**5. CLL**

sCD23 and sCD54 in B-cell chronic lymphocytic leukemia. Analysis of clinical significance.

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In 95 B-cell chronic lymphocytic leukemia (CLL) patients (44 stage A, 31 stage B, 20 stage C), followed-up in two hematological institutions, serum levels of either sCD23 or sCD54 were significantly increased in comparison to an age-matched control population. After setting a cut-off at the mean value for both these molecules(sCD23, 2834 U/ml; sCD54, 600 mg/l), a correlation with other prognostic factors was attempted. Increased levels of sCD23 and sCD54 in B-cell CLL reflected an accelerated clinical stage (i.e., clinical stages, pattern of BM involvement, absolute peripheral blood lymphocytosis) or disease progression (i.e., lymphocyte doubling time, Ki67 expression on BM lymphocytes, serum thymidine kinase activity). Life expectancy was significantly shorter in CLL patients with higher sCD23 levels (P < 0.001). The same applied for those with increased concentrations of sCD54 (P < 0.001).

After adjusting for the most important prognostic factors in CLL (i.e., clinical stages, BM histology) sCD23 lost its predictive power. In contrast, sCD54 seemed to be partially independent from other clinical stages or BM histology. Indeed, it could help to isolate two patient subgroups with different prognostic profile among stage B patients. After integrating sCD54 into Binet clinical staging patients could be separated into four groups whose observed/expected (O/E) ratios were as follows: (I) stage A, 0.37; (II) stage B with sCD54 < 600 mg/l, 0.51; (III) stage B with sCD54 ≥ 600 mg/l, 2.63; (IV) stage C, 3.37 (P < 0.005). When investigated in relationship to clinical outcome, serum level of sCD54 could predict progression to a more advanced clinical stage. The 5-year actuarial risk to progress to a more advanced clinical stage was 40% for stage A patients whose sCD54 levels at the time of diagnosis were lower than 600 mg/l and 87.5% for those with sCD54 levels higher than 600 mg/l (P < 0.001).

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**IMMUNOEHAEMATOLOGICAL PHENOMENA IN MALIGNANT LYMPHO-PROLIFERATIVE DISEASES: A POPULATION-BASED STUDY.**

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There is a well known association between immunohaematological phenomena (IH) and malignant lymphoproliferative diseases (MLPD). As previous studies are based on selected groups of patients, there is a lack of valid information regarding the incidence and prognostic significance of these phenomena in MLPD.

In this population-based study we included all newly diagnosed cases of MLPD in adults (> 14 years) from the Danish County of Funen (450,000 inhabitants) from 1.1.1983 till 31.12.1992. They consisted of: Non-Hodgkin's lymphoma (NHL) 504 pts., chronic lymphocytic leukemia (CLL) 244 pts., Hodgkin's disease (HD) 110 pts., Waldenström's macroglobulinemia (WM) 45 pts., acute lymphoblastic leukemia (ALL) 20 pts., hairy cell leukemia (HCL) 9 pts., and prolymphocytic leukemia (PLL) 4 pts.

IH were seen in 43 NHL pts. (8.5%), 40 CLL pts. (16.4%), 1 HD pt. (0.9%), 2 WM pts., 2 ALL pts., 1 HCL pt., and in none of the four PLL pts.

In the NHL group 18 pts. (3.5%) suffered from autoimmune haemolytic anaemia (AIHA), 10 pts. (2.0%) had thrombocytopenia of presumed autoimmune origin (AITP) and 7 pts. (1.4%) had Evans' syndrome. In 8 pts. (1.6%) a positive direct Coombs' test not associated with haemolysis (PCs), was found. In the CLL group the corresponding results were: AIHA 30 pts. (12.2%), AITP 5 pts. (2.0%), PCs 1 pt. (0.5%), and Evans' syndrome 2 pts. (1.6%). A total of 228 patients of the MLPD the following IH were found: HD 1 AITP, WM 1 PCs, 1 AIHA, ALL 1 AITP and 1 PCs, and HCL 1 AITP.

Univariate analysis showed IH to be associated with a shortened survival in NHL (p < 0.03) but not in CLL (p = 0.16). However, using a Cox regression model, NHL patients with IH did not differ from other NHL patients regarding survival.

In conclusion, immunohaematological phenomena are more frequently seen in CLL than in NHL, while they must be exceedingly rare in HD. Autoimmune haemolytic anaemia is mostly seen in CLL. In neither CLL nor NHL do IH influence survival.

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**EXPRESSION OF 4 ADHESION MOLECULES, CD54, CD11a/CD18, CD44 and LECAM-1 IN 89 B-CELL-LYMPHOPROLIFERATIVE DISORDERS RELATED TO MORPHOLOGICAL SUBTYPE AND CLINICAL STAGE.**


Four adhesion molecules (CD54 or ICAM-1, CD11a/CD18 or LFA-1, CD44, LECAM-1) have been investigated in 89 lymphoproliferative disorders (LPD) by flow cytometry and/or immunocytochemistry with the following objectives: 1) to define an adhesion profile characteristic of the main morphological subtypes; 2) to correlate with clinical behavior and especially bone marrow involvement. All cases were well-characterized immunologically and classified according to the REAL classification with slight changes for lymphomas, and to the recommendations of the Fab group for lymphoid leukemia. There were 25 CLL, 23 B-SLL, 14 lymphophaesmona lymphoid lymphoma/immunocyto (LPL), 18 follicular lymphoma, 7 FL, 4 mantle cell (MCL), 4 marginal-zone (2 MALT, 2 SLVL), 6 diffuse large cell (DLCL). 6 Burkitt/LAL3. Samples (fresh or frozen) originated from peripheral blood (35), bone marrow (7), and tissue biopsies (lymph node 43, spleen 8, other 19). Immunocytochemical analysis of lymph node and bone marrow biopsies was performed on formalin-fixed, paraffin-embedded sections and was scored semiquantitatively. The mean expression of each antigen in the whole group was calculated and the expression of each antigen in subgroups was compared with statistical methods (chi-square).

**2-chlorodeoxyadenosine (2-CDA) in pretreated low grade non Hodgkin's lymphoma (NHL) patients: lower frequency of infections with maintained high response rate after dose reduction.**


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2-CDA (cladribine) is effective in low grade lymphoproliferative disorders. To study toxicity and response in pretreated low grade NHL patients we started this phase I clinical trial. Ninety patients (male:59/31) with low grade NHL (IFC, IBC, chronic lymphocytic leukemia and Waldenström's disease excluded) were accrued from July 1992 - October 1995. The first 38 patients (group 1) received a total 2-CDA dose of 0.7 mg/kg/cycle as a continuous iv or sc infusion for 7 days; the dose was reduced further in 52 patients (group 2) to 0.5 mg/kg/cycle given as a sc bolus injection for 5 days. A maximum of 5 cycles were administered every 28 days until the best response or progression. Results: A total of 224 cycles were given (group 1: 85, group 2: 139). Response and toxicity were compared in both groups after a similar 2-CDA dosage (group 1: 2.1 mg/kg + 3 cycles; group 2: 2.5 mg/kg + 5 cycles) (median and range).

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**Conclusion:** The standard 2-CDA dosage of 0.7 mg/kg/cycle induced a high response rate in pretreated low grade NHL but was associated with a considerable incidence of severe infections (pneumonia, staphylococcus sepsicaemia, necrotising, brain abscess). The dose reduction by 30% led to an impressive decrease of the infection risk (3%, eradicated a higher incidence of sepsicaemia) while an equivalent response rate was maintained. Grade 3-4 myelotoxicity was acceptable in both groups and other severe adverse effects were rare. The results are not based on a randomized comparison. Even if we interpret them with the necessary caution, we conclude that 2-CDA dosage of 0.5 mg/kg/cycle should not be exceeded in this patient population.
RESPONSE AND TOXICITY OF CLADRABINE (2-CDA) AS FIRST LINE TREATMENT OF LOW-GRADE NON-HODGKIN’S LYMPHOMAS (NHL). PRELIMINARY DATA OF AN AUSTRIAN MULTICENTRAL TRIAL.


2-CDA is an effective drug in heavily pretreated low-grade NHL. In these patients serious infectious problems were reported. Aim of our trial is to evaluate efficacy and toxicity of 2-CDA in untreated patients with low-grade NHL.

Previously untreated low-grade NHL stage 3 or 4 were eligible to the trial. The protocol was approved by the local ethics committees. From June 1992 to October 1996 51 patients gave informed consent and were entered to the trial. 2-CDA was given as a 2-hour infusion 0.12 mg/kg daily for 5 consecutive days. Four treatment cycles were given every 28 days. After the last cycle of 2-CDA, patients were treated with interferon-α-2a for one year.

Twenty-eight of the 40 patients have completed the 2-CDA therapy. Of these patients one was excluded because of stage 2 disease, this patient achieved a partial remission. Median age was 55.4, range 24-74 years. Response rate was 60% (22/36), complete remission (19%), 520/6. After a median observation period of 110 days (27 to 692 days), 6 relapses occurred after 58, 60, 84, 138, 259, and 344 days respectively. Four patients died, all of progressive lymphoma. Toxicity WHO³⃣ 3 possibly related to 2-CDA occurred in 6 patients (23%) and in 12 of 86 cycles (14%). Grade 3 toxicities were hematological, except one infection. One WHO³⃣ 4 toxicity (polyneuropathy) was observed during 66 cycles (1%). Immunoglobulin G levels dropped from median 11.90 g/L to 10.89 g/L CD 4 counts from median 0.7 x10⁹ to 0.110 x10⁹. After a median time of 22 months after treatment start the median CD count still was 0.146×10⁹. Despite this considerable toxicity to CD 4 cells, only 6 infections were observed during 73 treatment courses (8%).

Conclusions: 2-CDA is an effective treatment in low-grade NHL. Infusion rate is low and treatment was well tolerated by previously untreated patients.

THREE-DAY THREE-WEEKLY ORAL CLADRABINE (2-CDA) FOR CHRONIC LYMPHOCYTIC LEUKEMIA. A PRELIMINARY REPORT FROM A EUROPEAN PHASE II MULTICENTER STUDY.

In our previous studies of 117 patients with symptomatic chronic lymphocytic leukaemia, five-monthly monthly cladribine courses resulted in an overall response rate of two thirds, and half the responses were complete. The median CR duration was 42 months, and the PR duration 18 months.

However, one third of the patients had major infections, and 13% developed thrombocytopenia. We therefore embarked on a schedule with lower total dose per course but the same dose intensity aiming at a reduced toxicity. From January 1995 through January 1996, 89 symptomatic patients from Brussels (B), Taunton (UK), and 18 Swedish institutions were entered. Oral cladribine 10 mg/kg/day was given days 1 through 3 every 3 weeks, for up to 10 courses. Stopping criteria were defined at various stages for patients with certain signs of toxicity, and/or insufficient improvement from therapy.

