete remission, CR, and 98/262 (37%) partial remission, PR. A total of 101 patients were eligible for iceberg irradiation, 32 in CR and 69 in PR after 8 courses of CVP. Of the 69 PR patients, 28 (41%) reached a CR after irradiation. So far, 228 patients have been randomised: 114 to IFN, 114 to "no further treatment". The remission status at the time of randomisation was 60% in CR and 40% PR/no change in the IFN arm versus 67% CR and 33% PR/no change in the control arm. IFN was well tolerated, i.e. IFN treatment was stopped in only 8 patients because of excessive toxicity (flu like syndrome:7; thrombocytopenia: 1). The overall and progression free 3-years survival are estimated at 84% and 43%, respectively (median follow-up: 2.5 years). The median progression free survival for all patients is 116 weeks. When the two curves are compared, the progression free 3-years survival is 48% in the IFN maintenance group versus 40% in the control group. However, there is a significant difference in the *duration* of the progression-free survival, i.e. 140 weeks in the IFN maintenance group versus 87 weeks in the control group (p=0.03). It is still too early to comment on possible differences in overall survival. In conclusion, in this longlasting randomised, multicenter study IFN maintenance treatment in the phase of "minimal residual disease" of low grade malignant NHL significantly prolongs progression free survival.

67 A CONCOMITANT TREATMENT WITH INTERFERON ALFA AND A DOXORUBICIN-CONTAINING REGIMEN IMPROVES SURVIVAL IN HIGH-TUMOR BURDEN FOLLICULAR NON-HODGKIN'S LYMPHOMAS.

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Interferon alfa (IFα) is active in follicular non-Hodgkin's lymphomas (NHL). Initial in vitro and clinical results have demonstrated synergistic or additive effects of IFα and cytotoxic drugs in NHL. In 1986, a clinical trial was designed to evaluate the benefit of a concomitant association of recombinant IFα to a doxorubicin-containing regimen in patients with clinically aggressive low-grade follicular NHL. Clinical, radiographic and biological criteria suggestive of a high-tumor burden were used to select 242 patients with follicular NHL. All patients were treated with a CHVP regimen (cyclophosphamide 600 mg/m^2 - doxorubicin 25 mg/m^2 - teniposide 60 mg/m^2 all on day 1 - prednisone 40 mg/m^2 D_1 to D_5; 6 monthly cycles followed by 1 cycle every 2 months during 1 year). After randomization, 123 patients additionally received α2b-interferon, INTRONA at a dosage 5 x 10^6 U three times weekly during 18 months. The remaining 119 patients were treated with chemotherapy only.
The median follow-up was 35 months (18-70). Compared to those treated with CHVP, patients treated with CHVP + IFα had a higher overall response rate (86 % vs. 70 %, p = 0.002), a longer median event-free survival (34.5 months vs. 18.7 months, p < 10^{-4}) and a higher 3-year overall survival (86 % vs. 69 %, p = 0.02). The following parameters had a negative influence on survival by a multivariate Cox analysis : CHVP treatment (p = 0.001), B symptoms (p = 0.03), bone marrow involvement (p = 0.06). Toxicity was significantly greater in patients treated with CHVP + IFα compared to CHVP alone : 5 % of patients in the CHVP arm and 30 % in the CHVP + IFα arm had neutropenias grade ≥ 3 during the induction phase (monthly cycles) but severe infections were very rare. There was no treatment-related death. Interferon has to be stopped because of toxicity in 17/123 (14 %) patients.
The addition of concomitant interferon alfa to a doxorubicin-containing regimen increases, the survival of patients with high-tumor burden follicular NHL.

68 A RANDOMIZED PHASE III TRIAL OF PROMACE-MOPP VS MACOP-B IN AGGRESSIVE NON-HODGKIN'S LYMPHOMAS (NHL). AN INTERIM ANALYSIS OF THE NON-HODGKIN'S LYMPHOMA CO-OPERATIVE STUDY GROUP.

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The aim of our study was to compare two regimens widely used in the treatment of high grade lymphoma and assess whether a III generation regimen were superior to II generation one as expected according to the dose intensity hypothesis.
Between January 1987 and August 1991, 224 patients (pts) with diffuse, intermediate-high grade NHL (Groups F,G,H,K/WF), not previosly treated, stage II bulky (≥10 cm),III IV,PS≤2 were randomized to receive: alternating PROMACE-MOPP x 6 cycles (Arm A), or MACOP-B x 12 weeks (Arm B), plus radiotherapy on the sites of bulky disease,if present at diagosis. 114 pts were treated according to Arm A, their median age was 50 yrs.(range 16-68),M/F ratio was 70/44, B symptoms were present in 55 pts and BM involvement in 32 pts. The stage was II bulky in 26, III in 29 and IV in 59 pts. 107 pts were treated according to Arm B, their median age was 46 yrs.(range 17-67), M/F ratio was 67/40, B symptoms were present in 35 pts and BM involvement in 23. The stage was II bulky in 24, III in 23 and IV in 60 pts. The others prognostic factors (PS, LDH, extranodal sites, mediastinal location) were balanced in both arms. Three pts after reviewing the slides turned out to be LD Hodgkin Disease and were considered inelegible for the study.Out of 221 eligible pts, 183 are presently evaluable in terms of response and disease free survival (DFS), all 221 pts are evaluable in terms of progression free survival (PFS) and survival (S).Current results are as follow :

		4-yrs		4-yrs	4-yrs
	n. pts	PFS(%)	CR (%)	DFS(%)	S (%)
PROMACE-MOPP	114	27	49/94 (52)	43	41
MACOP-B	107	40	50/89 (56)	55	56

Prevailing toxicities were medullary (grade III IV leucopenia 48 vs 39%; thrombocytopenia 8.5 vs 8.3; grade II IV sepsis 4.1 vs 12.4%) and gastroenteric (N/V 7.5 vs 8.3%, stomatitis 18.9 vs 34.4). Mortality treatment-related due to infections or major complications occurred in 12 pts. in Arm A (10.5%) and in 19 in Arm B (17.7%). In conclusion no significant difference in terms of efficacy between the two regimen a is presently evident. If longer experience with Arm B regimen will help reduce toxicity, the shorter treatment duration may be considered an advantage.

69 COMPARISON OF CHOP vs. PACEBOM IN DIFFUSE AND LARGE CELL LYMPHOMAS WITH AN ANALYSIS OF OUTCOME IN POOR PROGNOSIS YOUNGER PATIENTS: A BNLI RANDOMISED TRIAL.

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Between November 1987 and October 1992 485 adult patients less than 70 years old with Stage II-IV diffuse mixed and diffuse large cell non Hodgkin's lymphoma were entered into a randomised trial of monthly cycles of CHOP (minimum 6 cycles) or a weekly multiagent regimen (PACEBOM) given for 12 weeks. This preliminary report refers to the 414 patients entered up until the end of 1991 for whom adequate follow up is possible. 205 received CHOP and 209 received PACEBOM. Both arms of the trial were well matched for all risk factors. The median age in both arms was 53 years. The complete remission rates were 58% in the CHOP arm and 62% in the PACEBOM arm (difference NS). Of those achieving a CR the actuarial relapse free survival at 4 years was 68% and 66% respectively. The overall actuarial survival at 4 years in the CHOP arm was 53% and 61% in the PACEBOM arm (difference NS). Grade 3/4 haematological toxicity was more frequent with PACEBOM (49% vs. 35%) but the incidence of infections was similar (20% vs. 16%). For the whole group multivariate analysis revealed that the three factors predicting for poor survival were poor performance status (Karnovsky < 70), Stage III/IV and age. For patients under 60 years of age with at least 2 out of 3 of these factors, ie. poor disease performance status, Stage III/IV or a reduced albumin (21% of total patients) the CR rate was only 34% and the actuarial overall survival at 4 years was 41%. Of those attaining CR the actuarial relapse rate at 4 years was only 18%. This study shows 1) that PACEBOM and CHOP are equally effective and 2) that poor risk younger patients have a much reduced chance of obtaining a CR, but if this is attained, the relapse rate is not increased. This implies that if treatment is to be intensified to the younger poor risk patients, it must be directed at increasing the CR rate rather than consolidating an established first CR.

70 CHOP *vs* m-BACOD FOR ADVANCED DIFFUSE NON-HODGKIN'S LYMPHOMA: ASSOCIATION OF LONG-TERM OUTCOME WITH THE INTERNATIONAL INDEX (I.I.) AND WITH LDH ALONE.

