Memory stem cells

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Immunological memory lasts for a lifetime. It confers to primed individuals a certain level of immediate protection as well as the capacity to mount secondary immune responses. These aspects of immunological memory have a distinct cellular basis. Protective memory is mediated in peripheral tissues by "effector-memory" T cells and by antibodies, while reactive memory is mediated by "central-memory" T cells and memory B cells that respond to antigenic stimulation in secondary lymphoid organs. We are studying the mechanisms that control the generation of different types of memory cells and their maintenance in the absence of antigen. We found that lymphocyte activation by antigen is a progressive and stochastic process that leads to the generation of both effector cells and intermediates. The latter represent the central memory component of the immune response and have stem cell properties. In the absence of antigen central memory T and B lymphocytes continuously proliferate in response to signals delivered by cytokines, pathogens or T cells and, while self renewing, spill out terminally differentiated effector T cells and plasma cells. This mechanism is required to continuously replenish effector T cells and plasma cells that turn over or are eliminated, thus maintaining constant levels of protective memory. I will discuss the implications of the "stem cell model" of immunological memory for vaccination, immune reconstitution, autoimmunity and lymphomagenesis.

Following pathologic sub-classification, current management for HD involves staging and assessment of clinical prognostic factors. The emerging biology of LPHD is distinct from classical HD as is the treatment, including the potential for CD20-targeted therapy. Classical HD presents as early, non-bulky stage I-II in asymptomatic patients (pt) where complex staging and extended field radiotherapy (RT) has been replaced by brief chemotherapy (CT) and involved field RT. Major questions are which CT, number of cycles and whether RT can be eliminated. In intermediate bulky or symptomatic stage I-II pt, combined CT and RT is indicated but the optimal CT. Its duration and use of functional imaging to address these issues and the use and details of RT are important questions. In advanced HD, the risk of treatment failure as predicted by the International Prognostic score should be balanced against toxicity in the choice of CT. The ability to salvage pt who fail primary treatment with transplantation may influence overall survival. Studies in progress are evaluating different CT regimens, duration of CT and the role of consolidative RT for bulky or residual disease. In a recent study, RT did not influence the cure rate of advanced pt who achieved a complete response with CT. The risk of secondary leukemia after CT has been linked to genetic polymorphisms of enzymes involved in metabolic activation or detoxification of CT drugs. Similarly, genetic differences in radiation repair appear to predispose to adverse late effects of RT. The goal of HD therapy is the least complicated cure. In future, it should be possible to personalize HD care through increased understanding of individual tumor biology and individual predisposition to toxicity.

THE USE OF MONOCLONAL ANTIBODIES IN NHL


Following the original development of monoclonal antibodies by Kohler and Milstein, their potential as anti-cancer therapy has been explored, especially in lymphoma. The attraction lies in their specificity, leading to killing of malignant cells with relative sparing of normal tissue. Attention has focused on the chimeric (human-mouse) anti-CD20 antibody, Rituximab, which has shown activity in patients with follicular, mantle cell, and large B-cell lymphomas. Anti-CD20 has been successfully combined with conventional chemotherapy, particularly in the setting of germinal centre lymphomas. Anti-CD20 antibodies have also been chelated with 131Iodine and 90Ytrium with, in general, higher overall response rates and complete response rates than those seen with unlabelled antibodies. However, to date, these have not translated into longer event-free survival. Anti-CD20 is currently also undergoing evaluation in combination with anti-CD22.

Further interest has arisen from the observation that treatment with anti-CD20 can result in ‘molecular remission’ in a proportion of patients with follicular lymphoma. This is currently being investigated in a European study of high-dose treatment (HDT) in which patients with follicular lymphoma (at first or second recurrence) are randomised to receive chemotherapy +/- anti-CD20 prior to HDT. A second randomisation addresses the question of ‘maintenance’ anti-CD20 thereafter.

This presentation will review the published data and discuss ongoing trials in these areas.

DIFFUSE LARGE CELL LYMPHOMAS

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For the last decade, CHOP has been the best available standard of care based on equivalent therapeutic results with other multi-agent chemotherapy accompanied by lower costs and lesser toxicity. Furthermore, the International Prognostic Factor Index has permitted identification of subsets of patients with large variations in prognosis and thus prognosis specific therapy can now be tested.

Several treatment strategies have been commonly employed. A Phase III trial of CHOP + Rituxan by the GELA group has reported improved CR, DFS, and OS for the Rituxan treated patients. A similar large intergroup study from the United States should be presented in the near future. No randomized trials of CHOP + Rituxan have yet been presented in younger patients. Trials aimed at overcoming the multidrug resistance phenotype such as CVAD or EPOCH have been interpreted as having Jacobson, Elias Anaisie, Maurizio Zangari, Ashraf Badros, Athanasios Fassas, Firas Muwalled, Michelle Fox, John Crowley, Guido Tricot. University of Arkansas for Medical Sciences, Little Rock, AR.

To improve the results of TT I (CR 40%; 8 yr EFS 30%; 8 yr OS 50%), TT II (phase III trial + thalidomide), employed more intensive induction and introduced 1 yr consolidation chemotherapy after tandem autotransplants. Clinical outcome of the first 231 TT II patients, regardless of THAL (still blinded), was compared to results of all 231 TT I patients, whose characteristics were identical. Despite greater dose intensity, cumulative TRM with TT II versus TT I was lower at 4% versus 8% in patients <65 yr (p<0.05) and 9% versus 4% in those ≥ 65 yr (p<0.05). CR + n-CR with TT II versus TT I was higher at 67% versus 48% in younger patients (p<0.05) and 54% versus 42% in older patients (p<0.05). TT II was especially superior in good risk patients without del 13 and with normal LDH: 2 yr EFS 85% versus 70%, p=0.01; 2 yr OS 93% versus 80%, p=0.005. DVT occurred in 35% with THAL versus 10% without (p<0.001). Although several new agents (IMID, PS 341) appear promising in trials of advanced MM, dose intensity-based therapy has a proven track record of considerably improving CR rates and extending disease control up to 10 years in one-third of patients lacking CA 13. The potential contribution of THAL to the positive results of TT II will be examined upon completion of accrual of 660 patients.

Pursuit of dose intensity in multiple myeloma treatment: Total Therapy II versus Total Therapy I.

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8. The Increasing Role of Prognostic Factors in the Choice of Treatment

Diffuse large B-cell lymphoma (DLBCL), the most common lymphoid malignancy in adults, is currently curable in only 40% of patients. Clinical prognostic factor models such as the International Prognostic Index identify patients who are unlikely to be cured with standard therapy. However, these clinical models do not provide additional insights regarding more effective treatment strategies. In the absence of molecular insights into the observed heterogeneity of DLBCL, therapeutic approaches to "high-risk" patients have largely focused on modifying doses and schedules of conventional chemotherapeutic agents and adding stem cell support. However, these approaches have not significantly improved DLBCL patient survival, underscored the need to identify more rational, molecularly defined approaches to treatment. The clinical features used to identify "high-risk" DLBCL are likely to be surrogate variables for intrinsic molecular heterogeneity in the disease. The recent development of DNA microarrays provides an opportunity to take a genome-wide approach to identifying molecular signatures of previously unrecognized DLBCL subsets and prognostic categories. Recent studies indicate that supervised learning classification techniques can be used to predict outcome in DLBCL and identify rational targets for intervention.

**PROGNOSTIC RELEVANCE OF GENOMIC ABERRATIONS IN DIFFUSE LARGE B-CELL LYMPHOMA - ANALYSIS WITHIN A MULTICENTRIC TREATMENT TRIAL**

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In lymphomas, there are only few data regarding the prognostic significance or specific genomic aberrations. No analyses correlating genomic aberrations with the clinical course have been performed in homogeneous cohorts of patients treated within a clinical trial. We used the molecular cytogenetic technique of comparative genomic hybridization (CGH) to perform such an analysis in diffuse large B-cell lymphomas (DLCL). Panel-fish embedded tumor samples were obtained from patients, who were treated within the trial NHL-B of the German High-Grade Non-Hodgkin's Lymphoma Study Group. In this trial, all patients received similar therapy regimens (CHOP or CHOEP administered every 14 or 21 days). Two histopathological reference centers of the trial provided tumor samples from 316 patients. Due to formalin fixation, CGH analysis was successful in only 168 cases (53%). At the time of analysis, a clinical data set was available from 124 patients. 94 of these patients had a histology of DLCL according to the WHO classification and were further analyzed for the clinical relevance of genomic aberrations. The most frequent genomic gains and losses were gains on chromosome arms 1q, 3p, 3q, 7q, 11q, 12q, 18q and 8q as well as losses on 4q, 6q and 13q (all present in more than 10% of the cases). In univariate analysis, gains on 1q were significantly associated with an inferior tumor control (TC, p<0.008). In a multivariate analysis, this effect proved to be independent from the risk factors of the International Prognostic Index (IPI, p=0.024, relative risk RR 2.6). Similarly, 18q gains were associated with an inferior TC (p=0.047, RR 2.2). 18g gains predicted also for an inferior overall survival both in univariate analysis (p=0.022) and in a multivariate model containing the risk factors of the IPI (p=0.020; RR 2.8). These data demonstrate that molecular cytogenetic studies can be performed in the context of a clinical lymphoma trial. In DLCL, genomic gains and losses are predictive of clinical outcome, independent from clinical risk factors of the IPI. Novel molecular techniques, such as microarray based genomic DNA hybridizations, may allow a much more rapid screening for genomic aberrations in the setting of clinical trials.