Thirty-four patients with a median age of 64 (range 41-88) are currently evaluable for a preliminary analysis. Baseline conditions were as follows: A(5), B(13), C(16). Twenty-five (74%) were previously untreated. The overall response rate was 65%, with 7 CR (21%) and 15 PR (44%) after 5 to 10 courses. Seven patients had pneumonia, and one patient developed severe hemolysis.

The final analysis of the study will tell if this treatment schedule in combination with defined criteria for stopping therapy will reduce toxicity with retained response compared to the previously studied regimes. Studies in multi-institutional settings are required before proceeding into a phase-III comparison of cladribine, fludarabine and chlorambucil for symptomatic CLL.

2-CHLORODEOXYADENOSINE (2-CDA) THERAPY IN Hairy Cell Leukemia (HCL): COMPARISON OF 7-DAY CONTINUOUS IV INFUSION WITH A TWO-HOURS IV INFUSION ON 5 CONSECUTIVE DAYS.

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2-CDA is a potent analogue with excellent activity in HCL. A 7-day continuous i.v. infusion may be more convenient than a standard administration. Since a more convenient route of administration is desirable, we compared the activity of standard administration of a single 7-day continuous i.v. infusion (0.1 mg/kg/day) to (1) newly diagnosed, 6 pretreated with splenectomy and/or interferon-alpha, 15 with an outpatient regimen of 2-CDA (0.1 mg/kg/day) as a 2-hours i.v. infusion on 5 consecutive days (n=13); newly diagnosed, 6; pretreated, 5). All patients had at least Hb <10 g/dL, or granulocytes <1 x10⁹, or platelets <100 x10⁹, or symptomatic disease. Complete remission (CR) was defined as normalization of all abnormal parameters including HCL-negative bone marrow and negative immunophenotyping; hematocrit remission (HR) as normal peripheral blood counts and spleen size and at least 50% reduction of hairy cells in bone marrow; minor response (MR) as normalization of at least one peripheral blood cell count. There were 28 males and 6 females with a median age of 56 years (range 37-86).

<table>
<thead>
<tr>
<th>Response (%)</th>
<th>1-2 months</th>
<th>3-6 months</th>
<th>5-6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>7%</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td>PR</td>
<td>4%</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>NR</td>
<td>92%</td>
<td>91%</td>
<td>97%</td>
</tr>
<tr>
<td>7 day infusion</td>
<td>57%</td>
<td>58%</td>
<td>60%</td>
</tr>
<tr>
<td>5 day infusion</td>
<td>35%</td>
<td>35%</td>
<td>35%</td>
</tr>
<tr>
<td>5% in 1st month</td>
<td>7%</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>5% in 2nd month</td>
<td>7%</td>
<td>7%</td>
<td>7%</td>
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There were no relapses or primary failures with a median follow-up of 35 months (range 22-73) and 16 months (range 9-23) in the 7-day continuous infusion, respectively 5-day intermittent treatment. One patient in HR died after one month of 7-day continuous 2-CDA treatment from pneumonia. There were 2 deaths after one and four months respectively of 5-day intermittent CDA treatment due to cardiac arrest. Neutropenic fever developed in 13 patients (61%) with documented infection in 4 (19%), and 7 patients (35%) with documented infection in 2 (15%) during 7-day continuous respectively 5-day intermittent therapy. A general rule in the week of 7-day continuous infusion was seen in 5 (25%) and respectively 7 (45%) patients after 5-day intermittent therapy. In conclusion, 7-day continuous i.v. infusion induces rapid and durable remissions in patients with HCL. Responses to 5-day intermittent i.v. infusion are often delayed and though response quality may improve over months, almost none of the patients achieve complete remission.
6. High-dose chemotherapy

Neither CD34+ cell selection Nor B cell purging allow effective tumor cell purging of hematopoietic cell grafts from follicular non Hodgkin's lymphoma (NHL) patients.


Three different methods of purging tumor cells in graft harvested in 22 patients (pts) with bcl-2+ follicular NHL have been sequentially evaluated. In 7 pts CD34+ cell selection from peripheral blood progenitor cells was performed using a computer driven avidine immunofluorinity column device (CEPRATE, CellPro). In 11 pts marrow was purged using CD10, CD19 and CD20 monoclonal antibodies followed by 3 cycles of rabbit complement. In 4 pts B cell purging of the marrow used CD10, CD20, CD22, CD23 and CD37 followed by a magnetic cell separation (MAXSEP B-Cell Purging, Baxter). Recovery of CFU-GM and CD34+ cell (only after CellPro and Baxter purging) were evaluated as well as tumor purging efficiency. For detection of minimal residual disease (MRD), Nested oligonucleotide amplification was performed at the major breakpoint of the bcl-2 IgH hybrid gene (as described by Gribben et al (1991)). The limit of sensitivity of this technique, determined by serial dilution of KARPAS 422 cell line in 10ES normal cells. Median recovery of CD34+ cell were 48% and 34% after CD34+ selection and magnetic B cell purging respectively. The median number of CD34+ cells (x 10^6/kg) were 2.8 and 0.2 after CD34+ selection and magnetic B cell purging respectively. The median number of CFU-GM (x 10^3/kg) was 11(0-20), 2.8(0-3.5) and 1.8(0-3.4) after CD34+ selection, magnetic purging and complement dependent purging respectively. After conditioning with 12 Gy TBI and HD CTx the time to PMN and Plate recovery was 11(10-12), and 23(19-95) with CD34+ cell grafts (6 pts), 38(15-65) and 34(32-50) with magnetic purging BM (4 pts), 23(0-31) and 31(0-90) after complement dependent purging of the BM (11 pts). Fifteen patients have been evaluated for MRI 3m to 9m post transplant, 7 were bcl2 negative although 5 received bcl2 positive grafts. None of the patients progressed in 16 patients with a median follow up of 16 months after transplantation, 2 were relapsed. A second purging technique neither method appear to be effective in tumor cell purging. The exact prognostic significance of a very low tumor burden in the graft remains to be evaluated as well as more efficient purging techniques.

CAN INTENSIVE THERAPY WITH STEM CELL SUPPORT (ITwSCS) CHANGE THE NATURAL HISTORY OF FOLLICULAR LYMPHOMA PATIENTS?


Follicular lymphomas (FL) are characterized by multiple recurrences and the possible risk of histologic transformation (HT), duration of successive remissions becoming shorter. In the absence of randomized controlled studies, it remains difficult to know if ITwSCS may change this pattern of evolution. Between 08/90 and 10/95, 64 FL patients (pts) received such a treatment in our institution: 19 pts with adverse prognostic factors were in 1st partial remission (PR1); 32 pts in PR2 or in 2nd CR; 13 pts in subsequent progression. Median age was 48 y (25-63), median time from diagnosis to ITwSCS was 32 m (3-170). 12 pts had an history of HT and 8 pts had a composite lymphoma at diagnosis with coexistence of FL and diffuse aggressive lymphoma. 34 pts had persistent bone marrow involvement at time of the procedure. Conditioning regimen was Cy (60 mg/kg x 2d) + VP 16 (300 mg/m² x 3d) + TBI (10 Gy) in 51 pts and BEAM in 13 pts. There were 6 procedure-related deaths (9%). With a median follow-up of 17 m, 2-y overall survival (OS) was 85% and 2-y event-free survival (EFS) was 68%. In pts treated for recurrent disease, 2-y OS and 2-y EFS were 78% and 56% respectively. Outcome of pts treated after HT was not significantly different from that of an historical group of 15 FL pts who achieved CR or PR after salvage chemotherapy. The duration of ITwSCS-induced remission in pts treated in 2nd line or more was compared to the duration of the previous remission in each patient: among 36 evaluable pts in which follow-up is long enough, ITwSCS-induced remission was longer than previous remission in 25 pts (69%). ITwSCS in FL pts alters favorably the natural history of the disease.

PCR DETECTION OF IMMUNOGLOBULIN GENE REARRANGEMENTS IN NON-HODGKIN'S LYMPHOMAS AFTER HIGH-DOSE CHEMOTHERAPY AND BONE MARROW TRANSPLANTATION PREDICTS FOR RELAPSE

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In B cell NHL, clonal rearrangement of the third complementarity determining region (CDR3) on the immunoglobulin heavy chain gene (IgH) provides a useful marker for the detection of minimal residual disease (MRD) after treatment. This technique can be used for the detection of lymphoma cells independently to their expression of CD1418, which has previously been described as a target for PCR and a mean to detect MRD, but which is only expressed in 50% of the patients (pts) with NHL. To determine the clinical utility of IgH PCR, we analyzed PB and BM samples from pts with NHL (without CD1418) undergoing ABMT. As an initial strategy DNA was isolated for a variable VH and (joining) JR region primers. The clonal product was directly sequenced and clone specific probes constructed using VH region nucleotide sequences. In those cases failing to amplify using consensus region primers, PCR was performed using a panel of VH family specific framework region 1 (FR1) primers. Products were again sequenced directly for the generation of pts specific oligonucleotides. Patients with histological bone marrow infiltration were selected for study thus providing us with diagnostic samples. 24 pts with no (CD1418) were studied, and a clonal PCR product was obtained in 17 (71%). 6 pts had diffuse, and 9 pts had follicular NHL. 7 pts have relapsed after ABMT. Of these, 6 pts had detectable lymphoma cells prior to relapse, and one patient had no available sample for analysis. None of the 10 pts who are still in remission showed PCR detectable lymphoma cells later than one month after ABMT. Sequencing, and the use of patient specific IgH CDR3I oligonucleotides probes provides a simple and highly reliable method to determine the specificity of the IgH PCR technique. Persistence of PCR detectable lymphoma cells in these pts after BMT is associated with poor outcome.