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The results of EST 6483, a randomized comparison of CHOP (Cyclophosphamide, Doxorubicin, Vincristine, Prednisone) with m-BACOD (Methotrexate, Bleomycin, Doxorubicin, Vincristine, Dexamethasone) in patients with stage III,IV diffuse histiocytic and diffuse mixed histology NHL, demonstrated no difference between the regimens in the CR rate, DFS, time to treatment failure or overall survival, but greater toxicity with m-BACOD (NEJM 1992;327:1342). The I.I. (Shipp *et al.* Proc ASCO 1992,11:319) identified age>60, LDH>normal, performance status >1, ≥2 sites of disease, and stage III,IV as risk factors for poor outcome in diffuse histology NHL. Four risk groups were defined by the sum of poor risk factors: Low (0,1), Low-Int (2), High-Int (3), and High (4,5).

We have updated the results of EST 6483 with 5.3 years of follow-up for survival. Five-year DFS is 52%, 51% with CHOP and 54% with m-BACOD (p=.87), and 5-year survival is 46%, 43% with CHOP and 50% with m-BACOD (p=.43). 5-year results by the I.I. are presented below:

	5-yr DFS				5-yr Survival			
I.I.	(n)	CHOP	m-BACOD	All	(n)	CHOP	m-BACOD	All
1	(25)	43%	64%	50%	(35)	48%	67%	56%
2	(57)	54%	48%	51%	(102)	59%	58%	58%
3	(43)	70%	48%	58%	(97)	33%	42%	37%
4,5	(17)	29%	44%	38%	(52)	30%	31%	31%

There were no significant differences between CHOP and m-BACOD in any subgroups defined by the I.I.

Within this study of stage III,IV patients, the I.I. did not distinguish long-term outcome well among Low, Low-Int, and High-Int risk patients. An investigation in these data using exploratory diagnostics for proportional hazards regression identified an additional cut-point for LDH at 3 x normal: 5-yr survival was 57% if LDH<normal, 42% for LDH 1-3 x normal, and 21% if LDH > 3 x normal. LDH cut at 1 and 3 x normal was a far stronger predictor of outcome in a regression model than the I.I., and it will be interesting to test such analyses in subsets of the I.I. dataset.

71 *STAGE, SERUM LDH, AND PERFORMANCE STATUS PREDICT DISEASE PROGRESSION AND SURVIVAL IN HIV-ASSOCIATED LYMPHOMAS.*

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The best therapy for patients with AIDS and lymphoma has not been defined. However, to help determine the best therapy, we reviewed our experience at M. D. Anderson Cancer Center with 44 patients with positive HIV serology (positive HIV) and lymphoma. Of these 44 patients, 20 had diffuse large cell lymphomas (DLCL), and 18 had small noncleaved cell lymphomas (SNCCL). Three had Hodgkin's disease and three had diffuse small or mixed cell lymphomas. These patients received various intensive chemotherapy regimens for management of their disease; most of these regimens were those in use at our institution for other patients with lymphoma who did not have positive HIV. The complete response to treatment (CR) was 77% for all patients, 80% for those with DLCL, and 72% for those with SNCCL. Stage, serum LDH, and performance status were predictors of CR and freedom from progression. These patients had a high likelihood of infectious complications during chemotherapy. Though there was a tendency for patients with a T_4-cell count of ≤200 to have a higher risk of opportunistic infections while receiving therapy, most infections were controllable with appropriate antibiotic management. Most of the deaths in this study occurred after completion of therapy in complete remission, with a median survival of only 11 months, and were attributable to AIDS-related complications. Our data suggests that; (1) patients with lymphoma who have positive HIV have responses to chemotherapy similar to those expected for patients who are HIV-negative; (2) most infectious complications are manageable with appropriate therapy during treatment; and (3) after completion of chemotherapy, treatment should focus on control of progression of AIDS-related complications.

72 PRIMARY NASAL T CELL LYMPHOMA.

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Primary sinonasal lymphoproliferative lesions historically have been poorly characterized disorders, and the literature uses pathologic terms such as lymphomatoid granulomatosis, polymorphic reticulosis, and angiocentric T cell lymphoma and clinical terms such as lethal midline granuloma and midfacial necrotizing lesion. The incidence of sinonasal lymphoma is approximately 1.5% of lymphomas in the United States, but approximately 7% in Asian countries and in Peru. Although the majority of sinonasal lymphoma in the United States and Germany are of B lineage, non-B cell phenotypes represent the predominant phenotype in Asia and Peru. The non-B-cell lymphomas have a diffuse and sometimes angiocentric or angioinfiltrative pattern of involvement, and are commonly associated with extensive necrosis and mucosal ulceration. The neoplastic cells often show a wide range of nuclear size and atypia. These lymphomas are usually CD2, CD43, CD45RO, and CD56 positive and negative for many other T cell antigens (including CD3, CD4, CD5, CD7, CD8), suggesting aberrant T or natural killer cell lineage. Many of these cases lack detectable clonal immunoglobulin and β–T-cell receptor gene rearrangements. The vast majority of cases, regardless of country of origin, contain Epstein-Barr viral (EBV) genomes. Southern blot studies demonstrate the EBV to be present in a monoclonal population, despite germline antigen receptor gene rearrangement studies, and in situ hybridization studies have localized the EBV to the malignant cells. Although the median survival of patients with these lymphomas may be long, local recurrence or progression to systemic lymphoma commonly occurs, with death due to disease occurring in approximately 50% of patients.

73 T-CELL RICH B-CELL LYMPHOMA AND THEIR RELATIONSHIP TO HODGKIN'S DISEASE.

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The recognition of B-cell lymphomas with a strong reactive T-cell component simulating other disorders such as Hodgkin's disease (HD) or peripheral T-cell lymphoma is relatively recent. We report 16 cases, in which the diagnosis of diffuse lymphocyte predominance (LP HD) or mixed cellularity (MC) HD was the most frequent morphologic consideration. Clinicopathologic aberrancy drew attention to these cases. Clinical stage was unusually advanced (stages III and IV : 5 and 9 cases respectively). Splenomègaly was noted in 6/16 cases. M:F ratio was 15:1 and median age was 33 years (range 22-77 years). Follow-up was available in 12 patients. Response to chemotherapy was poor in most cases, and 6 patients died early of their disease (2 to 18 months after the diagnosis). In all cases, lymph node architecture was obliterated by the presence of large atypical cells in a diffuse background of small lymphocytes without a significant polymorphous infiltrate. Atypical cells, some resembling RS-cells and variants, were dispersed throughout the lymph node fields. In most cases small lymphocytes around large cells showed nuclear abnormalities consisting of moderate variation in size with hyperchromatic angulated nuclei. Large atypical cells were B-lymphocytes (CD20/L26+, CDw75/DNA.7+) expressing EMA ; a phenotype similar to nodular lymphocyte predominance HD. RS-cell (CD15, CD30) and T-cell-associated antigens were absent on large cells. The presence of kappa mRNA was detected in one case and in an additional case a clonal B-cell population was detected by PCR. No EB virus genome could be detected using in situ hybridization with EBER oligonucleotides.
These T-cell rich B-cell lymphoma represent a figure of 4-5 % with erroneous diagnosis of HD. Despite phenotypic similarity to nLP HD, the lack of lympho-histiocytic type cells (L&H cells) and the diffuse pattern, exclude the diagnosis of nLP HD for these cases. Aggressive and advanced disease at clinical presentation is also distinctly unusual for nLP HD. The most difficult differential diagnosis is diffuse LP HD. In the Rye classification the diagnosis of diffuse LP HD is based on the frequency of diagnostic RS-cells rather than lymphocyte population and its immunophenotype is not clearly established. Cases considered, in the past, as diffuse LP HD were probably heterogeneous and included not only LP HD but also MC HD (CD15+, CD30+, EMA-) and T cell-rich B-cell lymphoma as well as some non-Hodgkin's lymphomas of T-cell. Some cases previously reported with the diagnosis of diffuse LP HD with an aggressive course could correspond to T cell-rich B-cell lymphoma. Due to clinical implications we think there is a need for an immunomorphologic redefinition of diffuse LP HD.

74 MANTLE CELL LYMPHOMAS.

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Histological subtyping of Non Hodgkin's lymphomas is of prognostic significance and classification systems in use are subdividing these neoplasms in low grade, intermediate grade and high grade malignant disorders. This subgrouping is on its overall, largely supported by clinical findings but immunophenotyping and genotyping has clearly demonstrated that several of these histologically defined subcategories are heterogeneous and may comprise B cell as well as T cell lymphomas with neoplastic cells at different stages of maturation. This is clearly illustrated by the group of " diffuse small cleaved cell lymphomas" which comprises several B cell neoplasms related to different compartments of the B follicle as well as T cell lymphomas. Moreover, small cleaved B cell neoplasms have been differently named and interpreted in the States and in Europe and data on the natural history and therapeutic results on each of the various diseases included in this category, are largely missing.

