## High-grade Non-Hodgkin’s Lymphomas Treated with First Line VNCOP-B Regimen in 350 Elderly Patients: A Prospective Multicenter Study

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### Introduction
Age is a risk factor and a prognostic parameter in elderly aggressive histology non-Hodgkin’s lymphoma (NHL) patients. Several adapted chemotherapy regimens have recently been designed and tested on elderly patients. Several of these trials have shown that older aggressive histology NHL patients can benefit from specific and adequate treatment capable of curing a percentage of these patients.

### Methods
Between January 1992 and September 1997, 350 previously untreated aggressive histology NHL patients >60 years old were treated with a combination therapy including cyclophosphamide, mitoxantrone, vincristine, etoposide, bleomycin, and prednisone (VNCOP-B).

### Results
Complete remission (CR) was achieved by 202 (58%) patients, PR by 87 (25%), whereas the remaining 61 (17%) patients were nonresponders. Overall response rate (CR + PR) was 83%. Clinical and hematologic toxicities were modest, because 71% of the patients utilized granulocyte colony-stimulating factor (G-CSF). The CR rates for the three age groups (60-69, 70-79, and ≥80 years) were similar: 61%, 59%, and 56%, respectively. At 5 years, the relapse-free survival rate was 65% and the overall survival rate was 49%. In the multivariate analysis, prognostic factors associated with longer survival or longer relapse-free survival turned out to be localized disease stage (P=0.001) and good performance status (P=0.0002). The application of the International Prognostic Factor Index was significantly associated with the outcome (P=0.001).

### Conclusions
These data conform to a large cohort of patients that the VNCOP-B regimen is effective in inducing good CR and relapse-free survival rates with only moderate toxic effects in elderly aggressive histology NHL.


**Introduction:** Brief CX and IBRT has been shown to produce superior progression free and overall survival in patients with localized DLCL (Miller NEJM 98: 339-21). We present an 18-year experience with 3 consecutive regimens using brief CX and IBRT.

**Methods:** Eligible patients had limited-stage (I, II, IIIa, IIb, stage I-III, n<10 cm) DLCL. CX from 1/80-7/85 was CHOP x 3; from 8/85-1995, ACBO (doxorubicin 50 mg/m² and cyclophosphamide 320 mg/m² IV d1, w1,3,5, bleomycin 10 U/m² and vincristine 1.25 mg/m² IV d1, w2,4, prednisone 40 mg/m² po x 4) then taper with standard dose cimetidine, ranitidine and loraciguat; and from 9/96-7/99, ACOP-6 (same as ACBO but bleomycin eliminated, remaining IV drugs given q2 w x 3 and prednisone changed to d x 7, then qd x 5w). IBRT to the site of original disease was administered 3-6w later in a dose equivalent to 26Gy in 10 fr. Fractional prophylaxis was given to patients with sinus or epidual involvement.

**Results:** 310 pts (M/F=189/121), median age 64y (range 15-87), 33% ≥70y) received CHOP (65pts), ACBO (149) or ACOP-6 (96). 188 presented with stage I or II, 122 I/II, 204 with III, 215 extra nodal disease. PS was ≤1 in 279 (90%) pts and 252 (81%) had a normal LDH. Of 177 with available immunophenotype, 15% (48pts) were B, 20 T, and 2 null. 98% achieved CR. With a median F/U for living patients of 74mo, the 5 and 10y disease specific survivals (DSS) for all patients are 88% and 81%, and overall survivals (OS) are 80% and 62% with a median OS of 13.8y. The 3 regimens have similar DSS and OS (p=0.52). There were no ≥1 (3.1%) toxic deaths. When adjusted for modified IPil as per Miller the DSS OS are as follows:

<table>
<thead>
<tr>
<th>IPil</th>
<th>5y</th>
<th>10y</th>
<th>15y</th>
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<tr>
<td>0</td>
<td>83</td>
<td>77</td>
<td>54</td>
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<td>1</td>
<td>86</td>
<td>81</td>
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<td>86</td>
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<td>3</td>
<td>32</td>
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<td>59</td>
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The 5 and 10y DSS for patients ≥60y of age are 98% and 94% and for ≥60y are 83% and 73% (p=0.0004).

**Conclusions:** Long term outcome with brief CX and IBRT confirms this is a successful approach for patients with limited stage DLCL. Subgroups of patients with poor prognostic features do less well. A 6 week regimen appears as effective as CHOP.


**Introduction:** Age is a major adverse prognostic factor in patients with NHL. Compared with younger patients, elderly patients present with poor prognostic features, are less likely to respond to therapy and experience greater treatment related toxicity. Prior studies have demonstrated little difference in outcome among various chemotherapy regimens. We carried out a preliminary investigation of IPil (brief chemotherapy by COPA, a short duration low morbidity multi-agent regimen, and compare the outcome to our previously published chemotherapy regimens for elderly patients.

**Methods:** Between May 1993 and July 1998, 66 elderly patients (≤65yrs) were treated with COPA. All patients had biopsy proven diffuse large cell lymphoma with advanced stage disease (Ann Arbor stage III or IV, stage I or II in the head and neck or a ≤210 cm or disease that could not be encompassed in a radiation field). Patients with significant co-morbid illness that precluded the administration of multi-agent chemotherapy were excluded. COPA consists of cyclophosphamide 300 mg/m² IV, doxorubicin 35 mg/m² IV, and vincristine 1.2 mg/m² IV (no cap) every 2 weeks for 4 doses plus prednisone 40 mg/day daily for 7 days and then every other day for 7 weeks. Concomitantly, cetuximab and cetuximab and cetuximab are taken orally throughout the duration of chemotherapy. The comparison group included 170 elderly patients with advanced stage diffuse large cell lymphoma who were treated on one of three previously published protocols (low-dose ACOP-B, VAD and PODEX) from June 1982 to April 1993. Results: Median follow-up for living COPA patients was 14 mos (1-58) compared with 86 mos (26-188) for the comparison group. Median age for COPA patients was 75 y (57-91) and 53% were male. Prognostic factors were as follows: 30% had biliary disease (mass=10cm); 53%, PS ≥1; 67%, stage III or IV disease; 58%, LDH > normal; 30%, ≥1 extranodal site; 72%, IPil score in the high/intermediate or high category. There was no significant difference in age, sex or any of the listed prognostic factors between the COPA and comparison groups. There was only 1 treatment related death (1.5%) in the COPA group (due to sepsis), compared with 11 (6.5%) in the comparison group. Estimated 3-yr freedom from relapse was similar for the COPA and comparison groups, 50% and 33% respectively (p=0.364). Estimated 3-yr overall survival was also similar, 45% for the COPA group and 46% for the comparison group (p=0.877).

**Conclusions:** COPA is an 8-week easily administered chemotherapy regimen that is well tolerated and has low morbidity and mortality. Outcome following COPA is equivalent to that seen with our previously published regimens for the elderly and is similar to what was seen with CHOP. This study demonstrates that brief chemotherapy has efficacy similar to longer duration therapy in elderly patients with large cell lymphoma.
P-VABEC REGIMEN FOR ELDERLY AGGRESSIVE NON HODGKIN'S LYMPHOMA (NHL) PATIENTS. LONG TERM RESULTS OF 131 PATIENTS. M. Martelli, V. De Santis, L. Scracchi, F. Palombi, C. Goliglione, E. pecarmona, C. Torromeo and F. Mandelli. Dipartimento di Biocritica Cellulare ed Ematologia, Università "La Sapienza" Roma, Italy.

Purpose: To evaluate the long term results and the prognostic impact of the age-adjusted International Prognostic Index (IPI) in a continuous series of elderly patients (pts) with histologically aggressive NHL treated with the P-VABEC regimen.

Methods: From 10/1988 to 10/1995, 131 consecutive previously untreated pts with a median age of 66 years (range 65-80) and stage III-IV were enrolled in our study. Histology (according to REAL classification) was: Diffuse large B cells (DLBCL) 99 pts (75%), Burkitt-like (2.5%), Annular Large T cells (T-ALL) 2 (2%) and Peripheral T cell (PTCL) 14 (11%). Diffuse large cells not specified 14 (10%). The P-VABEC regimen was delivered on out-patients basis at Standard Dose (SD) in 101 pts or as increased Dose (ID) in 30 pts. The schedule consisted of doxorubicin (30' or 40' mg/m^2), etoposide (100' or 150' mg/m^2) and cyclophosphamide (330 mg/m^2) alternated weekly with vincristine (1.2mg/m^2) and, blycinomycin (501' or 1507' mg) for a total of 8 courses. Prednisone 50mg daily orally during the entire treatment period. From 10/88 to 12/90 60 pts were treated with P-VABEC-SD, from 01/91 to 12/92 30 pts with P-VABEC-ID and again from 01/93 to 10/95 41 pts with P-VABEC-SD. According to the IPI 131 pts were considered as Low Risk (IPI 0-1) and 45 as High Risk (IPI 2-3).