MYELOABLATIVE HIGH-DOSE THERAPY WITH PERIPHERAL BLOOD STEM CELL TRANSPLANTATION IN LOW-GRADE NON-HODGKIN'S LYMPHOMAS (NHL)

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Since July 1991, 90 patients (pts) with low-grade NHL received a TBI-containing high-dose therapy with PBSC transplantation in a single center study. There were 47 males and 43 females with a median age of 45 years (range, 22-60). According to the Kiel classification, 71 pts had centroblastic-centrocytic NHL, 13 pts centrocytic (mantle cell), 3 pts lymphoblastic, 2 pts immunocytic and 1 pt was classified as marginal zone NHL. A median of 2 leukaphereses (range, 1-7) were performed during filgrastim (r-methK-G-CSF)-supported marrow collection following high-dose cytarabine/mitoxantrone (HAM). A second cycle of HAM was administered for further tumor reduction in 42 pts. At the time of autografting, 56 patients were in first complete or partial remission, while 34 patients achieved a second remission after a history of relapse or progressive disease. A median number of 5.85 x 10^6 CD34+ cells/kg (range, 2.10 - 40.0) resulted in rapid and sustained reconstitution following high-dose therapy with TBI (hyperfractionated, 14.4 Gy) and cyclophosphamide (200 mg/kg). Five patients received BEAM (BCNU, etoposide, cyclophosphamide, melphalan) because of previous radiotherapy. The median time to reach a neutrophil count of 0.5 x 10^9/l and a platelet count of 20.0 x 10^9/l was 13 and 12 days, respectively. The rate of transplantation-related mortality was 5.6%. After a median follow-up time of 18 months, 72 patients are alive and in remission. Relapses were observed in 11 patients with previous history of treatment failure and in 2 patients transplanted in first remission. As a result, the probability of event-free survival for patients autografted in first remission was 85% at 40 months compared with 44% for patients with a history of treatment failure. Furthermore, patients with autografts containing PCR-(CD1418)-positive cells were more likely to relapse than patients who received a PCR-negative graft. In conclusion, myeloablative high-dose therapy with PBSC transplantation might be envisaged for patients in first remission when the tumor burden is low and before drug resistance develops. Purging may be considered to decrease the risk of re-infusing tumor cells, while interferon-a could be beneficial post-transplantation for controlling or eradicating minimal disease.
Molecular study of 48 follicular lymphoma (FL) patients treated with intensive-therapy supported with peripheral blood stem cell (PBSC) re-infusion.


From 09/90 until 12/94, 51 advanced poor-risk follicular lymphoma pts in first partial remission or 2nd (or subsequent) partial or complete remission (CR) received intensive myeloablative therapy (cyclophosphamide-VP16-12) or BEAM supported with PBSC re-infusion. PBSC were collected after priming with high-dose cyclophosphamide (4.5 to 5.25 g/m²) followed with GM-CSF. The majority of pts had bone marrow involvement either at diagnosis (89%) or at PBSC harvest (63%). Detection of bcl-2+ positive cells was performed using nested-PCR and oligonucleotides for both the major breakpoint region (MBR) and the minor clustering region (mcr) and results were confirmed by Southern blotting analysis with internal oligomers. Two pts did not have material available for this study. CSP harvests in 24/25 bcl-2+ informative pts were tested; 22 of them (92%) had bcl-2+ PCR-detectable DNA in apheresis sample; no test done on the bcl-2- non-informative pts had bcl-2+ PCR-detectable DNA in apheresis. Only 5/373 pts achieving CR experienced lymphoma progression after a median follow-up of 17 months (5-60 m). 18 pts bcl-2- informative pts had samples examined while in CR: 13 pts remained bcl-2- in follow-up of 15 months (5-56 m), including 2 pts that relapsed; 5 bcl-2+ informative pts had persistent bcl-2- negative samples in blood (3) or marrow (2) and none had relapsed with a median follow-up of 19 months (12-28). In conclusion, the vast majority of FL pts have tumour cell DNA detectable in PBSC harvests; however, the progression-free survival of these pts seems favorable with a low number of relapses. A limited number of them may convert to PCR negativity after myeloablative therapy.

RISK-ADAPTED CHEMOTHERAPY FOR LARGE CELL LYMPHOMA: VACOP-B FOLLOWED BY HIGH-DOSE CHEMOTHERAPY AND AUTOLOGOUS STEM CELL TRANSPLANTATION IN FIRST REMISSION.


Single institutions and transplant registries have reported excellent results on high-dose therapy alone, with 2-3 year survival of 40-70% in 60-80% of autologous bone marrow or peripheral blood stem cell transplantation (ASCT) in non-Hodgkin's lymphoma in first remission. These results might be overly optimistic, since they are based on selected patients (pts) able to undergo HDC, while the denominator of eligible pts was rarely reported. To prospectively determine the results of HDC with ASCT in high-risk non-Hodgkin's lymphoma, we undertook the following phase II study. Eligibility criteria for risk-adapted therapy included the presence of a large cell lymphoma at any stage, age 18-70 years, and absence of HIV infection, CNS manifestation at presentation, or second malignancies. All pts were treated initially with VACOP-B chemotherapy. Pts were defined to be at high risk of relapse and therefore to qualify for HDC with CBV and ASCT in first remission, if they had stage III/IV disease with an elevated LDH and/or tumor bulk >10 cm, or, for patients with mediastinal B-cell lymphoma with sclerosis, if they had stage III with an elevated LDH and/or bulk. Between August 1991 and October 1995 82 pts with large cell lymphoma participated in the study, including 10 with anaplastic Ki+ lymphoma and 8 with mediastinal B-cell lymphoma with sclerosis. The median follow-up is 27 months. The median age was 45 years (range 16-60). 53 pts were classified as low-risk according to our criteria (50% of them had a low or intermediate age-adjusted international index, A.I.I.). 29 pts qualified as high-risk under our criteria (24 of them had a intermediate-high or A.I.I.). 22 (75%) of the high-risk pts underwent HDC with ASCT in first remission. The median interval between the start of VACOP-B and HDC was 15.3 (range 12.7 to 30) weeks. Reasons for not undergoing HDC were progressive disease in 5 pts and refusal or toxicity of previous therapy in one pt each. 3-year event-free (3y-EFS), relapse-free, and overall survival of all pts was 59, 86, and 98%, respectively. One pt died during treatment of early disease progression, there was no mortality related to HDC. 3y-EFS in the low-risk group was 70% and in the high-risk group 47% (p=0.045). In a high risk group, relapses occurred within 18 months, whereas 3y-EFS was 91% for pts able to undergo HDC and 29% for the others. Thus, based on the intent to treat analysis in our prospective study, a 3y-EFS of just under 50% can be expected for high-risk large cell lymphoma intended to receive HDC in first remission. This number has to be taken into consideration for the planning of randomized phase III studies.

The international prognostic index (IPI) for diffuse large cell NHL at diagnosis (based on age, stage, performance status, IPI was designed to distinguish patients (pts) under 60 with a different prognosis (NEJM 329:987, 1995). The applicability of the IPI at relapse was evaluated on pts with intermediate/high grade (IHI) NHL treated in the PARMA trial. The IPI was available in 187 of the 215 pts. At inclusion, respectively 29%, 77 (41%), 45 (25%) and 16 (8%) pts had a risk index of 0, 1, 2 and 3, respectively (p=0.08). With a median follow-up of 63 months, overall survival (OS) at 5 years was 69%, 47%, 25%, 13% and 1% for pts with an IPI of 0, 1, 2 and 3 respectively (p=0.05). After 2 courses of DHAP, patients in partial or complete response (12/CR) were randomized to receive either BEAC and ABMT or 4 additional courses of DHAP. The OS of non randomized pts (i.e. in stable or progressive disease) was not significantly influenced by IPI (OS survival of 34%, 19%, 13%, 11% mos for pts to 3, respectively). However, the subgroup of non responding pts with an IPI of 0 at relapse had an unusually favorable prognosis for IHI NHL in relapse refractory to 2nd line treatment. Among the 109 randomized pts, pts IPI at relapse was found highly correlated to OS in pts treated in the DHAP arm (5-yrs OS: 58%, 20%, 38%, 0% for IPI=0 to 3 respectively, logrank=12.46, p=0.006). In contrast, IPI at relapse was not found correlated to overall survival in the BEAC arm (5-yrs OS: 55%, 69%, 56%, 50% for IPI=0 to 3 respectively, logrank=0.75, p=0.81). These results indicate that the IPI has a prognostic value for response and overall survival at the date of relapse in pts with IHI NHL. The IPI is correlated to overall survival in pts treated with conventional therapy but not with ABMT in this series. Although the numbers are small, ABMT dramatically improved the outcome of pts with an IPI of 0 to 1 in 3 in this series.

INTENSIFIED AND HIGH DOSE CHEMOTHERAPY WITH G-CSF AND AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) SUPPORT AS FIRST LINE THERAPY IN HIGH RISK DIFFUSE LARGE CELL LYMPHOMA (DLCL).


Purpose: In our previous study with MACOP-B and mitoxantrone we had identified a high risk group of DLCL. In a single institution we intensified our high risk group of DLCL, treating the advanced stage with high tumor burden and elevated LDH level or bone marrow (BM) involvement. Patients with BM involvement had the worst outcome with 3.5 year survival of only 12%. A novel therapeutic strategy was investigated to improve the outcome of these patients.

Patients and Methods: Since January 1992 through March 1995, 62 pts with high risk DLCL were enrolled. The therapeutic strategy included three phases: induction with 8 weeks of MACOP-B; intensification with a 3 day course of Mitoxantrone 8 mg/m² + HDACAR 2 g/m² x12h + Dexamethasone 4 mg x12h/24h (MAD protocol) and GCSF 4 x10⁶/kg days 4-17 to harvest peripheral blood cells (PBPC); consolidation with BEAM + ASCT with PBPC, marrow or both. Median age was 45 years (19-59). Fifty had high tumor burden, 50 elevated LDH level, 44 stage IV, 29 presented with 1 extranodal sites and 24 with BM involvement.

Results: Lymphopheresis after MAD and G-CSF yielded a median of 30 x10⁶/kg CD3+ cells and 70 x10⁶/kg CD19- cells. Fifty pts were autografted and twelve were not: 7 because of disease progression, 4 due to toxicity and one death. The median times to engraftment was 11 days to neutrophils > 0.5 x10⁹/l and 12 to platelets > 50 x10⁹/l. Forty seven patients (76%) achieved a CR, 12 (18%) showed a NR and 5 (3%) died of toxicity (disseminated mucositis, brain bleeding and acute hepatitis receiving 3HsAgreg). Among the 49 Pts with complete remission with MACOP-B, 65% achieved a CR with the following intensified therapy. With a median follow-up of 30 months DFS, OS and EFS were 69%, 50% and 52%. Patients with BM involvement had a lower CR rate (62% vs 84% p < 0.05) and OS was not significantly different between the two groups. These results compare favourably with those achieved in a historical control group with the same clinical characteristics treated with MACOP-B alone (CR 76% vs 43%, DFS 69% vs 41%, OS 60% vs 29%). All patients with BM involvement achieved better results with the sequential scheme than with MACOP-B alone (CR 62% vs 33% and OS 54% vs 12%). This scheme is feasible with moderate toxicity and may improve the outcome in high risk DLCL.

