14. Clinical Results in Lymphoma II

CONSOLIDATION ABMT AFTER STANDARD CHEMOTHERAPY vs CHVnmPB Alone for Primary Intermediate and High Grade NHL: A RANDOMIZED PHASE III EORTC STUDY.

A RETROSPECTIVE ANALYSIS OF 987 PATIENTS WITH FOLLICULAR LYMPHOMA (FL): A PREDICTIVE MODEL DEVELOPED BY THE ITALIAN LYMPHOMA INTERGROUP UPON A PROGNOSTIC INDEX (API).

THE CUP TRIAL: A RANDOMIZED STUDY ANALYZING THE EFFICACY OF HIGH DOSE THERAPY AND PURGING IN LOW-GRADe NON-HODGKIN'S LYMPHOMA (NHL).

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EARLY INTERIM REPORT OF THE LY03 RANDOMISED 
COOPERATIVE TRIAL OF OBSERVATION vs. CHLORAMBUCL 
AFTER ANTI-HELCOBACTER THERAPY IN LOW-GRADE 
GASTRIC LYMPHOMA

Zucca E., Roggero E., Trangulli C., Delcher J.C., Smith P., Pedrinis E., 
Motta T., Capella C., Copie-Bergmann C., Wotherspoon A. and 
Souhami R. for the International Extranodal Lymphoma Study Group 
(IELSG), the Groupe d’Etude des Lymphomes de l’Adulte (GELA) and 
the United Kingdom Lymphoma Group (UKLG)

Antibiotic therapy aimed at eradicating H. pylori infection has been 
shown in early trial to induce histological regression in the majority 
of low-grade gastric lymphoma. An international cooperative trial (LY03) 
is ongoing to ascertain:

- for how long tumor regression is maintained and whether this 
thrapy can permanently eradicate the lymphoma
- whether the addition of single-agent chlorambucil is of benefit in 
those patients who respond to antibiotics.

From March 1995 to September 1999, 183 patients with localized low-
grade MALT lymphoma of the stomach entered the trial. 100 men and 
83 women with a median age of 60 years (range 22-86).

Histological regression of the gastric lymphoma after anti-helicobacter 
triple therapy was observed in 57% of patients with about 75% of 
responses already evident in the first 8 months after antibiotic 
treatment; 70 patients (40%) have been randomised to observation vs. 
chlorambucil.

All cases undergo histological review, independently performed by two 
panels of expert pathologists. This review process is ongoing and the 
detailed analysis of the clinicopathological features associated with 
the response to anti-helicobacter therapy will be presented.

FACTORS DETERMINING FEASIBILITY AND OUTCOME OF 
AUTOLOGOUS STEM CELL TRANSPLANTATION FOR CLL

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Fifty-three patients were accrued to a single-center study investigating 
autologous stem cell transplantation (ASCT) for treatment of poor 
prognosis CLL. Binet stages were A=13, B=26, and C=14. The protocol 
comprises PBSC mobilization using the Dexe-BEAM regimen and 
myeloablative therapy with TBI/CY followed by reinfusion of immuno-
 magnetically purged stem cells. Results: Forty-three patients (81%) had 
successful PBSC collection (>1 x 10^6/kg CD34+ cells per leukapheresis) 
and were in a state of minimal disease after mobilization. Ten patients 
not achieving these goals were regarded as protocol failures. Factors 
associated with protocol failure were high Binet stage at mobilization 
(B/C=33% failure vs. A=7%, p=0.017), time from diagnosis to 
mobilization (>12 months 36% vs. <12 months 9%, p=0.08), and intensive 
chemotherapeutic pretreatment (p=0.025). To date, 38 patients have 
been autografted. With 1-59 months of follow-up, the estimated event-free 
survival at 2 years is 86% by clinical and 76% by molecular (polyclonal 
consensus primer CDR3 PCR) response criteria. Factors associated with 
inferior molecular progression-free survival (PFS) were short lymphocyte 
Doubling time (p=0.04), and failure to achieve dot blot negativity post 
transplant using clone-specific CDR3 probes (p=0.099); the patients with 
always positive dot blot also tended to have a reduced PFS (50% vs. 
100% at 2 years; p=0.1). Conclusions: ASCT in patients with CLL is 
feasible. Factors affecting successful completion of the protocol are advanced 
stage at mobilization and intensive pretreatment, suggesting that if SCT 
is considered, it should be performed early during the course of the disease. 
CDR3 PCR with clone-specific probes appears to be a useful tool for 
predicting disease recurrence after autografting.

MUCOSA-ASSOCIATED LYMPHOID TISSUE (MALT) – 
LYMPHOMA ARE DISSEMINATED DISEASE IN 1/3 OF THE 
PATIENTS. C. Thebilemont, C. Dumontet, G. Sailes, I. Moullet, 
Hospices Civils de Lyon, France.

159 patients with MALT lymphomas were analyzed according to 
their clinical presentation and outcome. At diagnosis, 53 (35%) of 
the patients presented a disseminated disease with multiple nodal 
and/or extra-nodal sites and/or bone marrow involvement. 79 
patients (50%) had gastrointestinal involvement and 80 patients 
(50%) had another involved extranodal site: 20 lung, 18 orbit, 18 
skin, 11 parotid, 6 thyroid, 5 breast, 4 Waldeyer's ring. No significant 
difference in clinical characteristics (sex, age, performance status, B symptoms) and in biological parameters 
(hemoglobin and LDH levels) was noticed between localized or 
disseminated MALT lymphoma patients. Only beta2 microglobulin 
was significantly more elevated in the disseminated disease 
patients than in the localized disease patients. Complete response 
after the first treatment was achieved in 73%, with no difference 
between the 2 groups. With a median follow up of 4 years, the 
predicted 5- and 10-year overall survival rates were similar in the 
2 groups 86% and 80% respectively. The median FFP survival 
was 5.56 years for all patients, surprisingly without any difference 
between localized and disseminated MALT lymphoma patients. Adverse prognostic factors for survival were high beta2 microglobulin level and multiple extranodal sites. A shortened FFP 
 survival was associated with localizations other than gastric 
involvement at diagnosis, anemia and high beta2 microglobulin 
level. In conclusion: 1/ MALT lymphoma is an indolent disease 
but presents as disseminated in 1/3 of the cases at diagnosis; 2/ 
the dissemination does not change the outcome of the disease; 3/ 
we confirm that non-gastric MALT lymphoma patients progress 
more often than gastric MALT lymphoma patients.

14. Clinical Results in Lymphoma II
15. Pediatric Lymphoma

CHILDHOOD HODGKIN’S DISEASE: EFFECTIVE MINIMAL TREATMENT.

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Objective To evaluate minimal bimodal treatment for Clinical Stages (CS) 1-3B childhood Hodgkin’s Disease.

Material From 1987-97 46 consecutive CS 1-3B children were treated in a pilot study using 3 cycles MOPP/ABV followed by extended field radiation treatment (EF RT) 15 Gy x 12 fractions. Intensification of both modalities was permitted when chemotherapy response was judged to be incomplete. In favourable CS 1 (upper one third neck) unilominal treatment with involved field RT (35 Gy) was allowed.(5 pts). Investigative studies included CT from mastic to genina. Staging laparotomy and lymphography were not used. The stage distribution was CS 1, 15; 2, 67; and 3 12 pts. Follow-up was for 0.1-14.4 (Med. 4.8) years.

Results Overall 5 yr progression free survival (5 PFS) was 90% and 5 year survival (5 S) 96%. No significant survival differences were observed by stage, B symptoms, mediastinal mass > 1/3 chest diameter, histology and age. From 1987-91 22/36 (61%) pts. received exactly 3 cycles MOPP/ABV and 21/36 (58%) a maximum of 15 Gy EF RT. From 1992-97 the respective data were 23/36 (91%) and 48/58 (83%). Respective 5 PFS was 88% and 91%. Poor prognosis was associated with the occurrence in a given patient of any two of the three factors: mediastinal mass > 50% of the chest diameter, pleural and/or pericardial effusion(s) and chest wall invasion. 5 pts. satisfied these requirements and 84 did not. The respective 5 PFS rates were 40% and 93% (P<.0001). No toxic deaths, life threatening toxicity or second tumours were observed. Overall these results were inferior to our earlier experience from 1973-86, with more intensive bimodal treatment: 6 cycles of MOPP and EF RT (25 Gy), also in 94 CS 1-3B children when PFS and SS were 83% and 96% respectively.

Conclusions 3 cycles MOPP/ABV and EF RT (15 Gy) is an effective treatment of low toxicity for children with CS 1-3B Hodgkin’s Disease.

STAGE IV HODGKIN’S DISEASE (HD) IN CHILDREN: RESULTS OF THE UNITED KINGDOM CHILDREN’S CANCER STUDY GROUP (UKCCSG).


Introduction: The standard treatment of children with stage IV HD in the UK is 6-8 cycles of CHVP regimen. Radiotherapy is not routinely used as its role in stage IV HD is unclear. In this study we report the UKCCSG results of children with stage IV HD treated between February 1982 and May 1998.

Methods: Eighty two patients aged less than 16 years with stage IV HD were treated with 6-8 cycles of CHVP/VPP and 7 had alternating CHVP/ABVD. Nineteen patients had involved field radiotherapy post-chemo, 35 Gy (n=8) and 20 Gy (n=9). Fifty two were male. Fifty one (61%) had B-symptoms. The main histological subtypes were nodular sclerosing (n=65) and mixed cellularity (n=12). In 66 patients, one extra lymphatic organ was involved, liver (n=20), bone marrow (n=12), liver (n=9) and bone (n=6). Total 50% had ≥2 organs involved.

Results: After a median follow up of 49 months, the overall and DFS are 78% and 50% respectively. Twenty eight patients relapsed, 7 died of HD. Five patients died of infection and one died of secondary AMH.

Conclusions: Although the DFS in this study is lower with this non-antracycline containing regimen than other studies, it is anticipated that survivors will have long term morbidity, although that remains to be seen. About 30% of relapsed patients could be salvaged with more intensive regimens.
BURKITT-LIKE LYMPHOMA IS IMMUNOPHENOTYPICALLY DIFFERENT FROM BURKITT LYMPHOMA IN YOUNG PERSONS

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State University of New York Health Science Center, Syracuse, New York, and the Pediatric Oncology Group

Introduction: Burkitt-like lymphoma (BLL) is a provisional histopathologic category of high-grade B-cell lymphomas which is morphologically intermediate between Burkitt lymphoma (BL) and large B-cell lymphoma (LBCL). The clinical significance of this morphology is controversial.