Results: The CR rate, the probability of OS and DFS at 5 years were respectively 67%, 44%, 35% for the entire group. The 5 yrs OS of the pts treated with P-VABEC SD or P-VABEC ID were 41% vs 31% (P=0.07), DFS 48% vs 22% (P=0.05) and EFS 49% vs 17% (P=0.01) respectively. Treatment-related mortality was 1/101(1%) pts for the P-VABEC SD vs 5/30 (16%) for P-VABEC ID (P=0.002). The 5 yrs OS in the Low Risk IPI compared to High Risk IPI group was 56% vs 34% (P=0.01) while EFS 51% vs 17% (P<0.001).

Conclusions: P-VABEC given on out-patient basis is an active and well tolerated regimen for elderly pts. The P-VABEC ID regimen mainly has increased the treatment-related mortality without an improvement of the efficacy. Patients with a High-Risk IPI score have a significant worse prognosis than Low-Risk IPI pts and for whom a modified treatment strategy may be explored.

AGGRESSIVE LOCALIZED LYMPHOMAS: LONG TERM RESULTS FROM 400 PATIENTS TREATED BY THE TWO GOELAMS 02 & 03 TRIALS. L. Delpratlma, P. Colombat, F. Choutard, A. Le Mevel, Ch. Berthoux, Th. Lamy, Ch. Candillou, F. Guillon, P. Cassen, N. Milpyed, J. Dupuy and S. Tabuteau for the GOELAMS group. Maladiere de Seng - Hôpital Sud - CEHU Amiens - France.

We treated 480 patients (pts) with a localized 'aggressive' NHL (from F to H types, annulat and T peripheral types). All sites were included except CNE, mucosal and cutaneous. DLBCL (238 pts), 232 extra nodal NHL, 232 CR 1A, 115 BI, 170 IA and 36 IB. Sex-ratio was 1.21 and median age 58 years (from 17 to 80). The 323 pts aged less than 65 years received 3 VAP (a double CHOP like regimen) and the 157 more aged pts 3 RMac-VECP (a CHOP like regimen) before a 40 Gray localized irradiation according to the GOELAMS 02 & 03 trials. There is no statistical difference among the two regimens looking at toxic deaths, failures and percentage of patients classified in high risk using chemotherapy and radiotherapy.

The prognostic of the 23 failures is very poor: median survival time is 11 months with only 2 pts alive after more than 2 years. With a median follow-up time about 8 years, we noted 2 non-related deaths (11 in each trials) and the DFS and 'specific' survival rates (SSR) are quite different among our two trials but we must remind that trials were age-dependent.

3. Aggressive Lymphoma and Pediatric Lymphoma


Introduction: The objective of the present study was to identify risk groups in adult patients (pts) with diffuse large cell lymphoma (DLCL) at first relapse (R1).

Methods: We studied 448 patients representing 90% of relapses observed in a decade (88-97) of prospective trials of initial chemotherapy by 4 multigroups and 3 centers in Italy. Median time to R1 was 381 days from diagnosis (Dx), 92% relapsed <3.5 yrs from Dx and 96% were initially treated >3.5 yrs ago. Median age at R1 was 55 yrs (16-85) and median follow-up is 3.3 yrs. Overall response (CR+PR) was 63% (similar in various salvage regimens) and high-dose stem cell transplant (HDSTC) was added in 89 pts. At 3 yrs, overall survival (OS) was 35% and progression-free survival (PFS) was 26%. OS and PFS were compared (log-rank by: histology (WF, hi vs intermedi), relative large B vs peripheral T vs anaplastic CD30+), phenotype (D vs T), time to R1 (<1yrs vs >1yrs from Dx), age at R1 (<65 vs >65), LODH at R1 (N vs >N), stage at R1 (I-II vs III-IV), performance status (PS) at R1 (0 vs 1-2). Age at R1, overall response to salvage chemotherapy and HDSTC intensification were included in the Cox models to adjust factors related to OS and PFS at univariate analysis. Results: Univariate OS and PFS were related with WF histology, with time to R1 and with age-adjusted IPI factors at R1 (LDH stage, age and PS). Multivariate: <1y vs R1 (RR=1.7, CI 95%=1.3-2.2) and age-adjusted IPI >1 at R1 (available in 399) (RR=2.4, CI 95%=1.8-3.2) were adverse factors (AFs). N vs APS at R1 (R,1.2) identified 3 risk groups: group A (APS=0), group B (APS=1) and group C (APS=2). In conclusion, in adults with DLCL at first relapse time to relapse and age-adjusted IPI should be balanced in comparative studies of salvage therapy since they predict risk independently from age, response to treatment and intensification with HDSTC.


Autologous stem cell transplantation (ASCT) has become a widely used treatment modality for primary refractoriness or relapsed NHL, but prognostic factors have not been well described in this setting. In this analysis, we examined the prognostic utility of patient, disease, and treatment characteristics in 170 patients who underwent cytokine-mobilized ASCT for NHL after induction failure or relapse at the University of Nebraska (41 low grade NHL (L NHL), 129 intermediate grade NHL (I-NHL)). The median follow-up of surviving patients is 47 months (minimum 24 months.) The estimated 20 day mortality rate is 2%, but the limited number of early deaths precludes meaningful analysis of their risk factors. I-NHL had a significantly higher risk of relapse (Relative Risk (RR) 3.7, p<0.03) than L-NHL. Among patients transplanted for L-NHL, intermediate risk (two or three risk factors) at the time of transplant by the International Prognostic Index (IPI) was the only statistically significant predictor of the risk of relapse (RR 7.6, compared to low risk, no high risk patients were transplanted, p=0.001). Among patients transplanted for L-NHL, extensive disease at transplant was the only statistically significant predictor of the risk of relapse (RR 1.9 compared to limited disease, p=0.004). Patients transplanted for L-NHL had significantly longer overall survival (OS) (median 83 months, p<0.0009) than patients transplanted for L-NHL (median 25 months.) Among patients transplanted for L-NHL, and treated within six months prior to transplant, resistant disease was suggestive of poorer OS (p=0.06). Among patients transplanted for L-NHL, extensive disease (p=0.008) and elevated LDH level (p=0.05) were significantly related to poorer OS in multivariate analysis. Among L-NHL patients, disease sensitivity, as well as IPI, should be considered in establishing prognosis at transplant. I-NHL patients with IPI intermediate risk may have limited benefit from ASCT and should be considered for allogeic transplant.
INTERFERON α2b VERSUS NO TREATMENT AFTER INTENSIVE THERAPY AND AUTOLOGOUS STEM CELL TRANSPLANTATION FOR RELAPSING LYMPHOMA. PRELIMINARY RESULTS OF AN INTERNATIONAL RANDOMIZED STUDY IN 174 PATIENTS.


High dose therapy (HDT) followed by autologous stem cell transplantation (ASCT) provides excellent survival in relapsing lymphoma compared with intensive chemotherapy. However, second relapse after HDT occurs frequently. Immunotherapy with interferon was chosen in this prospective multicentric (Europe, Australia, New Zealand) randomized trial because of its efficacy in phase II trials. Since October 95 to January 99, 174 patients were randomized to receive either IFNα2b 3.1×10^6 U TIW for 18 months (85 pts) or no further treatment (89 pts) after HDT + ASCT for patients in second remission. Forty-five pts had low grade lymphoma (NLG-1): 6 diffuse small lymphocytic, 2 follicular, 9 mantle cell, 1 mild lymphoma, 88 had high grade lymphoma (NLG-HL): 72 diffuse large B cell, 14 peripheral T, 1 leukemia lymphoma, 1 anaplastic large cell and 41 had Hodgkin’s disease (HD).

Median duration from diagnosis to randomization was 23 months (6 - 188). Seventy-two pts of the 85 randomized pts received effectively IFN. At this time, only 4 pts completed the 18 months of treatment. For these pts, a 90% of the planned dosage could be given.

Relapses after HDT were classified as very early (<3 months), early (3 <6 months) and late (>6 months) and occurred respectively in NLG-LG in 2, 25 cases, in NLG-HL in 12, 12, 12 cases and in HD in 0, 2, 3 cases. With a median follow-up of 10 months, the 2 yrs EFS was 42% (95 CI: 36-48).