High-dose chemotherapy
ROLE OF INDUCTION CHEMOTHERAPY (CT) AND BONE MARROW TRANSPLANTATION (BMT) IN ADULT LYMPHOMATOID LYMPHOMA (LBL)


We report the results of our experience in 62 adult LBL treated between January 1980 and December 1992. Characteristics of patients (pts) are: median age = 32 years (range 14 to 70); Ann-Tier classification stage II: 17, stage III: 6, stage IV: 39; pleural effusion (16 pts) and bone marrow involvement (14 pts) were the main involved extra-nodal sites. Induction CT to achieve Complete Response (CR) was: French Multicenter Acute Lymphoblastic Leukemia (ALL) protocols (38 pts), Non Hodgkin's Lymphoma (NHL) protocols (20pts), and 4 pts received CT without being included in protocols. Thirty-three pts underwent BMT after achieving CR to induction treatment (Allogeneic procedure 13 pts, Autologous procedure 20 pts). Forty-six pts (74%) achieved a CR to induction CT and 16 pts (25%) failed to respond. The pts who received an ALL induction CT had a 89 % CR rate, while CR rate was 52 % in pts who received a NHL induction regimen. With a median follow-up duration of 93 months (range 15 to 187), the actuarial overall survival (OS) rate for all patients is 49.20 % at 5 years and 41.30 % at 10 years, and actuarial event-free survival (EFS) rate is 45.30 % at 3 years and 37.40 % at 10 years. OS and EFS are significantly better in the grafted population (OS: 66 %, EFS: 56 % at 5 years). Comparison of results achieved with autologous or allogeneic transplant shows a trend toward a longer OS in allografted group.

In conclusion, induction CR in adult LBL must be similar to ALL. High dose CT to consolidate CR is superior to conventional CT. Allogeneic transplantation must be considered each time an histocompatible donor is identified.

A RANDOMIZED TRIAL OF FILGRASTIM (G-CSF) PRIMED PERIPHERAL BLOOD STEM CELLS (PBSCT) VS. BONE MARROW AS A RECONSTITUTION SOURCE FOR HIGH DOSE CHEMOTHERAPY IN PATIENTS WITH LUPHOMA AND HODGKIN'S DISEASE: A CLINICAL AND MOLECULAR ANALYSIS. D.P. Schenkelin, R. Kanzeti, I. McCann, D. Boilim, E. Berkman, J. Marcelli, C. Harkay, and K. Miller. Tufts-New England Medical Center, Bone Marrow Transplant Unit, Boston, MA.

The optimal source for hematopoietic reconstitution to support high dose chemotherapy with respect to engraftment and occult malignant contamination has not yet been determined. We initiated a randomized trial of either bone marrow support (2 x 10^6 MNC/kg) or PBSCT support (2 x 10^6 MNC/kg) for high dose chemotherapy (Thiotepa 300mg/m^2, Cyclophosphamide 7200mg/m^2, Carboplatin 160mg/m^2, and Etoposide 1600mg/m^2). The PBSCT were collected after 4 days of G-CSF priming at 10 mcg/kg/day. All patients received G-CSF at 5 mcg/kg/day following stem cell or marrow infusion. To date, 41 patients with either relapsed NHL (n=31) or HD (n=10) have been treated. Mean age was 44 years with a median follow-up of 18 months. Patients with any history of marrow involvement were assigned to a PBSCT-A arm while all others were randomized. Analysis reveals a significantly faster engraftment in either PBSCT arm while hospital stay, survival and freedom from relapse were not statistically significant in the two randomized arms.

Source: linc/10 plz/10 Im/M Surg/M Surv/M EFS/2/L

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(* day of last pt transfusion) (length of hospital stay)

Molecular analysis for occult malignant cells in bone marrow, PBSCT, and blood was performed using tumor specific oligonucleotide (TSo) PCR of the IgH CDR3 region in all NHL patients. A clonal CDR3 sequence was detected in 85% of cases analyzed. A high degree of clonal contamination was noted in both BM (65%) and PBSCT (82%) prior to infusion and in 78% of marrow samples obtained at 100 and 300 days post transplant. No statistical correlation between contamination and relapse was noted at this time. Competitive PCR studies suggest a higher load of CDR3 sequences in BM vs PBSCT.

ALLOGENEIC BONE MARROW TRANSPLANTATION FOR LOW GRADE LYMPHOMA.


We examined the outcome of allogeneic bone marrow transplants (BMT) for Low grade Lymphoma in HLA-identical siblings in 67 patients transplanted between 1984 and 1994. Median age was 37 years (range 14-53). 39 were males and 28 females. 50 patients (75%) had stage IV disease at the time of BMT. Median time from diagnosis to BMT was 29 months (range 5-88 months). 40 patients (60%) had never achieved complete remission. 20 patients (30%) had pretransplant Karnofsky performance scores (KPS) ≤ 80%. Most patients (97%) had received prior chemotherapy regimens (median 3, range 2-7). Kaplan-Meier survival (95% confidence interval) at three years is 58% (45%-70%) and disease-free survival, 58% (45-70%). Median follow-up for surviving patients is 27 months (range 5-89). Treatment-related mortality is 26% (15%-40%) and probability of recurrence, 8% (7%-18%). Factors associated with increased survival include age less than 38 at transplant (72% [55-86%] vs 40% [20-62%]; p = 0.01), sensitivity to chemotherapy (70% [53-84%] vs 46% [27-65%]; p = 0.02). 2 or fewer prior chemotherapy regimens (70% [53-85%] vs 42% [24-61%]; p = 0.02) and KPS>80% (64% [49-78%] vs 39% [18-63%]; p = 0.07). Allogeneic BMT can induce prolonged remissions in patients with recurrent and refractory low grade lymphoma. Among 22 patients surviving disease-free for more than 2 (range 2-7) years after BMT, only 1 recurred at 4 years, indicating that some patients may be cured.

FAVOURABLE OUTCOME AFTER ONE YEAR TREATMENT OF CHILDHOOD T-CELL LYMPHOMA/T-CELL ACUTE LYMPHOBlastic LEUKEMIA.

H. van den Berg, J. Zsiray, A. Veneberg, N. Schuttert, R.M. Slater, H. Behrendt, E. Emma Kinderziekenhuis AMC, Department of Anthropogenetics, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands.

For T-malignancies in children a poor prognosis is reported. In these malignancies a combination of lymphoma and leukemia is commonly seen at presentation and most patients are treated according to protocols for acute lymphoblastic leukemia (ALL). In pediatric lymphoblastic non-Hodgkin's lymphoma without bone marrow infiltration various protocols have been used. The most frequently reported LSA-L, regimen (and its modifications) shows variable survival rates between 40 and 75%. From 1989 we have treated 21 consecutive patients with T-cell malignancies, irrespective of localisation, with a protocol consisting of a 4 agent induction treatment followed by high doses of methotrexate and cytosine-arabinoside and intensified BACOP courses. Treatment duration for each patient was one year. Fifteen patients had stage IV disease. Follow-up ranged from 2 to 6 years (median 3.5 years). Overall event-free survival (EFS) was 81%, whilst in those with stage IV disease this was 74%. No therapy related deaths occurred. As prognostic factors, only a WBC > 100 x 109/L was marginally significant with respect to survival (p = 0.06). Evaluation of toxicity revealed a minimal decrease of CO-diffusion and cardiac shortening fraction. We conclude that a relatively short, but intensive chemotherapy can be used in T-cell malignancies. The EFS is satisfying, but larger studies are needed.

6. High-dose chemotherapy
SERO-EPIEDEMILOGICAL STUDIES RELATED TO EPSTEIN-BARR VIRUS IN HEALTHY TURKISH CHILDREN AND IN MALIGNANT LYMPHOMA PATIENTS


Dept of Pediatrics, Division of Pediatric Oncology, Hematology and Immunology, Ankara University Medical School, Ankara - Turkey

Malignant lymphomas constitute the second most common pediatric malignancies in Turkey. This study represents the sero-epidemiological analyses related to Epstein-Barr virus (EBV) in 120 children with malignant lymphomas. Fifty-one Hodgkin’s Disease (HD), 36 Burkitt’s lymphoma (BL) and 33 non Burkitt, non Hodgkin’s lymphoma cases were included in the study. There were 56 males, 64 females with an age range of 2-14 years. In HD group (M/F=40/11) median age was 8 years with 64% of them having mixed cellular histological subtypes. In BL group (M/F=22/11) median age was 5 years whereas in non Burkitt’s group (M/F=24/9) median age was 8 years. As far as the frequency of EBV infection is concerned, 84% of HD cases, 91.8% of BL cases and 78.7% of non Burkitt’s patients were found to be seropositive, respectively. Among healthy population, 311 children from different age groups were examined. In the age group of 6-18 months 41.8%, 2-6 years of age 60% and 7-18 years of age 81.6% of the children were found to be seropositive for EBV antigens, respectively. In HD and BL group the frequency of EBV infection was significantly higher when compared to non Burkitt’s and control groups. The highest antibody tiers to EBV were determined in BL (anti-EBV-VCA 1/300, anti-EBV EA 1/250, EBNA 1/200) and in HD (anti-EBV-VCA 1/150, anti-EBV EA 1/150, anti-EBNA 1/100) patients accordingly. These results were higher than control group (anti-EBV-VCA 1/93, anti-EBV-VCA EA 1/36, anti-EBNA 1/49) and non Burkitt’s group (anti-EBV-VCA 1/109, anti-EBV EA 1/33), respectively. Our data indicate that in Turkey the children are exposed to EBV infection starting from early ages of their lives. A growing body of evidence suggests that not only endemic BL, but type 1 epidemiologic pattern of HD, as well is commonly associated with EBV infection. More detailed studies, directed to predisposing factors and other environmental features are warranted in order to assess the groups who have increased risk of developing malignant lymphomas.

Hodgkin’s Disease in Children. Minimal Therapy for Clinical Stages (CS) I-IIIB

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From 1987-95 65 children with CS I-III Hodgkin’s Disease were treated bi-modally with MOPP/ABV followed by extended field irradiation (EFRT). Provided a satisfactory response was obtained MOPP/ABV was limited to 3 cycles and EFRT to 15 Gy in 12 fractions. Seventy-eight percent of patients received no more than 3 cycles and 92% 15 Gy EFRT, although 17%, in addition, received a mediastinal boost dose of 5-10 Gy. Stage distribution was CS I 16%, 2 63% and 5 17%. Follow-up duration of surviving patients was 1-87 (median 39) months. Overall 5 year event free survival was 89% and survival 95%. Of 3 deaths 2 were due to disease and 1 to a motor vehicle accident in remission.