With regard to the composition of the reactive B follicle several compartments may be recognised: a follicle centre, mainly involved in the second stage of the immune response with generation of IgG producing plasmacells and memory cells; a follicle mantel and a surrounding marginal zone, mainly responsible for the first step in the immune response resulting in the production of IgM producing plasmacells and recirculating B cells. Non Hodgkin's lymphomas may mimic this situation with tumours composed of neoplastic follicle centre cells (small cleaved cells admixed with a variable number of large non cleaved cells) and lymphomas of neoplastic mantle cells and marginal zone cells corresponding as well to "small cleaved cells". The latter two small cleaved cell lymphomas are of interest since both may display a "parafollicular" growth pattern mimicking a follicular growth, with remaining or residual, non neoplastic follicle centres. Marginal zone cell neoplasms are recognised as monocytoid B cell lymphomas or, if occurring in an extra nodal area, as MALT lymphomas.

Mantle cell lymphomas have been identified in the States as mantle zone lymphomas, if displaying a parafollicular growth, or as intermediately differentiated non Hodgkin's lymphomas if lymph node architecture is completely effaced by a diffuse neoplasm. In Europe the same neoplasm has been described as centrocytic lymphoma in the Kiel classification. Morphology, immunophenoting and cytogenetics reported in mantle zone lymphoma, in intermediately differentiated lymphoma and in centrocytic lymphoma support their similarity and underlines their distinction from follicle centre cell lymphomas. They all three are composed of a mixture of small round cells and small cleaved cells. The neoplastic cells express several B cell markers, surface immunoglobulines and CD5 but they lack CD10 expression and striking correlation with t (11;14) has been found with rearrangements of *bcl1* oncogen and PRAD1.

The behaviour and responsiveness to therapy of mantle cell lymphomas has not been fully documented yet and awaits more precise information to be distinguished from follicular lymphomas of predominantly small cleaved cells on the one end and from well differentiated lymphocytic lymphomas on the other end.

In order to obtain these data on mantle cell lymphomas as well as on other entities not recognised by the presently used classification systems, precise subtyping of non Hodgkin's lymphomas based on morphology and supported by immunophenotyping as well as cytogenetic analysis is now mandatory.

75 CD30/Ki-1 POSITIVE LYMPHOPROLIFERATIVE DISORDERS OF THE SKIN. CLINICOPATHOLOGIC CHARACTERIZATION OF 92 CASES (*).

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The CD30/Ki-1 activation antigen is expressed by atypical cells in Hodgkin's Disease (HD), anaplastic large cell lymphoma (ALC-L) and various non-Hodgkin's lymphomas (NHLs). Skin represents the most common site of extranodal CD 30+ lymphomas, but little is known about the clinical behaviour of these cutaneous CD 30+ lymphomas. Some authors suggested that CD30 expression in large cell cutaneous NHL is associated with a favourable prognosis. To further examine the prognostic significance of CD30 expression in cutaneous lymphomas, we analyzed the clinico-pathologic features of 92 cases of CD30+ cutaneous lymphoproliferative disorders. In all cases the majority of atypical cells expressed the CD30 antigen and histologically were classified as: 1) CD30 + ALC-L; 2) CD30+ NHL, non anaplastic, including mycosis fungoides, pleomorphic T cell and large cell lymphomas (immunoblastic, centroblastic); 3) HD and 4) lymphomatoid papulosis (LyP). Clinically, the cases included primary cutaneous disease (72 cases) and CD30+ lymphomas (9 cases), arising in patients with a previous history of cutaneous lymphoproliferative disease. In the other 11 cases, skin involvement followed or occurred simultaneously with extracutaneous CD 30+ ALC-L. Immunohistochemistry and molecular genetic analysis demonstrated a T cell lineage in 75 cases and a B cell lineage in 3 cases; 14 cases were null, non B non T, and 2 cases showed an ambigous immunoreactivity pattern on paraffin sections. Our observations suggest that cutaneous CD30+ lymphomas are heterogeneous neoplasms, characterized by different behaviour and prognosis. Specifically, we found that: 1) primary cutaneous CD30+ lymphomas have an indolent clinical course in most cases and lymph nodal involvement is frequently associated with progressive disease; 2) secondary cutaneous CD 30+ lymphomas are usually associated with poor prognosis and 3) interestingly ALC-L, HD and LyP can occur in the same patient (6 cases) and display overlapping cytological and immunohistochemical features, supporting the hypothesis of a common histogenesis for these disorders. Statistical analysis of histologic and immunophenotypic data is in course to investigate possible differences in prognosis among the various histologic subtypes of cutaneous CD 30+ malignancies.

(*) = collected from the Italian Cutaneous Ki-1 Lymphoma Study Group (L. Fiore-Donati, F. Menestrina, Verona; G. Vassallo, Piacenza; F. Facchetti, Brescia; S. Kindl, E. Boveri, U. Gianelli, Pavia; E. Bonoldi, Vicenza; V. Stracca, Venezia; T. Motta, Bergamo; M. Pilatti, Como; P. Fontana, Desenzano; C. Gambini, M. Truini, Genova; D. Remotti, Roma; M. Santucci, Firenze, A. Cossu, Cagliari; M. Bersiga, Cremona) and from the E.O.R.T.C. Cutaneous Lymphoma Study Group (P. Kaudewitz, Munich, Germany; E. Ralfkiaer Copenhagen, Denmark; C. Papadimitriou, Thessaloniki, Greece; U. Holecek, Essen, Germany; J. Wechsler, Creteil, France; M.L. Geerts, Gent, Belgium).

76 CORRELATION OF CYTOGENETIC FINDINGS AND HISTOPATHOLOGICAL DIAGNOSES ACCORDING TO THE UPDATED KIEL CLASSIFICATION IN 104 PERIPHERAL T CELL LYMPHOMAS. Brigitte Schlegelberger, Annekathrin Himmler, Alfred C. Feller°, Karl Lennert*, Werner Grote. Institute of Human Genetics, University of Kiel, Institutes of Pathology, University of Lübeck° and Kiel*, Germany.

Cytogenetic studies were performed on lymph node biopsies, skin biopsies and peripheral blood from 104 patients with peripheral T cell lymphomas (PTL). The diagnoses were made according to the updated Kiel classification.
Low grade PTL showed consistent cytogenetic features. Clones with inv(14) and trisomy 8q were found in all cases of T-CLL and T-PLL. The distal breakpoint of *clonal* inv(14) lay in 14q32.1 and differed from the distal breakpoint of *nonclonal* inv(14). It is supposed that band 14q32.1 contains an oncogene that is essential for the tumor development in T-CLL and T-PLL. AILD-type PTL was characterized by +3, +5 and +X clones. Trisomies 3 and 5 were also observed in T-zone and lymphoepitheloid lymphomas. However, different single cell aberrations and unrelated clones were exclusively detected in AILD-type PTL and appeared in 30 out of 50 cases.
High grade PTL did not comprise such characteristic cytogenetic findings as low grade PTL. Only in large cell anaplastic lymphomas a characteristic chromosome aberration, i.e. t(2;5)(p23;q35), was found. In contrast to low grade PTL, high grade PTL contained usually complex clones with many structural aberrations and often chromosome numbers in the triploid to tetraploid range. Recurrent aberrations of medium to large cell pleomorphic lymphomas were dup(6)(p12-p21/2), del(6)(q15q25), total or partial trisomy 7q and breaks in 13q14. Transition from low grade to high grade PTL was repeatedly accompanied by deletions in 1p, indicating a short survival.
In summary, the cytogenetic findings in our series of 104 PTL paralleled the histopathological diagnoses of the updated Kiel classification. Thus, cytogenetic findings can be helpful to clarify uncertain cases of peripheral T cell lymphomas.

77 POST-TRANSPLANT LYMPHOMAS THAT EXPRESS T-CELL MARKERS. E.K. Waller, M. Ziemianska, C.D. Bangs, I.L. Weissman, M. Cleary, and O.W. Kamel. Division of Oncology, Stanford University Medical Center, Stanford, CA 94305-5468

Lymphomas arising in organ transplant recipients usually are B-cell non-Hodgkin's lymphomas that contain Epstein-Barr virus DNA sequences. We investigated the characteristics of post-transplant lymphomas that lacked expression of the usual markers associated with EBV transformation. We describe four large cell lymphomas which expressed T-cell markers out of a group of 15 cases of post-transplant lymphoma seen recently at our institution. Two of these four cases were $CD4^+$ and one was $CD8^+$, and in one staining for CD4 and CD8 expression was not performed. One $CD4^+$ lymphoma was a $CD30^+$, EBV^- large cell lymphoma from a 65 year old kidney transplant recipient, the second was a EBV^+ large cell lymphoma from a 25 year old heart transplant patient. Two T-cell lymphoma were EBV^+ and had clonal T-cell receptor β gene rearrangements. The other two lymphomas expressed T-cell markers CD4 and CD43, and lacked expression of B-cell markers CD19, CD20, CD21, CD22, CD23, and surface immunoglobulin. Both $CD4^+$ lymphomas were tumorigenic following their heterotransplantation into severe combined immunodeficient (SCID) mice. Cytogenetics, immunophenotyping and genotyping of the secondary tumors from SCID mice demonstrated their clonality and identity with the patients' primary tumors. Novel $CD4^+$ lymphoma cell lines, LH521/4 and LK418/4, were established from tumors that had been passaged in SCID mice. An immunodeficient environment may facilitate the growth of these T-cell or biphenotypic lymphomas; the etiology of their genesis can include transformation with EBV and other, as yet unidentified mechanisms.