**THE COMBINATION OF BCL-6 PROTEIN AND CD10 EXPRESSION PREDICTS OUTCOME IN DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) INDEPENDENTLY OF IPI SCORE**

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1 BC Cancer Agency, Vancouver, Canada; 2 Institute of Human Genetics, Kiel, Germany; 3 Stanford University, California. Introduction: Better molecular biologic determinants of outcome in DLBCL are needed to guide treatment and development of new agents. We determined the impact of the presence of the Bcl-6 protein and CD10 expression on long-term outcome in DLBCL for all patients and by IPI group.

Methods: Bcl-6 protein and CD10 expression were determined by standard immunohistochemistry and the impact of positivity on survival determined for all patients and by IPI group.

Results: Specimens from 100 patients with newly diagnosed DLBCL (median age 61 year, range 15-92; male:female 52:48; stages I+II=28, II+III=12, IV=21; IPI 0-1=42, 2-3=25, 3-5+10) were tested. 42 were found to be positive for Bcl-6 protein and CD10 expression: 4 negative for Bcl-6 and positive for CD10; 47 positive for Bcl-6 and negative for CD10; and 7 were negative for both. The expression status strongly predicted survival (follow-up for living patients 2-159 mos [median 62]).

Conclusions: The combination of Bcl-6 protein and CD10 expression is a major impact on outcome and is independent of the IPI score. Both should be incorporated into molecular biologic prognostic models.
A SINGLE NUCLEOTIDE POLYMORPHISM IN THE IL-10 GENE PROMOTER IS ASSOCIATED WITH AN ADVERSE OUTCOME OF DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) PATIENTS (PTS).

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Introduction: Interleukin-10 exerts pleiotropic effects in regulating the immune response and promotes B-cell survival in various models. The adverse prognostic value of high IL-10 levels at diagnosis has been well documented in Hodgkin and non-Hodgkin's lymphoma and CLL pts. A single nucleotide polymorphism (G/A) located at the position -1082 in the promoter region of IL-10 gene has been associated with differences in cytokine production in vitro and with several pathological situations where IL-10 may play a pathophysiological role (asthma, EBV infection, graft versus host disease). We already demonstrated that the -1082G allele was more frequently found in lymphoma patients (Lech-Maranda, ASH 2001) suggesting that inherited control in IL-10 gene regulation may predispose to lymphoma onset. Here we show that this polymorphism also markedly affects the outcome of DLBCL patients.

Patients and Methods: The -1082 polymorphism of IL-10 gene was analyzed using allele specific PCR and independently confirmed using fluorescent PCR genotyping in a cohort of 211 DLBCL pts.

Results: Observed allele G frequency was 0.48 in the cohort and was equally distributed (Chi2 test) according to usual clinical and biological prognostic parameters with the exception of age and hemoglobin level. In 199 pts treated with an anthracyclin containing regime, a complete response was more frequently observed in pts carrying -1082G allele (RR=1.85; CI 95% 1.03-3.33). Moreover, progression free, relapse free and overall survivals in pts carrying this allele were significantly improved (Log-Rank p=0.05; =0.01; =0.003; respectively). A Cox multivariate analysis confirmed the independent prognostic value of IL-10 G allele for DLBCL pts overall survival (RR=1.95; 95% CI 1.16-3.26).

Conclusions: These results demonstrate the major contribution of genetic background controlling IL-10 gene expression in diffuse large cell lymphoma patients outcome, further emphasizing the IL-10 pathway as a molecular target for future therapeutic interventions.

THE INCREASING ROLE OF PROGNOSTIC FACTORS IN THE CHOICE OF TREATMENT -- MANTLE CELL LYMPHOMA

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Despite an indolent (centrocytic) morphology, mantle cell lymphoma (MCL) is characterized by an aggressive clinical course with a median survival of less than 3 years and virtually no long term survivors. Histological diagnosis may be ambiguous and is frequently based on the additional (immunohistochemical) detection of the characteristic cyclin D1 overexpression. Because of the extremely poor prognosis, more aggressive therapeutic approaches like myeloablative high dose therapy with subsequent autologous stem cell transplantation or allogeneic transplantation with dose-reduced conditioning regimens are frequently applied and an early identification of high risk patients is therefore essential.

In the majority of retrospective studies, parameters of the international prognostic index (originally established in diffuse large cell lymphoma) have some prognostic impact in mantle cell lymphoma. Although a rough risk profile may be estimated to some extent, in most series only age, performance status, and leukemic generalization or spleen involvement remain as independent prognostic determinants in multivariate analysis. Cases with diffuse growth pattern and blastoid variant may also have a slightly worse outcome of disease. However, in almost all series published, these factors were inferior to cell proliferation markers (either Ki67 immunostaining or number of mitoses per high power field).

In the largest series so far presented almost all of these patients died within two years of follow-up. Interestingly, despite the characteristic overexpression of cyclin D1 in virtually all MCL, alterations of other cell cycle regulators (p16INK4a, p53) seem to additionally deteriorate the clinical course of disease and are frequently associated with a secondary transformation to aggressive histology.

The recently established European MCL Research Network aims at the prospective evaluation of these and additional molecular alterations to identify the critical genetic markers of lymphoma progression in MCL. Future concepts will be based on the individualized selection of therapeutic options according to the risk profile of the lymphoma patient.
9. Is There a Role for Allo-transplant in Any Type of Malignant Lymphomas?

Is there any Role for Allogeneic Stem Cell Transplantation in Malignant Lymphoma?
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In contrast to other indications the number of allogeneic transplants in lymphoma is low. This was at least partly due to the high transplant-related mortality seen in patients with advanced disease treated many years ago. Attempts to perform allogeneic transplantation earlier in the course of disease have been even more limited because patients with indolent lymphoma or CLL may run a relatively benign course and it was feared to shorten life-expectancy of these patients. In recent years, however, it has become clear that patients with mantle cell lymphoma as well as subgroups of patients with CLL or aggressive and indolent lymphoma do not well with conventional chemo- and/or radiotherapy; autologous transplantation may postpone relapse in some cases and OS be improved; cure of the disease is generally not achieved. Therefore, the interest in allogeneic transplantation has increased recently and more results in patients with early disease become available. In particular, interest has focussed on the graft vs. lymphoma effect which should help to eradicate the malignant disease. Preliminary data on non-myeloablative transplantation for patients with CLL and low grade NHL look promissing because the traditionally high transplant-related mortality could be reduced and GvL-effects were indeed observed. Further refinement of the technique will hopefully help to improve the results of allo-transplantation in lymphoma. Only long-term follow up of patients treated with allogeneic transplantation after non-myeloablative conditioning will tell if the results are truly better with this new modality than after classical conditioning.

ALLOTRANSPLANTATION IN LYMPHOMA: LIMITED BENEFITS FOR A LIMITED POPULATION AND CONTINUING CHALLENGE FOR THE FUTURE.

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Allogeneic transplantation has not made a major impact on the median survival of patients with malignant lymphoma. The reasons for this are many.
First, the median age of onset for non-Hodgkin's lymphoma especially continues to rise due to the aging population.
Second, toxicity-related morbidity and mortality is limiting in these older age groups.
Third, the relative impact of allogeneic transplantation cannot be appreciated from the literature since most series have intrinsic selection bias, often with short follow-up, and rarely with quality of life assessments.
Fourth, there are limitations in the availability of histocompatible donors, especially in minority populations.
When compared to autologous transplantation, the treatment-associated mortality is considerably higher, but the durability of remission for these patients who survive the toxicity is reportedly better than that achieved by autologous transplantation.
Extensive prior therapy, clinical drug resistance and relatively poor performance status leads to poorer results with transplantation.
The earlier applications of allografts might yield better results, however, the treatment-related mortality and morbidity continues to emerge as a limitation in offering allograft to suitable patients.
The introduction of new biological treatments in the armamentarium against lymphoma continually places the more toxic option further back in the line of salvage treatments, especially if these new treatments are non-toxic.
The scientific challenge to separate graft vs. host from graft vs. tumor if possible will expand the possibilities for mini allografts. The potential, however, is enormous with current therapy to reduce the tumor burden considerably to a point where allografts could effectively eliminate microscopic residual disease.
10. Epidemiology, Imaging