Six patients relapsed, 2 on treatment with progressive disease after 4 and 5 cycles of MOPP/ABV and 4 after a complete remission and standard treatment. Two of these patients died of disease and 4 are alive post transplant in a second continuing remission. To date there has been no life threatening toxicity and no second tumour.

These survival results are not inferior to our previous results using MOPP (6 cycles) and EFRT (25-30 Gy), when for 94 CS I-III patients 5 and 10 year event free survival was 81 and 78% and survival 92 and 90%. Six deaths were due to toxicity. The objective of this single institution pilot study, to maintain event free survival and decrease toxicity has been achieved to date. It is too early to evaluate long-term toxicity.

SERUM ICAM-1 (CD54) AND CD44 LEVELS AND THEIR TISSUE EXPRESSION IN PEDIATRIC MALIGNANT LYMPHOMA


Levels of soluble intercellular adhesion molecules ICAM-1 (CD54) and CD44 were measured in serum samples obtained from 37 children with M. Lymphoma (ML) at diagnosis and remission with a sandwich enzyme immuno-assay (ELISA) method. Sixteen cases with Hodgkin’s disease (HD), 15 non Hodgkin’s lymphoma (NHL) and 8 Burkitt’s lymphoma (BL) were included in the study. There were 22 males and 15 females ranging in age from 3 to 15 years. Twelve age matched children were used as controls. Expression of adhesion molecules in tumor tissue samples was assessed by APAAP technique. Median levels of serum ICAM-1 were significantly higher in HD than in controls and other ML cases. However, no correlation was found between disease stage, histology, B symptoms and ICAM-1 levels in HD. Serum CD44 (sCD44) was also elevated in all patients with ML, highest being in HD before treatment. sCD44 levels correlated with the stage of the disease, B symptoms and increased ESR in HD. Tissue ICAM-1 (CD54) and sCD44 expressions were also found to be increased in some stages of the diseases. Serum CD44 and ICAM-1 levels were decreased significantly in patients with complete remission. These preliminary results suggest that determinations of serum ICAM-1 and CD44 may be useful in evaluation and monitoring of treatment response in patients with ML.

PRELIMINARY REPORT ON THE DCLSG-NHL-94 STUDY


Since 1972 the Dutch Childhood Leukemia Study Group (DCLSG) has coordinated the treatment of all children with leukaemia in the Netherlands. In April 1994 the DCLSG-NHL-94 study was implemented. The aim of this study is to central registration and central coordination of the diagnosis and the treatment of all children in the Netherlands with non-Hodgkin's Lymphoma (NHL). In a retrospective study the incidence of NHL in the Netherlands over the period 1973-1985 remained constant at 0.75 per 105 children under 15 years of age per year, which means ± 30 new patients each year (Cobergh, 1991). Although the DCLSG owns a well-organized trial bureau for central registration of all data of NHL patients in the Netherlands. We are now comparing the current clinical data of all NHL patients in the Netherlands with our old data.

We therefore asked the Dutch paediatricians to take care of the coordination of the diagnostic procedures, the treatment as well as the registration towards the DCLSG. All data managers of the DCLSG received an extensive educational training on this subject. 20 months after the implementation of the DCLSG-NHL-94 protocol, 46 patients were registered. The diagnosis was made by the local pathologist: 22 patients as B-NHL, 9 patients as non-B-NHL and 5 patients as LCL. Until 01/09, the trial bureau received not yet complete data of the remaining 10 patients. The diagnosis was made on biopsy-material in 18, 5 and 5 patients with B-NHL, non-B-NHL and LCL exp. In the remaining 7 cases (3 B-NHL patients and 4 non-B-NHL patients) with cytomorphological examination on pleural fluid or ascites. Up to 01/09 the pathologist review panel has confirmed the diagnosis in 25 patients.

We conclude that the intake of 46 patients in 20 months is in accordance with the aforementioned epidemiological data. Although the DCLSG has a long experience in collecting data for leukemia patients the implementation of a nation-wide NHL-study proved to be more cumbersome than expected.

6. High-dose chemotherapy
REDUCED THYROID VOLUME IS FREQUENTLY ASSOCIATED WITH THYROID DYSFUSSION AFTER TREATMENT FOR CHILDHOOD HODGKIN DISEASE

G. DESAI, D. LARIZZA, G. SOMMARUGA, F. CORBELLA, A. BADO, V. SPICA RUSOTTI, MAURICE DEPAPERSI, RADIOLOGY, ONCOLOGICAL RADIOTHERAPY, UNIVERSITY, INRCS Policlinico San Matteo, Pavia, Italy

Current management of childhood Hodgkin disease (HD) rests on combined treatment comprising low-dose radiotherapy (RT) and multiagent chemotherapy. Irradiation of the neck is associated with increased incidence of thyroid cancer (after 6 to 30 years) and possibly of hypothyroidism. Increased levels of TSH due to primary thyroid failure may result in an additional risk of neoplastic growth of thyroid cells.

We evaluated 26 patients (16 males and 10 females) with HD diagnosed between 1983 and 1993 (median age at diagnosis 10 years, range 2-16 years) who were treated according to protocol AIEOP-MH 1983 (n=14) or AIEOP-MH 1989 (n=12) (Cancer 72:2049,1993). At the time of evaluation (median time of 76 months after RT), 25 patients were in first complete remission and one in second remission after a rescue therapy including a second course of neck RT. The RT dose was 26 Gy or less (median 20 Gy) in 20 patients and greater than 26 Gy (27 to 43) in the remaining. In all but one case RT fields partially included the thyroid gland. Thyroid function studies included T3,T4,TFT,TSHTLTHB,autoantibodies (TgA, TPO) and TSH responses to TRH. Thyroid gland structure and volume were assessed by ultrasonography (US).

Normal thyroid function was observed in 7 of the irradiated patients and in the only patient who did not receive neck irradiation. 6/25 patients (25%) had low thyroid hormones with increased basal TSH; increased TSH response to TRH was present in 5/6. 3/25 (12%) had increased both basal and stimulated TSH with normal thyroid hormones concentrations. 8 patients (32%) had low thyroid hormones levels with normal basal TSH or increased after TRH (n=2); one patient had increased FT3 levels with TSH and T4B values were normal in all patients. TgA and TPO were absent in all patients. US study of 25 patients showed one or more cystic nodules in 4 patients, without any correlation to thyroid function. Thyroid volume was inferior to age-standards in 14 patients with significantly longer median follow-up time (79 vs 42 months from irradiation, p<0.01) and no significant difference in RT dose (p=0.17); of these 14 also had thyroid dysfunction requiring thyroxine therapy in six. A significant (p<0.05) association between follow-up duration and reduction of thyroid volume was observed also in patients with normal thyroid function.

Thyroid dysfunction is frequent (72%) in pts treated for childhood HD. Primary hypothyroidism with high TSH was the most frequent pattern. Evidence of low thyroid hormones despite normal TSH suggests that basal TSH is not a specific marker for screening of hypothyroidism in such patients. Patients with longer follow-up are at significant risk for reduced thyroid volume. Its frequent (78%) association with thyroid dysfunction is in favour of direct thyroid damage. The pathogenic role of chemo- and/or RT is not clarified.

IMPROVEMENT OF THE TREATMENT RESULTS WITH THE USE OF LMB-89 PROTOCOL IN B-NHL IN CHILDREN. PRELIMINARY REPORT BY POLISH PEDIATRIC LEUKEMIA LYMHPHOMA STUDY GROUP (PPLLSG).


Published data by the French SFOP Group has shown that in large series of patients on protocols LMB - 88 and in LMB - 86 intensification of chemotherapy is associated with significant improvement in outcome, with around 80% 2 years survivor for Murphy-stage III and RT to the stage IV. In 1993 the PPLLSG adopted the LMB-89 regimen to improve the results of advanced stages of NHL in children in Poland. Thirty three patients aged from 21 months to 17 years are evaluable. Sixteen children presented with the stage III and fourteen stage IV, 11 patients have BM involvement, 3 CNS disease. The majority were Burkitt's type Primary Malignant were abdominal in 21 pts (63.6%), nodes in 5 pts (13.2%),tonsils in 2 pts (6.1%). Remaining 5 primaries sites were bone, groma,textes and mediastinal. The median time of follow up was 17 months. Complete remission was achieved in 10 from 33 pts (90.9%). Two children relapsed : the first pt with initial liver tumor and BM involvement, the second with primary tonsil tumor and bone invasion. The relapses occured in BM. Five patients died. One due to refractory dis ease, two because of the toxicity of chemotherapy and two because of relapse.

In 65% of the patients the deep fall of granulocytes, platelets and red blood cells was observed 7 - 10 days from the start of treatment cycle. Inspite of this deep pacotopenia, the life threatening infections or deaths due to infections were not observed. Conclusion:

1. the protocol LMB-89 resulted in a high percentage of remissions, 2.EFS was 91.2% and the percentage of relapses 6.1%, 3. the aggressiveness of the protocol with the administration of supportive treatment does not caused life threatening complications.

DISSEMINATED BONE INVOLVEMENT IN PEDIATRIC BURKITT LYMPHOMA: A PEDIATRIC ONCOLOGY GROUP (POG) STUDY.

DESAI S., BOWMAN W.P., SCHWENK M., BERARD C., SHRUTER J., MURPHY S., Cross Cancer Institute, Edmonton, Canada, Cook Children's Hospital, Fort Worth, Texas., Pediatric Oncology Group, Chicago, Ill., and St. Jude Children's Research Hospital, Memphis, TN.

In an effort to further improve outcome for children with advanced B-cell malignancies, a treatment plan consisting of four courses of fructose, cyclophosphamide, doxorubicin and vincristine alternating with sequential high-dose methotrexate and cytarabine, was given in conjunction with intrathecal methotrexate and cytarabine. From October 1986 to October 1992, 133 eligible patients were enrolled: 74 with B-cell (Sig) acute lymphoblastic leukemia (B-ALL) and 59 stage IV small noncleaved cell lymphoma (SNCLL - including Burkitt lymphoma). Seventeen patients were identified from the latter group to have disseminated bone but not bone marrow involvement. In addition to involvement at other sites (jaw, abdomen, chest, kidneys and liver), a median of 3 (1-8) bony sites were involved. These sites of involvement were defined on the basis of clinical and radiographic (bone scan) findings. Also, 2 patients had central nervous system involvement at diagnosis. There were 13 male and 4 female. Sixteen patients achieved complete remission(CR). One patient died of complications 3 weeks from study entry. Two patients relapsed: 1 at 5 months and 1 at 8 months from diagnosis. One patient developed a second malignancy - Acute myelomonocytic leukemia 4 years from diagnosis. A subset of 4 patients received only 3 courses of therapy with G-CSF support - all are alive and disease free. A total of 13 patients are in CCR. The patient who developed secondary acute myelomonocytic leukemia is in remission post allogeneic bone marrow transplantation. Three year EFS (SE of this group of patients is comparable to the larger group of stage IV SNCLL patients 82%+/-12% vs 79%+/-8%). Logrank comparison is inconclusive about the prognostic importance of bone involvement (p=0.7, two-sided).