78 **OCCURENCE OF t(14;18)-POSITIVE, MONOCLONAL PLASMA CELLS FOLLOWING TREATMENT WITH IL-3, IN A PATIENT WITH FOLLICULAR LYMPHOMA.** M.H.H. Kramer, J.C. Kluin-Nelemans, Ph.M. Kluin, W.E. Fibbe. Department of Pathology and Hematology, University Hospital Leiden, P.O.Box 9603, 2300 RC Leiden, The Netherlands.

Follicular lymphomas are tumors of mature B cells, as judged by their functionally rearranged Ig genes and cell surface expression of Ig. However it appears that the t(14;18) translocation of follicular lymphoma cells occurs at the pre-B cell stage. We present a case of a t(14;18)-positive, IgM-kappa follicular B cell lymphoma, treated with high dose chemotherapy, followed by an autologous bone marrow transplantation (ABMT). The pre-transplant bone marrow biopsy showed a minimal localization of small lymphoma cells. Posttransplant Interleukin 3 (IL-3) was given to study its potential to enhance hematopoietic recovery. Directly after a two week treatment with IL-3 the patient developed a marked plasmacytosis in blood and bone marrow (up to 30% plasma cells). The bone marrow histology was compatible with multiple myeloma. The plasma cells expressed cytoplasmic IgM and kappa light chains, e.g. the same isotypes as the original lymphoma. Paraproteinemia with the same specificities was found. Kappa light chains were detectable in a urine specimen. Cytogenetic analysis of these cultured plasma cells revealed, amongst other abnormalities, a clone with a t(14;18) translocation. The plasmacytosis disappeared within 8 weeks after discontinuation of IL-3 and was followed by a transient lymphocytosis in the peripheral blood, with 79 % T-lymphocytes and only 3 % B-lymphocytes (CD4/CD8 ratio=0.4). The patient is now in a stable clinical complete remission 32 months after transplantation. Bone marrow histology and cytology does not show infiltration of lymphoma and no increase of plasma cells. The paraprotein is not detectable anymore.

With PCR and Southern Blot analysis it was shown that both the follicular lymphoma cells from a lymph node at presentation of the disease, and the plasma cells during IL-3 treatment contained a translocation within the minor cluster region (mcr) of the bcl-2 oncogene on chromosome 18 and the IgH gene region on chromosome 14.

IL-3 has been shown to be an **in vitro** growth- and differentiation factor for follicular lymphoma cells (C. Clayburger et al. J Exp Med 1992, 175:371). We suggest that IL-3 may play a role in inducing **in vivo** proliferation of the malignant clone as has been described before (A. Ganser et al. Blood 1990, 76:666). An additional effect reported here may be the **in vivo differentiating** capacity of IL-3. Under influence of this cytokine a t(14;18)-positive clone of mature, malignant B-cells, expressing s-IgM-kappa, gave rise to a transient monoclonal plasmacytosis with the same immunophenotype and a similar t(14;18) translocation. These results indicate a prominent role for IL-3 in the biology of follicular tumors, and stresses that this growth factor must be used with caution in the treatment of follicular lymphoma.

79 YOUNG "STUDY" AND "NON-STUDY" PATIENTS WITH NHL IN SWITZERLAND 1976 - 1991. H.P. Wagner, I. Dingeldein-Bettler, R. Angst, B. Arnet, C. Baumgartner, D. Beck, W. Berchtold, E.A. Bleher, J. Briner, U. Caflisch, B. Delaleu, A. Feldges, E. Frey, I. Glanzmann, A. Hirt, P. Imbach, H. Kuechler, K. Leibundgut, A. Meister, A.M. Morin-Bertrand, L. Nobile, J. Plaschkes, H.J. Pluess, A. Ridolfi Lüthy, F. Selz-Felix, E. Signer, E. Stettler, N. von der Weid, M. Wyss, V. Ziehli. Swiss Pediatric Oncology Group SPOG, Inselspital, 3010 Bern, Switzerland

Of 162 pts <17 yrs old with immunocytologically or histologically proven NHL registered by SPOG, 120 were enrolled on SPOG or POG protocols (=study pts) while 42 were not (=non-study pts). 81 (67%) of the study pts had Murphy stage III or IV disease, 45/81 (56%) B- and 27/81 (33%) T-NHL. 25/42 (60%) of the non-study pts had stage III or IV disease, 15/25 (60%) B- and 4/25 (16%) T-NHL. 1976 - 1983 13/82 (16%) were non-study pts, 1984 - 1991 29/80 (36%). 81/120 (76%) of the study and 22/42 (52%) of the non-study pts survive.

The reasons for not becoming a study pt varied: in 11/42 (26%) the treating physician/parents/patient prefered a non-SPOG non-POG protocol; 16/42 (38%) were treated according to a SPOG or POG protocol but could not be enrolled officially due to pretreatment, inability to comply with protocol requirements or anticipated difficulties with follow-up. 7 of the remaining 15 pts were initially treated for Hodgkins disease (4), rhabdomyosarcoma (2) or Ewing sarcoma (1). In 8 pts the strategy of treatment was not clear.

Our results demonstrate that one fourth (26%) of all NHL occuring in young residents of Switzerland were not treated according to the recommendations of SPOG. It appears, however, that in approximately 75% of these cases conditions excluding an enrollment on an official protocol prevailed. Since the survival rate of non-study pts appears to be smaller than that of study pts, treatment results of protocol studies may be biased and should be compared to population-based analyses of outcome.

80 CHILDHOOD NON-HODGKIN'S LYMPHOMA OF THE NON-B-CELL TYPE (NB-NHL): TREATMENT RESULTS OF THREE BFM TRIALS.

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178 children (75% males) of up to 18 years of age with non-B-cell non-Hodgkin's lymphoma (NB-NHL) were enrolled from 1981 to 1990 in the three consecutive trials NHL-BFM 81 (n=39), NHL-BFM 83 (n=62), and NHL-BFM 86 (n=77). The diagnosis according to the Kiel classification was lymphoblastic (152 T-cell, 9 B-precursor-cell), peripheral T-cell type (n=4), and unclassified (n=13). The distribution of clinical stages according to the Murphy's staging system was 4.5%, 6.2%, 61.2%, and 28.1% in stages I-IV, respectively. Treatment was stratified accordingly: Pts. with stage I and II disease received an 8-drugs induction therapy (protocol I) with prednisone, vincristine, daunorubicin, L-asparaginase, cyclophosphamide (CYC), cytarabin (ARA-C), 6-mercaptopurine (6-MP) and i.t. methotrexate (MTX) followed by extracompartment therapy with MTX and 6-MP, and maintenance therapy with oral 6-MP and MTX. Total therapy duration was 18 months. Pts. with stage III and IV disease received an additional reinduction element (protocol III/II) similar to protocol I and cranial irradiation. The treatment plan was almost identical to the protocols ALL-BFM 81, 83 and 86 for non-B ALL. Major modifications in the evolution of the three therapy regimens consisted of the introduction of intermediate dose MTX (0.5g/sqm/24h x 4) for all pts. in trial 83, the 10-fold increase in MTX dosage, the intensification of reinduction therapy (protocol II with CYC), as well as the reduction in the dosage of preventive cranial irradiation from 18 to 12 Gy for stage III/IV pts. in trial 86. Local irradiation was an optional element of treatment. After a median observation time of seven years 125 of 167 pts. (74.8%) are in continuous complete remission (CCR), 11 pts. are lost to follow-up. The probability for event-free survival by life table analysis is 0.69 (SD=0.08), 0.76 (SD=0.06), and 0.77 (SD=0.05) for all pts. in trials NB-NHL-BFM 81, 83, and 86, respectively. These results indicate that treatment intensification did not further improve the outcome. The results according to stage do not reveal a statistically significant difference. Adverse initial events such as early death or nonresponse were encountered in 7 pts., and two pts. died while in CCR. The majority of relapses (n=33) occurred with local tumor involvement (n=16) followed by bone marrow recurrence in stage III and IV pts. (n=11). Only five pts. relapsed with CNS disease. In the ongoing trial NHL-BFM 90, the treatment regimen remained essentially unchanged but the initial response to therapy will be evaluated as a potential prognostic factor. Pts. with inadequate response to induction therapy (less than 70% tumor reduction and/or persistent systemic disease) are treated with early reintensification elements utilizing HD-ARA-C, dexamethasone, ifosfamide, etoposide, and vindesine. 67/74 pts. with NB-NHL are presently in CCR.