At the time of analysis, 153 pts were evaluable with a median follow-up of 11 months. Twenty-four (35) in NLG-LG, 41 (80) in NLG-HL and 31 (35) in HD were alive without progression (aP) after HDT + ASCT. Two-year event-free survival (EFS) was: 87% (95 CI: 40-51) for all the population. EFS for NLG-LG, 32 % (25-39) for NLG-HL and 74 % (65-83) for HD. Separate analysis between the two randomized groups will be performed this year with a longer follow-up.

INTERMEDIATE-DOSE SEQUENTIAL CHEMOTHERAPY IN ELDERLY PATIENTS AFFECTED BY ADVANCED DIFFUSE LARGE-CELL LYMPHOMA.

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Introduction CHOP or similar anthracycline-based chemotherapy regimens induce CR in 45%-50% in elderly patients selected by different criteria (DCLL). The two-year event-free survival, however, is poor ranging between 15% and 35%. Other regimens based on a weekly scheduled sequential chemotherapy, such as P-VEBEC or VAPE-CL, yielded similar or inferior results.

Methods Between February '93 and September '99 96 consecutive untreated elderly patients affected by advanced-stage DCLL were enrolled in a phase II study with the administration of a novel intermediate-dose sequential chemotherapy regimen (IDS) based on six bi-weekly administrations of Cyclophosphamide 40mg/m2 (cycle 2 and 4), VP16-1.5 gm/m2 (cycle 3 and 5) and Fluorouracil in 60 mg/m2. Complete response was achieved in 22 pts (45%) and 7 in 1 pt. with an overall response rate of 88%. Two pts were resistant and died for progressive disease, and 1 died for acute respiratory insufficiency secondary a Gallab-Byrd syndrome. Chemotherapy was given as scheduled, without delay or dose reduction in all pts. Among 22 pts attaining CR, 15 pts were in complete continuous remission with a projected 42-month disease free survival of 54%. 7 pts relapsed and 4 died for progressive lymphoma. After a median follow-up of 23 months 19/20 pts are alive, with a projected 44-month overall survival of 78%.

Conclusions IDS is an intermediate-intensity chemotherapy regimen particularly suitable for elderly pts with advanced stage DCLL. In this pts subgroup IDS proved to be highly effective in inducing a high CR rate and a prolonged survival in absence of severe toxicity.
B-2M has been identified as an important independent prognostic variable for survival in aggressive non-Hodgkin's lymphoma. B-2M is a part of the IPI which is the most widely used prognostic staging system for diffuse large cell lymphoma (DLCL). Since age is part of the IPI, and B-2M levels vary with age, we analyzed the prognostic impact of B-2M on the IPI as well as in 3 age groups. We studied 400 pts with DLCL treated at our institution from 1984-92 treated with conventional doxorubicin-based regimens (or protocols). B2-M and IPI were analyzed for their correlation with survival. Both B-2M and IPI were shown to be statistically significant independent prognostic correlation in the <60 y/o and 60-69 y/o age groups but not in the >70 y/o group. The 5 year survival of pts in the low risk (risk group 0-1) and low-intermediate (risk group 2) of the IPI who presented with low B-2M (<3.0, normal ≤2.0) was 75% and 62% as contrasted with those with high B-2M (≥3.0) in the same risk groups who had 47% and 34% survival (p<0.001 and 0.19 respectively). However, B-2M did not provide any further discrimination within the unfavorable risk groups of the IPI ie risk groups ≥3. We analyzed 3 age groups within the favorable risk categories and found that B-2M correlated well with survival within the <60 and 60-69 age categories but not in the >70 group. We conclude that B-2M is an independent variable which adds further capacity to discriminate prognosis in the favorable categories of the IPI. By incorporating this variable into the favorable groups of the IPI, it is possible to identify a subgroup of patients with elevated B-2M whose survival is as poor as those in the unfavorable IPI categories. On the other hand those with a low B-2M and favorable IPI have an even more favorable outcome than expected if only the IPI without the B-2M had been used. If confirmed in an independent population, these data might justify the use of more intensive

TREATMENT RESULTS OF THE FRENCH NEUROSURGICAL SOCIETY SERIES.

In order to precisely the outcome of patients with primary CNS lymphoma, a large neurological survey was undertaken. A questionnaire was sent to the French & Belgian neurosurgical physicians to get results in the records of 248 cases. All patients were HIV- and had a pathological proven diagnosis. There were 127 women and 121 men. The mean age was 61 years (range 2-88 years). Initial clinical signs were focal neurologic deficit; 70%; neuropsychiatric disorder: 45%; intracranial hypertension: 33%; and epistaxis: 8%. The histological diagnosis was obtained either after surgical resection in 116 patients (46%), or after stereotactic biopsy (54%). 129 patients received chemotherapy + radiotherapy, 60 patients radiotherapy alone and 35 patients chemotherapy alone. 117 patients were in remission after treatment. Survival rates for the 248 patients at 1, 2 & 3 years after diagnosis were 48%, 37% & 27% respectively. Radiotherapy was found to have an impact on survival. Chemotherapy + radiotherapy significantly increased the survival duration. One year survival rate for 5 different treatment groups is shown below:

<table>
<thead>
<tr>
<th>Group</th>
<th>Protocol</th>
<th>Survival rate (1 year)</th>
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<tbody>
<tr>
<td>A</td>
<td>No chemotherapy</td>
<td>37% ± 5%</td>
</tr>
<tr>
<td>B</td>
<td>Miscellaneous chemotherapy without anthracycline, methotrexate, Cytarabine</td>
<td>29% ± 10%</td>
</tr>
<tr>
<td>C</td>
<td>Chemotherapy with anthracycline without methotrexate nor Cytarabine</td>
<td>64% ± 5%</td>
</tr>
<tr>
<td>D</td>
<td>Chemotherapy without anthracycline with methotrexate or Cytarabine</td>
<td>54% ± 6%</td>
</tr>
<tr>
<td>E</td>
<td>Chemotherapy with anthracycline and methotrexate or Cytarabine</td>
<td>65% ± 10%</td>
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In Cox multivariate analysis, 3 independent factors were found to have a favorable impact on survival: age < 60 years, radiation therapy, use of chemotherapy (group C) or methotrexate (group D). The results of this study could be used to elaborate prospective clinical trials.

3. Aggressive Lymphoma and Pediatric Lymphoma

Un治 aggressive mantle cell lymphoma (MCL) presents with frequent gastrointestinal involvement and has high complete response (CR) rates with intensive chemotherapy (IC) without stem cell transplant. JE Romaguera, JP Khouri, HM Kantarjian, PB Hagemeister, MA Rodriguez, PW McLaughlin, AH Sarris, A Younes, J Rodriguez, O Tate, MJ Keating, CA Koller, SA Riggs, R Champlin, and F Cabanillas.

MCL has poor prognosis. We investigated a previously described regimen of fractionated cyclophosphamide with doxorubicin, vincristine and dexamethasone (Hyper-CVAD) alternating every 3 weeks with high dose methotrexate and Ara-C (M-A) for up to 8 cycles. All courses included the use of growth factors and prophylaxis with antibacterial, antifungal, and antiviral therapy. Thirty consecutive previously untreated patients with diffuse or nodular MCL or its blastic variants were enrolled in 2 sequential phase II studies. Median age was 67 with 85% being over 65 years. Eight of 17 patients tested (47%) had gastrointestinal involvement of whom 88% did not have presenting symptoms. Overall response rate was 87% (95% CI 69-96) and the CR rate was 67% (95% CI 47-83). With a median follow-up of 17 months, the 3-year failure-free survival (FFS) for the entire group is 20% and the overall survival is 58%. Hematologic toxicity was significant but only 8% of the cycles were associated with grade 3-4 infection. Treatment related death occurred in 3 patients (10%). In conclusion, gastrointestinal involvement by MCL is more frequent than previously estimated. Hyper-CVAD alternating with M-A is an active regimen. Strategies for eradicating minimal residual disease are needed.

TREATMENT OF INTERMEDIATE AND HIGH GRADE NON-HODGKIN'S LYMPHOMA (NHL) USING CEOP VERSUS CNOP.


Introduction: During the last few years Epstein-Barr (EB) and human cytomegalovirus (HCMV) have been used in the treatment of NHL because of their favourable priliminary clinical profile. Especially M has less severe non-hematologic toxicity.