CHANGES IN INCIDENCE BY HISTOLOGIC SUBTYPES IN THE USA IN THE LAST 20 YEARS.
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Clinical investigations have shown prognostic heterogeneity within the non-Hodgkin’s lymphoma (NHL) according to histology, but few descriptive studies have considered NHLs by subgroup. Our earlier analysis assessed the demographic patterns and trends in population-based rates of different histologic subgroups of NHL. Using data collected by the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute, we calculated incidence rates for the major clinicopathologic categories of NHL, by age, race, sex, geographic area, and time period. Among the more than 60 000 NHL cases diagnosed during the period from 1978 through 1992, total incidence (per 100 000 person-years, age-adjusted world standard) was 14.2 and 9.3 among white males and females, respectively, and 11.2 and 6.2 among black males and females, respectively. However, rates for follicular NHLs were two to three times greater among whites than among blacks, with little sex variation. Blacks demonstrated much higher incidence than whites for peripheral T-cell NHL, with the incidence rates higher in males than in females. For other NHL subgroups, the incidence rates for persons less than 60 years of age were generally higher among males than among females, with little racial difference; at older ages, the rates were higher among whites than among blacks, with little sex difference. High-grade NHL was the most rapidly rising subtype, particularly among males. Follicular NHL increased more rapidly in black males than in the other race/sex groups. Overall, the broad categories of small lymphocytic, follicular, diffuse, high-grade, and peripheral T-cell NHL emerged as distinct entities with specific age, sex, racial, temporal, and geographic variations in rates. Findings from our larger population-based study revealed differing demographic patterns and incidence trends according to histologic group. We will update the incidence data to include several additional years of cases and present the incidence patterns according to the broad categories suggested by our previous analysis. Future descriptive and analytic investigations should evaluate NHL risks according to subtype, as defined by histology and new classification criteria.

INCIDENCE TRENDS FOR NON-HODGKIN’S LYMPHOMAS (NHL) IN WESTERN DENMARK OVER THE LAST TWO DECADES.
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on behalf of the Danish Lymphoma Group, LYFO

Introduction: An increasing incidence of NHL in western countries has been reported through the last 10 years and does not seem to be solely attributable to AIDS-related cases or improved diagnostic practices. The reported increment seems mostly due to a rise in the number of cases diagnosed in older age groups and displaying germinal center-derived histology.

Aim of the study: To investigate the incidence trends of NHL in western Denmark on the basis of a Danish population-based lymphoma registry.

Methods: The present analysis relies on data from the population-based Danish LYFO registry, where almost all new cases of NHL diagnosed in western Denmark (2.8 mio inhabitants) have been registered since 1983, and on the data from the Danish National Institutes of Statistics for reference demographics. This study covers the period 1982-1999.

Results: In the study period, a total of 5143 patients (2756 men and 2387 women; M:F ratio 1:2) were registered. The median age was 66 yrs (range 15-98 yrs); 4000 patients (80%) were aged <50 yrs and 1053 (20%) were aged >=50. The total number of cases diagnosed in 1983 was 199 and in 1999 was 197 and 341, respectively (Y hatch 1983-1999: P<0.05). The combined number of cases and deaths during the 16 year period was 3017 cases (2756 men and 2387 women; M:F ratio 1:2). The total median age at death was 66 yrs (range 15-98 yrs). The distribution of NHL subtypes did not change significantly during the study period. Regressions analysis showed an overall yearly incidence rise of 2.5% corresponding to an incidence rate (IR) in 1983 of 10.6/100,000 persons and in 1999 of 15.6/100,000. No significant differences in geographic distribution were observed within the region. The most marked increase was seen for diffuse large B-cell lymphomas (DLBCL) with a yearly incidence increase of 6.1% (7.7% per year for patients under 50 and 5.3% per year for those aged >=50 yrs). Follicular lymphomas (FL) showed a yearly incidence increase of 2.5% occurring almost entirely within the older age group (>=50 yrs). No incidence changes were observed for T-cell lymphomas or for cases of extranodal origin (taken either as one group or according to specific anatomic sites).

Conclusions: DLBCL and, to a lesser extent, FL are the NHL subtypes contributing to the incidence increase observed in western Denmark. In contrast to FL, the increment seen in DLBCL was also evident in the younger (<50yrs) age groups.

MEDICAL HISTORY RISK-FACTORS FOR NON-HODGKIN’S Lymphoma (NHL) BY MAJOR SITE
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Introduction: Molecular and genetic evidence indicate that the etiology of NHL is likely to differ by histologic subtype. However, there is little epidemiologic data for risk of NHL by subtype. We investigated the association between self-reported personal medical history factors and risk for working formulation NHL subtypes.

Methods: We conducted a population-based case-control study between 1988 and 1995 in the San Francisco Bay Area. In-person interviews were completed for nearly 1600 patients and >2500 controls who were between 21 and 75 years of age. These analyses included the HIV negative participants (1304 patients and 2402 controls) and, to reflect more recent classifications, follicular subtypes were combined, as were diffuse large-cell and immunoblastic. Medical history topics included allergies, diseases, vaccinations and medicucation use. Pairwise polytomous multivariable models that focused on a specific subtype were fit based on results from the initial age and sex-adjusted analyses. Results: Of the NHL patients, 12% had small lymphocytic, 27% follicular, 5% diffuse small, 6% diffuse mixed, 40% diffuse large, 1% lymphoblastic, 3% Burkitt-like, 4% mycosis fungoides and 5% not otherwise-specified lymphomas. Few factors were associated with >1 subtype and none with >=3 although this may have been a reflection of small numbers associated with less common subtypes. Increased risks for subtypes included increased body mass index; BCG vaccination; use of cimetidine and another histamine H2-antagonist; sulfonamide use; beta-blocker use; history of heart disease; and childhood eczema. Decreased risks for subtypes included vaccines for hepatitis, diptheria-pertussis-tetanus, and measles; use of nonsteroidal anti-inflammatory drugs; calcium channel blockers; history of mononucleosis; fever blisters; plant allergens; and bee and wasp stings. Conclusions: These results provide preliminary but thought-provoking data to consider in our efforts to determine potential pathways of lymphomagenesis that may be distinct by subtype. Immune surveillance is implicated in these results.

GENETIC PREDISPOSITION TO LYMPHOMA DEFINED USING A POPULATION-BASED EPIDEMIOLOGICAL STUDY
Molecular Epidemiology Programme, University Research Fund Centre, University of Leeds, University of Hertfordshire, University of California, USA.

Understanding the genetic predisposition to lymphoma demands an analysis of the interaction between environmental exposure and the genetic makeup of the exposed individual. Important hypotheses to test in this regard include the effects of organochlorines, solvents and organophosphates which are metabolised by xenobiotic metabolism enzymes systems. The second is the relation of infectious exposure and genetic variation within the immune system governing the T/Th2 responses. The third addresses the relationship of the capacity of the cell to repair DNA double strand breaks occurring as a consequence of antigen receptor rearrangement, somatic hypermutation and class switch recombination and their interaction with environmental stresses.

We have addressed these issues in a large population based study carried out in Northern and Southern England. This study was designed to capture incident cases of Follicular lymphoma, diffuse large B cell lymphoma, Hodgkin disease. Over 300 cases in each of these groups have been recruited as have age sex matched controls, from the same GP practice. The study has been closed for these larger groups but continues to recruit the less frequent groups of mantle cell, marginal zone lymphoma and peripheral T cell lymphoma. For all of the cases somatic and tumour DNA together with serum and tumour sections are stored and have formed the basis for molecular analyser. All of the cases and controls have had an extensive face to face interview assessing exposure and in addition GP note extinction has been performed on the same groups looking at infectious exposures.

We will present the preliminary results of this study together with a comprehensive IL10 polymorphism analysis. Data relating to an extensive array of xenobiotic and DNA repair genes relevant to lymphoma risk will be presented as derived from DNA pooling experiments. We will also present data showing a protective effect against developing lymphoma for 2 novel amino terminal polymorphisms within the Ig IV gene.
HEPATITIS C VIRUS (HCV) AND LYMPHOPROLIFERATIVE DISORDERS: A MULTICENTRE CASE-CONTROL STUDY

From GIMEMA Cooperative Group and Istituto Superiore di Sanita, Italy

Hepatitis C virus (HCV) has been found associated with mixed cryoglobulinemia and with B cell non Hodgkin lymphoma (B-NHL). The studies reporting an association between HCV and B-NHL are not univocal and have several limitations such us the use of prevalent cases and use of inappropriate control groups. The present study is a multicentric case-control study conducted from January 1998 until February 2001.

Methods: All cases were new diagnosis of not pre-treated Lymphoproliferative disorders and the controls were enrolled during the study period from department of traumatology, orthopedic, ophthalmology, surgery, gynecology, otolaryngology, medicine, dermatology and dentistry in the same hospitals where cases were identified. Anti-HCV antibodies were detected by 3rd generation ELISA and RIBA tests. A commercial PCR test was used for detection of serum HCV-RNA and genotyping was performed by Inno-LIPA. Adjusted odds ratios and their 95% confidence intervals were computed using multiple logistic regression model.