81 B-CELL NEOPLASIA IN CHILDHOOD: RISK GROUP STRATIFICATION, TREATMENT STRATEGY AND PRELIMINARY RESULTS OF TRIAL NHL-BFM 90.

A. Reiter[1], D. Henzler[1], M. Schrappe[1], S. Sauter[2], W. Ebell[1], A. Brandt[1], E. Odenwald[1], E. Yakisan[1], M.R. Parwaresch[3], M. Tiemann[3], G. Mann[4], W.-D. Ludwig[5], H. Riehm[1] for the BFM Group. Depts. of Pediatrics, [1]Hannover, [2]Freiburg, [4]Vienna, [3]Dept of Hematopathology Kiel, [5]Dept. of Internal Medicine Berlin, FRG and Austria.

Our conclusions from trials ALL/NHL-BFM 81, 83, 86 for B-NHL/B-ALL were: 1) patients (pts) with complete resection had an excellent outcome; 2) pts had an increased risk for failure if they had extensive abdominal tumors (LDH $\geq$ 500 U/L) regardless of bone marrow (BM) involvement, or residual manifestations after 2 courses of therapy, or overt CNS disease; 3) high dose methotrexate (HD-MTX) 24 h infusion is an important component for treatment of B-cell neoplasms (Blood 80:2471, 1992). In trial NHL-BFM 90 therapy intensity is stratified into 3 branches. Branch 1: completely resected; branch 2: not resected, extra-abdominal localization or abdominal localization and LDH < 500 U/L; branch 3: not resected and abdominal localization and LDH $\geq$ 500 U/L, and all pts with BM or/and CNS involvement. After a 5-days' prephase (cyclophosphamide (CY)/prednisone), pts of branch 1, 2, 3 receive 2, 4 or 6 alternating courses of therapy, respectively. Course 1: vincristine, dexamethasone (DEXA), ifosfamide (IFO), cytarabin (ARA-C), etoposide (VP16), MTX 5 g/m²/24h (in branch 1, 500 mg/m²), MTX/ARA-C/prednisolone i.th. Course 2: IFO is replaced by CY, ARA-C and VP16 replaced by doxorubicin. In comparison to our previous trials therapy is reduced from 3 to 2 courses for pts with complete resection, and HD-MTX is introduced for all pts except for those in branch 1. Pts with stage III (St. Jude) with abdominal localization and LDH $\geq$ 500 U/l (40 % of stage III pts) are now included in branch 3 with the most intensive therapy. CNS pos. pts receive MTX/ARA-C/prednisolone applied intraventricularly. No radiotherapy is used. Pts with incomplete response after 2 courses receive an intensification (DEXA, Vindesine 3 mg/m², Ara-C 2 g/m²/12h x 4, VP16 150 mg/m²/d x 3). Pts with viable residual tumor after the intensified course receive megadose chemotherapy (busulfan, VP16, CY or thiotepa for CNS neg. or pos. pts, respectively) with autologous BM rescue (ABMT). From 4/1990 to 12/1992, 214 pts with B-cell neoplasms were registered; no patient is excluded from evaluation. The Kaplan Meier estimate of event free survival (pEFS) at 2 years is .89 ($\pm$.02) (median observation time 17 months). The results are as follows:

Branch	Pts	Early Death	Failure	CCR	pEFS	SD
1	32	0	1	31	.92	($\pm$.07)
2	88	0	1	87	.99	($\pm$.01)
3	94 (51 BM+, 17 CNS+)	8 (2 NHL, 6 Toxicity)	10	76	.74	($\pm$.06)

With this stratification approximately 60 % of the pts can be easily defined at diagnosis that have an pEFS of >95% with a very short treatment. pEFS for pts with stage III abdominal disease and LDH $\geq$ 500 U/L increased from < .50 in the preceeding studies to .80. Two pts had persistent viable residual tumor after 3 courses, and received ABMT; both are alive after 18 and 25 months. Of the 17 CNS pos pts, 3 sufferred a very early death, 14 are in complete continuous remission.

82 LARGE CELL ANAPLASTIC LYMPHOMA IN CHILDREN - OUTCOME USING HIGH GRADE B CELL CHEMOTHERAPY.

CR Pinkerton, M Gerrard. On behalf of United Kingdom Children's Cancer Study Group (UKCCSG)

The optimal management of large cell anaplastic Ki-1 positive lymphoma (LCA) in children remains uncertain. Treatment regimens varying from those used for B cell non-Hodgkin's lymphoma to common acute lymphoblastic leukaemia have been reported.

A regimen based on the SFOP LMB '89 B cell NHL protocol has been used by the UKCCSG since 1990. This regimen comprises high dose methotrexate, cyclophosphamide, doxorubicin, cytarabine, vincristine and prednisolone. Radiotherapy is not given electively. Between August 1990 and October 1992 14 patients out of 176 registered on the UKCCSG NHL 900 series were found to have Ki-1 positive LCA. Seven were boys. Multiple lymphadenopathy was the commonest site of disease. Bone was involved in three, skin in four and mediastinum in three cases. No patient had bone marrow or central nervous system involvement. Murphy stages were; stage III (11), stage II (2) and stage I (1). On immunophenotyping six were T, six indeterminate and two not known.

Two patients with localised disease were treated with a less intensive regimen containing similar drugs but omitting cyclophosphamide and one patient with stage III disease received a T cell leukaemia regimen. Of 11 patients given the more intensive B cell regimen 8 achieved complete remission and all of these remain disease free. None of the three who failed to achieve remission survived.

These data are too preliminary to conclude whether the outcome in this tumour is different from that for B lymphoblastic lymphoma given the same treatment. It also remains to be demonstrated to what extent within the category of LCA there are sub-groups based on clinical features, i.e. localised disease, immunophenotype or cytogenetics, who require more or less intensive therapy.

83 Immunophenotype Influences Survival In Pediatric Large Cell Lymphoma. A Pediatric Oncology Group Study.

Robert E. Hutchison, Costan W. Berard, Jonathan J. Shuster, Michael P. Link, Terry E. Pick and Sharon B. Murphy.

69 cases of pediatric large cell non-Hodgkin's lymphoma (NHL) were analyzed by paraffin-section immunochemistry for evidence of T-cell, B-cell, histiocytic, myeloid, and Hodgkin's-associated lineages. All cases had been previously classified histologically according to the Working Formulation for Clinical Usage (WF), staged in a uniform manner (Murphy system) and treated with a modern chemotherapy regimen according to one of two protocols for localized (stage I and II) NHL or advanced (stage III and IV) large cell NHL. Tissue sections from paraffin-embedded blocks were reacted with a panel of antibodies including anti- CD45, CD20, CD45Ra, MB-2 (not clustered), CD3, CD45Ro, CD43, CD15, CD30, and CD68. H&E stained sections from the same blocks were also examined for the histologic features of Anaplastic Large Cell Lymphoma (ALCL) according to the updated Kiel Classification. Statistical analysis utilized the Exact Conditional Chi-Square and Kruskall-Wallis tests for clinical features and logrank test to evaluate survival. Histology (WF) showed 36 diffuse large cell and 33 immunoblastic lymphomas. Immunophenotypic results demonstrated 25 T-cell, 25 B-cell and 19 non-T, non-B cell lineage. 29 cases showed the Hodgkin's associated antigen CD30 (19 T-cell and 10 non-T, non-B) and of these 22 were classified as ALCL. 2 additional cases showed ALCL features without CD30 expression. Phenotype (T-cell vs. B-cell vs. non-T, non-B) showed significant correlations with age and with survival. B-cell patients were older (median = 14.4 yrs.) than T-cell (median = 9.5 yrs.) or non-T, non-B (median = 10.4 yrs.), ($p = .019$). B-cell phenotype was also associated with more favorable survival with only one failure versus 7 for T-cell and 7 for non-T, non-B ($p = .030$). B-cell was more frequently limited stage but was also associated with favorable survival when analyzed with stratification for stage ($p = .036$). Neither CD30 expression ($p = .81$) nor ALCL histology ($p = .95$) showed association with survival. We conclude that among pediatric large cell lymphomas, T-cell and B-cell lineages are approximately equally distributed, non-T, non-B cases are also frequent and CD30+ ALCL is common among both T-cell and non-T, non-B cell types. B-cell lymphomas tend to occur in older children and are associated with superior survival.