Patients and Methods: A randomised multicenter phase III study was conducted in order to compare the efficacy and toxicity of CEOP and CNOP in intermediate and high grade NHL. CEOP (arm A) consisted of cyclophosphamide 1600mg/m², E 70mg/m²q 2 days and prednisone 50mg/m²q days 1-5. The CNOP regimen (arm B) was identical to CEOP except for replacement of E by 12mg/m² M. Randomization was stratified according to risk factors defined by IPI (low, low intermediate, high intermediate and high). From September 1993 to November 1998, 228 patients registered for the trial, 216 were evaluable. Patients characteristics were evenly distributed in the two arms, except of age which slightly favoured CEOP arm. Results: There were significant differences between the two groups in the rates of complete remission (CR) and partial remission (PR). The overall response rate was 77% in arm A (56% CR, 20.8% PR) and 80% in arm B (58.2% CR, 22.7% PR). With a median follow-up time of 27.3 months, the median survival has not reached yet in arm A, while it was 34 months in arm B (p=0.03). There was no significant difference regarding the time to progression between the two groups (25.6 months vs 19 months). The therapeutic efficacy of both regimens was equivalent among the four IPI groups. More alopecia was observed in arm A WHO grade 2 neuropenia was more frequent in arm B. Supportive treatment with G-CSF was given to 12 and 15 patients respectively.

Conclusion: There were no significant differences in the rates of CR and PR between CEOP and CNOP in the treatment of intermediate and high grade NHL. Lymphopenia was more frequent in the CNOP group. There was a trend for better survival in the CEOP arm, but further follow up is needed to assess the efficacy of both regimens, especially among IPI risk groups.
FACTORS PREDICTIVE OF EARLY DEATH IN PATIENTS RECEIVING ACV FOR ACTIVE HODGKIN'S LYMPHOMA


Patients treated in the LNH-87 and LNH-93 treated with the intensive third generation ACV protocol were analyzed to determine risk factors of early death. Early death was defined as death for any cause occurring within 3 months of randomization. Among the 183 (7.1%) early deaths. Identified causes of death involved disease progression in 51 patients, treatment-related toxicity in 118 patients, and sepsis in 43 patients. Poor performance status (ECOG>1), disseminated stage, age >50 years, liver involvement, pleural involvement, malignant ascites or pleuritis were all found to be significantly associated with an increased risk of early death. Adverse biological factors at diagnosis included serum albumin <30g/L, increased total serum LDH, serum beta-2-microglobulin >3mg/L, lactate dehydrogenase >850IU/mm3, platelets <100,000/mm3, leukocytes >10,000/mm3, lymphocytes <750/mm3, presence of a monoclonal component in serum. Groups of patients with the highest risks of early death were: PS of 3 or 4 (70% risk of early death), LDH >500 of normal values (20% risk), platelets <100,000 (15% risk), malignant ascites or pleuritis (14% risk), hemoglobin <85g/L (13% risk). The other parameters were associated with an increased risk ranging between 8 and 17%. In a multivariate analysis PS, spleen involvement, serum LDH and beta-2 microglobulin and aspartate transaminase retained prognostic value. The simplified IPI also had a prognostic value for early death, with a risk of 1.5 % for patients with no adjuvant risk factors, 4.3% for patients with 1 factor, 7.1% for patients with 2 factors and 20.3% for patients with 3 factors. Older patients with a poor performance status were at increased risk of early death, with a 11% risk in patients age >65 years and a 50% risk in patients age >70 years. In the subgroup of 32 patients with PS 3-4 and decreased platelets had a 47% risk of early death. Conversely patients under the age of 40 with a PS of 0 or 1 had a 1.6% risk of early death and only one early death was observed in patients under 65 years of age with a factor of the IPI. Some factors were not associated with early death: sex, tumor diameter >10 cm, lung involvement, mediastinal involvement. There was no significant improvement in the incidence of early death between the first inclusions in 1987 to the last in 1997, in spite of the widespread use of growth factors during the last time period. The IPI was the best indicator of risk of early death, in particular in elderly patients and the IPI has prognostic value for occurrence of early death in NHL patients treated with aggressive chemotherapy.

MULTICENTER PROSPECTIVE RANDOMIZED TRIAL OF CHOP VERSUS INTENSIFIED CNOP IN PATIENTS WITH AGGRESSIVE NON-HODGKIN’S LYMPHOMA (ANHL)


For the Hellenic Cooperative Lymphoma Group (HCLG)

INTRODUCTION: ANHLs have been treated with CHOP combination chemotherapy with few modifications of its (CR) rates of aggressiveness. M1 Hodgkin’s lymphoma is an aneurinodendrome, which causes DNA strand breakage mediated by its effects on DNA polymerase II.

PATIENTS AND METHODS: In this preliminary analysis we report on 116 newly diagnosed patients enrolled from 6 centers in Greece. Patients with ANHL were randomized to receive either CHOP (Cyclophosphamide 750mg/m2 iv d 1, Doxorubicin 50mg/m2 iv d 1, Vincristine 1.4mg/m2 iv d 1 and Prednisone 100mg/d for 6 cycles) or CHOP (Cyclophosphamide 750mg/m2 iv d 1, Mitoxantrone 20mg/m2 iv d 1, Vincristine 1.4mg/m2 iv (maximum 2mg) d 1 and Prednisone 100mg/d for 6 cycles). Randomization was stratified according to the international prognostic index (IP: 0-1 vs ≥2). The inclusion criteria were age 15-70 years, intermediate or high grade history other than lymphoblastic or Burkitt’s lymphoma. Primary end points were the objective response rate and the assessment of toxicity. The secondary end points were failure free survival (FFS) and overall survival (OS). All patients were scheduled for 6 cycles of CHOP or CHOP and were subsequently reevaluated. Response was evaluated according to known criteria. Patients achieving a CR were again randomized either to receive interferon-alpha (IFN-α) maintenance (MU thrice weekly s.c.) or not.

RESULTS: Among 116 enrolled patients, 106 were eligible for the study. Their median age was 48 years. ICNOP and CHOP arm were balanced with regard to the potential prognostic factors and FSI. ICNOP rate was 74% in the ICNOP and 70% in the CHOP arm, while overall response rate was 87% and 84% respectively (p=0.66). The 2-year disease-free survival (DFS) was 83% and 74% in CHOP and ICNOP arm respectively (p=0.02). The 2-year FFS and OS were 57% vs 54% (p=0.69) and 72% vs 65% (p=0.21). IFN-α maintenance was administered in 83% of complete responders (23%) of the ICNOP and 15.7% (30%) of the CHOP arm. IFN-α maintenance did not appear to prolong DFS. Toxicity was significantly greater in the ICNOP arm (10 grade 3 and 4 compared to 10% and 6% in CHOP arm respectively).

CONCLUSIONS: ICNOP was equally effective to CHOP in patients with ANHL, as far as CR and short term FFS and OS are concerned. Toxicity was more pronounced in the CHOP arm.

AGGRESSIVE TREATMENT OF HIV-RELATED NON-HODGKIN’S LYMPHOMA WITH THE THIRD GENERATION REGIMEN PROMAC-E CYTOMAB, LONG-TERM RESULTS

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INTRODUCTION: Optimal treatment for HIV-related non-Hodgkin’s lymphoma (NHL) is still uncertain. Intravenous chemotherapy (IC) is the conventional therapy. HIV infection might alter the toxic side effects in HIV-infected patients (pts), and in a recent randomized trial half-dose CTG gave similar results with less toxic side effects than full-dose CT. Since the onset of HIV epidemics we have consecutively treated patients with HIV-related NHL and CTG is our current treatment. Fifteen pts died of HIV-related complications while in CR and 9 are currently alive in continuous CR after a median follow up of 45 months (6-97). At 5 years the DFS is 36% and the OS 25%.

RESULTS: A total of 7 patients were treated with Promac-E-Cytomab (Pro-MAC-E). Five patients of the 53 pts treated with Promac-E-Cytomab were as follows: age 32 (21-47), IDU 40 (75%), CD4 count <500 cells/mm3 in 13/19, previous AIDS 12/19 (63%), WPFI history 32/41 (78%), stage 3 8/12 (67%), 4/12 (33%) high-grade not classifiable; 8 (15%), others: 5 (9%), stage III/IV 40 (75%), LDH1<34 (64%), and did not differ from those of pts enrolled in multistitutional protocols. According to the International Prognostic Index (IP) 57 (70%) were at high risk. Of 48 patients evaluable for response (2 early deaths and at follow up, 2 still on treatment), 36 (63%) achieved complete remission (CR) and 7 (13%) partial remission; the overall remission rate was 77%; 8 pts were non responders and 2 died of toxicity. Six (18%) pts reached current incomplete response, 2 of them died of AIDS. The other 10 died of HIV-related complications while in CR and 11 were currently alive in continuous CR after a median follow up of 45 months (6-97). At 5 years the DFS is 36% and the OS 25%.