Methods: To investigate the biology of BLL and determine objective criteria for distinction between it, BL and LBCL in children, we examined 41 cases of pediatric B-cell lymphoma by immunohistochemistry for proteins associated with proto-oncogenes c-myc, BCL-2 and BCL-6 and a subset of cases (with adequate slides) for a proliferation-associated marker (Ki-67) and for apoptosis (Apoptag). Paraffin sections of 16 cases of BLL, 13 cases of BL and 12 cases of LBCL were examined. Each was registered since January 1995 through April 1998 on Pediatric Oncology Group studies for treatment of small noncleaved cell (Burkit) or large cell lymphoma.

Results: Our results showed BCL-6 expression (more than 20% of cells) in 16/16 BLL, 4/13 BL, and 9/12 LBCL; c-myc expression in 14/15 BLL, 9/13 BL, and 12/12 LBCL; and BCL-2 expression in 2/16 BLL, 9/13 BL, and 6/12 LBCL. Mean apoptotic index for BLL was 10.3% (n=6); for BL was 17.1% (n=5); and for LBCL was 19.6% (n=6). Ki-67 was reactive in >80% of cells in each case also tested for apoptosis. There was a significantly higher proportion of BLL than BCL which expressed BCL-6 (p = 0.0001).

Conclusion: We conclude that BCL-6 aids in the identification of BLL versus BL. BCL-2 protein is infrequently expressed in BLL compared to LBCL, and rare to absent from BL. Each histologic type expresses c-myc and shows high proliferation, while BL may show slightly greater apoptosis. It is likely that in children in North America, BL is biologically distinct from BL and more closely resembles a subset of LBCL.

Childhood Lymphoblastic Lymphoma - can we improve outcome?

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Since the studies by Wolters et al (1979) and the CCSG (1983) the recommended treatment for both T and precursor B-cell lymphoblastic lymphoma has been with sustained leukaemia therapy including for the relatively rare localised forms. Five year EFS figures have been stuck obstinately at 70-75% in single centre and 65-70% in collaborative unslected series with little difference reported between Stage III and IV disease. Relapses are rare in Stages I and II. Unlike B-cell disease relapses do occur late and recent improvements are not impressive. The maturity of T cell phenotype more closely predicts sites of disease (eg mature and skin/bone) than likely outcome. Speed of response may predict outcome. Shephard et al reported 5 year EFS of 84% for those in CR at Day 60 compared with 56% for those with one or more residual mediastinal disease. As for ALL such slow responders might benefit from intensification (eg. Phipp et al 1988 - HD C/T + stem cell rescue) and/or local irradiation (eg. Mott et al 1984). Understanding the biology might lead to greater advances:

1. By monitoring for M.R.D. by probing for TAL1 deletions, if(1/14) or for T cell and b gene receptors.
2. Manipulating known T cell responsiveness to specific drugs eg. steroids, aspirinase, rabepracymes, alkyators.

The results of collaborative trials will be presented to highlight ways in which further advances might be made.

FAVORABLE OUTCOME FOR FOR CHILDREN AND ADOLESCENTS WITH T-CELL Lymphoblastic Lymphoma (T-LBL) WITH AN INTENSIVE ALL-TYPE THERAPY WITHOUT LOCAL RADIOThERAPY

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Introduction: In trial NHL-BFM 90, we investigated the efficacy of an ALL-type treatment with moderate dose prophylactic cranial irradiation but without local radiotherapy for childhood T-cell lymphoblastic lymphoma (T-LBL).

Patients and Methods: From April 1990 to March 1995, 101 evaluable patients, (pt) 1.1 - 16.4 (median 8.8) years of age, with T-LBL (2, 7, 18, 9 pts with stage I, II, III, IV, respectively) were enrolled in study NHL-BFM 90. Pts received an 8-drug induction over 9 weeks followed by consolidation including 4 cycles of MTX 5g/m^2. Pts with stage I and II continued with maintenance up to a total therapy duration of 24 months. Pts with stage III and IV received an 8-drug intensification and cranial radiotherapy (RT) (12 Gyc for prophylaxis) between consolidation and maintenance. Cumulative doses/m² of anthracyclines/cyclophosphamide were: 100mg/m² for pts with stage III; 240 mg/m² for pts with stage IV. Residual tumor after completion of the induction phase had to be resected. No local RT was applied. In case of less than 70% tumor regression at day 33 or residual tumor after the completion induction phase, pts received intensified chemotherapy.

Results: The estimated event-free survival at 5 years is 92±6% for the total group, 97±6% for pts of stage I, 96±2% for pts of stage II, and 94±2% for pts of stage IV (median follow-up 4.5 years, (up-date Sept. 1, 1998). Events were one early death, 7 local tumor failures (3 combined with BM-relapse), and one secondary AML. Two pts had less than 70% tumor regression at day 33 and received intensified chemotherapy, one of them failed. Of 16 pts with residual tumor after induction, 9 had surgical intervention which did not reveal vital tumor in any of them. Two of these 16 pts suffered from local progress as compared to 4 of 80 pts with complete tumor regression after induction.

Conclusion: Event-free survival of 90% can be achieved in childhood T-LBL with ALL-type chemotherapy including moderate cumulative doses of anthracyclines and cyclophosphamide, and moderate dose prophylactic cranial irradiation but without local radiotherapy. Providing tumor regression within 5 weeks is sufficient, tumor remnants after induction have weak prognostic impact.

THERAPY FOR PEDIATRIC ANAPLASTIC LARGE CELL LYMPHOMA (ALCL) - RESULTS FROM THERAPY-TRIAL NHL-BFM 90


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Introduction: Anaplastic large cell lymphoma (ALCL) accounts for approx. 10% of all childhood NHL. Treatment varies according to previous described favourable outcome (trial NHL-BFM 86) in a larger series of patients.

Methods: From 04/90 to 03/95, 98 pts <18 yrs of age with newly diagnosed ALCL were registered as eligible for multicenter-trial NHL-BFM 90. Pts were stratified according to stage: K1 (stage I and II-completely resected), K2 (stage IIIa-completely resected, stage IIIb), K3 (stage IV or multifocal bone disease). Therapy consisted of 2 alternating 5-day courses of steroids, VCR, MTX (0.5 g/m² in K1+K2, 5g/m² in K3), ARA-C, VP-16, Doxorubicin, and i.d. therapy; total number of courses was 3 in K1, 6 in K2 and 6 in K3 (courses 3-6: HD-Ara/Cy/VP-16).

Results: 38/89 ALCL were of T-cell-type, 5/89 of B-cell-type, 31/89 of B-type, 2/89 of histiocytic type, 13/89 of unknown immunology. Stages were: I: n=8; II: n=20; III: n=55; IV: n=6. Extraneal manifestations were: lung n=13, skin n=16, soft tissue n=13, bone n=14, CNS n=1. BM n=3. 28 pts had mediastinal involvement. PFS at 5 years was 0.76 (SE 0.05). Events were: 2 pts did not respond and died of progress (both in branch K2), 18 pts relapsed (13 in K2, 5 in K3), 1 pt suffered from 2nd malignancy (K2). Skin-, lung-involvement and T-cell-type were associated with increased risk of failure. Median time from diagnosis to relapse was 0.74 years. Overall survival was 0.85 (SE 0.04). 71/89 pts. are alive after a median observation time of 3.7 years.

Conclusions: Short-pulse chemotherapy with moderate cumulative dosage of drugs is an effective treatment of pediatric ALCL. For further improvement and evaluation of prognostic factors, large cooperative trials at an international level are required.
PROGNOSTIC FACTORS IN CHILDHOOD ANAPLASTIC LARGE CELL LYMPHOMA (ALCL): RESULTS OF THE EUROPEAN INTERGROUP STUDY MC: La Deley1, A Rainer2, D Willaim3, A Roses4, K Seidemann5, R Pinkerton6, C Patte7, L Brugière1 1SFOF (France), 2BFM group (Germany), 3UKCGO (UK), 4AIEOP (Italy) Purpose and methods In order to study prognostic factors, the data on 235 children enrolled for ALCL in the BFM (33pts), SFOF (82pts) and UKCGO (80pts) studies were included in a retrospective study of the « European Intergroup Group of ALCL ». All these children have been treated according to protocols designed to treat childhood ALCL with a short and intensive chemotherapy treatment, similar to those used for B-cell lymphoma. Slides have been reviewed by the national pathology panel for 228 patients (96%). Hodgkin-like ALCL were excluded from this series. Results Among the 235 patients included in the study, 206 patients (88%) achieved a CR and 49 relapsed. The probability of survival and disease-free survival at 3 years of the whole population is of 82% (76 - 88%) and 71% (64 - 76%) respectively, with a median follow-up of 47 months. Several factors seem to be prognostic of the DFS in univariate analysis: E-symptoms, mediastinal involvement, skin lesions, visceral involvement, high staging in the II St Jude or Ann Arbor classification, or elevated LDH. Patients with bone lesions seem to have a better prognosis than others. Soft tissue masses do not worsen the prognosis. Moreover, a country adjusted for country has permitted the highlighting of three poor prognostic factors: - mediastinal involvement (relative risk of failure of 2.1 [1.3-3.6] -p = 0.004) - visceral involvement defined as lung, liver or spleen involvement (relative risk of failure of 2.1 [1.2-3.4] - p = 0.006) - skin lesions (relative risk of failure of 1.9 [1.3-3.6] - p = 0.02 Based on the results of the Cox model, it is possible to define: - a good prognostic group (85 patients without skin or mediastinal or visceral involvement) with a 3-year event-free survival of 87% (78-93%): - a group with poor prognosis (150 patients with skin and/or mediastinal and/or visceral involvement) with a 3-year event free survival of 61% (53-69%). Conclusion: This type of regimen demonstrated efficacy in childhood ALCL. However, therapeutic results have to be improved for patients with adverse prognostic parameters such as visceral involvement and skin lesions.