Results: The anti-HCV prevalences and adjusted odds ratios are presented in the table 1.

When genotype distribution was analysed in NHL and controls, 1b and 2a/1c were present in the 42% and 45% respectively of NHL, and in 50% and 44% of control group.

Table 1. Prevalence of HCV infection and Adjusted O.R. in T-cell NHL, B-cell NHL and HD patients

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of patients</th>
<th>Anti-HCV antibodies(%)</th>
<th>O.R.</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>402</td>
<td>22(5.5)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>HD</td>
<td>156</td>
<td>5(3.2)</td>
<td>1.1</td>
<td>0.4-3.2</td>
</tr>
<tr>
<td>NHL</td>
<td>395</td>
<td>68(17.2)</td>
<td>3.1</td>
<td>1.8-5.4</td>
</tr>
<tr>
<td>B-cell</td>
<td>28</td>
<td>4(14.3)</td>
<td>2.0</td>
<td>0.6-7.1</td>
</tr>
</tbody>
</table>

**adj for area of residence, age and sex.

**95% Confidence Interval

Comment: Our study, conducted in different geographical areas of Italy using incident cases, confirms an association between anti-HCV and NHL. No role of specific HCV genotype was found.

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PROGNOSTIC VALUE OF INTERIM AND POST-TREATMENT FDG-PET SCANNING IN HODGKIN LYMPHOMA

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Introduction: We have previously reported on the role of FDG PET in predicting treatment outcome following therapy for aggressive NHL. [1] We have shown that FDG-PET is an accurate method of assessing remission and estimating prognosis following treatment and is more accurate than CT in this respect. An interim PET after 2-3 cycles of chemotherapy predicted the long-term outcome early on and had a high negative predictive value (NPV) (100%). This study assesses the prognostic value of interim and post treatment PET in Hodgkin lymphoma (HL).

Patients & Methods: 65 adult patients with biopsy proven HL underwent a whole body FDG-PET scan as part of the initial staging procedure and after completion of the planned course of treatment. 33 of these patients also had an early "interim" scan (after 2-3 cycles of chemotherapy). Results of PET were correlated with remission and Progression-Free survival (PFS).

Results: In 57/65 (88%) patients the PET returned to normal after treatment. 5/57 (9.3%) remained in continued complete remission with a minimum follow-up of 14 months and a median of 36. 4(7%) relapsed with a median PFS of 15 months. 8 patients had persistent abnormal uptake on post-treatment PET, all of whom (100%) demonstrated persistent relapsed disease with a median PFS of 3 months. A subgroup (32 patients) underwent a post-treatment CT as well as a PET. Comparison of the CT & PET in this subgroup revealed a PPV of 80% and 90% and a positive predictive value (PPV) of 12% and 75% for the CT & PET respectively. In the 32 patients who had early interim scans; relapse rate was 100% (6/6) for partial remission and 8% (2/26) for complete remission. An updated analysis with PFS curves will be presented at the meeting.

Conclusions: These results suggest that FDG-PET has a prognostic value in HL similar to that which we reported for aggressive NHL. Persistent abnormal uptake of FDG on PET after completion of treatment is associated with a high risk of persistent disease or early relapse. PET has higher PPV & NPV than CT. An interim PET after 2-3 cycles of chemotherapy predicts the long-term outcome early during treatment.

Molecular Pathogenesis of Malignant Lymphomas: What's New?

ADVANCED IN THE MOLECULAR BIOLOGY OF HODGKIN AND REED-STERNBERG CELLS IN HODGKIN'S LYMPHOMA

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Hodgkin and Reed/Sternberg (HRS) cells represent the malignant cells in classical Hodgkin's lymphoma (HL). Since their immunophenotype cannot be attributed to any normal cell of the hematopoietic lineage, the derivation of HRS cells has been controversially discussed, but molecular studies established their derivation from germinal center B cells. Gene expression profiles generated by SAGE and DNA chip microarrays from HRS cell lines were compared with those of normal B cell subsets, focusing here on the expression of B lineage markers. This analysis revealed decreased mRNA levels for nearly all established B lineage-specific genes. In particular, multiple components of signaling pathways active in B cells, including B cell receptor (BCR) signaling, were severely affected. We propose that the B lineage identity in HRS cells may explain their survival without BCR expression and reflect a previously unrecognized fundamental defect in maintaining the B cell differentiation state in HRS cells, which is likely caused by a novel, yet unknown, pathogenic mechanism. The genes specifically upregulated in HRS cells are currently under investigation.

Molecular single cell analysis of HRS cells from the recently defined lymphocyte-rich classical subtype of HL revealed clonal HRS cell expansions carrying mutated Ig gene rearrangements without significant intrasomatic diversity in all five cases analyzed and indicated stringent selection for functionality. Thus, HRS cells in lymphocyte-rich classical HL show differences to HRS cells of classical and lymphocyte predominant HL.

Abstract: ALCCL: An update

Harel Sinet

Viewed a number of years after their first description, anaplastic large cell lymphoma (ALCL- lymphoma, ALCCL) now represents a generally accepted group of large cell lymphomas. Essential defining features comprise of a proliferation of large lymphoid cells with a strong expression of the cytotoxic receptor CD30, and a characteristic growth pattern. Three entities of ALCL-lymphomas were identified using molecular and clinical criteria: primary systemic anaplastic lymphoma kinase (ALK)-positive ALCCL-lymphoma, primary systemic ALK-negative ALCCL-lymphoma and primary cutaneous ALCCL-lymphoma. The ALK expression in the primary systemic ALCCL-lymphoma entity is caused by chromosomal translocations, most commonly t(2;5), and can nowadays be reliably detected by immunohistochemistry. ALCCL-lymphoma predominantly affects young male patients and if treated with chemotherapy has a favourable prognosis. They show a broad morphological spectrum, with the "common type", the small cell variant and the lymphoepithelioid variant being the most commonly observed. Knowledge of the existence of these variants is essential in establishing the correct diagnosis. ALCCL-lymphoma occurs in older patients, equally affecting both genders and has an unfavorable prognosis. The morphology and the immunophenotype of primary cutaneous ALCCL-lymphoma shows an overlap with that of lymphomatoid papulosis. Both diseases have an excellent prognosis and secondary systemic dissemination is only rarely observed.

The ALCCL-lymphomas described above derive from T cells and are generally accepted as biological entities. In contrast, large B-cell lymphomas with anaplastic morphology are now believed not to represent an own entity, but a morphological variant of diffuse large B-cell lymphoma. Malignant lymphomas with morphological features of both Hodgkin- and ALCCL-lymphomas were formerly classified as ALCCL. Hodgkin's-like. Recent immunohistochemical analyses using new marker molecules suggest, however, that ALCCL-Hodgkin's-like does not represent an own lymphoma entity. Most of these cases are likely to be examples of tumour cell rich classical Hodgkin lymphoma, while a minority of these cases appear to fall into either the category of ALCCL-positive or ALCCL-negative ALCCL-lymphomas.

MOLECULAR PATHOGENESIS OF MALT LYMPHOMAS: WHAT'S NEW?

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Low-grade MALT lymphomas are unusual in that they are characterized by two distinct cytogenetic alterations that are not found in nodal or splenic marginal zone lymphomas, but have been reported in several different mucosal sites. The most frequent is the t(11;18) found in 30-35% of cases. This results in a variable-sized fusion of 2 novel genes, API2 on chromosome 11 and MALT1 on chromosome 18. API2 is an inhibitor of apoptosis and MALT1 is a paracaspase. The t(11;18) has been found in mucosa diffuse large B-cell lymphomas (DLBCL). The other cytogenetic abnormality in MALT lymphomas is the t(1;14) found in only 1-2% of cases. This translocation brings bc-10 under control of enhancer elements of the Igk locus resulting in over-expression of bc-10. Although mutations were initially thought to be important in pathogenesis, these have only been found infrequently. Thus, over-expression of wild-type (wt) Bcl-10 appears to be more important. A search for normal binding partners of Bcl-10 revealed MALT1, one of the genes involved in the t(11;18). Bcl-10 transgenic animals develop profound splenic marginal zone hyperplasia and bcl-10 knockout mice have normal apoptotic signaling, but show defective NF-kB activity following engagement of the antigen receptor complex. Thus, these 2 very disparate translocations are involved in the same signaling pathway. These data suggest that a MALT lymphoma may develop following a t(11;14) resulting in up-regulation of wt Bcl-10, which activates I kappa B kinase (IKK) and results in transcription of NF-κB into the nucleus where it induces transcriptional up-regulation of a number of wild-type genes. Alternatively, a t(11;18) produces an API2-MALT1 fusion, which bypasses normal Bcl-10 to activate IKK directly and similarly results in increased nuclear translocation of NF-κB. Both translocations result in the nuclear expression of Bcl-10 protein, a finding that correlates with resistance to antibiotic therapy.