CONCLUSIONS: Pro-MAC-E-Cytomab in this series of 53 AIDS with advanced prognostic features (75% IDU, CD4 count <500 cells/mm3, 75% high-risk IP index score) was feasible and worthwhile, giving satisfactory results in terms of remission rate and DFS, with possibility of long-term survival and cure. The recent introduction of HAART can contribute to ameliorate the long-term prognosis of these pts, that remains mostly related to the underlying HIV infection.

3. Aggressive Lymphoma and Pediatric Lymphoma
3. Aggressive Lymphoma and Pediatric Lymphoma

The efficacy of the MEMID regimen for aggressive NHL in the elderly with mitoxantrone 10 mg/m²/day (d) 1, etoposide 100 mg/m² d1-3, mitoguazone 100 mg/m² d1-4, ifosfamide 1 g/m² d1-3, dexamesthanol 40 mg d1-3 has been published previously (ASH 1993, abst. 2288). A multicentric randomized trial was performed comparing MEMID and CHOP like regimens (cyclophosphamide 750 mg/m² d1, epirubicin 70 mg/m² d1, vincristine 1 mg/m² d1 and prednisone 60 mg/m² d1-5). Chemotherapy courses were repeated every 3 weeks in both arms and G-CSF 300 μg was systematically used after each cycle from d6 to d14. From 03/04 to 06/98, 160 patients over 65 years old, with stage II to IV aggressive NHL (groups E,F,G or H of the Working Formulation) and WHO performance status 0-2 were randomized by 23 institutions. Median age was 73 years (65-87). Response and toxicity are assessable for 145 patients (CEOP 75, MEMID 70). The two groups are well balanced for age, stage, pathologic subgroups, B symptoms, internatal prognostic index, LDH level, [B microglobulin level. After 6 cycles, CR or PR > 75 % were reported in 65 % of CEOP patients and 52 % of MEMID patients: difference not significant. With 14 months of median follow-up (0.5-56): median overall survival is 20.6 months with CEOP and 15.3 months with MEMID (log rank, ns).

Neutropenia, anemia, thrombocytopenia and febrile neutropenia occurred significantly more frequently in MEMID group, and lead to the early interruption of this phase III study (ASH 1998, abstract 2563).

The data confirm that CHOP or CHOP-like regimen remains the standard treatment for advanced aggressive NHL in elderly patients.

The POOR PROGNOSTIC SIGNIFICANCE OF BONE MARROW INVOLVEMENT (BM) IN DIFFUSE LARGE CELL LYMPHOMA (DLCCL).

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Intradermal Conventional chemotherapy in advanced stage DLCCL allows prolonged survival in about half of patients (90%), especially those with favorable prognostic factors. The International Prognostic Index (IPI) stratifies pts in risk groups. The adverse prognostic significance of bone BM involvement is not always unequivocal. Patients and methods: Between 1986 and 1993, 246 patients with advanced-stage DLCCL were treated with two conventional chemotherapy regimens: MACOP-B (100 pts) or MACOB (46 pts). The median age was 45 years (range 15-65) and clinical characteristics were: 81% of pts had a performance status (PS) 0-1 and 19% a PS=2, 47% of pts had a LDH level greater than normal, 46% had stage II disease, 21% stage III and 37% stage IV, 52% had a bulky disease and 10% had large cell BM involvement, 19% had focal extranodal sites. According to the Age-Adjusted IPI score, 25% were at low risk, 36% at low-intermediate (LI) risk, 37% at intermediate-high (IH) risk and 8% at high risk (HI) risk.

Results: Median follow-up from 15 months, 35% of pts achieved a complete remission (CR) at the end of the treatment; CR rate decreased significantly through IPI groups: 90% in the LI group, 77% in the LI group, 65% in the IH group and 56% in the HI group. Also 9-pts overall survival (OS), 8-pts disease free survival (DFS) and 7-pts failure free survival (FFS) rates decreased from the low risk group to the high one. OS was 78%, 66% 42% and 22%, DFS was 83%, 00%, 50% and 40% and, finally, FFS was 76%, 54%, 39% and 22% respectively. A Cox multivariate analysis with FFS as end-point was performed. Variables analyzed were sex, age, performance status, PS, LDH level, stage, bulky BM involvement, extranodal sites and Age-Adjusted IPI score. In the whole series of pts the multivariate analysis showed that BM involvement and IPI score were the only significant independent factors affecting FFS rates (P<0.001). Nine-pts FFS rates were 8% and 38% respectively in pts with or without BM involvement (P<0.001). In the LI and HI risk groups BM involvement independently related with FFS in multivariate analysis: BM involvement in IPI (P<0.001) and stage (P<0.05). In the group of pts with an IPI score, FFs were 0% and 65% in pts with or without BM involvement. In the same group BSS was 0% in pts with stage II disease. In the BM and HI risk groups BM involvement remained the only independent prognostic factor in multivariate analysis (P<0.01). In this second group, 9-pts FFS were 42% in pts without BM involvement and 11% in pts with BM involvement.

Conclusions: pts with bone marrow involvement have a poor outcome and they must be considered as factor of worse prognosis. Our data suggest that BM involvement and IPI score should be considered as important factors in chemotherapy for advanced-stage DLCCL. The results are considered in pts at LI and HI risk with further adverse factors such as bulky disease and advanced stage disease.

CONFIRMATION OF A LONG-TERM SURVIVAL ADVANTAGE OF MACOP-B OVER CHOP IN INTERMEDIATE-GRADE NON-HODGKIN'S LYMPHOMA (NHL).

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Introduction: Early reports of randomized studies comparing MACOP-B and CHOP in patients with intermediate-grade NHL have concluded that MACOP-B was more toxic than CHOP but had no overall survival advantage. The ANZLGI trial, presented at the VI International Conference on Malignant Lymphoma in 1996, demonstrated a significantly increased 5-year survival for MACOP-B compared to CHOP and decreased 3-year rate of disease progression. The current report extends the follow-up period by another 3 years.

Methods: The trial accrued 236 eligible patients with intermediate-grade NHL between October 1996 and June 1991. Patients were randomized to receive MACOP-B or CHOP. In the present analysis, the close-out date was 1 July 1998. The estimated median duration of follow-up was 9.4 years.

Results: There is a significant difference in both the 5 year and 10 year overall survival rates between the two arms (P= 0.037 and 0.021 respectively). The MACOP-B survival rate was 55% at 5 years and 46% at 10 years compared to CHOP 41% at 5 years and 31% at 10 years. The estimated percentage of patients who are progression-free at 5 years is also significantly higher for MACOP-B (P=0.004) 43% vs 27% for CHOP. The difference at 10 years is not quite statistically significant (P=0.056), 38% vs 27%. There was no evidence that the superior results for MACOP-B depended on patient's age, nor their International Prognostic Index.

Conclusions: In this update of the ANZLGI randomized trial, patients with intermediate-grade NHL who received MACOP-B continued to show superior long-term results compared with those who received CHOP.
"VANDA" PROTOCOL AS TREATMENT FOR LYMPHOBLASTIC LYMPHOMA (LL) RELAPSES IN CHILDREN TREATED BY SFOP LMT 89 PROTOCOL.


Introduction: The prognosis of relapsed T-cell LL remains poor. A combination of drugs called "Vanda" (Bertrand Y et al, MPO, 1993, 21: poste 157) has been used since 1993 to treat LL patients (pts) after relapsing on the SFOP LMT89 protocol.

Patients and Methods: 22 (1 stage II, 9 at III, 12 at IV) of 88 pts with T-LL treated on the SFOP LMT 89 protocol relapsed. 8 pts relapsing before 1993 were treated with miscellaneous combinations (MC) and 14 pts after 1993 were treated with "Vanda" (VP16: 150mg/m² d, 3, 4, 5; Ara-C: 2mg/m² x 2 d 1, 2; Novantrone: 8 mg/m² d 3, 4; daunomycin: 20 mg/m² d 1, 5 and L-Asparaginase: 10000 U/m² d 7, 9, 11, 13; intrathecal methotrexate and ara-C at 5 if CNS- and twice a week if CNS+). Fisher exact test was performed.