84 CHARACTERISTICS AND TREATMENT OUTCOME FOR 18 CHILDREN WITH CD30 POSITIVE LARGE CELL NON-HODGKIN LYMPHOMA (NHL). J. Sandlund, C-H Pui, V. Santana, H. Mahmoud, W. Crist, J-S Lin, L. Mao, R. Ribeiro, C. Berard, R. Hutchison. St. Jude Children's Research Hospital (SJCRH), Memphis, TN, the University of Tennessee, Memphis, College of Medicine, Memphis, TN and State University of New York, Syracuse, NY.

We examined 45 cases of large cell NHL in children treated at SJCRH from 1975-1990 to determine the incidence, clinical features, immunophenotype, histiotype (NCI working formulation vs. Kiel), and impact on outcome associated with CD30 expression. Eighteen cases (40%) expressed CD30. Of the thirteen boys and five girls, four had limited stage (I or II) disease and fourteen had advanced stage (III or IV) disease. While nodal disease was common in both $CD30^+$ (16/18) and $CD30^-$ (18/27) cases, $CD30^+$ cases were significantly more likely to have skin involvement ($p=0.007$). Although there was no significant association between CD30 expression and NCI working formulation subtypes ($p=0.435$), $CD30^+$ cases were more likely to have anaplastic histiotype by Kiel classification (15/18 vs. 1/27 in $CD30^-$ cases, $p<0.001$). Moreover, all $CD30^+$ cases had either T-cell or null-cell phenotype, while the majority of $CD30^-$ cases (16/27) were B-cell ($p<0.001$). Among patients with limited stage disease , the 5 year event-free survival was 75% ± 22% for $CD30^+$ cases and 92% ± 9% for $CD30^-$ cases ($p=0.1$). Among patients with advanced staged disease, the 5-yr event-free survival was 57% ± 17% for $CD30^+$ cases and 29% ± 17% for $CD30^-$ cases ($p=0.096$). However, the overall 5-yr survival rate for advanced stage patients was significantly better for $CD30^+$ cases (86% ± 12% vs. 29% ± 14%, $p=0.0014$). Thus CD30 is frequently expressed in large cell NHL of childhood, and is significantly associated with T or null-cell phenotype, anaplastic morphology, skin involvement and better overall survival.

85 **PRIMARY ANAPLASTIC LARGE CELL NON HODGKIN LYMPHOMA (ALC-NHL) IN CHILDREN.** M. Massimino, M. Gasparini, L. Rottoli, R. Luksch, F. Lombardi, R. Giardini, F. Rilke. Divisions of Pediatric Oncology, Radiation Therapy, and Pathology. Istituto Nazionale Tumori, 20133 Milan, MI, Italy.

Of 260 consecutive children treated for NHL from 1979 to 1992, 32 (12%) had ALC-NHL both on morphological and immunocytochemical grounds. In 16/32 the phenotype was determined on frozen sections and all of them were CD30-immunoreactive. Conversely, the remaining 16 cases were Ber-H2 positive on paraffin embedded sections. The initial diagnosis for the 16 pts admitted before 1987 was malignant histiocytosis in 14 and immunoblastic NHL in 2. There were 20 males (62%) and 12 females with a median age of 9 yrs (range 2-16 yrs). Only 4/32 presented with one single site involved. Nodal involvement was evident in 23 (72%), in 7 associated with infiltration of covering soft tissues and skin. Multiple deposits in the subcutaneous tissue were palpable in 9/32. Bone lytic lesions were observed in 10 and spleen involvement in 9. Less commonly involved sites were mediastinum (6), lungs (6), liver (3), GI tract (2) and meninges (1). BM aspiration and needle biopsies as well as CSF cytology were normal. Fever was present in 21 (65%), LDH levels were slightly increased in 3. 28/32 were considered evaluable for therapy and treated according to a program similar to that in use for childhood lymphoblastic NHL, consisting of a 2-month polychemotherapy induction followed by a 22-month maintenance (Am J Ped Haematol Oncol 5:161, 1983) but without any form of CNS prophylaxis. 4 were not considered evaluable for therapy because of different treatments. 27/28 underwent CR and one died during induction because of treatment-related complications. 7/27 (26%) relapsed in a median time of 7 mos (range 5-47 mos) from treatment start: 4 subsequently died because of progressive disease, 2 are in CR after salvage chemotherapy and one is on treatment after relapse. 22/27 (81%) were alive in CCR from 5 mos to 13 yrs (median FU 5 yrs). Bad prognostic indicators were involvement of the liver and lungs. First relapses never occurred in BM or CNS (except for the patient with meningeal involvement at diagnosis). ALC-NHL in children represents a subgroup of NHL with a peculiar behaviour and relatively good prognosis. Treatment program can be refined according to the initial extent of disease.

86 LARGE CELL ANAPLASTIC LYMPHOMA IN CHILDREN : THERAPEUTIC RESULTS IN 75 PATIENTS TREATED WITH 3 CONSECUTIVE POLYCHEMOTHERAPY REGIMENS.

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Between January 1975 and April 1992, 75 children with large cell anaplastic lymphoma (LCAL) confirmed histologically were treated with a polychemotherapy regimen according to 3 consecutive protocols (COPAD, HM89, HM91). 25 of these patients (pts) were initially diagnosed as malignant histiocytosis and further reviewed as LCAL.

The COPAD regimen, used between 1975 and 1989, combined vincristine, cyclophosphamide, doxorubicin and prednisone for a total duration of 12 months. In HM89, methotrexate (3g/m²) and VP16 were added to previous drugs and total duration of treatment shortened to 8 months. Since 1991, vinblastine and bleomycin were given in maintenace therapy in addition to the other drugs.

28 children were treated according to COPAD protocol, 22 in the HM89 and 25 in the HM91.

Ages ranged from 17 months to 15 years (median 10 y). The male : female ratio was 44:13.

According to the Murphy classification, 4 pts had stage I disease, 2 stage II, 54 stage III and 15 stage IV. 55 pts had B symptoms. Lymph nodes were present in 35, skin lesions in 33, visceral involvement in 35 and bone marrow involvement in 15. No patient had central nervous system involvement at diagnosis.

Initial chemotherapy resulted in a complete remission in 22/28 pts in COPAD protocol, 20/22 in HM89 and 21/25 in HM91. 23 pts relapsed 3 months to 5 years after diagnosis (mean 8 months) : 10 in the COPAD protocol, 9 in HM89 and 5 in HM91. Most of the relapses were nodal or cutaneous. None of them was in CNS. 9 of them are alive in second complete remission after a second line chemotherapy (vinblastine, bleomycin and BCNU) with a follow-up of 14 m to 17 years (median 7y). Overall 55 pts are alive with no evidence of disease with 8 months to 18 years follow-up (median 4 y), 14 died 2 months to 7 years after diagnosis and 6 are alive with progressive disease. Event free survival is 52 % at 5 years and crude survival is 88 % at 5 years.

No significant difference in outcome appeared according to the protocol.

Study of pronostic factors is in progress and might help to distinguish the patients requiring a more agressive therapy.

87 LARGE CELL ANAPLASTIC LYMPHOMA (LCAL) OF CHILDHOOD: A REPORT OF 45 PATIENTS UNIFORMELY TREATED ACCORDING TO THE BFM B-NHL STRATEGY.