P80 AND VISCERAL INVOLVEMENT IN CHILDHOOD KII ALCL M. Massimino, F. Spessato, R. Lukisch, R. Giardini. Istituto Nazionale Tumori, Milan, Italy

Introduction: Between 1976 and 1998, K11+ ALCL was diagnosed in 144 children (28 males, 16 females, age range 27-16.1 yrs, median 10). Up to 1993, 32 such children were treated according to a common chemotherapy protocol, without considering prognostic factors (Annals of Oncology 6:915-920, 1995). Thereafter, patients presenting with visceral (lung, spleen, liver, GI tract) or mediastinal involvement were assigned to a high-risk treatment protocol with induction intensification. Considering the whole cohort of patients divided into Group A) 21 evaluable patients with visceral/mediastinal involvement, and Group B) 22 evaluable patients with other ALCL locations, S and EFS survival at 5 years were 57% and 38%, respectively, for group A, and 83% and 100% (94% at 6 years), respectively, for Group B.

Methods: To investigate a possible correlation between ALCL locations and NPM-ALK protein expression, we tested for p80 immunoactivity 17/22 cases of Group A, and 16/22 of Group B.

Results: Fourteen of 17 specimens in group A and 16/16 specimens in Group B were positive for p80.

Conclusions: Differently from adults' series so far reported, p80 positivity did neither correlate with prognosis nor with ALCL sites of involvement in a series of 37/44 childhood ALCL. Tailored treatment according to prognostic factors does not have to rely on NPM-ALK protein expression.

RELAPSES OF CHILDHOOD ANAPLASTIC LARGE CELL LYMPHOMA: TREATMENT RESULTS IN A SERIES OF 41 CHILDREN - A REPORT FROM THE FRENCH SOCIETY OF PEDIATRIC ONCOLOGY

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Purpose To study response to chemotherapy and the outcome of children treated for a relapsed ALCL, and to evaluate the role of ABMT in these patients.

Methods Clinical data of the 41 relapses that occurred in 119 patients with ALCL enrolled in 3 consecutive studies since 1975 were analysed. The histopathologic material was reviewed in the reference laboratory for all the patients. First line treatment consisted of intensive chemotherapy according to the COPAP protocol for the first series of 12 patients treated between 1975 and 1986 and to the SFOP HM protocols for the 30 patients treated between 1989 and 1997. Treatment of the relapse was heterogeneous: 18/41 patients were treated with CVB (CCNU, vinblastine, bleomycin, Ara-C), 10/41 with CVA (CCNU, vinblastine, bleomycin, Ara-C) and the other 13 patients with miscellaneous protocols. Fifteen patients underwent ABMT while in CR2.

Results 36/41 (88%) patients achieved CR2. With a median follow up of 5 years, 12 pts died, 9 of their disease and 29 patients are alive in CR2 (20 pts), CR3 (3pts), CR4 (2pts), CR5 (1pt) or CR6 (1pt). Overall and event-free survival are respectively 69% (53-82%) and 44% (29-61%) at 2 years. In univariate analysis, patients treated with ABMT while in CR2 did not appear to have a better outcome than those treated with conventional chemotherapy. Two factors were found to be associated with a higher risk of failure: an interval of less than 12 months between the diagnosis and the treatment of relapse and the first treatment with the HM protocol. Remarkably, a long-lasting remission was obtained in 8/13 patients treated with weekly vinblastine for a relapse including 6 relapses occurring after ABMT.

Conclusion Relapsed ALCL are highly chemoresistant but over 40% of the patients experience several relapses. Prolonged conventional chemotherapy based on vinblastine might prove as efficient as short intensive treatment with ABMT.
16. Clinical-Pathological Correlations


Introduction: TCRBCL is a heterogeneous disorder lacking precise diagnostic criteria, as is histocytosis-rich B-cell lymphoma (HRBCL). Both may be related to each other and to nodular lymphocyte predominant Hodgkin's disease (NLPHD).

Methods: 50 cases of "paragranuloma-like" TCRBCL were compiled from the files of 3 centers based on the recognition of a common histologic appearance. All authors reviewed the cases, paraffin-section immunostains were performed and the clinical data was collected.

Results: A total of 50 cases were studied, all with similar features. Biopsies revealed diffuse architecture with a polymorphous infiltrate composed mostly of small lymphoid cells and histocytes. In some cases the large neoplastic cells resembled "popcorn" cells of NLPHD. These cells tended to cluster, but without obvious nodularity in H&E sections. Stains for CD57 and folliculodendritic cells were negative. The large neoplastic cells were CD20, CD43, CD75, CD79a and EMA. The background small lymphocytes were CD3+ and occasionally demonstrated nuclear irregularity. The median age of the patients was 43 y (range 19-77 y). 91% had stage III/IV disease and the majority of the patients were male (81%) with hepatic involvement (21%), elevated LDH (74%) and frequent bone marrow (BM) involvement (53%). The 5 year overall survival was only 20%.

Conclusions: Paragranuloma-type TCRBCL and HRBCL are identical based on morphology, phenotype and clinical features. Several features, including histologic transformation suggest a histogenesis related to NLPHD. The poor clinical outcome of these patients is likely related to frequent BM involvement and advanced stage.

European Mantle Cell Lymphoma Study Group: Pathology, proliferation indices and survival in 304 patients M. Tiemann1, C. Schrader1, M. Dreiling1, W. Hiddemann1, R. Parwaresch3 for the EEC MCL Study Group. 1Department of Pathology, Heinrich-Heine-University, Dusseldorf, Germany 2Department of Hematology, University of Kiel, Germany 3Department of Hematology, University of Munich, Germany.

Introduction: Since 1995, the European Mantle Cell Lymphoma Study Group has met four times at the Lymph Node Registry in Kiel to review the MCL cases of 11 European panels with respect to morphology and clinical outcome. 590 MCL cases from Germany, Switzerland, France, Italy, Great Britain, the Netherlands, Belgium and Spain were registered. Here, we report on the pathological features and their prognostic significance in 351 cases which were available for a retrospective study by two interactive panels of 5 and 6 hematopathologists, each.

Patients and Methods: Conventional histological slides and immunophenotype were evaluated according to the Anacyte criteria. Cytology of MCL was classified using 4 groups. Growth pattern was divided into 3 groups. Consensus was defined as agreement between at least 3 of 5 or 3 of 6 pathologists. Cases lacking consensus were reevaluated by all 11 pathologists.

Results: A consensus diagnosis of MCL was reached in 340 cases (97%). In 26 cases (7%) the diagnosis was uncertain and in 21 cases (6%) a diagnosis other than MCL or no diagnosis was made. The vast majority (206 cases) of MCL showed the classical cytology originally described for the centrocytic lymphoma of the Kiel classification. The small cell variant (B-CLL type) was found in 6 cases. In 18 cases the pleomorphic variant (similar to large B-cell lymphoma) and in 8 cases the blastic variant (lymphoblastic lymphoblastic lymphoma) was found. In 10 cases the pleomorphic variant a mixture of classical and pleomorphic morphology was present. Two percent of MCL showed a nodular growth pattern with prominent germinal centers, 21% had a nodular pattern, 30% were diffuse and 19% showed a nodular mixed pattern. Complete remission rates for all patients were 40%, 50%, 40% and 30% for the nodular, diffuse and mixed growth pattern, respectively. For the entire group the mean overall survival (OS) was less than 3 years, and 90% of patients died within 7 years after diagnosis.

No significant difference in OS was found between the classical variant and the variant subtypes. Nodal MCL had a marginally more favorable prognosis than diffuse MCL (P=0.051). In 185 MCL cases the proliferation index was determined by staining with the antibody Ki-55/MIB-1 (Ki-67). Using a cutoff level of 36%, the 15 cases with a high index fared significantly worse than the 171 other cases with low proliferation index (P=0.0001).

A similar association was observed for the mitotic index. Hot spots of proliferation did not influence the clinical outcome. Conclusion: The classical type of mantle cell lymphoma represents a distinct entity. Variant types of MCL are rare and pose mainly a diagnostic problem. Proliferation indices seem to be more objective and are thus important prognostic factors that are superior to cytology and growth pattern.

Distribution of Various Subtypes of Non Hodgkin's Lymphoma in India: A Study of 2773 Lymphomas Using REAL and WHO Classification.

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Introduction: The distribution of the major subtypes of non Hodgkin's lymphoma (NHL) differs across geographic regions. There has been no previous study from India which has incorporated immunophenotypic findings and addressed this issue.

Material & Methods: All cases diagnosed as NHL between January 1995 to June 1998, in the Dept. of Pathology and Lymphoma Registry were selected for the study. Only cases where paraffin blocks were available were included and immunohistochemistry was carried out on paraffin sections of all cases. The cases were reviewed by three pathologists and diagnostic problems were discussed by a panel of pathologists with special interest in lymphoma pathology. Of a total of 2831 cases, 58 cases were excluded on review and a diagnosis of NHL was accepted in 2773 cases.

Results: B-cell lymphomas formed 79.1% of NHLs whereas T-cell lymphomas formed 16.2% of the total. Diffuse large B-cell lymphoma was the most common subtype forming 34% of all NHLs. Follicular center cell lymphomas, B-cell small lymphocytic lymphoma, mantle cell lymphoma and marginal zone B-cell lymphomas (including MALT lymphomas) amounted to 12.6%, 5.7%, 3.4% and 8.2% respectively. Among the T-cell lymphomas, T-cell lymphoblastic lymphoma, anaplastic large cell lymphomas of T/null-cell type and other nodal peripheral T-cell lymphomas accounted for 6%, 4.3% and 2.9% of all cases respectively.

Conclusion: The distribution of NHL subtypes in India shows important differences with those from the rest of the world. Follicular lymphoma is less common in India as compared to Europe and the United States of America. Peripheral T-cell lymphomas and T/NK-cell lymphomas of nasal and nasal types, which are common in many other Asian countries, are also less prevalent.

PROLIFERATIVE ACTIVITY AS A PROGNOSTIC FACTOR IN AGGRESSIVE NON-HODGKIN'S LYMPHOMAS: AN IMMUNOHISTOCHEMICAL STUDY WITH MIB-1 ANTIBODY OF 891 CASES FROM THE GELA-LNHTrial.


Introduction: The prognostic value of growth fraction determination in aggressive non-Hodgkin's lymphomas (NHL) remains debated. The nuclear protein Ki-67 is expressed in cycling cells and is recognized on paraffin sections by the monoclonal antibody MIB-1. The aim of this study was to analyze cellular proliferation in a large series of 991 aggressive NHL patients included in the GELA-LNHT trial and to assess the prognostic significance of MIB-1 labelling.