Results: The median time to relapse was 15 months (7 - 48) 11 pts had local relapse (8 with BM+, 1 with CNS+ and 1 with BM+CNS+). 5 pts had isolated BM relapse, 4 pts had isolated CNS relapse; 1 had CNS/ BM relapse and 1 had breast relapse. 2nd complete remission (CR2) was obtained in 1/8 pts (12%) treated with MC which was consolidated by mismatch allogeneic bone marrow transplantation (BMT). All these 8 pts died, 7 from disease and 1 from toxic death. CR2 was obtained in 1/14 pts (78%) treated with Vanda. 1 had a 2nd relapse prior to BMT. BMT (TBI-Ara-C-melphalan) was performed in 10 pts (8 autologous and 2 allogeneic) 4/10 relapsing after BMT and 6 pts (1 isolated BM relapse, 4 with local/BM relapse and 1 with breast relapse) are alive in CR2 (52, 40, 70, 58 and 40 months after BMT). The prognostic factor is the time at relapse > 18 mo (p = 0.009). All the pts with CNS relapse (n = 7) died. No toxic death was reported with Vanda but grade 3 gut toxicity is frequent and all pts had grade 4 hematological toxicity. Conclusion: The toxicity of "Vanda" is acceptable, and the efficacy is good for patients with LL late relapse (> 18 months). BMT may be required to maintain CR and TBI-Ara-C-melphalan is well tolerating option.

MEDIALSTINAL LARGE B-CELL LYMPHOMA WITH SCEROSIS IN CHILDHOOD - REPORT OF 26 PATIENTS FROM THE BFMI-TRIALS.

K. Seidenmann, R. Parwaresch, C. Niemeier, B. Ritte, C. Urban, A. Reiter University children's hospital of Hannover, Freiburg, Munich (Germany) and Graz (Austria). Introduction: Primary mediastinal large B-cell lymphoma with sclerosis (PMLC) is a rare entity of Non-Hodgkin's lymphoma (NHL) arising from thymic mature B-cells. Clinical data and outcome of this rare entity was analysed in a population of pediatric patients with NHL.

Methods: From 04/86 to 03/98 (trials NHL-BFM 86, 90 and 95), 26 patients younger than 18 years with newly diagnosed PMLC have been registered. Treatment was stratified by stage and tumor mass (serum-LDH) and consisted of 4-6 courses of polychemotherapy for B-cell lymphomas (Dexamethasone, MTX (0.5, 1, and 5 mg/m²), Vincluzin, VP-16, CPM, Ifosfamide, Doxorubicine and Ara-C). Radiation therapy was not part of the protocol.

Results: PMLC accounts for approximately 2% of childhood B-NHL. Median age was 14.4 years (range 3-17 yrs). There was no difference in gender distribution (16 female, 12 male). Mediastinal involvement only was observed in 10 patients, additional lung involvement in 7 (27%). Renal involvement was the most frequent extrathoracic manifestation (n=5). CNS- or bone marrow involvement was not observed. 2 pts. diagnosed prior to recognition of PMLC as separate entity received non-B-NHL therapy for lymphoblastic lymphoma and died of progression. Of 24 pts. receiving B-NHL therapy, 1 patient (disseminated disease, vital tumor after 3 courses) died of early progression. 2 pts. relapsed 8 and 14 months after initial diagnosis; one died, the other is alive in 2 remission for 2 years. 20 patients are in 1 CR after a median observation time of 3.4 years; 1 pt was LFP after 5.9 yrs. In 11/20 pts. in 1 CR, residual tumor was still present after 3 therapy-courses, being availed in all 6 cases in which 2nd look-OP was performed.

Conclusions: PMLC is a rare NHL-entity in childhood with a good prognosis. High-dose polychemotherapy for B-cell lymphoma yields an EFS of 79% (SE 0.08). Clinical response is usually excellent after 1-2 courses, small residual mediastinal remnants seem to be of no prognostic relevance. In a minority of cases, response to therapy seems to be extremely poor, however.

NHL IN PEDIATRIC PATIENTS WITH CHROMOSOMAL BREAKAGE SYNDROMES (AT AND NBS) - EXPERIENCE FROM THE BFMI-TRIALS.


University children's hospitals of Hannover, Berlin, Erlangen, Freiburg, (Germany). St. Anna children's hospital Vienna (Austria).

Introduction: Lymphoma and leukemia are the commonest malignant diseases in patients with chromosomal breakage syndromes and immunodeficiency (Ataxia telangiectasia, AT and Nijmegen breakage syndrome-NBS). With improved management of infections, malignant disease is more frequently diagnosed and has become one of the commonest causes of death in pediatric AT and NBS.

Methods: In three consecutive multicenter therapy trials for pediatric NHL (NHL-BFM), 1569 pts. with newly diagnosed NHL have been registered between 04/86 and 10/1997. 9 pts with AT (n=5) or NBS (n=4) were identified and analyzed.

Results: Median age of pts. with AT and NBS at diagnosis of NHL was 9 years; 5 pts were female, 4 male. NHL-entities differed from non-AT/NBS-patients: Diffuse large B-cell lymphoma: n=7, ALC: n=1; lymphoblastic T-cell lymphoma: n=1. Cervical nodes, paranasal sinuses and epipharynx were the sites most frequently involved. Stages were: I and II in 3 pts., III in 5 and IV in 1 patient. All patients received postchemotherapy according to tumor-entity and stage, none received radiation. Dose reductions according to individual tolerance concerned mainly MTX (50% dose, maximum dose 1 g/m²) to reduce corticosteroid toxicity, alkylating agents and epipodophyllotoxines. Outcome and events are:

<table>
<thead>
<tr>
<th>Patients (n=9)</th>
<th>Toxic death</th>
<th>Progr./Rel.</th>
<th>2nd malignancy</th>
<th>1. CR*</th>
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<td>1</td>
<td>2</td>
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* median follow-up of 5 years (range 1-10 years)

Conclusions: Diffuse large B-cell lymphoma is the predominant subtype of NHL in patients with AT and NBS. Curvilinear treatment is possible all patients should be attempted with intensity of therapy adjusted to individual tolerance. Alkylating agents, epipodophyllotoxines should be omitted, dose of MTX should be limited to 1 g/m². Further cooperative trials using standardized approaches are required.

RELAPSE OF CHILDHOOD B-CELL LYMPHOMA (BCL) AFTER INTENSIVE FIRST LINE TREATMENT (T1). EXPERIENCE OF THE FRENCH SOCIETY OF PEDIATRIC ONCOLOGY (SFOP) IN THE LMB89 PROTOCOL.

C. Patte, D. Frappaz, Y. Bertrand, G. Leverger, C. Coze, J. Michon, P. Boulard, A. Babin-Bouillet, A. Beruchel, A. Thys, L. De Lumley, on behalf of the SFOP.

Introduction: with intensive polychemotherapy regimens, outcome of the pediatric patients (pts) with BCL improved greatly and relapses became rare. Are these relapses still curable?.

Purpose: to review clinical data, treatment and outcome of the pts who relapsed in the LMB 89 protocol.

Methods: 555 pts with previously untreated BCL were treated between July 1989 and June 1996 in the LMB 89 protocol. Initial T1 was stratified in 3 groups (g): A, B and C, depending on stage and resection. In g A and B, 1st CR of relapse was the CYVVE regimen (Ara-C high dose (HD) and continuous infusion + VP16). In g C, T1 was more heterogeneous as CYVVE was part of the initial T1. After 2nd CR was achieved, pts underwent HD chemotherapy (CT) with hematopoetic stem cell rescue.

Results: 28 pts relapsed: 1 g (2% of pts of the g), 19 g B (5%) and 8 g C (8%). Histology was Burkitt's, <1 middle size or BCL, 4 large cell, 4 and not subclassified BCL. 4. Site of relapse was isolated in 16 pts (local or regional), 5 bone marrow, 1 CNS, 7, and multiple in 12. Median time of relapse was shorter in Burkitt's and in 26 in large cell. 3 pts died of toxicity, 8 did not achieved CR and subsequently died. 17 pts (1 g A, 14 g B and 2 g C) achieved 2nd CR and received HD CT (13 BEAM + radiotherapy, 3 Busulphan+Melphalan+Ara-C, 1 TBI+Melphalan+Ara-C). Presently, 7 pts (25% of the relapses) (1 g A, 5 g B, 1 g C) (4 Burkitt's, 1 middle size BCL, 2 large cell) are alive in CR with median follow-up of 5 years (2-8y). All had only one site of relapse (local or regional, 5 CNS: 2) and all but one needed only one line of relapse T1 to enter 2nd CR.

Conclusion: with present effective polychemotherapy regimens, relapses of BCL are difficult to cure all the more relapse sites are multiple and previous T1 more intensive. More efficient T1 still needs to be found.
Treatment Results Of Childhood Anaplastic Large Cell Lymphoma. Ten-year Experience of Polish Pediatric Leukemia / Lymphoma Study Group.