Recent data suggest 2 possible pathways of MALT lymphoma development based on differences in chromosomal instability. The t(11;18) pathway is cytogenetically and histologically stable. The other pathway involves gains at chromosome 3q26-27 or more rarely at t(1;14) and results in a MALT lymphoma at risk for transformation to DLBCL. The latter type shares clonal cytogenetic alterations with de novo DLBCL at mucosal or epithelial sites.

MEDULLARY SCLEROSING LARGE B-CELL LYMPHOMA

An overview based on the results of a pathologic trial supported by the International Extranodal Lymphoma Study Group (IELSG).

Stefano A. Pilotti1, Gianluca Gallo1, Pier Luigi Zinzani1, Brunangelo Falini1, Philippe Gaulard2, Emanuele Zucca3, Federica Pieri1, Claudia Vaili4, Eva Berra5, Elena Salvadoni1, Stefano Ascari2, Milena Piccioli1, Peter Johnson6, Roberto Giardini1, Edoardo Pescarmona1, Domenico Novero7, Piero Paolo Piccilia7, Teresa Marafioti1, Miguel A. Alcalde8, Franco Cavalli9. On the IELSG behalf.

1Università di Bologna, Italy, 2Università dei Piemonte Orientale "Amedeo Avogadro", Novara, Italy, 3Università di Perugia, Italy, 4Hospital Henri Mondor, Creteil, France, 5Istituto Oncologico della Svizzera Italiana, Bellinzona, Switzerland, 6Southampton University, United Kingdom, 7Istituto Nazionale dei Tumori, Milan, Italy, 8Università di Roma "La Sapienza", Italy, 9Università di Torino, Italy, 10Università Autonoma de Madrid, Spain.

Background. PMBL has been the object of numerous reports, which have provided conflicting results in terms of phenotype, molecular characteristics, and histogenetic interpretation. During an IELSG study carried out from 1997 to 2000, 137 PMBLs were collected for exhaustive pathologic, phenotypic and molecular evaluation. Results. At light microscopy, they mostly consisted of large cells with a predominantly diffuse growth pattern, varying degrees of nuclear polymorphism and to basophilic cytoplasm. The lymphomatous growth evoked a focous reaction with frequent compartmentalization. On immunohistochemistry, tumour cells showed the following phenotype: CD45+, CD20+, CD79a+, PAX5/BAEP+, BOB1+, OCT-2+, BCL2+, BCL6+, HLA-DR+, MAL protein+, BOB1+, MUM1/IRF4+, CD10+, CD21+, CD15+, CD138+, CD68, and CD23. The search for immunoglobulins (Ig) as well as for the corresponding mRNA provided negative results. At molecular analysis, carried out in 45 cases, some novel findings were observed, which expand the spectrum of our knowledge on PMBL. In fact, more than half of the tumors displayed BCL-6 gene mutations, which usually occurred along with functioning somatic IgVH gene mutations and Bcl-6 and/or MUM1/IRF4 expression. Conclusions. The present study suggests that the concept of PMBL is mostly derived from activated germinal center or post-germinal center cells. However, the tumor differs from other aggressive B-cell lymphomas in that it shows defective Ig production in spite of an intact transcription machinery and lack of IgVH gene rearrangement.

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Novel mechanisms in the pathogenesis of diffuse large cell lymphoma and their clinical implications

Riccardo Dalla-Favera, Institute for Cancer Genetics, Columbia University

B cell derived diffuse large cell lymphomas (DLCL) derive from the germinal center (GC), the structure where naive B cells encounter the antigen, undergo immunoglobulin (Ig) V region somatic hypermutation (SH) and class switch recombination (CSR), and are selected to become memory B cells or plasma cells. SH and CSR mechanisms are involved in the generation of specific chromosomal translocations, which contribute to the pathogenesis of DLCL by deregulating the expression of oncogenes like BCL2 and BCL6. New findings indicate that: i) the somatic hypermutation mechanism is aberrantly activated in >50% of DLCL leading to the mutation of multiple proto-oncogenes and, possibly, to the generation of chromosomal translocations; ii) the BCL6 proto-oncogene, which is normally downregulated by CD40 signaling, becomes constitutively expressed in the majority of DLCL cases; iii) the function of BCL6 is controlled by three distinct pathways that can be modulated for therapeutic purposes.
ONCOGENE Deregulation in B-Cell Lymphomas

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Malignant transformation of B cells can occur at various stages of lymphocyte development, from early B-cell progenitors to mature B cells, reflecting the heterogeneity of B-cell neoplasms with regard to their biologic and clinical behavior. The genetic characterization of B-cell neoplasms performed over the past two decades has now elucidated the mechanisms underlying most B-cell lymphomagenesis and led to a more precise definition of lymphoma subgroups for both the Hodgkin and non-Hodgkin lymphomas. Many of these molecular abnormalities are being incorporated into classification systems, such as the World Health Organization classification for hematologic malignancies, reflecting their importance in the diagnosis of these neoplasms. This presentation will seek especially to update information regarding several of the more recently identified genes that are deregulated in the Hodgkin or non-Hodgkin lymphomas including various 1q21-q22 loci such as BCL9, MUC1, FCgammarIIB and the IRTA genes, as well as the API2-MLT/MALT1 and BCL10 genes, among others. In addition, recent findings using microarray technology to assess global gene deregulation in B-cell oncogenesis and the use of this methodology for further defining distinct lymphoma subtypes will be addressed.
13. Clinical Results in Lymphoma

FOUR WEEKS OF VAPEC-B CHEMOTHERAPY BEFORE INVOLVED FIELD RADIOTHERAPY MINIMIZES THE RELAPSE RATE IN EARLY STAGE, LOW RISK HODGKIN'S DISEASE AND IS NOT ASSOCIATED WITH AN EXCESS OF SECOND MALIGNANCY. IA Radford, RA Cowan, WDJ Ryder, RJ Johnson, SS Banerjee, DP Deakin, PM Wilkinson, RD James and D Crowthor for the Manchester Lymphoma Group, Christie Hospital, Manchester, UK.

Between August 1989 and February 1997, a total of 125 patients with clinical stage I/IIA Hodgkin's disease and no mediastinal bulk were randomised between radiotherapy alone and four weeks of VAPEC-B chemotherapy (doxorubicin 35mg/m² iv on weeks 1 and 3, cyclophosphamide 150mg/m² iv week 1, etoposide 100mg/m² po daily for five weeks week 3, vincristine 1.4mg/m² iv and bleomycin 10,000 IU/m² iv weeks 2 and 4 with prednisolone 50mg daily for four weeks and prophyllactic co-trimoxazole and ketaconazole) followed by radiotherapy. The field of radiotherapy to be employed was decided before randomisation and this and patient characteristics were well balanced between the two trial arms. For the patients receiving chemotherapy, 4 developed significant toxicity (grade III stomatitis in 2 patients, grade III neutropenic sepsis in 1 patient and exaggerated skin reaction to subsequent radiotherapy in 1 patient) but otherwise the treatment was well tolerated.

A median follow-up of 8 years (range 3.0-12.3 years) there have been 30 progressions (RT alone 23, CT + RT 7), 7 deaths from Hodgkin’s disease (RT alone 4, CT + RT 3), 9 deaths from second malignancy (RT alone 6, MDS 1, CML 1, NHL 1, carcinoma 3; CT + RT 3, AML 1, NHL 1, carcinoma 1), and 6 deaths from other causes (RT alone 2, CT + RT 4). These data translate into a highly significant difference in freedom from progression (FFP) at five years (RT alone 63%, CT + RT 93%, p<0.0005) but no significant difference in survival (RT alone 90%, CT + RT 94%, p=0.5). The effect on FFP was observed in both favourable and unfavourable patients as defined by EORTC prognostic criteria.