We conclude that the majority of children with Burkitt lymphoma disseminated to bone can be cured with intensive chemotherapy of short duration (6 - 8 months).

IS DOXORubicIN OF THERAPEUTIC VALUE IN CHILDREN WITH SNCLL LYMHPHOMA TREATED ON NCI PROTOCOL 89-C-41 - PRELIMINARY RESULTS

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From June 1992 to January 1996, 17 children with SNCLL lymphoma were treated at Hadassah University Hospital in Jerusalem. The chemotherapy protocol was a modified version of NCI protocol 89-C-41 in which doxorubicin(DOX) was omitted completely but all other drug dosages were unchanged. Eleven patients(pts) with prolonged neutropenia received G-CSF. The median age was 5 years(range 2-16). The distribution by stage(St.Jude)-II-4, III-10, IV-3. 14 pts were treated on the high risk arm with 4-8 cycles of alternate CODOX-M (A) and IVAC(B). Three children were treated on the low risk arm with 3A cycles. All 17 pts achieved a complete remission (CR). One pt relapsed on therapy and one pt died of sepsis while in CR. Fifteen children out of 17 remain in first CR 1-43 months after diagnosis with median follow up of 29 months. Toxicity was noticeably different from that reported from the NCI protocol 89-C-41. Mucositis was above grade II in only 10 out of 46A cycles and the incidence of documented septicemia was only 5 in 86 cycles. These rates are markedly lower than those observed in the original protocol. Although the number of pts treated without DOX is still small, these preliminary results are consistent with the possibility that DOX adds toxicity without therapeutic benefit to NCI protocol 89-C-41. Further larger randomized cooperative group studies would need to be done to determine the role of DOX in the treatment of SNCLL lymphoma.
Further abstracts

1. Epidemiology / Diagnostic

EPIDEMIOLOGY OF MALIGNANT LYMPHOMAS IN SARDINIA, 1974 - 1993.

All cases of malignant lymphomas (ML) newly diagnosed in the 20 years from 1974 to 1993 have been collected from all Pathology Institutions of the island of Sardinia. Resident population was 1,394,175 inhabitants in the 1981 and 1,648,248 in the 1991 census, with a similar male to female ratio but with a decrease of about 2.5% in age class 0-14 in the 1991 census. In all cases age, sex, residence, histological diagnosis have been taken into consideration; the incidence has been divided in two decades.

HODGKIN'S DISEASE (HD): Mean incidence for year was 34 cases (range 20-49, median 34) in the period 1974-1983 and 44 cases (range 36-53, median 44) in the period 1984-1983. Age adjusted incidence rate (x 105/5 x year) was 2.6 for male and 1.8 for female in the first ten years of our survey and 2.9, for male and 2.2 for female in the second one.

NON-HODGKIN'S LYMPHOMAS (NHL): Mean incidence for year was 63 cases (range 49-80, median 62) in the period 1974-1983 and 124 cases (range 91-161, median 121) in the period 1984-1993. Age adjusted incidence rate (x 105/5 x year) was 5.1 for male and 3.7 for female in the first ten years of our survey and 8.6 for male and 6.4 for female in the second one.

The increase was evident from age groups over 14 years of females and over 24 years in males and was similar in the other age groups and in both sexes. NHL/HIV+ cases accounted for about 1% in period 1984-1993.

The almost stable incidence rate of HD indicates that effects of potential artificial agents (as improvement in diagnostic evaluation or in population access to medical facilities etc.) are likely to have had a small influence on the observed increase in incidence of NHL.

These data demonstrate that also in the Sarдинia population it is evident an increase in incidence of NHL as previously observed in USA and other countries.

The Italian multicenter study on hematolymphopoietic malignancies: incidence rates of non-Hodgkin's lymphomas (NHL) in different Italian areas

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All newly diagnosed cases of NHL, aged 20-74 years, were identified in 11 Italian areas in a three-year period (1991-1993) in the frame of the "Italian multicenter study on hematolymphopoietic malignancies" funded by the U.S. National Cancer Institute (CA 51086). This population-based study included industrialized areas (town of Torino, province of Varese), agricultural areas (provinces of Novara, Verceili, Alessandria, Imperia, Forlì, Siena, Latina and Ragusa) and areas with a mixture of industrial and agricultural activities (provinces of Verona and Fienza). Incident cases were identified through periodic surveys in all the Hematological and Pathological departments of the study areas. Overall, 1823 NHL (55.5% males, 44.5% females) were identified and classified according to Working Formulation (WF). All reported diagnoses were re-examined by one of us (S.d.L) in order to reach a homogenious classification. Diffuse large cell NHL (WF G) and small lymphocytic NHL (WF A) were the most frequent histotypes in this series classified respectively for 21% and 14.4% of cases; 9.8% of cases were not classifiable according to WF. In different areas, NHL incidence rates x100,000 (truncated 20-74 years, standardized on Italian 1991 population) varied among males between 25.4 (Forlì) and 9.3 (Alessandria) and among females between 17.0 (Varese) and 5.4 (Imperia). In the two highest incidence areas, the most frequent NHL histotypes were, respectively, small lymphocytic lymphoma (WF-A, incidence rate 6.4) in Forlì males and diffuse large cell lymphoma (WF-G, incidence rate 3.5) in Varese females.

HISTOPATHOLOGICAL AND MOLECULAR FINDINGS OF NON HODGKIN'S LYMPHOMAS IN ADULTS IN SOUTH VIET-NAM.

In order to study histopathological findings and molecular aspects of non hodgkin's lymphomas (NHL) in south Viet-Nam, 84 cases were collected with paraffin blocks, imprints and frozen tissues from Ho Chi Minh Cancer Center. All cases were classified according to the criteria of the REAL classification. Immunohistopathological studies to detect B and T-cell antigens have been done on paraffin sections, genotypic studies, detection of gene rearrangements (c-myc, bcl-6) and of Epstein-Barr virus (EBV) were performed using Southern blot technique. In situ hybridization with EBV1 has been done to localize EBV positive cells.

Several categories of NHL belonging to precursor and peripheral B and T-cell neoplasms were observed as following:
- 9 cases from precursors: B-lymphoblastic (LB): 3 cases, non-B non-T-LB: 2 cases, T-LB: 4 cases
- 69 cases were peripheral B-cell neoplasms: follicular center cell lymphoma, follicular, 12 cases (2 predominantly small cell, 3 mixed, 7 predominantly large cell), 1 diffuse predominantly small cells, mantle cell lymphoma: 6 cases with "blastic" aspect in 3, 1 diffuse plasmacytic proliferation, 46 cases of diffuse large B-cell lymphoma (LC) with a mixture of centroblasts and immuno blastoids (in 3 cases immunoblastoids were widely predominant), Burkitt's lymphoma: 3 cases.
- 6 cases were peripheral T-cell lymphoma (PTCL) with plasmocytoid aspect ranging from small cells to large cells.

The overall detection of EBV positive in 54 cases was 14%, EBV was absent in LB and BL, observed in 429 LC, and in 3/5 PTCL.

C-myc rearrangement was not detected in the 18 tested cases, but bcl-6 was rearranged in 41% of LC (10/24 tested cases).

This study of adult NHL in south Viet-Nam shows the high incidence of LC NHL with bcl-6 rearrangement, the low frequency of BL and EBV association, except in PTCL.

EPIDEMIOLOGIC ASPECTS OF LYMPHOMA IN JERUSALEM AND ISRAEL.
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The incidence of lymphoma (LY) is increasing in Israel as it is worldwide. The Israeli population is composed of a variety of ethnic/racial groups, native-born and immigrant populations. Population-based data from the Israel Cancer Registry reveals that LY is among the ten most frequent cancers in both sexes. An increase in the incidence of Non-Hodgkin's lymphoma (NHL) is evident among Jewish males, from 7.5/100,000 in 1960-66 to 13.1/100,000 in 1991; among Jewish females the incidence has increased from 5.3/100,000 to 11/100,000 in 1991. During the same period the incidence of Hodgkin's Disease (HD) has been relatively stable, ranging from 2.4-3.4/100,000 in males and 1-2.5/100,000 in Jewish females.

Among the Jewish population, rates of NHL are low in Asian-born men and women, and high in all other groups, including North African-born women (15.1/100,000 in 1991). Rates for HD are low amongst those born in Asia/Africa and high for European/American and Israeli-born Jews. In the latter group the usual male predominance of HD is not evident. Among non-Jews there has not been a substantial change in the incidence of the LY over the last 30 years. A hospital-based audit of demographic, histologic and survival characteristics of 724 LY patients treated at Hadassah University Hospital and diagnosed between 1987 and 1992 was performed. The proportion of cases of HD (27%) was higher than the national figures. A shift toward high grade NHL (20% of cases) among non-Jews, with a relatively paucity of chronic lymphatic leukemia and low grade NHL was noted. For both HD and NHL overall survival was similar to that in the published literature from world centers.
ASSOCIATION OF HODGKIN'S DISEASE WITH EPSTEIN BARR VIRUS IN EGYPTIAN PATIENTS.

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The present study explores the possible role of Epstein Barr Virus (EBV) in pathogenesis of Hodgkin's Disease (HD) in Egypt and the possible prognostic factors monitoring course of the disease. The material included 83 patients with HD with following subtypes: 75 NS, 7 MC and 1 LP. Diagnosis of HD was confirmed by markers studied including Leu M1, Ber H2 and L2. Viral identification was done on formalin fixed paraffin embedded sections by In Situ hybridization technique (ISH), to detect EBV EBER1. IHC was positive in 55/77 cases; a frequency of 71.4%, with no significant difference between nodular class HD versus adult cases 38/53, whereas normal and non-lymphoid malignancy were positive by IISH in 0/8 and 6/42 consecutively. Correlation of stage of the disease with ISH positive staining revealed positive cases in 1/2 stage I, 1/1 stage II, 10/19 stage III and 1/1 stage IV. In 41 ISH positive cases, p53 overexpression was seen in 29 cases (71%), whereas 14 negative ISH cases manifested positive p 53 overexpression in 7 cases (50%). The initial response to therapy was analyzed, 17 patients manifested complete remission, 12 were children, 5 adults. 12 were positive by ISH and 5 were positive for p53. Six patients manifested partial remission, 5 were adults, 2 were positive by ISH and 4 were positive for p53. On follow up, 12 patients manifested no relapses for 12-50 months, 10 were children, 8 were positive by ISH and 4 were positive for p53. Seven cases manifested bad course with frequent relapses and early deaths, 5 were adults, 4 were positive by ISH and 2 were positive for p53. It is concluded that EBV has possible role in pathogenesis of HD through epigenetic mechanism involving p53 overexpression, moreover information of ISH and p 53 have prognostic significance.