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Anaplastic large cell lymphomas (ALCL) constitute the particular clinical and histological entity. The cure rates of this type of NHL is evidently less satisfactory than for B lineage NHL. For these reasons there is need to search newer and more effective treatment strategies for children with ALCL. The retrospective study was undertaken to evaluate clinical treatment results of children with ALCL registered in 9 oncohematological centers of Polish Leukemia/Lymphoma Study Group during the years 1987–1988. The studied group comprised 55 children with ALCL aged from 5 to 18 years (median: 12.8 years). The diagnosis was based on histomorphological investigation supplemented with immunophenotyping. The clinical staging system of S. Murphy was used for prognostic stratification. Twenty-six patients (pts) diagnosed in years 1991-1998 were treated according to BFM-90 regimen for ALCL; nine children before 1992 were treated according to BFM-86 protocol (6: B-NHL, 3: NB-NHL).

Six children presented in stage I (17.7%), 27 in stage III (47.2%) and 2 in stage IV (5.3%, both with bone involvement). The primary sites of disease included: mediastinum - 12 pts (34.3%), abdomen - 12 pts, lymphnodes - 7 pts (20%), skin - 2 (5.7%). Two children had disseminated disease at presentation. Twenty-nine pts entered complete remission (82.9%) and 3 partial remission (8.6%). Two pts (5.7%) with extensive tumor of mediastinum and lung involvement did not respond to therapy and died because of progression. One early toxic death due to infection immediately after the first course of intensive chemotherapy occurred. Ten pts (34.5%) experienced a recurrence: 5 pts under therapy and 7 pts in 2-8 months after the completing of the treatment. In five cases the relapse occurred in primary site. Three of 10 relapsed pts achieved II remission following second line therapy, 5 pts died of progression. A total of 8 pts died (22.9%). Causes of death were progression in 2 non-responder pts, sepsis in 1 pt before complete remission and progression after relapse in 5 pts. The 10-year event free survival rate in the whole group, with a median follow up of 46 months (range 1 - 125), is 54±5%. Conclusion: The long-term prognosis in pts with ALCL remains unfavorable. There is a high risk of relapses observed in the short time after the cessation of therapy. New treatment approaches for this group of patients is to be found.
MOLECULAR RESPONSE RATE OF FOLLICULAR LYMPHOMA TO CENTRAL LYMPHATIC IRRADIATION (CLI) AS MEASURED BY FLUORESCENCE CHAIN ALEXA FLUOR® 488 (F(488)) INVOLVING Bcl-2 ONCOGENE

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**Introduction:** More than eighty percent of patients with follicular lymphoma have t(14;18) (q32;q21) at the major breakpoint region (MBR) or minor cluster region (MCR) deoxyribonucleic acid (DNA) changes. A study was undertaken to assess molecular complete response rates of stages I-II follicular lymphoma to CLI by PCR evidence of this marker in the bone marrow and peripheral blood.

**Methods:** Thirty three patients with stages I-II follicular lymphoma were treated with CLI. Bone marrow and peripheral blood samples were obtained before and after CLI for PCR analysis for the DNA sequences that flank the bcl-2 MBR or MCR of this translocation. In PCR-positive patients, bone marrow and blood samples were followed at regular intervals during and after CLI and the results were correlated with clinical findings.

**Results:** All 33 patients achieved complete clinical response after CLI. Median follow-up was 42 months (range 9 to 64 months). Ten patients relapsed. A total of 71 PCR results were available. Pre- and post-CLI PCR results were available in 27 patients, 21 of which were positive before CLI. Nineteen of the 21 patients had at least one follow-up PCR three or more months after CLI started. For all the patients with positive pretreatment PCR, (1) there was a clear, monotonic decreasing trend toward a lower proportion of PCR positive tests (35% at 4 years) with increasing time after treatment, (2) there was a trend toward earlier relapse among patients who still had a positive PCR 9 months, though these differences were not statistically significant. Further experience with the different types of the PCR results in these patients is needed to determine which patients were truly positive and those who did not.

**Conclusion:** These data suggest that molecular complete response is gradually achieved over years after CLI. The prognostic significance of the observed conversions would require longer follow-up.

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RESPONSE DURATION (RD) IS THE MOST IMPORTANT FACTOR TO PREDICT OVERALL SURVIVAL (OS) IN FOLLICULAR LYMPHOMA (FL)

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**Introduction:** FL patients in advanced stage are not curable with current therapies, but they can survive for a long time, with a median OS of 8 years. Although several new treatments may improve these figures, its toxicity is considerable and they should be used in selected cases. In addition to standard prognostic factors, evolutive variables, such as RD, may be important to select patients candidates to intensive new therapies.

**Patients and Methods:** Patients (N=57 M/55 F; median age: 55 yrs) consecutively diagnosed in a single institution of advanced stage (III-IV) FL (grade: 1; 42%, II; 49%, III; 4%, undifferentiable, 1%) were analysed. Extramedullary involvement was diagnosed in 81%, including bone marrow in 76%. Treatment consisted of alkylating agents in 28 cases, combination chemotherapy in 25, adriamycin-containing regimens in 96, and other in 12.

**Results:** Among 153 assesseable patients, 53 (35%) reached complete response (CR), and 75 (49%) partial response (PR). After a median follow-up of 5.4 yrs, 80 patients presented with relapse/progression, the median failure-free survival (FFS) being 2.6 yrs. Eighty-year-OS was 45% (SE: 5.2). The main initial variables predicting both FFS and OS in multivariate analysis were age (p<0.01), and serum LDH (p<0.01). No differences were found according to the treatment. Patients responding to therapy had OS longer than nonresponders (median OS: 3 yr. 8 yr. 7 yrs: p<0.001). Among responders, patients in CR showed a trend of longer OS than those in PR. Median OS not reached and 7.5 yrs, respectively). The OS from the time of response (CR/PR) was analyzed using a landmark method. Patients in whom DR<1 year had a OS from response significantly shorter than those with DR>1 year (8-yr OS from response: 22% and 44%, respectively, p<0.001). The initial prognostic factors, the response to treatment (CR or PR) and DR were included in a multivariate analysis, with DR emerging as the most important variable to predict OS from response (p<0.001).

**Conclusions:** DR<1 year is the most important unfavorable variable to predict OS from response in advanced stage FL patients and, therefore, it may be useful to select candidates to intensive treatments.

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IMMUNOPHENOTYPIC CHANGES AND HISTOLOGICAL PROGRESSION OF NON-HODGKIN'S LYMPHOMA (NHL) FOLLOWING ANTI-CD20 MONOCLONAL ANTIBODY (MoaB) THERAPY WITH RITUXIMAB (MoAb)

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**Introduction:** CD20 is present on virtually all B-cell NHLs, and is the target of rituximab (Rmb), a chimeric MoAb. Following an observation at SBH of CD20-negative (CD20-) disease after therapy (Rmb with Rmb, & late progression with peripheral T-cell lymphoma) (PTCL), an analysis of phenotype and histology at progression after Rmb was undertaken.

**Materials:** 67 patients (pts) with CD20-positive (CD20+) NHL, (n=33); lymphoplasmycytoid, n=14; mantle cell, n=12; small lymphocytic, n=4; & diffuse large-cell lymphoma (DLCL), n=4) received Rmb at SBH between 12/96 & 7/99. The median age was 56 years (range 35-63 years), and 72% were male. Relapse at progression (PD) following Rmb was undertaken whenever feasible. Immunophenotyping was performed following Rmb in 28 pts using the diagnostic MoAb L20, which recognises the intracytoplasmic portion of CD20 in fixed tissue. The specimens studied include; bone marrow (BM) in 2/7 pts with persistent NHL infiltration; lymph node (LN) in 19/20 other pts who developed PD and underwent biopsy; and post-mortem (PM) examination in 1 pt following splenic rupture before the last infusion of Rmb.

**Results:** Changes in CD20 phenotype were seen in 5/28 pts after Rmb. In 1/5, persistent BM infiltration following Rmb was CD20-, and in another the tumour cells were heterogeneously CD20+ (ie. some were CD20+). At LN biopsy at PD, tumour cells in 1 pt were heterogeneously CD20+ (ie. some were CD20+), and another died of an aggressive and disseminated PTCL (CD2+, CD3+, & CD4+, CD8+). CD20+ in 1 pt at PD was in 1 pt. The remaining, 1 at PM immediately following Rmb, all tumour cells were CD20+ (ie. B cells), but heterogeneously CD20+ (most were CD20+). CD20+ adenocarcinoma pts with PD after Rmb developed histologic transformation to CD20+ DLCL.