Four weeks of VAPEC-B chemotherapy before involved field radiation treatment in patients with clinical stage I/IIA Hodgkin’s disease is associated with a high response rate, a low incidence of toxicity, and a highly significant improvement in freedom from progression compared with RT alone. Second malignancy has occurred in both arms of the trial but no excess has been observed in patients receiving CT.
HIGH DOSE ORAL CHLORAMBUCIL +/- EPURINIC IN PATIENTS WITH INELIGIBLE NON FOLLICULAR LYMPHOMA: RESULTS OF A RANDOMIZED TRIAL


Background: Few randomized trials have been carried out on the treatment of specific subtypes of indolent non follicular lymphoma (INFL). In 1993 we started a multicenter randomized trial to assess the usefulness of Epurinic in addition to High dose oral Chlorambucil for the treatment of this lymphomas. Methods: Patients with histological diagnosis (IST) of Small Lymphocytic/ Lymphoplasmacytoid Lymphoma (SLL/CL), Immunocytoma (IC) and marginal zone lymphoma (MZL) or with an immunohistomorphological (ICM) diagnosis (on blood and/or bone marrow samples) of mature B-Cell non follicular lymphomas were eligible for the study. Patients with chronic Chronic Lymphocytic Leukemia or Mantle Cell Lymphoma were excluded. Advanced disease was required and defined by the presence of stage II (with more than three involved sites), III or IV and at least one of the following: systemic symptoms, bulky disease, ascites, thrombocytopenia, lymphocyte doubling time <12 months. The study compared 8 cycles of HDHC-P (chlorambucil 15 mg/m2/day and prednisone 100 mg/m2 p.o. for 5 days every 28 days) arm A) with 8 cycles of HDHC-P + epurinic 60 mg/m2 iv on day 1 (arm B). Response pte were randomized to 1 year of iFEN maintenance treatment or observation. The aim of the study were to evaluate: a) the efficacy in terms of complete response and time to, b) the toxicity and c) the effect on of response duration. Results: The study was closed on December 2001 with the enrolment of 170 pts: 26 pts were excluded from study due to dizagreement (15), unconfirmed aggressive disease (3) or missing data (6). Of the 144 eligible patients response was available in 119 pts (median age 62 years (37-77), M/F 68/71; arm A 66pts, arm B 73 pts; IST 98pts, (CM 41pts, leukemia presentation, 32 pts) induction therapy led to 42 CR (30.2%, 95% CI 22.6 to 37.0), 62 PR (44.6%, 95% CI 33.5 to 55.5), 32 SD-PO (22.8%, 95% CI 16.2 to 32.4) with 18 pts (12.3%) not evaluable due to the arm of treatment, RCHP+R in 4 pts (6.8%) treated with HDHC alone vs 9 pts (8.1%) treated with HDHC-EP (P=0.08). A significant higher incidence in terms of hematologic toxicity was observed among patients treated with epurinic. After induction 58 of the 103 responsive patients were randomized to iFEN (33 pts) or observation (21). No difference between these two groups was observed in terms of disease free survival (DFS), P=0.32. After a median follow up of 40 months (2-104) non inference to overall survival (P=0.26) and DFS (P=0.25) was observed between the two induction treatment arms. The outcome was not influenced by diagnostic approach (IST vs CFM) or by leukemia presentation. Conclusions: Epurinic doesn't add any advantage to high dose oral Chlorambucil in the outcome of patients with INFL. Furthermore 1 year of iFEN maintenance does not seem to prolong survival among patients responsive to induction treatment.

THE LONG TERM IMPACT OF A WATCH AND WAIT POLICY VS IMMEDIATE SYSTEMIC TREATMENT FOR ASYMPTOMATIC ADVANCED STAGE IDOLENT NON HODGKIN LYMOPHMA: RESULTS OF A BRITISH NATIONAL LYMPHOMA RANDOMIZED TRIAL. K. M. Andrews, P. North, A. Nonnan, R. Boardman, P. Jackims, S. A. Mackness, R. E. Marcus, DC Linch on behalf of the BNIJL. The CRC and UCL Cancer Trials Centre, London UK.

The inability of either single alkylating agent chemotherapy or aggressive combination chemotherapy to cure low grade non-Hodgkin's lymphomas (LGLNHL), even if combined with radiotherapy, has questioned the necessity of any treatment in advanced stage disease. Initial studies comparing the outcome of patients with asymptomatic advanced LGLNHL who were either treated immediately or carefully followed without initial treatment have been limited by small patient numbers and short periods of follow up. Here we describe the outcome of 309 patients with asymptomatic, advanced (stage III and IV), LGLNHL who were recruited between 1980 and 1990. The histology was centrally reviewed, 66% had LGLNHL and 34% had diffuse lymphocytic lymphomas. Only 3 patients (1%) have been lost to follow up. 138 patients were randomised to immediate systemic therapy with chlorambucil (10mg/day continuously). The remaining 151 patients were randomised to observation with systematic therapy being delayed until disease progression. In both arms local radiotherapy to symptomatic nodes was permissible. The median follow up is 16 years. There was no significant difference in overall survival (OS) or cause specific survival (CSS) between the two arms (OS p=0.84, CSS p=0.44). Multivariate analysis showed age >60 years and stage III disease conferred a significant survival advantage (OS and CSS). In the observation arm, 26 patients have died without receiving chemotherapy, the major causes of death being solid tumours and cardiovascular disease. 19 patients were alive and had not received chemotherapy at 10 years follow up. The actuarial chance of not requiring chemotherapy (non-Lymphoma deaths censored) at 10 years was 19%. The histology has been further reviewed in 18 of these 19 and a diagnosis indolent lymphoma was confirmed in 17. In one case the material was insufficient to confirm a diagnosis. The indolent group included 2 patients (enlarged thyroid, cervical nodes and splenomegaly) the thyroid biopsy was now thought to show chronic thyroiditis.

HIGH DOSE THERAPY IMPROVES PROGRESSION FREED Survival in RELAPSED NON-HODGKIN'S LYMOPHMA: RESULTS FROM THE RANDOMIZED EUROPEAN CUP Trial

Harry C. Schouten, Wendi Qian, Matthew R. Sydes, Steve Kvaloy, Adolfo Porcellini, once from Sweden, Hans Erik Johnson, Jannet Dooroij, Gunnar Kvalheim, on behalf of the CUP trial committee. University Hospital Maastricht, Maastricht, the Netherlands.

Purpose: To determine in a randomized clinical trial whether high dose therapy followed by autologous stem cell transplantation is more effective than standard treatment with regard to progression-free survival and overall survival in patients with relapsed follicular NHL and to assess the additional value of immuno- magnetic ex vivo purging of the stem cell graft with regard to progression-free survival and overall survival.

Methods and patients: Patients received 3 cycles of chemotherapy, and responding patients with limited bone marrow infiltration were randomized to either further 3 cycles of chemotherapy (C) or unpurged high dose therapy (U) or purged high dose therapy (P) Treatment. Results: Between August 1993 to April 1997, 140 patients were registered from 36 centers internationally and 89 were randomized. Reasons for failure to randomize included patient refusal, early progression or death on induction therapy. The trial closed at this point when the sample size for the CP comparison was achieved, but slow accrual prevented the other comparisons being addressed adequately. With a median follow up of 44 months, the p-value of log-rank test for progression-free survival and overall survival is 0.01 and 0.31, respectively. For progression-free survival, the hazard ratio (95%CI) for U vs C, P versus C, P versus U is 0.36 (0.17, 0.78), 0.44 (0.21, 0.91) and 1.01 (0.50, 2.04), respectively. These are 0.59 (0.22, 1.53), 0.48 (0.18, 1.26), 0.58 (0.24, 1.43) for overall survival.

Conclusion: High dose therapy significantly improves progression-free survival.

Despite this being an old trial, the study provides definite and useful data. The study provides definite and useful data. The study provides definite and useful data.
THE OUTCOME OF FOLLICULAR LYMPHOMA GRADE 3A AND 3B-18 ANTHOCYRINE N ECESSARY AS FRONT LINE THERAPY? L. Chu, R. Jones, A. Norman, Alan Horwich, Daniel Cavoisky, A. Womerspoon, D. Cunningham

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BACKGROUND: A 3-grade system for follicular lymphomas (FL) is used in the recently introduced WHO classification for lymphoid malignancies based on the absolute number of centroblasts in the neoplastic follicles. Grade 3 FL is further subdivided into 3a and 3b for investigational purposes according to whether centrocytes are present. PATIENTS AND METHODS: 231 patients with FL, referred from 1972 to 2001, were identified from our prospectively maintained database. Original diagnostic materials were available to review on 215 patients. They were re-classified according to the current WHO grading system. Long term outcome of these patients was analyzed from the database. RESULTS: FL grade 1, 2 and 3 accounted for 92, 68 and 35 patients respectively. Among the 55 grade 3 patients (M: 29 F: 26), 44 had 3a and 11 had 3b FL. Median age was 53 (range: 18-81). Initial staging was stage I-II: 18 patients (ps) and stage III-IIV: 37 ps. Initial management was: radiotherapy (RT) alone 12 ps, chemotherapy alone 34 ps (15 patients under chemotherapy based chemotherapy, chemotherapy and RT-2 ps and “watch and wait” policy-7 ps. The overall response rate to first treatment was 78.2% (95% CI 68.8-83.5). After failure, patients were stratified into 3 groups based on their histological characteristics allowing for different salvage strategies. Results were stratified as follows: Grade 3a, 13 patients with a 2-year progression-free survival of 43% (95% CI 11-77). Grade 3b, 22 patients with a 2-year progression-free survival of 14% (95% CI 0-39). Conclusion: Grade 3 FL requires specific strategies. In the majority of cases, radiotherapy is the first-line treatment. When progression occurs, chemotherapy is recommended, but outcomes are poor in grade 3b FL.