Methods: The percentage of MIB-1 positive cells (MIB-1 index) was estimated among 500 cells at x40 magnification in selected fields of highest MIB-1 expression. The manual counting was validated in 278 cases by an automatic counting method using image analysis, with a high concordance between the two methods (r = 0.75, p = 0.0001).

Results: MIB-1 index was linked to histological subtype. The mean percentage of MIB-1 positive cells was 67 ± 16% for the entire series (B-NHL 68 ± 15%, T-NHL 57 ± 17%), with the highest and the less dispersed values being observed among lymphoblastic and Burkitt's subtypes (82 ± 11%). In the most representative subgroup of polymorphous centroblastic NHL (n = 436), the MIB-1 index ranged from 17 to 85% with a mean value of 68 ± 13%. In this subgroup, the percentage of MIB-1 positive tumor cells was not significantly correlated with either the overall survival or event-free survival (EFS). Five-year EFS was 32 ± 10% and 46 ± 6% for cases with MIB-1 positivity 50% (n = 103) and > 50% (n = 88), respectively (P = 0.06). After multivariate analysis, MIB-1 index did not provide any additional prognostic information when challenged with the factors of the International Prognostic Index (IPI).}

16. Clinical-Pathological Correlations
IMMUNOBLASTIC LYMPHOMA (IL): A SUBTYPE OF B-CELL DIFFUSE LARGE-CELL LYMPHOMA (DLCL) WITH DIFFERENT INITIAL FEATURES AND POOR OUTCOME.


Introduction: Under the name of DLCL, the REAL classification includes different entities that can be separated in the future. Although IL has been traditionally differentiated from DLCL, the lack of consensus criteria for diagnosis makes difficult its consideration as a specific subtype. Nevertheless, IL patients have particular clinicopathological features and different prognosis.

Patients and methods: Two-hundred thirty-nine patients (M/F: 124/115; median age: 56 yrs), HIV-negative, were consecutively diagnosed of DLCL according to the REAL classification in a single institution between 1983 and 1996. The definition of IL was based on the presence of >20% of immunoblastic cells in the biopsy. Main initial and evolutive data were recorded and used for uni- and multivariate analysis.

Results: Thirty-eight patients (16%) were diagnosed of IL. The most important features according to the histologic subtype are detailed in the table:

<table>
<thead>
<tr>
<th>IL-CL vs IL</th>
<th>IL</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range)</td>
<td>56 (14-89)</td>
<td>56 (24-84)</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>49</td>
<td>66</td>
</tr>
<tr>
<td>Performance status ECOG ≥2 (%)</td>
<td>38</td>
<td>60</td>
</tr>
<tr>
<td>B-symptoms (%)</td>
<td>40</td>
<td>58</td>
</tr>
<tr>
<td>Primary extranodal (%)</td>
<td>33</td>
<td>32</td>
</tr>
<tr>
<td>Stage III-IV (%)</td>
<td>46</td>
<td>55</td>
</tr>
<tr>
<td>High serum LDH (%)</td>
<td>48</td>
<td>66</td>
</tr>
<tr>
<td>High-risk international index (%)</td>
<td>16</td>
<td>29</td>
</tr>
<tr>
<td>Complete response rate (%)</td>
<td>68</td>
<td>49</td>
</tr>
<tr>
<td>5-y overall Survival (%)</td>
<td>58</td>
<td>30</td>
</tr>
</tbody>
</table>

The treatment was not different between the groups. After a median follow-up of 3.4 yrs, the overall survival of IL patients was significantly shorter. In the multivariate analysis, IL subtype (p=0.001), along with age, performance status, bone marrow infiltration and serum LDH, maintained its prognostic importance.

Conclusions: To consider IL patients as a specific subset of DLCLs could be of interest, since they have different initial characteristics and poor prognosis.

CD56 IS AN INDEPENDENT PROGNOSTIC FACTOR FOR T-NULL CELL TYPE OF ANAPlastic LARGE CELL LYMPHOMA


Introduction: Anaplastic large cell lymphoma (ALCL) is a subset of non-Hodgkin’s lymphoma characterized by a peculiar anaplastic morphology and an expression of Ki-1 (CD30) antigen. Recent progress has identified that ALCL with p80/ALK + ALK expression constitute a distinct subset of ALCL. p80/ALK + ALCL has been characterized with younger age distribution, nodal predilection and fair clinical course, but some of them pursue a poor prognosis. CD56 has been reported to be expressed in a subset of ALCL.

Methods: To identify major prognostic factors, we investigated the clinical features of 87 cases of ALCL with T-null cell phenotype. ALCL with B-cell phenotype and primary cutaneous ALCL were excluded from this study.

Results: There were 56 men and 31 women; their ages ranged from 2 to 85 years (median age, 30 years). Of 85 cases tested p80/ALK was positive in 53 cases (62%), and of 77 cases CD56 was positive in 13 cases (17%). p80/ALK + group showed significantly younger age predominate. Median overall survival was 3.1 years. Univariate analysis identified that a longer survival was significantly associated with younger age (<50 yrs, p=0.004), early stage (IC, p=0.01), good PS (0-2, p=0.001), p80/ALK positivity (p=0.002) and CD56 negativity (p=0.03). By multivariate analysis, advanced stage (p=0.005, RR=24.0), CD56 positivity (p=0.001, RR=7.53), bad PS (p=0.001, RR=5.69) and p80 negativity (p=0.001, RR=4.08) were identified as major prognostic factors. CD56 cases showed worse prognosis in both p80-positive and -negative subgroups.

Conclusion: These data suggest that CD56 is an independent prognostic factor for ALCL. Appropriate therapy for ALCL should be explored based on the prognostic model including CD56.
y6 T-CELL LYMPHOMAS
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Human y6 T lymphocytes represent a minor subset of T-cells which exhibit a tissue-restricted repertoire, with predilection for the red pulp of the spleen and some mucosal tissues such as the gastrointestinal tract, have a broad antigen specificity and can develop cytotoxic activity.

Among T-cell neoplasms, a proportion of T lymphoblastic leukemia/lymphomas express a y6 T-cell receptor (TCR) whereas only a small percentage of peripheral T-cell lymphomas are of y6 origin. Among them, hepatosplenic y6 T-cell lymphoma (HSTL) is a rare but distinct entity. HSTL is characterized by its common occurrence in young adults, sometimes in a context of immunosuppression (such as solid organ transplantation), with hepatopeliosis but no lymphadenopathy, frequent B symptoms, thrombocytopenia and a poor prognosis. Neoplastic cells are clonal medium-sized y6 T-cells which have a non activated cytotoxic profile (TIA1+, Granzyme B-), infiltrate the sinuses of the bone marrow, the sinuses of the liver, the cord and sinuses of the spleen and frequently show isochromosome 7q.

Non hepatosplenic y6 T-cell lymphomas have been recently reported. Most of them are characterized by an initial site of involvement in mucosal tissues (nasal cavity, gastrointestinal tract, lung, larynx, thyroid) or skin. They show a broad cytopathological appearance and have a constant activated cytotoxic (TIA1+, Granzyme B+, Perforin+) phenotype. The potential role of y6 T-cells in the immune response in the epidermal and epithelial linings and the past history of chronic antigen exposure in some patients, these lymphomas can be regarded as a model of activated cytotoxic lymphomas originating from the normal y6 T-cells that are present or can be induced by inflammatory states in different mucosa-associated lymphoid tissues (MALT) as well as in the skin.

The importance of cell lineage (TaBu, Th6, NK) in the definition of disease entity in T/NK cell neoplasms is unclear. Whereas HSTL is a distinct clinicopathologic entity which strongly resembles y6 origin, several cases of non hepatosplenic y6 TL are likely to belong to different clinicopathologic entities of extranodal T/NK cell lymphomas.

PRIMARY CUTANEOUS CD3-POSITIVE EPIDERMOTROPIC CYTOTOXIC T-CELL LYMPHOMAS: A DISTINCT CLINICAL-PATHOLOGIC ENTITY WITH AN AGGRESSIVE CLINICAL BEHAVIOUR
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Introduction: Primary cutaneous T-cell lymphomas (CTCL) generally have the phenotype of CD3+, CD4+, CD45Ro- memory T-cells. CTCL expressing a CD8+ T-cell phenotype are extremely rare and ill-defined. To elucidate if CD8+ CTCL represent a distinct disease entity several CD8+ CTCL cases were reviewed.

Methods: 17 cases were selected from the files of the 1st dept. of Dermatology, IRCSS, of the University of Milan and from the dept. of Dermatology and Pathology of the Free University Hospital of Amsterdam. The clinical, histological and immunophenotypic features were all reviewed. Further, 15 cases were investigated not only for TCR gene rearrangement but also for EBV genome integration in the DNA of neoplastic T-cells by using nested PCR and ISH.

Results: Eight cases formed a homogeneous group showing presentation with generalized plaques, papulonodules and tumors mimicking disseminated广电 evolve reticulosis; metastatic spread to unusual sites, such as the lung, testis, CNS and oral cavity, but not to the lymph nodes, and an aggressive course (median survival, 32 months). Histologically, they were characterized by a band-like lymphoid and strongly epithemepathic infiltrate of medium-sized to large pleomorphic T-cells or immunoblasts with expression of CD3, CD8, CD7, CD45RA, CD3, and TIA-1 markers, whereas CD2 and CD5 were quite constantly lost. TIA-1 expression pointed out a derivation from cytoktic T-cells (CTL). The other 9 cases formed an heterogeneous group with the characteristic clinical and histological features as well as the expression of well defined types of CTCL such as mycosis fungoides, postkeratotic reticulosis, lymphomatoid papulosis, CD30-positive large T-cell lymphoma, and one case of subcutaneous panniculitis-like T-cell lymphoma. Phenotypically neoplastic T-cells were CD2, CD3, CD4, CD45Ro, CD8+ positive whereas CD5, CD7, and TIA-1 were variably expressed from case to case.

Fourteen out of 15 analyzed cases showed monoclonal configuration of TCR γ-gene whereas none of the tested cases were EBV+.
17. Vaccines and Monoclonal Antibodies

CURRENT AND FUTURE ROLE OF VACCINES IN LYMHPHMA

Introduction: The aim of vaccination of patients with lymphoma is to induce a continuing immune response to suppress emerging tumor cells. Many candidate tumor antigens are being defined at the gene level, and the challenge is to use these to activate a weakened, and possibly tolerant, immune system to attack tumor. Genetic vaccines can be rationally designed and manipulated, and encoded antigen can gain access to a range of processing pathways.