INCIDENCE OF NON-HODGKIN LYMPHOMA IN SWEDEN 1958-1992

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In recent years, there has been many reports from Europe and North-America describing non-Hodgkin-lymphoma (NHL) as one of the most rapidly increasing malignancies. The reasons for this are poorly understood. This material describes the incidence pattern of NHL in Sweden during 1958-1992. A total of 26,925 cases (14,854 men and 12,071 females) aged 15 years or older reported to the Swedish Cancer Registry between 1958 and 1992 were analysed. The increase in the age-adjusted incidence during this period was 433% among men and 389% among women, a mean yearly of 4.3% in men and 3.5% in women. The highest rates were seen during the most recent years and in the oldest age group although there was a clear trend with increased age-adjusted incidence over time in both the male and the female groups in ages over 55. The incidence was low in the ages below 35 years. Known etiologic factors are viruses, environmental exposures and immunosuppression. There has been a true increase in the age-adjusted incidence of non-Hodgkin lymphomas in Sweden during the years 1958-1992.

In the age group between 35-54 the increase was about 3.4% among men and 2.7% among women. Between 55-74 years the increase was 3.8% among men and 2.9% among women. In the oldest age group 75 years and older the increase was 4% among men and 3.3% among women. Within a given age group, the age-adjusted incidence rate increases steadily over time in both the male and female group. The highest rate were seen in the most recent years and in the oldest age group, although in the younger age groups the trends are harder to judge because there are less cases. The incidence is low in ages below 30 and after that an increase was seen, with a sharp increase beginning at 55 years and a peak at the age of 80-84 men and 85 or older women. The median age at diagnosis increased from 61 to 71 years in women and from 62 to 69 years in men during 1990 to 1990. This change can only in part be explained by an increased median age of the population.

1. Epidemiology / Diagnostic

IMAGE-GUIDED CORE NEEDLE BIOPSY IN MALIGNANT LYMPHOMA: EXPERIENCE WITH 100 PATIENTS.

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In an initial evaluation of 1500 CT guided core-needle biopsies performed in our institute during the period 1989-1994, we encountered 100 with the diagnosis of lymphoma. Here we review the clinical impact of 109 image-guided needle biopsies in these 100 patients with NHL and HD. Eighty six patients received therapy based on the results of the needle biopsy alone. Fourteen patients received therapy after undergoing surgical biopsy performed because of a suspected diagnosis of lymphoma in an earlier core-needle biopsy. In 78% of the patients the needle biopsy saved a further surgical procedure.

Of the 29 patients with HD, 25 received treatment based on the needle biopsy results alone and 4 after undergoing subsequent surgical biopsy. In all the 25 HD patients with a positive core-needle biopsy the histological subtype could be determined accurately. Ten of the 71 patients with NHL underwent surgical biopsy, after core-needle biopsy proved inadequate, while 61 were treated on the basis of the needle biopsy results alone. In 14 of the 61 positive needle biopsies for NHL, the diagnosis of lymphoma was established definitely however the histopathologic subtype could not be defined with certainty. Nevertheless these 14 cases were eventually diagnosed as nodular and large cell type NHL but nodular and diffuse, patterns could not be distinguished.

It seems from our experience in this study, that image guided core-needle biopsies provide sufficient information for the diagnosis and subsequent therapeutic decision to treat, in most cases of lymphoma.
ULTRASOUND GUIDED FINE-NEEDLE BIOPSY (FNB) OF THE SPLEEN FOR DIAGNOSIS OF LYMPHOPROLIFERATIVE DISORDERS (LPD): REPORT OF 18 CASES.


We report 18 patients with suspected LPD, in whom the spleen was the only or the most accessible organ in which to establish a correct diagnosis. In all cases spleen FNB were performed under ultrasound guide, preferably on focal lesions, using a cutting needle yielding both histological and cytological samples (Histocut 20 gauge, 1 mm diameter).

No complication occurred in this series. A diagnosis of non-Hodgkin lymphoma (NHL) could be established in 11 cases (5 low/intermediate-grade, 4 high-grade, 2 unspecified; 10 B- and 1 NK-phenotype). In one patient a diagnosis of suspected NHL on spleen FNB was confirmed by invasive biopsies. Three other subjects were diagnosed as having Hodgkin’s disease, hairy-cell leukemia, and sarcoïdosis, respectively.

The procedure failed to provide diagnostic informations only in three patients, in one of whom, brucellosis could be diagnosed during the follow-up. We conclude that FNB of the spleen is a safe and highly effective diagnostic approach for patients with suspected LPD without other easily accessible sites or uneligable for more invasive procedures.

THALLIUM-201 MYOCARDIAL TOMOSCINTIGRAPHY (201Tl SPET) BEFORE MANTLE FIELD RADIOTHERAPY FOR Hodgkin’s DISEASE.

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Mediastinal irradiation for Hodgkin’s disease (HD) may predispose patients to premature coronary artery disease. We have previously reported a high rate of abnormalities of 201Tl SPET in conjunction with exercise in a series of 25 patients who had received mantle radiotherapy for HD several years before, supporting silent myocardial ischemia (J-Y Piergl et al. Int. J. Radiat. Oncol. Biol. Phys., 25, pp 871-876, 1993). In order to compare these results to reference explorations, 201Tl SPET has been performed in 13 other HD patients before irradiation. Median age was 25 years (range: 16-39). Ten patients were female, 3 male. There were two stage I, 10 stage II and one stage III. All patients had mediastinal involvement. Nine of them had large mediastinal masses. Of them, 3 had lung involvement (2 stage IE, and one stage IIE). Twelve out of 13 had received chemotherapy before radiotherapy, with anthracycline in all cases (10 MOPP/ABV, 1 ABVD, 1 EBVP). 201Tl SPET have been done before chemotherapy in five patients and after chemotherapy in seven. In all cases, Thallium scintigraphies were performed before mediastinal irradiation. Scintigraphies were assessed in conjunction with exercise except in two cases due to poor general condition of the patients. All exercise electrocardiograms were normal. Scintigraphies were totally normal in 7 patients. In three cases, anterior or infero-apical defects were observed without clear redistribution at rest. In 3 cases, all with bulky mediastinal involvement, anterior defect with redistribution at rest was noted, suggesting reduced myocardial infusion during stress. In one of those three, progressive regression of the defect until normalisation could be observed on scintigraphy performed each year (follow-up: 3 years).

Large mediastinal masses in HD may reduce myocardial infusion and be responsible for ischemia-like cardiac scintigraphic pictures. In addition they could be partly responsible for long-term cardiac scintigraphic abnormalities.

GA-67 SCINTIGRAPHY IN LYMPHOMA

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Ga-67 is an indicator of the viability of lymphoma after treatment. When using modern techniques of SPECT and delayed studies at 7 and 14 days, gallium scintigraphy plays an important role in the management of patients with lymphoma. In our study population of 596 patients, the sensitivity for Hodgkin’s disease and aggressive non-Hodgkin’s lymphoma was 85% and the specificity was 98%. Diagnosis of response to treatment had a sensitivity of 93%, and the sensitivity for diagnosis of recurrence was 90%. In 12 of 41 events of recurrence, Ga-67 scintigraphy was abnormal before all other tests. In low-grade lymphoma, the accuracy was somewhat lower but still useful: sensitivity was 79% and specificity was 94%. Ga-67 is used clinically to determine the nature of a residual mass after treatment and for early diagnosis of recurrence after continuous clinical remission when all other tests are negative.

Scintigraphy after one course of chemotherapy predicts response and could be used potentially to select early patients who are not sensitive to first-line chemotherapy. In conclusion, Ga-67 appears to be a clinically useful test in patients with lymphoma after treatment.

THE ROLE OF Ga-67 SCINTIGRAPHY IN THE DETECTION OF MEDIALNTAL DISEASE IN HODGKIN’S HD/ AND NON-HODGKIN’S LYMPHOMA/HLH


Ga-67 scanning is particularly useful in the staging and monitoring response to therapy of malignant lymphoma. As a dynamic examination it provides information about the nature of residual masses in mediastinum. X-ray and CT scanning are less useful for monitoring therapy in oncologic patients.

Our aim was to compare Ga-67 scan with X-ray and CT scanning done in a group of patients in studies in previously treated HD and NHL patients in order to detect persisting active disease or before therapy to determine prognostic value of Ga-67 scan.

The study involved group of 36 patients with histologically proven HD and 6 with NHL in the age of 17 to 65 years.

The examinations were limited to mediastinum. Planar Ga-67 scans were performed 48 and 72 h post iv injection of 259-370 MBq.

<table>
<thead>
<tr>
<th>HD</th>
<th>NNL</th>
<th>Ga-67 X-ray</th>
<th>Ga-67 X-ray</th>
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</thead>
<tbody>
<tr>
<td>True positive</td>
<td>15</td>
<td>17</td>
<td>13</td>
</tr>
<tr>
<td>False positive</td>
<td>0</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>True negative</td>
<td>13</td>
<td>5</td>
<td>1</td>
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<tr>
<td>False negative</td>
<td>2</td>
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Conclusion: Ga-67 is helpful in determining whether or not a residual lesion in CR represents active lymphoma or fibrotic tissue.
GALLIUM-67 -SPECT IN LYMPHOMA WITH GASTRIC INVOLVEMENT

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Accurate staging of Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL) is important for treatment management. The gallium scan (GS) is significant indicator of disease activity. Both Hodgkin's and non-Hodgkin's lymphoma may involve gastric wall. Traditionally fibrogastroscopy has been used to detect such involvement.

The present study aimed to show the value of Gallium-67 SPECT in lymphoma patient with gastric involvement. We evaluated 30 patients with proven lymphomas using Ga-67 citrate (17 with Hodgkin's disease and 13 with non-Hodgkin's lymphomas). All patients had been verified and staged by histology and imaging methods. In two of them (1 with Hodgkin's disease and 1 with non-Hodgkin's lymphoma) we found gastric involvement before other investigations.

We can conclude that Ga-67 scintigraphy is a sensitive method for detecting extranodal localisation of malignant lymphoma.