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RADIOTHERAPY IS UNNECESSARY IN ELDERLY PATIENTS WITH LOCALIZED AGGRESSIVE NON HODGKIN’S LYMPHOMA: RESULTS OF THE LNH 91-3 STUDY

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For the GELA, CHU San Timol, Lodge, Belgium.

ChOP combined with radiotherapy is considered as the standard treatment for localized aggressive non-Hodgkin lymphoma (NHL) (Miller et al. NEJM 1998. 339 21: Tamara et al. JCO 2002, 20:197). However, few randomized prospective trials have compared chemotherapy alone to the same chemotherapy plus involved field radiotherapy (IFRT).

The LNH 91-3 study compared 4 courses of CHOP to 4 courses of CHOP followed by 40 Gy involved-field radiotherapy in patients 70-60 years with localized good prognosis aggressive NHL (0 factor in the age-adjusted IPI score). At randomization, patients were stratified on bulk (< vs > 10 cm).

From 03/93 to 06/00, 528 ps were included and 464 were eligible for analysis. Forty-five percent of patients were >70 yrs of age or older.

Clinical characteristics were well balanced between the 2 treatment groups: median age 68 yrs, stage I-IV B66%, bulky disease 10%, T-cell phenotype 8%. 56% pts had extranodal sites of disease. Complete response at the end of treatment was identical in both groups (99% and 93% respectively). Toxicity occurred in 2% of both groups. With a median follow up of 49 months, the 5 yrs event-free survival (EFS) and the 3 yrs overall survival (OS) did not differ significantly (66% for CHOP alone vs 67% for ChOP plus IFRT, p = 0.6 and 76% for CHOP above vs 67% for ChOP plus IFRT, p = 0.1).

When patients of both arms were split into subgroups according to age (60-64 yrs, 65-69 yrs, 70-74 yrs, 75 yrs and over), the CR rate was the same in the different age groups. However, for patients over 69 yrs, the OS was better in the group treated by chemo only (p = 0.02).

We conclude that in limited stages of disease, 4 cycles of standard-dose CHOP alone produce acceptable CR and survival rates in elderly patients with little life threatening toxicity. Involved field radiotherapy following chemotherapy does not increase CR rate, EFS or OS. On the contrary, in pts over 69 yrs, radiotherapy following chemo might have a negative impact on survival.

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SUPERIORITY OF THE ACVBVP REGIMEN OVER A COMBINED TREATMENT WITH THREE CYCLES OF CHOP FOLLOWED BY HIGH-DOSAGE CHIMEROIDIOPLASIA IN LOW RISK LOCALIZED AGGRESSIVE NON-HODGKIN’S LYMPHOMA: THE LHNB-3 STUDY


Combined chemotherapeutic approach is considered as the standard treatment for localized aggressive lymphomas. Because published series appear heterogeneous with regard to prognostic factors, we aimed to determine the optimal treatment of low risk localized lymphomas. From 03/93 to 06/00, 631 patients (pts) under 60y were included with aggressive lymphomas (WF histology: F,G,M or anaplastic) and an adverse Event-Free Survival Index that was randomized between a chemotherapy arm consisting in 3 cycles of ACVBVP (doxorubicin 75 mg/m2 day 1, cyclophosphamide 1.2g/m2 day 1, vindesine 2 mg/m2 days 1 and 5, bleomycin 10 mg days 1 and 5, prednisone 60 mg/m2 day 1 to 5) given every 2 weeks followed by sequential consolidation (methotrexate, ifosfamide, VP16, cytarabine) and a cycle of chemotherapy every 3 weeks for a total of 20-Cycles. Chemotherapy was defined as firstly treatment on bulk (> 10 cm). Pts were eligible for analysis. Clinical characteristics were well balanced between the 2 treatment groups: median age 47y, stage I-IV 67%, bulky disease 10%, T-cell phenotype 10%. 50% of pts had extranodal sites of disease, mainly Waldeyer ring (37%) and gastrointestinal tract (13%). Complete response at the end of treatment was identical in both groups (93%). By stratified log rank test, we found that pts treated with the ACVBVP regimen had significantly better 5-year event-free survival (EFS) (p = 0.004) than pts treated by the combined modality (83.5% vs 74.9%, respectively). With a median follow-up of 55 months, the 5y-survival significantly differed in favor of the ACVBVP arm (40% vs 29.5%, respectively, p = 0.02). Mediation of the ACVBVP regimen was independently affected by three adverse factors: bulky disease (p = 0.005), R2.3, stage I (p = 0.001, RR:1.0) and treatment arm (p = 0.01, RR:1.7). No patient died from toxicity in either arm. Only one grade 4 infection was observed with ACVBVP.


Introduction: Treatment results in aggressive NHL might be improved by shortening treatment intervals of and/or adding etoposide to CHOP. Methods: Between 1994 and 2000, 831 patients 61-75 yrs were randomized in a 2x2 factorial design to 6 x CHOP-21, CHOP-14, CHOP-21 (CHOP plus etoposide 100 mg/m2 day 1-3), or CHOP-14. Patients in the 2-weekly regimen received G-CSF starting from day 4. Patients received radiotherapy (36 GY) to sites of initial bulky disease (57 cm) and extranodal disease. The primary end-point was time to treatment failure (TTF) with events defined as disease progression or relapse, death or initiation of an alternative treatment arm. Results: This interim analysis includes 612 evaluable patients and about 75% of all expected events. Median age was 67 years, and adverse prognostic factors were well balanced between the treatment arms. Median relative dose intensity was 95% for CHOP-21, 95% for CHOP-14, 93% for CHOP-14 and 87% for CHOP-14. CR rates were 63.2% for CHOP-21 (n=152), 69.6% for CHOP-14 (n=150), 77.0% for CHOP-14 (n=153) and 73.2% for CHOP-14 (n=157), p = 0.055. For patients with elevated LDH, CR rates rose from 48.6% with CHOP-21 to 70.4% with CHOP-14. At a median time of observation of 40 months, TTF (33% vs 42.3%) and overall survival (64.3% vs 49%) are significantly better for CHOP-14 than for CHOP-21. Covariates taking into account interval shortening, addition of etoposide and an interaction term showed that these differences were significant (TTF: p=0.03, OS: p=0.04). CHOP-14 was associated with the lowest rate of leukopenia (42%, CHOP-21:59%, CHOP-14:66%, CHOP:21-83%). Fatal toxicities were similar in the CHOP regimens (3.9% and 3.3%) but markedly higher in CHOP-21 and CHOP-14 (5.3%, 7.6%). Conclusions: In patients >60 yrs with aggressive NHL, time to median relapse (CHOP-14) improves results significantly over standard CHOP-21, whereas no improvement was achieved by the addition of etoposide, in part due to its toxicity in this population. After 25 years of CHOP-21, CHOP-14 should be considered as the new reference standard for elderly patients due to its excellent efficacy/cost-effectiveness profile. Supported by Deutsche Krebshilfe.
SURVIVAL ADVANTAGE OF ACVB REGIMEN OVER STANDARD CHOP IN THE TREATMENT OF ADVANCED AGGRESSIVE NON-HODGKIN'S LYMPHOMA (NHL). THE LNH 93-5 STUDY.


Introduction: The ACVB regimen consists of an induction phase of intensified CHOP with CNS prophylaxis followed by a sequential consolidation. Previous studies suggested that ACVB could be mostly beneficial for patients with advanced disease.

Methods: Between 03/93 and 09/96 we conducted a randomized multicenter phase III study comparing the ACVB regimen (dexamethasone, cyclophosphamide, vindesine, bleomycin, prednisone and intrathecal methotrexate), four cycles given every 3 weeks followed by sequential consolidation therapy (methotrexate plus leucovorin, ifosfamide, etoposide, and Ara-C) to a standard CHOP (eight cycles at a 3-week interval) in patients with aggressive NHL aged between 61 and 69 with at least one adverse prognostic factor of the age-adjusted international Prognostic Index (AAI-PI).

Results: 706 pts were randomized and 635 were eligible. Median age was 65 yr. The number of risk factors of the aa-PI was respectively 1 in 34% of the pts, 2 in 43% and 3 in 23%. Prognostic factors were equally distributed between the treatment groups. The rate of complete response was 58% in the ACVB group and 56% in the CHOP group (p=0.5). The incidence of grade 3 and 4 leukopenia and thrombocytopenia was higher in the ACVB group (p<0.001) leading to a higher incidence of severe or life-threatening infections (p<0.001). Treatment-related deaths were more frequent in the ACVB group (p=0.014). At three yrs, EFS was 48% (95% CI, 41 to 51%) in the ACVB group and 35% (95% CI, 29 to 39%) in the CHOP group (p=0.002). In a Cox regression model, the treatment group was found to affect EFS independently of the aa-PI (p=0.005). Overall survival at three yrs was 53% (95% CI, 48% to 58%) in the ACVB group and 45% (95% CI, 40% to 49%) in the CHOP group (p=0.03).