Methods: We focused initially on the idiotypic determinants of B-cell tumors, encoded by V\(_\text{H}\) and V\(_\text{L}\) genes, and assembled as single chain Fv (scFv) in a DNA vaccine format. However, these sequences alone were poorly immunogenic in mice. We therefore fused the gene encoding the Fragment C (FvC) of Tetanus Toxin to the scFv sequence. Fused scFv-FvC genes were tested in mouse models of B-cell lymphoma and myeloma. To investigate if gene fusion vaccines could be used for other tumor antigens, we also linked FvC to the gene encoding carcinoembryonic antigen (CEA).

Results: Fusion of FvC to scFv dramatically increased the anti-idiotypic immune response, and led to protective immunity in B-cell lymphomas. Fusion was required for the promotional effect, with separate genes ineffective. This fusion gene design is now being used in a small clinical trial of patients with low grade lymphoma. Surprisingly, a scFv-FvC fusion vaccine also induced protective anti-idiotypic immunity against myeloma, likely to be mediated by CD4+ T cells. A CEA-FvC construct gave a similar promotional effect of antibody responses against CEA.

Conclusions: Fusion of FvC to a weak tumor antigen is a device to activate immunity against the tumor. The promotional effect is probably operative at several levels, including recognition by dendritic cells, and activation of strong T-cell help. Intramuscular delivery leads to secretion of antibodies and cross-priming of cytotoxic T cells. The strategy may be applicable to a wide range of tumor antigens.

UNCONJUGATED MONOCLONAL ANTIBODY THERAPY OF LYMPHOMA.
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The approval of the chimeric anti-CD20 monoclonal antibody (mAb) Rituximab (Mabthera, Rituxan) for the treatment of patients with relapsed low grade or follicular B cell lymphoma (NHL) represents a milestone in the development of immunologic based, tumor specific therapy. The CD20 molecule has many properties that make it an attractive target for mAb based therapy. It is stable in the membrane, does not modulate, and is not shed. It is nearly B cell restricted in expression and found in high copy number especially in follicular histologies. Rituximab has augmented interaction with the human immune effector systems (complement and antibody dependent cell mediated cytotoxicity) and may directly induce apoptosis and augment chemotherapy.

Multiple studies have now demonstrated single agent activity in patients with follicular, mantle cell, diffuse large cell, Waldenstrom's, and post-transplant lymphoproliferative diseases (PTLD) histologies. Application to patients with newly diagnosed low-grade NHL and in combination with or following standard chemotherapy in nearly all types of B cell histologies is being explored with promising early results. The moderate toxicity profile, and single agent activity have prompted these combination studies. It is reasonable to expect that the use of this new treatment in the setting of minimal residual disease may lead to prolongation of disease free survival, and the results from randomized clinical trials are eagerly awaited.

Additional areas of interest include in vivo purging of stem cell collections, adjuvant use with or following high-dose therapy and stem cell transplant and augmentation of the immune mediated effects by treatment with cytokines such as IL-2, Interferon or cytokine growth factors.

RADIOACTIVE MONOCLONAL ANTIBODIES
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Radioisotope-labeled monoclonal antibodies can have theoretic advantages over unlabeled antibodies in the treatment of lymphomas. This is because external radiation can destroy antigen-positive and negative tumor cells, as well as untargeted antigen-positive tumor cells within a tumor that unlabeled antibodies may miss. Also, the radio-labeled antibodies can still recruit cytokytic host immune mechanisms or directly effect tumor-cell proliferation.

Several radiolabeled antibodies against different B-cell surface antigens are under study. The largest experience is with antibodies directed against CD20. Anti-B1, a mouse IgG2a antibody, has been labeled with I-131 and studied in patients with relapsed disease as well as in patients with previously untreated advanced low-grade lymphomas. Using a single-cycle regimen consisting of a tracer and a non-myeloablative therapeutic dose one week apart, single and multicenter phase II and III studies have demonstrated an overall response rate of approximately 72% and a complete response rate of 39% in patients with low-grade and transformed lymphomas who had had a median of 4 prior chemotherapy regimens. A phase III trial showed I-131-Anti-B1 was superior to the last chemotherapy received in a highly chemotherapy-refractory population. In previously untreated patients, a 100% overall response rate and 71% complete remission rate has been reported in 24 patients.

Another antibody (ZS8) labeled with Y-90 has been shown to have similar response rates in relapsed patients as the I-131-labeled antibodies, although in a somewhat less heavily pretreated population. With both radiolabeled antibodies, myelosuppression is the dominant toxicity. Patients treated with I-131 Anti-B1 have been able to be retreated. No information regarding retreatment with Y-90 antibodies is yet available.

Myeloablative doses of I-131 Anti-B1 with stem cell rescue have been given to 29 relapsed patients with a 86% overall response rate and 79% complete response rate. More recent studies are combining high-dose radiolabeled antibody with high-dose chemotherapy and promising results are being obtained.

Iodine-131 Anti-B1 Antibody (iodine I 131 tositumomab) is a new agent undergoing study for the treatment of patients with low-grade and transformed low-grade NHL. Efficacy and safety have been demonstrated in Phase I, II, and III trials. This abstract describes the therapies received subsequent to iodine-131 Anti-B1 Antibody. Two hundred and forty-eight patients with NHL were treated on trials, with 10% of these patients receiving additional therapy. Of the 10% who received additional therapy, 40% of these patients had active lymphoma as part of their conditioning regimen, a median of 13 months following iodine-131 Anti-B1 Antibody. These patients did not receive additional therapy following progression (within 90 days of progression (n=10), rapidly progressive disease (n=6), refractory to therapy (n=1), low partial response (n=11), and was lost to follow-up. At study withdrawal, the 10% patients who did not receive additional therapy had median ANC and platelet counts of 3.9 cells/mm$^3$ and 141,000 cells/mm$^3$, respectively. Subsequent therapy can be administered following iodine-131 Anti-B1 Antibody. This has included combination chemotherapy regimens, radiation therapy, rituximab, re-treatment with Iodine-131 Anti-B1 Antibody, and high dose therapy with autologous or allogeneic bone marrow transplant.

**IMMUNOTHERAPY OF MANTLE CELL LYMPHOMA (MCL) WITH RITUXIMAB (Rmb): DURATION OF RESPONSE & ANALYSIS OF FACTORS ASSOCIATED WITH RESPONSE**

**Introduction:**

A retrospective analysis was performed to delineate the factors associated with response, and the duration of response, in patients with MCL following treatment with Rmb. **Methods:**

- **Patients:** 87 patients (pts) with MCL [newly-diagnosed (MCL1) n=39, previously-treated (MCL2) n=48; median age 62 years (range 33-83); 76% male], were treated (Fx) with single agent Rmb at 200 mg/m$^2$ in 2 studies in 1996-97 (375 mg/m$^2$, n=47, 750 mg/m$^2$, n=40; 500 mg/m$^2$, n=30). Fx was conducted in the absence of WHO performance status (PS) 2 or 3, and only patients with extensive disease (94%). Statistical modeling of factors associated with response was performed by logistic regression. Duration of response was calculated from the date of complete remission (CR) or partial response (PR), and censored if further Rx was given prior to progression (PD) of MCL.

**Results:**

- The overall response rate (RR) was 42% (34/81, 3 events, CRR 15%). On multivariate analysis, inducers, LHD (p<0.003, PS 0 vs. 1 vs. 2, p=0.03), MCL2 refractory to last prior Rx (p=0.04), and splenomegaly (p=0.01) at the time of Rx with Rmb, but not MCL1 or dose effect, were significantly associated with a lower RR. On multivariate analysis, only LHD retained statistical significance (p=0.001), and age had borderline significance (p=0.09).

- The median follow-up was 1.3 years, and the 1 year survival was 90%.

**Conclusions:**

The RR to single agent Rmb in MCL is 42%, whether MCL1 or MCL2; elevated LHD at the time of therapy was associated with a 9-year OS. The duration of response was longer for pts achieving CR, and was similar to that previously reported in follicular lymphoma.

**AUTOLOGOUS LYMPHOCYTES AS VECTORS TO TARGET THERAPY LOW GRADE NHL AND CLL**


**Introduction:**

Diffusely lymphocytic non-Hodgkin lymphoma (DLNHL) and chronic lymphocytic leukemias (CLL) remain incurable with conventional therapy. In these diseases the malignant lymphoma is exquisitely sensitive to radiation, but traditional radiation therapy techniques have been limited by normal tissue toxicity, particularly myelosuppression. We have developed a novel technique incorporating autologous lymphocytes to target a plasmacytoid undifferentiated, inducer 114m, to lymphocyte traffic areas in patients with lymphoma malignancy. We present a pilot study of this technique in patients with refractory disease.

**Methods:**

Nineteen patients (10 DLNHL and 9 CLL) median age 66 (51 - 87) were treated with a single infusion of autologous lymphocytes labeled with a median activity of 100 MBq of inducer 114m. All patients had progressive disease refractory to conventional chemotherapy including chlorambucil, CVP oxacloprinum and fludarabine. 17/19 patients had a heavy lymphoid burden in terms of hepatosplenomegaly and multiple lymphadenopathy. The median lymphocyte count at the time of therapy was 140 x 10^9 /L (15-300), median platelet count of 90 (27 - 160).

**Results:**

At three months post-infusion 2/19 patients showed a complete remission (CR) 8/19 partial remission, 3 stable disease and 6 patients were treatment failures. The median duration of response for the 10 responders was 12 months (6 to 36 months). The median survival for the 19 patients was 12 months. The major toxicity was myelosuppression, particularly thrombocytopenia and anemia. 3/19 patients had a platelet count below 20 x 10^9 /L at the time of death. There were no infective deaths.

**Conclusion:**

This represents a new approach to targeting therapy in lymphoid malignancy. We observed a significant anti-lymphoma effect in a group of patients with late stage refractory disease. The dose limiting toxicity is myelosuppression which may be less marked if this treatment was delivered earlier in the disease process or if the infusions were delivered as a lower dose intermittent therapy titrated against response and in bone marrow depression.