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LCAL is now a well recognized clinicopathological entity (Kadin, J Clin Oncol 9:533, 1991). However, an optimal treatment strategy is not established yet. Due to the rapid proliferation properties of the disease, LCAL pts entering the trials NHL-BFM 81/ 83/86/90, were treated according to the strategy for B-cell NHL. From Sept. 1983 to March 1992, 45 pts were enrolled (30 males, 15 females; median age 10 y, range 11 m - 16 y/11 m). The presence of CD 30 antigen was determined in 44 cases. The immunophenotype was T in 26 pts, B in 1, non-B/nonT in 7, and not available in 11 pts. Extranodal involvement was observed in 26 pts: bone lesions (10 pts), soft tissue (11), skin, (5), lung (4), effusions (5), bowel (2), others (3). 13 pts presented with hepato(spleno)megaly and 17 had B symptoms. No patient had bone marrow (BM) involvement, and only one had CNS involvement. According to the St. Jude´s staging system, 6 pts had stage I disease, 11 stage II, 27 stage III, and 1 stage IV disease. Therapy consisted of two different 5-day courses composed of corticosteroids, cyclophosphamide/ifosfamide, medium dose methotrexate (MD-MTX) (0.5 g/m²), ARA-C, VM 26, adriamycin and i.th. therapy, administered to a total of 3 (pts with complete primary resection) or 6 courses. 6 pts with bone lesions received intensified therapy: MD-MTX was replaced by high-dose-MTX (5 g/m²), and 4 of these pts received HD-Ara-C and VP16. None of the pts received local radiotherapy and only one received CNS irradiation. 3 pts failed to achieve remission, one pt suffered toxic death. Six pts relapsed (4 stage II, 2 stage III), among them 3 of 5 pts with skin involvement. 35 pts (78 %) are in CCR for periods between 9 and 111 months (median 31 months). All relapses occurred within 8 months after diagnosis. The sites of first recurrence were: previous manifestations in one, different sites in three, and skin lesions at different sites in two pts with initial skin involvement; CNS or BM was never involved. Our preliminary conclusions are: a therapy strategy, originally designed for the rapid proliferating B-cell neoplasias, is also effective in LCAL treatment. CNS irradiation or local therapy seem to be of no advantage. Stage or initial tumor mass are likely to be of no prognostic importance. Initial skin involvement, however, may characterize a distinct subgroup.

88 In vitro drug sensitivity testing of tumour cells from patients with non-Hodgkin's lymphoma (NHL) using the Fluorometric Microculture Cytotoxicity Assay (FMCA)

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The automated FMCA, based on cleavage by viable cells of fluorescein diacetate to fluorescent fluorescein (Larsson & Nygren, Int J Cancer 46:67, 1990), was used for cytotoxic drug sensitivity testing of 75 samples of freshly prepared or cryopreserved tumour cells from patients with high or low grade NHL at diagnosis and relapse. Up to 30 cytotoxic drugs or drug combinations were tested and for all samples the technical success rate was above 90%. Enough cells for testing the most important drugs could often be obtained from needle biopsies. FMCA data showed good correlation to the well established Disc assay.

When comparing high and low grade NHL samples there was no significant difference in sensitivity to the most important cytotoxic drugs, and as a group the NHL samples were generally much more drug sensitive than tumour cells from solid tumours clinically well known to be more drug resistant, e.g. carcinomas of the breast, ovary, lung, kidney and adrenal. There was also a good correlation between *in vitro* drug sensitivity and clinical outcome for individual patients. Cross-resistance between drugs used for treatment of NHL was a common *in vitro* finding, but the currently used drug combinations for NHL all contain components that are non-cross-resistant *in vitro*. Addition of the resistance modulating agents Verapamil, Cyclosporin A (CsA) and the non-immunosuppressive CsA analogue PSC significantly potentiated the effect of Vincristine and Doxorubicin in 10 - 40% of the samples, with samples from relapsed patients being most sensitive.

It is concluded that the FMCA with a minimum of effort and with a high technical success rate report clinically relevant drug sensitivity data for NHL. *In vitro* drug sensitivity testing could thus perhaps serve as a tool for optimization of chemotherapy for NHL in the future.

89 IMMUNOTOXINS: IS THERE A POTENTIAL CLINICAL VALUE?

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Since the first description of so called "Magic bullets (Zauberkugeln)" by Paul Ehrlich nearly hundred yers ago, oncologists have been searching for treatment modalities that would specifically kill the malignant cell thereby leaving normal tissue unharmed. However, it was not until the advent of monoclonal antibody (MoAb) technology that tumor selective reagents became available in limitless supply. A large number of MoAbs with selectivity for tumor cells have been prepared particularely for hematopoietic malignancies. Many of these were linked to the ribosome damaging A-chain of ricin or other toxins like abrin, saporin, pseudomonas-exotoxin, or diphteriatoxin to form immunotoxins which combine the selectivity of the antibody moiety with the potency of the toxin. The first generation of these immunotoxins showed impressive results *in vitro* but in most cases disappointing antitumor effects in in animal systems or patients. In contrast, the second generation of immunotoxins consisting of recombinant toxin molecules with ligands that are genetically engineered or ricin A-chain immunotoxins with a greatly improved stability and selectivity have been demonstrated to be extremely effictive in several animal models. The results of the current clinical trials in lymphoma patients suggest a possible clinical use of immunotoxins.

90 THERAPY OF REFRACTORY HODGKIN'S DISEASE WITH ANTI-CD30/SAPORIN IMMUNOTOXIN

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In Hodgkin's disease (HD), Hodgkin (H) and Reed-Sternberg (R-S) cells consistently express on the surface the antigen CD30. We investigated the potential terapeutic role of an immunotoxin (IT) prepared by covalently linking the anti-CD30 monoclonal antibody Ber-H2 to saporin (SO6), a type-1 rybosome inactivating protein from Saponaria Officinalis, in 8 patients with refractory HD. Therapy was well tolerated at total doses ranging from 0.4 mg/Kg (given as 3-hour infusion at day 1) to 0.8 mg/Kg (given as two single 0.4 mg/Kg doses at days 1 and 7). Side effects included fever, fatigue, slight thrombocytopenia (3 cases), 4-5 time increase in liver enzymes (AST and ALT), and signs of mild capillary leak syndrome in half of the patients (average increase of 3 Kg in body weight and mialgias). All clinical signs and laboratory changes reversed within 7-10 days. Currently, additional patients are being enrolled to determine the maximum tolerated dose (MTD). Pharmakocinetic studies were performed in three patients. The T1/2 ranged from 18 to 25 hours. In these cases, the circulating IT was immunoreactive and biologically active, as determined by the ability of patients' serum samples to selectively bind to their own H and R-S cells in vitro (frozen sections from pre-treatment tumor biopsies) and to kill CD30+ HD-derived human cell lines in vitro. A rapid and remarkable reduction in the size of tumor masses (ranging from ≥50% to ≥75%) was documented by CT scans performed 7 and 30 days after the infusion of IT in 5 out of the 8 patients. The duration of the response ranged from 2 to 4 months. Most patients developed an immune response to both the antibody and toxin moieties. Our preliminary results suggest a role for the Ber-H2/SO6 IT in the treatment of minimal residual disease in selected categories of patients with HD and CD30+ anaplastic large cell lymphomas.

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91 Prospects for Anti-Sense Therapy

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Antisense molecules are oligonucleotides that bind to messenger RNA in a sequence specific manner and interfere with translation. These oligomers are highly specific and normally inhibit the production of a single protein. Antisense oligonucleotides can even be rendered tumor specific since some tumors contain abnormal messenger RNA molecules that result from genetic changes pertinent to pathogenesis and which represent a tumor-specific target. In tumors in which viral genes are relevant to pathogenesis (e.g. EBV associated tumors) operationally tumor-specific antisense molecules may be targeted to viral genes. We have demonstrated the feasibility of these approaches in the small non-cleaved cell lymphomas in which we have used two tumor specific targets. 1) c-myc intron sequences which are present in the mRNA of a subset of tumors defined by the chromosomal breakpoint locations resulting from the 8;14 translocation, and 2) the EBNA-1 gene of EBV which, we believe, is capable of collaborating with the 8;14 translocation. If antisense molecules are to be used therapeutically, means must be developed of ensuring that these oligomers are delivered at high enough concentration to the intracellular target sequences.

92a THE PARMA INTERNATIONAL RANDOMIZED PROSPECTIVE STUDY IN RELAPSED NON HODGKIN LYMPHOMA : SECOND INTERIM ANALYSIS OF 172 PATIENTS AND UPDATE (as 20/11/92: 200 patients).

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In order to compare conventional therapy with massive chemotherapy + ABMT in relapsed non Hodgkin's lymphoma, a randomized multicentre study was initiated by the PARMA group. Between July 1987 and November 1992, 200 consecutive patients from 49 worldwide institutions were included in the study. They were all intermediate or high grade non Hodgkins lymphoma with previous complete remission and included at time of first or second relapse. Age was between 16 and 60 years. Central nervous system and bone marrow relapses were excluded. Histological proof of relapse was mandatory. They all received after a complete staging the same rescue protocol i.e. DHAP (Dexamethasone, Cisplatin and Cytarabine) for 2 consecutives courses at 3-4 week interval.

200 were pre-included and 198 were evaluable for response (2 patients were to early to be evaluated). 111 were in CR (23,2%) or PR (30,8%) after 2 courses of DHAP (56%). Patients relapsing on therapy have a lower response rate than patients relapsing off therapy. Among these 111 patients, 98 were randomized between 4 additional courses of DHAP or massive therapy (BEAC : Carmustine, Etoposide, Cytarabine, Cyclophosphamide) and autologous bone marrow transplantation. Radiotherapy of involved fields was performed after 6 courses of DHAP in the first arm, and before massive therapy and ABMT in the second one. Reasons for no randomization were : 85 non responders (42,9 %), and 13 responders (patients refusal (3 patients), technical problems (3 patients), protocol violations (2 patients), abnormal bone marrow cellularity (2 patients), hepatic dysfunction (1 patient), ileum perforation (1 patient) and renal failure (1 patient)).