LOW GRADE NON HODGKIN LYMPHOMAS AND GALLIUM-67 SCAN AS A PROGNOSTIC FACTOR

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We retrospectively evaluated 53 patients (pts) affected by low grade non Hodgkin Lymphoma (LGL), classified according to Working Formulation as A (21), B (6), C (19) and D (8), admitted to our hospital from 1985 to 1995. The mean age was 61 years (34-81). Conventional staging was performed with clinical evaluation (CE), bone marrow trephine biopsy, CT and Gallium-67 (Ga-67) scan. A semiquantitative scale modified from Wuxman was used for grading Ga-67 uptake by the tumour. The determination of CD1 antigen expression on fresh nodal specimen was performed in 53/53 pts. Most of A pts were watchfully observed without any therapy (15/21), while maturational-based chemoaphoresis was offered to the majority of B, C and D pts (23/32). Overall, Ga-67 scan identified 37/37(100%) of the nodal sites identified by CE and CT. A cut-off value of 3 + in two sites or 4 + in a single site was able to identify pts with poor prognosis. After a mean follow up of 41 months (1-133), the mean survival time (MST) was 67 months in the whole population, 36 in the high score group and 82 in the low score group (p=0.0001). Mean CD 71 values were 8.9 ± 2.7% in the former and 27.4 ± 14.9% in the latter (p=0.0001). The prognostic value of Ga-67 scan was particularly evident in follicular lymphomas (group B, and D) where all but 3 of the 13 pts with high score were dead after a follow up of 41 months (in 2 out of the 3 patients still alive the follow up was shorter than two months), conversely, 13 out of 19 pts with a low score were alive after the same follow up. The predictive value for death of a positive and negative scan was respectively 77% and 79% By contrast, in the lymphoepithelial lymphomas group (A) 1/2/21 pts had a negative scan, and half of them (9/17) died. Thus the predictive value for death of a negative scan was low (47%). We attempted to define a modified WI prognostic score for LGL replacing the stage of disease (5/13 pts were staged III or IV) with Ga-67 scan score (high score=1, low score=0). Accordingly, four groups of pts with different outcome were defined: group 1: score 0, MST 114 months; group 2: score 1, MST 82 months; group 3: score 3, MST 30 months; group 4: score 5, MST 10 months (p=0.0001). In the same population of patients the MST for conventional WILI stage 3 and 4 groups was respectively 42 and 28 months (p=0.001). Thus the proposed prognostic model, although applied to a very small series of pts, more properly identifies a subset of pts that are very bad, as compared to conventional WI.

We conclude that: 1) Ga-67 scan is inappropriate for staging LGL pts; 2) the degree of Ga-67 uptake roughly correlates to the CD 71 expression on lymphoma cells; 3) high score in Ga-67 scan is associated with a poor prognosis in LGL pts, giving new insights in the definition of prognosis of these "indolent" neoplasms.

IS POSSIBLE A NON INVASIVE DIAGNOSIS OF PRIMARY CEREBRAL LYMPHOMA IN HIV POSITIVE PATIENTS? DESCRIPTION OF TWO PARADIGMATIC CLINICAL CASES

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BACKGROUND

The introduction of antiretroviral therapy and opportunistic infections (OI) prophylaxis has greatly reduced the number of HIV infected patients on a longer survival in a condition of progressively higher immunosuppression, and since 1985 an increasing incidence of HIV related tumors has been reported: during the course of HIV disease, 10% of patients (pts) develop Non Hodgkin Lymphomas (NHL) and, among this group, Primary Central Nervous Lymphomas (PCNL) make 15% - 20% of cases, corresponding to 6.4% of focal brain diseases (FBDs).

PATIENTS, METHODS AND RESULTS

Two pts with AIDS and PCNL are considered. Case n° 1: male, age 25 yrs, inacurenant drug user (IDU), in 1993 AIDS IV CDC, in 1994 diagnosis of FBD on neuroradiology, unsuccessful empiric antimicrobial treatment, cerebral biopsy (CB) gave histological proof of PCL and radiotherapy (RT) was undertaken with clinical and radiologic remission; case n° 2: male, age 28 yrs, IDU, in 1993 IV CDC, in 1995 diagnosis of FBD on neuroradiology, unsuccessful empiric antiinfectious treatment, not eligible for CB, EBV-PCR found in the liquor. Histological proof was not available, but, based on clinical features and laboratory and radiological findings, in order to improve life quality of the pts, a 4 GY fraction of RT was undertaken; patient's compliance didn't allow completion of the RT; diagnosis was confirmed only by necropsy. Differential diagnosis of FBDs is based on histological proof. In AIDS pts clinical features and laboratory are specific, but in preliminary studies the presence of the virus in the liquor (EBV-PCR) has been demonstrated in 100% of PCL histologically confirmed. Radiologic findings per se are unreliable, but experiences are growing on the specificity of central Single Photon Emission Tomography (SPECT) in PCL.Tissueplasminogen activator has high prevalence in FBDs in AIDS: it justifies a therapeutic approach ex adveneitais in first, but, in non responsive pts with technically unobtainable FBDs, liquor EBV-PCR and central SPECT can be proposed. If these give a positive result, the antimicrobial treatment be proposed in absence of histological proof?

CONCLUSION

In case n° 1 the classic diagnosis and therapy algorithm for FBDs was followed, the pt died due to OI. In case n° 2 the histological proof for PCL was not obtained in vivo and the possibility of antimicrobial treatment was considered, based on suggestive data from liquor EBV-PCR and neuroradiology. Further controlled studies are warranted to assess the contribution of these diagnostic tools in a possible non invasive diagnosis of PCL.

TUMOUR INHOMOGENEITIES ON MR IMAGING, A NEW FACTOR WITH PROGNOSTIC INFORMATION IN NON-HODGKIN LYMPHOMAS

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Lymphoma infiltrated tissues have different appearance on magnetic resonance imaging (MRI). High grade NHL are often more or less inhomogeneous, most often depending on necrotic areas, while low grade NHL usually have an homogeneous appearance.

The prognostic importance of the inhomogeneities on MRI in NHL was evaluated in 46 consecutive patients with high-grade NHL, and in 13 patients with low-grade NHL at the time of diagnosis. The degree of inhomogeneity was measured with a quantitative method (HOM) (Acta Radiol. 1993, 34: 3-9) and the appearance was also evaluated subjectively.

Patients (n=12) with localized disease (stage I), who had all been treated with radiotherapy, had an excellent prognosis, which was independent of the degree of tumour inhomogeneity, in generalised NHL (stages II-IV), treated with chemotherapy, the appearance on MRI provided prognostic information among all patients and in high-grade NHL. Patients with pronounced tumour inhomogeneity, all high grade NHL, had a very poor prognosis. The histological subtype, viz. low and high-grade NHL, did not influence survival. In a multivariate analysis including all stages, HOM provided prognostic information when tumour stage and grade was considered. In a multivariate analysis among only generalized NHL, including grade, stage and HOM, HOM was the strongest prognostic variable.

The inhomogeneities, easily detected on MRI, may indicate a mechanism for failure to chemotherapy, but not to fractionated radiotherapy.

1. Epidemiology / Diagnostic
POSITRON EMISSION TOMOGRAPHY VERSUS CONVENTIONAL RADIOLOGICAL EXAMINATIONS IN PATIENTS WITH MALIGNANT LYMPHOMAS.

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In order to investigate whether positron emission tomography (PET) may be able to replace conventional staging by a number of examinations as CT-scans, ultrasoundography, x-rays of thorax, abdomen and gastrointestinal tract and thus, may save substantial efforts by the patients without major increases of costs, we designed a comparative study using PET with F-18-FDG versus conventional staging in patients with malignant lymphomas. Patients were examined before treatment, after 3 or 4 cycles of chemotherapy and after completion of radio/chemotherapy. So far, 17 patients were entered into the study. 2 patients suggested to have lymphomas by PET and CT-scans had to be excluded, because the histology revealed tuberculosis. Of the remaining 15 patients, 8 had Hodgkin's disease (7 nodular sclerosing, 1 mixed type) and 7 patients non-Hodgkin’s lymphomas (2 large cell anastrica, 1 MALT, 1 T-zone, 1 B-lymphoblastic, 1 B-cell lymphoma and 1 cl-lymphoma). At diagnosis, in 2/15 cases the different examinations completely corresponded. In 10/15 patients, the procedures showed slightly different results, not influencing tumor stage or treatment.

In 3 patients there were differences concerning the stage: 1. a malignant pleura effusion demonstrated by CT but not by PET; 2. lymphoma of the lung shown by PET but not by other exams and 3. a nodule in the abdomen described by PET, which turned out to be within the thorax by CT scan. 8 patients were studied after 3 or 4 cycles of chemotherapy and 3 patients after finishing chemotherapy. The latter and 4/8 patients after chemotherapy had CR in all procedures. Of the remaining 4 patients 3 had CR by CT-scan, but showed high metabolism in F-18-FDG in several lymph nodes. One patient with MALT lymphoma was described to have residues of lymphoma in the liver and the colon and CR in the stomach by PET. This patient was demonstrated to have only partial remission in the stomach by x-ray of the stomach.

In conclusion, the data so far demonstrate comparable results using PET or conventional diagnostic procedures.

PET-FDG SUBDIAPHRAGMATIC NODAL ASSESSMENT IN HODGKIN’S DISEASE: A COMPARISON WITH LYMHOGRAPHY


Background. Different radiopharmaceuticals have been suggested as potentially evaluable tools for staging different tumors including lymphomas. In the assessment of subdiaphragmatic disease in lymphomas, PET studies with the glucose analogue (F-18) fluoro-deoxy-glucose (FDG) may overcome the limitations of tracers showing a physiologically high abdominal uptake such as Ga-67 citrate.

Aims. To compare prospectively the reliability of PET imaging vs lymphography in evaluating subdiaphragmatic nodal involvement in newly diagnosed HD pts.

Patients and Methods. Whole-body PET studies were performed 30-40 minutes following IV administration of 370 MBq FDG. Up to now 12 patients have been studied (M/F = 5/7; age range 14-65). Bipedal lymphography has been successfully performed in 11 cases. Lymphographic images were evaluated by conventional criteria, and whole body PET-FDG images were assessed for presence of abnormal uptake corresponding to iliac and paraaortic nodal regions.

Results.

<table>
<thead>
<tr>
<th>PET-FDG</th>
<th>Normal</th>
<th>Possibly abnormal</th>
<th>Definitely abnormal</th>
<th>Non-diagnostic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphography</td>
<td>6</td>
<td>2</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

Conclusions. While lymphography remains the gold standard for evaluation of fine structural changes in lymph nodes, our preliminary findings suggest that PET - FDG images can noninvasively provide valuable information for staging HD and can reliably rule out subdiaphragmatic nodal involvement.