**THE EFFECT OF RITUXIMAB IN PATIENTS WITH FOLLICULAR AND MANTLE CELL LYMPHOMA**


**Introduction:**

Clinical activity of the anti-CD20 monoclonal antibody Rituximab has been observed in patients with follicular lymphoma (FL) and mantle cell lymphoma (MCL). We present the results of a preliminary analysis of an ongoing prospective trial in patients with these diseases.

**Methods:**

120 patients with bimodally measurable FL or MCL (REAL classification) were treated with Rituximab 375 mg/m²/week for 4 weeks. A central pathology review confirmed the diagnosis of FL in 76/78 and of MCL in 38/42 cases. Response was evaluated after 8 weeks and continued 12 weeks after treatment.

**Results:**

Patients characterize FL and (MCL) median age 57 (55), time from diagnosis 2.6 (4.0) years and time since last chemotherapy 7.1 (4.3) months. (90%) had advanced (stage III-IV) disease, ECOG performance status = 0 in 73% (32%) and = 1 in 23% (33%) of cases 55% (69%) had an involved bone marrow at some time in the course of disease. 24% (21%) were previously untreated, while 23% (21%) had received one and 53% (57%) more than one chemotherapy regimen. 23% (19%) had been irradiated before and 90% (85%) of the pre-treated patients had responded to previous systemic or local therapy. Toxicity of the treatment was grade 1-2 fever and rigor during the first infusion and mild asthenia in approximately 15% during the treatment period. Due to unacceptable side effects one patient interrupted treatment, and another needed a dose reduction. 8/78 of the FL and 8/42 of the MCL patients experienced serious adverse events (not necessarily due to rituximab) during treatment or shortly thereafter, resulting in death in 5 cases. At week 12 the response rates for FL and MCL patients were 51% (4% CR) and 22% (2% CR) respectively. In a multivariate analysis including the most relevant patient characteristics, disease and previous treatment variables, no factor was found independently predictive for response. Baseline bone and marrow were positive for PCR for the translocation t(14;18) in 41% FL and for t(11;14) in 38% MCL patients, becoming negative in 62/71 FL and 27/27 MCL evaluated after treatment. The follow up of the blood cell immunophenotype showed the disappearance of all B-lymphocytes from the blood after the first treatment week, while CD4, CD8 and NK lymphocytes remained unchanged up to 12 weeks thereafter.

**Conclusion:**

Rituximab is an active agent for the treatment of FL, while its efficacy is modest in MCL. The likelihood of responding seems to be independent from the number of previous treatments or from responses to previous therapy.
EARLY MOLECULAR RESPONSES IN NEWLY DIAGNOSED
FOLLICULAR LYMPHOMA PATIENTS WITH RITUXIMAB AS
FIRST LINE TREATMENT.

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Deconinck, F. Guilhot, C. Bastard, J-Y. Blay, O. Blanchet, B. Mahé, F. Boud, G.
Garnier, P. Ledentin, A. Najman, A. Mathieu-Boud, A. Benzahra, and P. Solal-Celigny.
France.

Introduction: Fifty patients (pts) with newly diagnosed follicular lymphomas and low
sized tumor burden criteria were treated with 4 weekly injections (375 mg/m²) of Mabthera
(Rituximab®; F. Hoffmann-La Roche, Basel) (see other abstract for clinical responses).
Methods: Molecular analyses of bcl2-Ig heavy chain rearrangements were performed in one
central laboratory with PCR using MBR/mcr and Lc consensus specific oligonucleotides. At diagnosis, a single PCR amplification was performed with a
sensitivity ≥10⁵ on lymph node (17 pts), bone marrow (BM; 47 pts) and peripheral
blood (PB; 49 pts), while during follow-up (day 50 and month 6), nested PCR with a
sensitivity ≥10³ was used to monitor molecular markers in pts positive at diagnosis.
Results: One pt was excluded after pathological review and 1 pt could not be evaluated
by PCR at study entry. Out of the remaining 48 pts studied, 32 (67%) were PCR
positive (PCR+ve) in PB and 9/27 pts PCR+ve in BM. In details, 9 pts were PCR-
ve both in PB and BM, 7 pts PCR+ve in PB while PCR+ve in BM; 11 remained
PCR+ve both in PB and BM and 2 pts were PCR+ve and 1 PCR+ve in PB (BM not
done). Among day 50 PCR+ve pts in PB, 8 were in CR, 4 in PR, and 5 with no change
while in PCR+ve pts in BM, none was in CR, 7 were in PR, 5 with no change and 1 had
progressive disease. At 6 months (23/32 informative pts evaluated), 15 pts were found
PCR+ve in PB while 8 were PCR+ve. Interestingly, 12 patients that were PCR+ve in PB
at day 50 remain PCR+ve in PB at 6 months while 2 returned to PB PCR+ve (both
were PCR+ve in BM at day 50). In 10 pts that were PB PCR+ve patients at day 50, 4
converted in PB to PCR+ve at 6 months and 6 remain PCR+ve. Finally, 4 out of 5 pts
were PCR+ve in PB and BM at 12 months.
Conclusion: This preliminary analysis indicates that 4 courses of Rituximab induce
rapid and sustained PCR negativity in PB in a substantial number of patients (17/20 at
day 50 and in 19/23 at 6 months) and seem to correlate with early clinical responses.
The duration of this molecular response and its significance for outcome remains to be
determined with a longer follow-up (updated results will be presented).

INTERFERON-γ (IFN-γ) INDUCES CD20 EXPRESSION ON MULTIPLE
MYELOMA (MM) PATIENT AND HEALTHY Donor (HD) PLASMA CELLS
AND B-CELLS AND AUGMENTS BINDING OF RITUXIMAB (RITUXAN)
TO MM PLASMA CELLS.

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A.R. Belch, L. Pilaraki and K.C. Anderson, Dana Farber Cancer Institute and
Massachusetts General Hospital, Harvard Medical School, Boston MA, U.S.A.,
and Cross Cancer Institute, University of Alberta, Edmonton, Alberta, CANADA.

Introduction: In view of recent successes with anti-CD20 directed radiotherapy in
other B-cell malignancies, we recently initiated a Phase II trial to study single agent
Rituxan in MM. It remains controversial as to which cell (B-cell or plasma cell) acts as
the clonogenic cell in MM. Circulating CD20+ clonotypic B-cells bearing identical Ig
rearrangements as autologous plasma cells have been detected in the circulation of
most MM patients. In contrast, plasma cells from most (though not all) MM patients
lack CD38, or express it weakly. As such, identifying agents which induce CD20
expression on plasma cells may improve the binding to anti-CD20 directed MoAbs
therapies and augment responses to these agents.
Methods: RPMI 8226 MM plasma cells, freshly obtained plasma cells (CD38+, CD45+)
from the bone marrows (BM) of 7 MM patients and 2 HD, along with circulating B-
cells (CD19+, CD20+) from the peripheral blood (PB) of 5 MM patients, and 3 HD
were cultured for 48 hours with and without recombinant human IFN-γ (1 U/ml
up to 1000 U/ml). Changes in CD20 expression were characterized by flow cytometry using
the B1 (CD20) and Rituximab (Rituxan) MoAbs with appropriate isotype controls.
Results: IFN-γ significantly induced CD20 expression on RPMI 8226 MM cells, as
well as on CD20 plasma cells taken from 5 of 7 MM patients and 2 of 2 HD. Induction
of CD20 expression on plasma cells occurred in a dose dependent manner, with an EC₅₀
of 1 U/ml of IFN-γ, with a plateau reached at 100 U/ml at 48 hrs. Rituxan binding to
RPMI 8226 MM cells, as well as MM patient plasma cells was significantly augmented
by IFN-γ at these concentrations. Both the percentage of B-cells expressing CD20,
and the intensity of CD20 expression on B-cells was also induced by IFN-γ on
circulating B-cells taken from 5 of 5 MM patients, and 3 HD.
Conclusion: IFN-γ induces CD20 expression on CD20+ MM and HD plasma cells, and
increases CD20 expression on circulating MM and HD B-cells. Moreover, IFN-γ
augments Rituxan binding to MM plasma cells. These data provide the rationale for
the use of IFN-γ to enhance responses to CD20 targeted therapeutics in MM.
18. Future Developments

POLYamine ANALOGUE THERAPY WITH DIETHYLMORPHOSPERMINE (DEHP) FOR HIV-ASSOCIATED NON-HODGKIN’S LYMPHOMA (HIV-NHL): TARGETING PROLIFERATING MACROPHAGES

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Introduction: Macrophages are known to secrete a variety of cytokines that may play a role in B-cell proliferation and the pathogenesis of HIV-NHL. We have previously demonstrated the presence of clonally integrated HIV in the macrophages associated with HIV-NHL which may result in cytokine overproduction as an initial step in lymphomagenesis. Preliminary studies suggested that these proliferating macrophages were killed in vitro by polyamine analogues. We studied the tolerance and antitumor activity of DEHP, a polyamine analogue.

Methods: Ability to induce proliferating macrophages in peripheral blood was studied by identifying the percentage of CD14 cells positive for proliferating cell nuclear antigen (PCNA) in HIV patients relative to HIV-negative controls. Five patients with refractory HIV-NHL were treated as one dose of DEHP and serial peripheral blood specimens collected to evaluate pretreatment sensitivity to DEHP and correlations between antitumor response and the proportion of PCNA positive CD14 cells macrophages present in peripheral blood.

Results: Abnormally high levels of PCNA expression were identified in all five peripheral blood specimens from HIV-NHL patients. PCNA+ macrophages from three patients with HIV-NHL all accumulated bromodeoxyuridine (BrdU) as markers of DEHP therapy and pre-treatment DEHP sensitivities of PCNA+ CD14+ cells are shown below:

<table>
<thead>
<tr>
<th>Patient</th>
<th>% PCNA+</th>
<th>Pre-treatment Sensitivity</th>
<th>DEHP Dose (mg/m²)</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>41</td>
<td>+</td>
<td>25</td>
<td>PD</td>
</tr>
<tr>
<td>2</td>
<td>48</td>
<td>++</td>
<td>25</td>
<td>PD</td>
</tr>
<tr>
<td>3</td>
<td>90</td>
<td>+++</td>
<td>25</td>
<td>PD</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>+++</td>
<td>50</td>
<td>PD</td>
</tr>
<tr>
<td>5</td>
<td>100</td>
<td>++++</td>
<td>50</td>
<td>PR</td>
</tr>
</tbody>
</table>

Both responding patients had reduction in PCNA+ CD14+ cells in peripheral blood after DEHP therapy. Increased expression of these markers was observed just prior to relapse in both. No significant cytotoxicities were encountered.