The main end point is the failure rate at 2 years (i.e. relapse or death wathever the cause). There is no statistical difference in term of toxic death rate. The survival of the randomized patients is 50% at 3 years.

This second interim analysis shows that initial hypotheses are still valid after 5 years. The observed difference between the 2 arms needs more patients to be statistically significant. Thus, the Steering Committee has decided to pursue the recruitment period in order to included more patients.

92b THE LYON CONSENSUS CONFERENCE ON HIGH DOSE THERAPY AND STEM CELL TRANSPLANTATION. RESULTS FOR LYMPHOMAS.

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An international consensus conference on intensive chemotherapy plus hematopoïetic stem cell transplantation was organized in Lyon June 4th - 6th 1993. Lymphomas were reviewed extensively by a group of experts and an international jury.

Experts reviewing the fact were J. Armitage and C. Gisselbrecht for lymphomas, A. Carella and A.H Goldstone for hodgkin's disease.

Jury chairmen were M.Symann and A.K Burnett and members were M.D. Abeloff, C. Bennett, P. Biron, F. Chauvin, J. Crowley, V. Diehl, J.P Droz, A. Hagenbeek, D.P Harrington, D. Maraninchi, J.A. Neidhart, H.M Pinedo, J. Reiffers, B. Salles, J. Simons, A.M. Teller.

questions were :

Lymphomas : What is the place of high dose therapy with hematopoïetic stem cell transplantation in NHL (children excluded) ? Role in first CR (low grade, intermediate and high grade) ? Which patients ? Role in first PR (low grade, intermediate and high grade) ? Which patients ? Role in primary refractory patients (low grade, intermediate and high grade) ? Which patients ? Role in relapse patients (low grade, intermediate and high grade) ? Which patients ? Sensitive relapse patients ? Resistant relapse patients ? Source of stem cell to choose ? In which circumstances an allogenic donor be preferable ?

Hodgkin : What is the place of high dose therapy with hematopoïetic stem cell transplantation in the treatment of hodgkin's disease ? Patients not responding after 3 courses ? Patient not CR after first line therapy ? Patient relapsing from CR ? Does disease free interval matter ? Is chemosensitivity important ? A role in first CR ? A role for allogenic ?

Reports of the jury conclusions will be given to the audience.

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FLUDARABINE IN MALIGNANT LYMPHOMA: PRESENT STATUS AND FUTURE POSSIBILITIES. M.J. Keating, P. McLaughlin, L. Robertson, W. Plunkett, F. Cabanillas. Department of Hematology, University of Texas M.D. Anderson Cancer Center, 1515 Holcombe, Houston, Texas

Fludarabine is an adenine nucleoside that has recently been studied in the management of indolent lymphoproliferative diseases. Most activity has been noted in chronic lymphocytic leukemia (CLL), the leukemic counterpart of diffuse small lymphocytic lymphoma. In indolent lymphoma, phase I studies demonstrated a 25 - 30% partial response (PR) rate. Subsequent phase II studies have reported complete and PR rates of more than 50% in a number of series of low grade lymphoma. Follicular lymphomas appear to have higher response rates. Complete remissions (CR) were obtained even in patients (pts) who had received extensive prior therapy. The response rate in pts with intermediate grade lymphoma is <10%. An association was noted with the degree of prior treatment. The major morbidity was related to infection and myelosuppression. Subsequent studies have combined fludarabine with mitoxantrone and dexamethasone (FMD). In human acute leukemia, fludarabine has been demonstrated to enhance DNA damage caused by mitoxantrone. In phase I studies 9/21 pts achieved a CR and 7/21 a PR for an overall response rate of 76%. In more recent phase II studies, the response rate in low grade lymphoma is more than 90%. Fludarabine has been used in the management of Waldenstrom's lymphoma (macroglobulinemia) with a response rate of 40%. Patients with no prior treatment or primary refractory disease had a higher response rate than refractory relapsed pts (8/14 vs 2/11). Strikingly these responses have been very durable and have been noted even in pts with anemia and thrombocytopenia. The response rate of fludarabine in previously treated CLL is >50% being more than 75% in those who are possibly still sensitive to alkylating agents. The CR rate in pts who receive fludarabine as their initial therapy is 65 - 70%, suggesting that fludarabine would have marked activity as a single agent in previously untreated small lymphocytic lymphoma. Fludarabine has been demonstrated in vivo to enhance the uptake and retention of the triphosphate of cytosine arabinoside (ara-CTP). Both fludarabine and ara-C have been demonstrated to be synergistic in the LoVo cell line and fludarabine can reverse cisplatinum resistance in a platinum resistant LoVo line. Combinations of fludarabine, ara-C, and cisplatinum have been developed in pts with CLL refractory to fludarabine with a 30 - 40% response rate and two out of the three pts with large cell lymphoma transformation of CLL (Richter's syndrome) have obtained a CR with this regimen. This combination appears worthy of study in intermediate grade lymphoma. Fludarabine has been studied in vitro and demonstrated to inhibit repair of radiation-induced DNA damage. Studies of fludarabine as a radiation sensitizer have demonstrated additive and synergistic activity in three solid tumor models. The striking activity of fludarabine as a single agent in indolent lymphoproliferative diseases and its interesting in vivo interaction with cytosine arabinoside and in vitro interaction with radiation and DNA damaging agents such as cisplatinum and mitoxantrone suggests an expanding role of this agent in combination regimens in low grade lymphoma and possibly intermediate grade lymphoma.

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2-CHLORODEOXYADENOSINE ACTIVITY IN THE LYMPHOID MALIGNANCIES. L.D. Piro and A. Saven. Division of Hematology and Oncology, Ida M. and Cecil H. Green Cancer Center, Scripps Clinic and Research Foundation, La Jolla, California, USA.

2-Chlorodeoxyadenosine is an adenosine deaminase-resistant purine nucleoside agent effective in the treatment of lymphoid malignancies. 2-CdA accumulates in cells with a favorable ratio of deoxycytidine kinase to 5'-nucleotidase activity such as lymphocytes. Once phosphorylated by deoxycytidine kinase it is converted into a 5'-triphosphate derivative which is a potent inhibitor of both ribonucleotide reductase and DNA polymerase alpha. In resting cells, the progressive accumulation of deoxynucleoside 5'-triphosphates causes profound deoxyribonucleotide pool imbalances. Combined with inhibition of DNA polymerase alpha, the deoxynucleotide pool disturbances prevent proper DNA repair. Consequently, DNA strand breaks gradually accumulate with time. The result of this accumulation is two-fold: 1) activation of a poly(ADP-ribose)-polymerase that consumes both NAD and ATP, and 2) activation of a Ca^{++}/Mg^{++}-dependent endonuclease that produces double-stranded DNA breaks at internucleosomal regions. The cleavage of DNA into oligonucleosomal fragments is the hallmark of apoptosis. 2-CdA is cleared largely through the kidney and has a two-phase clearance, with an initial half-life of about 30 minutes followed by a second-phase half-life of 7 hours. Phase I studies have been conducted with 2-CdA in a variety of administration schemes including continuous infusion intravenously over 5 and 7 days, and one- and two-hour bolus administration for 5 consecutive days intravenously. Recently, pilot studies with oral and subcutaneous administration have been performed. Myelosuppression is the dose-limiting toxicity of 2-chlorodeoxyadenosine. When administered via the continuous infusion scheme, the maximum tolerated dose (MTD) was established to be 0.1 mg/kg/day for 7 days inducing a 25% incidence of myelosuppression. In phase II studies, adopting this dosage and administration, 2-CdA has been shown to have activity in hairy cell leukemia, chronic lymphocytic leukemia, low-grade non-Hodgkin's B-cell lymphomas, cutaneous T-cell lymphomas, and Waldenström's macroglobulinemia. The overall response rate in hairy cell leukemia is 97%, with 85% complete remissions following a single cycle of therapy. Activity in chronic lymphocytic leukemia is 44%, with 4% complete remissions requiring a median of two treatments. Activity in low-grade non-Hodgkin's lymphoma is 43%, with 20% complete remissions and in cutaneous T-cell lymphoma is 47%, with 20% complete remissions. Activity in phase II testing in previously untreated patients with these disorders is currently underway and phase I testing of 2-CdA in combination with other agents is ongoing. 2-CdA is a new purine nucleoside agent which is active in most lymphoid malignancies and is likely to play a major role in the therapeutic armamentarium of lymphoid malignancies.