Conclusions: ACVB is a more toxic regimen than CHOP in this population of rather elderly patients but it significantly prolongs EFS and overall survival.

FRONTLINE HIGH-DOSE CHEMOTHERAPY (HDC) WITH AUTOLOGOUS STEM CELL TRANSPLANTATION VS STANDARD CHOP REGIMEN FOR PATIENTS (≥60yr) WITH NON-HL RR INTERMEDIATE OR HIGH GRADE LYMPHOMAS (NHL). FINAL RESULTS OF A RANDOMIZED TRIAL by the GOELAMS.


Introduction: CHOP remains the standard therapy for intermediate and high-grade NHL. We performed a randomized trial of CHOP vs ASCT in pts age 15 to 60 yrs with newly diagnosed non-Hodgkin's B-cell lymphoma not responding to initial chemotherapy or high-grade NHL. Methods: pts were randomized between CHOP (C=70 mg/m2, II = 50 mg/m2) for 8 courses or high dose chemotherapy (HDC) consisting of courses of CEC (C=1.3 g/m2, etoposide =1000 mg/m2, vindesine 3 mg/m2; and PMD) every 15 sr supported with GM-CSF, followed by a course of high dose Methotrexate (5 g/m2) with cytarabine 100 mg/m2 x 5 d (CEP). Patients then received at lest 1 to 2 CEP in order to support a BEAM regimen (Etoposide 400 mg/m2 x 4; d 4; cytarabine 400 mg/m2 x 4, d 2; CEP x 4) sheduled on d 66 of 1st CEP. Results: 207 pts were included, 177 eligible pts (99 CHOP; 90 HDC) are evaluable. The median age was 67 yr, 71% had diffuse large cell histology. At dg: AA stage was II with Abdominal bulk, III and IV in 19%, 21% and 60% of pts respectively. According to age adjusted IPI, 6% of the pts were in the low, 41% in the intermediate low, 55% in the high intermediate risk category. Characteristics were matched between the two groups. The program was completed in 72% and 81% of CHOP and HDC groups respectively. In an intent to treat analysis, with a med FU of 46 mo the 5 yr probability of survival (SV), event free survival (EFS) and freedom from progression (FFP) are as follow: SV (%) EFS (%) FFP (%) CHOP 55/+6 36/+5 37/+5 ASCT 71/+5 55/+5 56/+5 p 0.076 0.037 0.018 Conclusion: HDC with frontline ASCT is superior to standard CHOP for pts < 60 yr. EFS and FFP. There is a trend for better overall survival which is significant (74% vs 63% p=0.003) for pts with intermediate high risk IPI.

PROPHYLACTIC GRANULOCYTE-COLONY STIMULATING FACTOR (G-CSF) ADDED TO CHOP IN THE TREATMENT OF ELDERLY PATIENTS WITH AGGRESSIVE NON-HODGKIN'S LYMPHOMA (NHL). FINAL RESULTS OF A MULTICENTRE PHASE 3 STUDY.


Introduction: the result of treatment of aggressive NHL in elderly patients is relatively poor. Dose reduction or postponement of chemotherapy occurs frequently. The objective of the study was whether G-CSF may prevent leukopenia, infections and dose reduction, and improve the relative dose intensity (RDI) and outcome of treatment.

Methods: a multicenter phase 3 study was initiated to compare the result of standard CHOP q 3-weeks with CHOP + G-CSF days 2-11 in elderly patients (≥ 65 years) with a stage IVb S aggressive NHL. The study included quality of life (QOL) and cost analysis.

Results: 389 eligible patients were included by 63 centers. Patient characteristics were evenly distributed between the treatment arms. Bulky disease was more prevalent in the CHOP + G-CSF arm (P=0.04). The median age was 72 years. According to the AAIP 43 patients were low risk, 134 were low intermediate risk, 167 high intermediate and 45 high risk. 65% completed the protocol treatment. The median follow-up of patients still alive is 33 months. Prophylactic G-CSF improved the RDI of cyclophosphamide and doxorubicin, median 93% versus 96%, P=0.05. The CR rate was 55% with CHOP and 52% with CHOP + G-CSF (P=NS). The disease free survival from CR was 43% and 49% respectively (P=NS). G-CSF significantly reduced infections (15% to 11% of the cycles) and days with antibiotics (median 6 and 0 days, P=0.002), but not the number of hospital admissions. CHOP was well tolerated: from start of treatment the QOL did not decrease, and it improved in patients achieving a CR or PR.

Conclusions: Prophylactic G-CSF increased the RDI and decreased the number of infections and antibiotic prescriptions. The outcome of treatment did not improve.

A RANDOMISED TRIAL OF CHOP x 6-8 vs CHOP x 3 + BEAM + ASCT IN 4 PATIENTS WITH HISTOLOGICALLY AGGRESSIVE NON-HODGKIN'S LYMPHOMA.


Between January 1993 and October 2001 457 patients with newly diagnosed histologically aggressive NHL and poor prognosis disease defined as age-adjusted IPI score of high and high-intermediate risk were entered into this trial. Histology included diffuse large B-cell lymphoma, grade 3 follicular lymphoma, anaplastic large cell lymphoma and peripheral T cell lymphomas. Lymphoblastic lymphomas and Burkitt lymphoma were excluded.

Patients were randomised to receive standard CHOP therapy (6-8 cycles with at least 2 cycles beyond CR) or CHOP x 3 followed by BEAM and ASCT (n=225) providing there had been an objective response to CHOP with no progression at any site, and the bone marrow was morphologically clear of lymphoma after 3 cycles of CHOP. Consolidation radiotherapy was at the discretion of the individual centres.

The median age was 48 years (range 16-65) with 278 males and 179 females. The primary endpoint was overall survival (OS) and with a median follow-up of 24 months there is no difference between the two arms (χ²=0.15, p=0.7). The actuarial overall survival in the CHOP arm was 54% at 5 years and in the CHOP + BEAM arm was 50% at 5 years. In the CHOP + BEAM arm only 62% of the randomized patients proceeded to BEAM. Reasons for failure to receive BEAM included: inadequate response to CHOP (40%), persisting marrow disease (10%), patient choice (27%), physician choice reflecting the patients' poor general condition and other (8%). An analysis of progression free survival (PFS) will be presented.

This study shows that high dose therapy after only 3 cycles of CHOP is not of overall benefit in poor risk patients. The lack of adequate response to the initial 3 cycles of CHOP in nearly 20% of patients indicates that future trials must address early intensification of therapy.

Aim: to compare feasibility, toxicity and outcome of HDS regimen with ASCT vs an outpatient intensified chemotherapy regimen (MegaCEOP). Patients and methods: from January 1996 to September 2000, 130 patients <60 years with DLCL with age-adjusted IPAG intermediate-high (IH) or high (H) risk and/or bone marrow (BM) involvement were enrolled. They were randomized to: group A: HDS (APO plus intensification with CTX 7 g/m² + MTX 8 g/m² + VCR 1.4 mg/m² + VP-16 2 g/m² + 2 DHAP in BM+ pts) + ASCT (MITOX 60 mg/m² + MEL 180 mg/m² + EPI 130 mg/m² + VCR 1.4 mg/m² d 1 and PDN 40 mg/m² d 1 to 5) 6 or 8 courses (BM+ pts) every 14 days with G-CSF 5 support. Results: 4 pts were excluded due to major violations. 126 pts were evaluated: 60 randomized to HDS + ASCT and 66 to MegaCEOP; median age 43 years (18-60), 63% at IH and 37% at H risk. Clinical characteristics were well balanced. CR rate was superimposable: group A 58% vs group B 70%. With a median follow-up of 43 months no differences in the outcome were observed. DFS, OS and FFS rates at four years were respectively: group A 77%, 52%, 46% vs group B 69%, 62%, 44%. FFS rates were not different between A and B in pts without BM involvement (group A 46% vs B 50%) whereas pts with BM+ did better if treated with HDS + ASCT (FFS 56% vs 31%, p<0.05). Fifteen pts did not complete the program: 10 group A (3 toxicities 7 progressions), 5 group B (2 toxicities and 3 progressions). Severe toxicities (WHO >2) were (A vs B): cardiac 5% vs 2%; peripheral neuropathy 5% vs 9%; infections 18% vs 9% and mucositis 10% vs 3%. Four pts died of toxicity: two (HDS) due to aspergillosis and bacterial pneumonia and two (MegaCEOP) due to sepsis. Two secondary AMLL and MDS were observed at 23 and 30 months after ASCT in group A. Conclusions: HDS + ASCT or an intensified outpatient chemotherapy (MegaCEOP) are effective in high risk DLCL and feasible in a cooperative setting without severe toxicity. MegaCEOP is easier to administered and its effective as HDS + ASCT.