Conclusions: Proliferating macrophages can be detected in peripheral blood of HIV-NHL patients. DEHP was well-tolerated and demonstrated some evidence of antitumor activity which seemed to correlate with in vitro sensitivity of peripheral blood PCNA+ macrophages.

LIPOSOMAL VINCristINE IN RELAPSED NHL: EARLY RESULTS

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Objective: Vincristine is an active agent in NHL and ALL, but full doses are often precluded by neurotoxicity. Since liposomal encapsulation of vincristine (LV) allows administration of higher doses, we explored its activity in relapsed NHL. ALL. Methods: Eligible patients (pts) with relapsed NHL (CR or PR during initial RA) or ALL, age ≥16 years, with no HIV or other serious infection, no CNS disease, normal renal function, neutrophils >500, and platelets ≥300. After informed consent, pts received 2.0 mg/m² of LV (VBP q14d). Responses were scored up to 12 injections, with dose adjustment for toxicity. Results: Of the 51 registered pts, 35 are currently available for response. Median age is 62 years (range 19-86), and 21 are males. Histology was follicular in 12, transformed follicular in 7, diffuse large cell in 11, mantle cell in 3, NK cell in 1, and ALL in 1. Clinical grade was high in 1, aggressive in 17, indolent in 10, and transformed in 7 pts. Serum LDH was high in 16/35, and β2-microglobulin > 3.0 mg/l in 19/30 pts. All 35 pts received prior VCR, median number of prior regimens was 3 (range 1-10), and 1/35 pts were refractory to the regimen immediately preceding LV. The 1 pt with ALL did not respond. Responses were seen in 14/34 (41%) of pts with NHL (95% CI 21%-59%). Responses according to clinical grade are shown below:

<table>
<thead>
<tr>
<th>Inpatient</th>
<th>Transformed</th>
<th>Aggressive</th>
<th>Transformed or Aggressive</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>10</td>
<td>17</td>
<td>28</td>
</tr>
<tr>
<td>% CR/PR</td>
<td>10</td>
<td>71</td>
<td>47</td>
</tr>
<tr>
<td>95% CI</td>
<td>1-45</td>
<td>29-96</td>
<td>23-72</td>
</tr>
</tbody>
</table>

Median response duration was 4 months. Grade 3/4 toxicity included sensory neuropathy in 11 pts, and motor neuropathy in 1. Neurotoxicity caused termination of treatment in 5 pts, all of whom had some prior neuropathy and prior vincristine.

Median response duration was 4 months. Grade 3/4 toxicity included sensory neuropathy in 11 pts, and motor neuropathy in 1. Neurotoxicity caused termination of treatment in 5 pts, all of whom had some prior neuropathy and prior vincristine.

KI-3(S-CFV)-ETA', A NEW RECOMBINANT ANTI-CD30 IMMUNOTOXIN FOR THE TREATMENT OF HODGKIN LYMPHOMA CELLS

Laboratory of Immunotherapy, University Hospital of Cologne, Germany

Introduction: The CD30 antigen is highly overexpressed in Hodgkin's and large cell anaplastic lymphoma can serve as a good target antigen for a selective immunotherapy. We thus produced a new recombinant anti-CD30 immunotoxin fusing a high-affinity binding moiety to a potent bacterial toxin.

Methods: We constructed a single chain variable fragment (scFv) from the murine anti-CD30 antibody KI-3, fusing heavy chain variable (VH) and light chain variable (VL) domain of the monoclonal antibody by a flexible peptide sequence. We cloned the assembled VH- and VL- genes into a plasmid vector to receive functional high affinity scFv. Produced filamentous phages were purified and screened for binding on the Hodgkin cell line L540C. A binding Ki-3 scFv clone was characterized by sequencing, whole cell ELISA experiments and FACS analyses. The recombinant antibody was genetically fused in a deletion mutant of Pseudomonas exotoxin (ETA) using an improved new pET-derived expression vector (pBMM1).

Results: The resulting Ki-3(scFv)-ETA' immunotoxin was directed to the perisomatic space of E.coli. After purification we could demonstrate a high binding activity in FACS analysis to L540C cells. Ki-3(scFv)-ETA will be further investigated in vitro and compared with another recently evaluated anti-CD30 immunotoxin (Ki-4(scFv)-ETA'), which binds to a different CD30 epitope.

Conclusions: The best of these new immunotherapeutic agents will be used for the treatment of patients with Hodgkin's lymphoma and other CD30-positive malignancies.

PBPC MOBILIZATION, HARVEST AND REINFUSION FOR CHEMOTHERAPY INTENSIFICATION IN ELDERLY NON-HODGKIN'S LYMPHOMA PATIENTS


Introduction: Mobilized peripheral blood progenitor cells (PBPC) are now widely employed for chemoradiotherapy intensification in patients with advanced-stage non-Hodgkin's lymphoma (NHL). This strategy is generally employed in patients aged 60-65 years. Few data are available on the potential use of PBPC in elderly NHL patients.

Methods: PBPC mobilization, harvest and reinfusion was evaluated in 21 NHL pts. (15 at onset, 6 relapsed) aged between 61 and 80 yrs. (median 68). Their main clinical features included: histologic subtypes: Burkitt's1, DLCL in 9, mantle-cell in 3, low grade in 8, BM involvement in 11, high LDH in 14, Stage III-IvB in 14, Performance Status 3 in 4-8. Mobilization was induced by intermediate-dose chemotherapy + G-CSF (5μg/kg/day).

Results: PBPC mobilization could be elicited in 17 out of 21 pts. The extent of progenitor mobilization and harvest was as follows:

<table>
<thead>
<tr>
<th>Peak values of CD34+/HL</th>
<th>CFU/GM/mL</th>
<th>No. of Aphereses</th>
<th>Total harvest/kg of CD34+ CFU-GM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>23</td>
<td>1.416</td>
<td>2</td>
</tr>
<tr>
<td>Range</td>
<td>4-120</td>
<td>450-62,900</td>
<td>1-3</td>
</tr>
<tr>
<td></td>
<td>3.9 x 10⁷</td>
<td>13.5 x 10⁴</td>
<td>0.3-46</td>
</tr>
<tr>
<td></td>
<td>1.6-209</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

So far, harvested PBPC have been reinfused in 14 pts. following intensified chemotherapy. There was one fatal pneumonia in a pt. with cerebral disease progression, no other fatal complication occurred. Marked tumor regression could be documented in all but 2 patients.

Conclusions: The use of autologous PBPC is a feasible option in elderly NHL pts. as a support for intensified chemotherapy.
FEASIBILITY OF TANDEM AUTOLGOUS STEM CELL TRANSPLANTATION (ASTCT) IN VERY UNFAVORABLE (UF) RELAPSE FROM HODGKIN'S DISEASE (HD).


Methods: Between 01/85 and 11/87, patients under 50 years old with very UF relapse from HD (e.g., primary refractory patients or early and delayed relapse were included in a pilot study of double ASCT). They were planned to receive two courses of IVAVO (ifosfamide 4500 mg/m² etoposide 450 mg/m², adriamycin 75 mg/m² with GCSF and blood stem cell collection. ASCT1 was conditioned with CBV + mitoxantrone (30 mg/m²) and ASCT2 (cytarabine 6 g/m², melphalan 140 mg/m²) and total body irradiation at 12 Gy or busulfan 16 (n = 8) > 12 mg/kg). Patients: 43 patients (median age: 29 y) met the inclusion criteria. The median time between diagnosis and progression was 11 mo and 19 patients had refractory disease whereas 24 patients were in relapse. 28 patients had documented histological progression. At progression extra nodal site was present in 23 patients and previously irradiated site in 12 patients. 87% received 2 cures of IV AVD and response > 50% was observed in 72% of patients. Among the 43 patients, 3 had no ASCT for disease progression and died. 9 patients had only ASCT1 (refusal n=1, progression n=5, low stem cell collection n=3). 31 patients (%) received the double ASCT and are available for toxicity, in 2 cases a bone marrow cryopreservation was necessary. Results: Hematologic recovery was normal after ASCT1 but delayed platelet recovery was observed after ASCT2. The interval between the 2 ASCT was at 88 days. 2 VOD and one fatal were observed with busulfan 16 mg/kg, one hemorragic event. Detailed toxicity will be presented. 5 patients received involved field radiotherapy after ASCT2. After ASCT2, 83% were in good remission and 20% relapsed within the first year. Overall survival at 2 years is at 82% and at 70% for patients receiving the 2 ASCT with a disease free survival at 56% (including 8 patients with primary refractory disease). Conclusion: double ASCT is feasible in very UF relapse from HD and may lead to some prolonged remission.

ALLOGENEIC BONE MARROW TRANSPLANTATION (ALLO BMT) FOR LOW GRADE LYMPHOMA (LGL) AND CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)


Strategies with curative potential are needed for young patients (pts) with advanced stage LGL and CLL. alloBMT shows promise for such patients at disease progression following initial therapy. Between Sept 85 and Jan. '99, 29 pts with these diagnoses (LGL: n=14, CLL: n=15) received alloBMT from matched related donors. Median age at BMT was 42 (range 20 to 52) years. Fourteen pts were male, 15 female. Median interval from diagnosis to BMT was 21 (range 4-154) mon. Histology in LGL pts included follicular small cleaved cell (13), follicular mixed (4) and small lymphocytic (2). Seven pts had B-CLL, 2 T-CLL, and 1 T-cell prolymphocytic leukemia. Marrow involvement at diagnosis was present in twenty six pts (90%). Prior therapy included alkylating agents in 17 pts, cyclophosphamide alone in 11, and none in 1. In number of prior episodes of therapy was 0 in 1 pt, 1 in 11 pts, 2 in 6 pts, and 3 or > in 11 pts. Disease status at transplant was induction failure (IP) (9), RII (1), PR (2), CR (1), PR1 (1), CR1 (1), and induction (1). Twenty-three of 29 pts (79%) were stage IV at the time of transplant; 24 (83%) had never achieved CR. Donor source was HLA matched sibling (20), unrelated (UD) (8) and syndigeneic (1). The conditioning regimen included cyclophosphamide, total body or lymphoid irradiation +/- others (9), and busulfan, cyclophosphamide +/- others in 3 pts with extensive prior radiotherapy. Prophylaxis for GVHD included cyclosporine + methotrexate (22), cyclosporine + methylprednisolone (2), T cell depletion (TCD) +/- others (4), and none (1). Regimens related toxicity was tolerable; 20 of 29 pts sustained a Grade C in all other systems. Median (range) days to engraftment, ANC > 5.0 x 10⁹/L BWC > 1.0 x 10⁹/L and platelets > 20 x 10⁹/L was 18.5 (10-33); 18.3 (10-32); and 26.5 (10-68) respectively. Cumulative incidence of acute GVHD (A1+2) was 30%. Sixteen pts are currently alive, a median of 22 mos (range 1-45) post BMT with a median KPS of 90. Death occurred related to transplant complications in 9 pts and underlying disease in 4. Twenty-three of 37 evaluable pts (85%) achieved CR post-BMT. Four pts had persistent disease/relapse. Overall and event free survival for the whole group is at 13 and 14% respectively. Allo BMT for young pts with advanced stage LGL or CLL is a feasible strategy that can result in achievement of durable remissions with tolerable toxicity and low relapse rate.

ALLOGENEIC TRANSPLANTATION FOR MANTLE CELL LYMPHOMA: MOLECULAR REMISSIONS AND EVIDENCE OF GRAFT-VERSUS-MALIGNANCY


Introduction: The presence of graft-versus-tumor effect has been well established for various hematological malignancies but not for mantle cell lymphoma (MCL). Sixteen patients with the difuse type of MCL received allogeneic transplantation. Three had additional blastic features. All had an HLA-identical sibling donor. Fifteen had stage IV disease. Eleven patients were previously treated, including one who failed prior autologous transplantation. Five patients were newly diagnosted.

Methods and Results: Fourteen patients received high dose chemoradiotherapy. Twelve (85%) achieved complete and 2 (14%) partial response. Two additional patients had nonsalvage preparative regimen. Once failed to engraft and later relapsed. The other patient had progressive disease one month post transplant but after developing graft-versus-host disease (GVHD) he later achieved complete remission now durable for 14+ months (mos). Residual lymphoma was assessed in seven patients studied by polymerase chain reaction assay (PCR) for BCL-1. All had detectable disease at the time of transplant. When tested within four months post transplant, four of these patients attained a molecular response. One of the 3 molecular non-responders converted to a negative PCR status 7 mos later and one fluctuates between positive and negative PCR 14 mos post BMT.

Overall survival (OS) and freedom-from-progression (FFP) at 3 years were both 55% (95% confidence interval CI), 28 to 83%. For the patients with chemosensitive disease, the FFP and OS at one year were 90% (95% CI, 71 to 100%) compared with 44% (95% CI, 1 to 88%) (P=0.04) for those who were refractory to conventional chemotherapy at the time of transplantation. There were six deaths. These were related to GVHD (three cases), infection (one case), multorgan failure (one case), graft failure (one case).

Conclusions: This report provides the first evidence suggestive of graft-versus-malignancy in MCL. Data supportive of this concept include 1) the ability to achieve remission using nonablative chemotherapy as preparative regimen, 2) the conversion from PCR (+) early after transplant to PCR (-) several months later and 3) a markedly lower relapse rate than occurs after autologous transplantation in similar patients.

Allogeneic Bone Marrow and Blood Cell Transplants to Treat Patients with Lymphoma

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Since the cure of aggressive non-Hodgkin's lymphoma was reported using autologous bone marrow transplantation in 1975, autologous rather than allogeneic stem cells have been the primary source to rescue patients after high-dose therapy for lymphoma. However, there are patients in whom adequate cells free of lymphoma are hard or impossible to collect, and others in whom a graft vs. lymphoma effect would be an advantage. This has led to studies of allogeneic bone marrow or blood cell transplantation in patients with lymphoma. In North America in 1995-96, approximately 400 allogeneic transplants were done for lymphoma in contrast to more than 2,000 autologous transplants. However, the proportion of allogeneic transplanted has been increasing. Allogeneic transplantation has been tested in patients with diffuse large B-cell lymphoma, follicular lymphoma, small lymphocytic lymphoma, mantle cell lymphoma, Hodgkin's disease, and in patients failing in autotransplant. In relapsed diffuse aggressive lymphoma (i.e., usually diffuse large B-cell lymphoma), autologous transplantation appears superior to allogeneic transplantation with a superior overall survival and progression-free survival. In follicular lymphoma, the relapse rate after allogeneic transplantation appears to be lower than with autologous transplantation (approximately 20% vs. greater than 50%). A similar finding has been described in small lymphocytic lymphoma and might be true in mantle cell lymphoma. Allogeneic transplantation has been reported to have a surprisingly high death rate in Hodgkin's disease. Some patients failing autotransplant for lymphoma can be cured with a second allogeneic transplant, although the death rate with this approach is high.

It is possible that allogeneic transplantation, when feasible, could become the treatment of choice for younger patients with follicular lymphoma, small lymphocytic lymphoma, and mantle cell lymphoma when bone marrow transplantation is performed.
ANTISENSE OLIGONUCLEOTIDE THERAPY
P. E. Cotter, J. Waters, D. Fennell, A. Webb, P. Clark, D. Cunningham
St Bartholomew's and the Royal London Hospital, London, EC1N 1BB, U.K.

Introduction: Antisense oligonucleotides represent a new therapeutic approach based on the "silencing" of genes involved in the prevention of programmed cell death (apoptosis). In the field of lymphoma obvious targets included follicular lymphoma with the t(14;18) translocation, resulting in deregulated expression of the BCL-2 gene, chemoresistance and subsequent protection against lymphoma cell death.

Methods and results: Using an 18 base AO sequence to BCL-2 (G3139 - Genta USA) with a thioate chemistry to protect against nuclease activity, cellular internalisation is good, in vivo toxicities are minimal and pharmacokinetics show tissue availability maximal with continuous subcutaneous infusions. In a human phase I antisense study (21 patients) the G3139 is well tolerated with minimal toxicity. Some evidence of efficacy has been observed including a responder with stage IVB follicular lymphoma who has achieved complete clinical and radiological response in excess of two years. The main dose limiting toxicity has been reversible thrombocytopenia and is related to the thioate backbone. In the cancer setting AO may eventually be used in combination with chemotherapy to overcome the chemoprotective effect of anti-apoptosis genes. Both BCL-2 and BCL-xl are such genes. BCL-2 and BCL-xl (developed by ISIS Pharma, USA) AO's have been administered to xenograft models of t(14;18) lymphoma and acute biphenotypic leukaemia (with the t(4;11)), both with high BCL-2 and BCL-xl expression. Following the antisense therapy Etoposide was infused IV. A considerably enhanced tumour reduction, and increased apoptosis was observed with lower chemotherapeutic doses. A third AO against Protein Kinase C Alpha RNA (ISIS Pharma, USA) in a human Phase I study has reported efficacy in low grade lymphoma. AO may also have an application in tumours expressing mutant TP53. The use of AO against the MDM2 gene has shown the ability to restore wild type TP53 expression, suggesting that as we may be able to restore normal cell growth and death patterns by molecular manipulations.

Conclusion: Downregulation of anti-apoptosis by antisense oligonucleotides in the human setting has low toxicity and anti-lymphoma activity where conventional chemotherapy has failed.

GENE THERAPY OF LEUKEMIAS AND LYMPHOMAS
Division of Hematology/Oncology, University of California, San Diego, CA

Introduction: Despite expressing class I and II major histocompatibility antigens, leukemia and lymphoma II cells are ineffective antigen presenting cells. However, we have demonstrated that chronic lymphocytic leukemia (CLL) B cells modified to express recombinant CD40-CD40-ligand (CD154) using a replication defective adenovirus vector (Ad-CD154) are induced to express immune co-stimulatory molecules that render these cells proficient in antigen presentation. Moreover, such modified leukemia cells can induce autologous cytotoxic T lymphocytes in vivo that are specific for infected and non-infected leukemia B cells. Thus, we have developed a strategy for gene therapy for CLL whereby neoplastic B cells are infected with Ad-CD154 ex vivo and then administered to the patient as a single intravenous injection.

Methods: We are completing a phase I dose-escalation study in patients with progressive, intermediate or high risk CLL by the modified Ralt staging criteria. To date, ten patients have received autologous Ad-CD154 transduced CLL cells. Two patients (Pilot Group) received 3.3 x 10^8 autologous leukemia cells of which <8% expressed the CD154 transgene. Three patients received 3.3 x 10^9 (Group I), three received 1 x 10^10 (Group II), and two received 3.3 x 10^9 (Group III) autologous Ad-CD154 CLL cells, of which approximately 50% expressed the CD154 transgene.

Results: The intravenous injection of transduced cells was well tolerated with no immediate toxicity experienced by any of the patients. The patients in the Pilot Group did not experience any toxicity or substantial clinical response. Two of the three patients in Group I had >50% reduction in leukemia counts occurring three days after receipt of the transduced cells. Moreover, these patients experienced clinically noticeable reductions in lymph nodes and/or spleen size. Two of the three patients had significant increases in peripheral blood T-cell counts by one week. The one patient who did not experience any toxicity or significant early response to therapy had been pre-treated heavily with fludarabine and had CD4+ T cell counts less than 35/mm^3 prior to therapy. All patients in Groups II and III had >50% reduction in leukemia cell counts occurring within days after receipt of their modified leukemia cells. These patients experienced clinically notable softening of lymph nodes and reduction in lymph node size. Four of the five patients had 2-5 fold increase in blood T-cell counts one week after treatment. No dose limiting toxicity has been observed in any patient to date. Clinical toxicity consists of fever, fatigue, malaise, and anorexia (flu-like symptoms) that are transient and resolve within three days after treatment. Minor transient laboratory abnormalities have been observed.

Conclusions: Overall, significant reductions in leukemia cell counts and lymph node size have been observed following a one-time infusion of Ad-CD154 modified autologous leukemia cells. A further and more durable response is hypothesized with repeat dosing. This forms the basis for modifying the current trial to include repeat doses. In addition, clinical trials based on this approach are being developed for patients with B cell leukaemias or multiple myeloma.