**Conclusions:** CD20-negative post-Rmb NHL may develop in some pts early after Rmb and there is a risk of late progression with PTCL. Pts with PD after Rmb should therefore undergo re-biopsy and immunophenotyping whenever possible, particularly re-treatment with Rmb was contemplated.
A PHASE II STUDY TO EVALUATE THE COMBINATION OF FLUDARABINE, MITOXANTRONE AND DEXAMETHASONE (FMD) IN PATIENTS WITH P polycoccic LYMPHOMA (FL). C.R. Crowley1, J.M. Foran1, A.Z.S. Rohatiner1, J.A. Radford2, S. Johnson1, P.W. Johnson1, J. Matthews1, T.A. Lister1. 1ICRF Medical Oncology Unit, St. Bartholomew’s Hospital, London, UK. 2Christie Hospital, Manchester, UK, 3Taunton and Somerset Hospital, Taunton, UK, 4Royal South Hants Hospital, Southampton, UK.

Aims: An open Phase II Study of FMD has been conducted in patients with FL to confirm the previously reported response rate.

Patients and Methods: Fifty six patients (median age 50 years, range 27-69 years, 48 with recurrent or resistant FL, 8 with newly diagnosed FL) have received FMD. Previously treated patients had received a median of two prior regimens (range 1-10); the most recent having failed in 16 pts. Treatment comprised a maximum of 7 cycles of Fludarabine: 25 mg/m2, days 1-3, mitoxantrone: 10 mg/m2, day 1 and dexamethasone: 20 mg, days 1-5. Routine Pneumocystis prophylaxis was given.

Results: Outcome data are available on 44 pts; 2 are not evaluable for response, the remainder are still receiving treatment. The overall response rate was 27/44 (61%), complete responses being seen in 9 pts (20%). The response rate in newly diagnosed pts. was 5/7 (71%), in chemosensitive relapse 13/16 (81%) and in chemoresistant disease 6/16 (38%). Initial toxicity has been moderate and primarily haematological. Thirty-eight percent of pts. required admission during treatment; there were no treatment-related deaths. In 12 pts, subsequent mobilisation of peripheral blood progenitor cells (PBPC) using G-CSF alone (16 µg/kg/day x 4 days) was attempted prior to high-dose therapy. Adequate numbers of CD34+ve cells (>1 x 10^7/kg) could not be collected in 6 pts. Clinical data will be presented on all 56 pts., with molecular follow-up for those with evidence of a bcl-2 rearrangement.

Conclusions: FMD was well tolerated. However, the response rate in this patient population was lower than expected and collection of PBPC subsequently was difficult.

STAGE I AND II POLYCHROMATIC LYMPHOMA: LONGTERM OUTCOME AND PATTERN OF FAILURE.

T. Lipuner, M. Gospodarowicz, M. Pittile, B. Patterson, A. Bezjak, R. Tsang, W. Wells and the PMH Lymphoma Group

Princess Margaret Hospital, The Toronto Hospital and University of Toronto, Toronto, Canada.

Introduction: Localized follicular lymphoma (FL) has an indolent course with a long median survival. The purpose of this review is to assess the ability of radiation therapy (RT) to control disease.

Methods: We analyzed the records of 596 patients (pts) with stage I and II FL treated between 1967-1996. Median age was 58.9 years (range 17-86). Median follow-up was 10.3 years (range 0.7-28.3). Stage of disease was: 379 IA, 41 IB, 199 IIA and 14 IIB. Histology was: 197 follicular small cell (FSC), 189 follicular mixed (FM) and 210 follicular large cell (FLC) lymphoma. 462 pts presented with nodal and 134 pts with extranodal sites. 717 of pts were treated with involved field RT alone to a median dose of 35 Gy.

Results: Median overall survival (OS) and disease free survival (DFS) was 15.3 and 6.8 years respectively. 336 pts were alive at time of analysis, 152 died of lymphoma. In the RT alone cohort OS and DFS were 15.7 and 6.6 years respectively. 93% of relapses occurred in distant sites. In a multivariable analysis age >50, bulk >2cm and stage IIA ext disease predicted for high risk for relapse and a poorer cause specific survival (CSS). Time to relapse following RT alone was predictive for long term survival: median CSS for relapse at ≤ 2 years was 6.1 years, for relapse at > 2 years was 13.5 years.

Conclusions: Younger patients with small bulk (<2cm), stage I or IIA localized and FSC-FM with PHL at a lower risk for relapse or death of lymphoma. No significant survival differences were observed between FSC, FM and FLC. RT alone provides long-term disease control in localized FL in over 40% of pts.
Radioimmunotherapy of Relapsed or Refractory Non-Hodgkin's Lymphoma

L. Elezovic, A. Pecoraro, J. Kordula, M. Tschopp, F. Pfister, and M. Durrant

INCIDENT OF HISTOLOGICAL TRANSFORMATION AT FIRST RELAPSE IN FOLLICULAR LYMPHOMA PATIENTS INCLUDED IN THE PROSPECTIVE GELF 86 PROTOCOL

C. Belanger, D. Simon, P. Brice, B. Bouabdallah, C. Hainaut, H. Tilly, O. Romain, C. Martin, N. Broussesh, Ph. Solal-Celigny, GELA, Centre Hayem, Hospital Saint Louis, Paris, France

Preliminary Results from a Prospective Randomised Phase III Trial of Fludarabine vs CVP Chemotherapy in Newly Diagnosed Patients with Ann Arbor Stage II or IV Low Grade NHL

R. Mancuso, E. Dabaghian, R. O'Meara, G. Huguenin, A. Anagnostopoulos, M. von van Ginkel and A. Hagenbeek on behalf of the EORTC Lymphoma Group, HOVON (NL), NBLI (UK)

We present the preliminary results of a randomised comparison of Fludarabine vs CVP in 381 patients with low grade NHL. Patient eligibility criteria for entry were: age older than 18 years, histology IWF groups A, B or C (CLL excluded) and stage III or IV disease. Patients were randomised between Fludarabine 25 mg/m^2 daily for 5 days and 5 days CVP chemotherapy; Cyclophosphamide 750 mg/m^2 day 1, Vincristine 1.4 mg/m^2 day 1, Prednisolone 40 mg/m^2 days 1-5. Both were given every 4 weeks for 8 courses. Patients were randomised and treated either immediately after diagnosis or after a period of 'watch and wait'. Patients were only allowed to be staged by entry and after the last course of treatment by clinical examination, CT scan and bone marrow biopsy. 381 patients were entered by 60 centres in 9 countries between April 93 and January 97. 72 patients were excluded because of inadequate or inappropriate histology. Patients were analysed in the two groups according to intention to treat analysis. In the Fludarabine group the overall response rate was 69% (39% CR, 30% PR) and in the CVP group the overall response rate was 53% (17% CR, 36% PR) (p = 0.01). Response rates were not different between the groups treated at diagnosis or after a period of 'watch and wait'. The median follow-up is now 570 days since randomisation. Who haematological toxicity was observed more frequently in the Fludarabine arm with more patients suffering from grade 2+granulocytopenia and thrombocytopenia (p = 0.01). Significant alopecia occurred only in the CVP group. Overall 50 patients have died; 24 from NHL, 2 from secondary malignancy, 3 from complications of treatment, 4 from another disease and 17 from a variety of other causes which have not yet been fully analysed. Fludarabine is an effective single agent for newly diagnosed patients with low grade non-Hodgkin's lymphoma, with a higher response rate than CVP. Its impact on overall survival remains to be established. If these results are confirmed on longer follow-up, Fludarabine may be a useful single agent in the treatment of low grade NHL but have impact on long term survival. It should now be evaluated in new combination regimens to assess its true role in the management of low grade NHL.

Introduction: Between 01/93 and 03/96, 81 consecutive patients (pts) (NMF: 42/39) up to the age of 60 yr (median 48 yr, range 24 to 59) with advanced stage low grade and mantle cell lymphoma were enrolled at diagnosis on treatment with CPF: cyclophosphamide 1 gm/m² iv and prednisone 40 mg/m²/d po x 5 was followed in 3 weeks by fludarabine 25 mg/m²/d iv x 5. CP was reintroduced 4 weeks later and therapy thus alternated to a total of 8 cycles (4 of each). 62 pts had follicular histology, 9 small lymphocytic and 7 mantle cell. 57 pts had stage IV disease, 19 stage III and 5 extensive stage II. 14 pts had B symptoms, 53 bone marrow involvement, 9 serum LDH > normal and 17 bulky disease (> 10 cm). 73 pts had an ECOG performance status of 0 or 1.

Results: 79 pts completed the planned treatment. There was no alopecia, febrile neutropenia or toxic death. With a median follow-up of 45 months (range 1 to 72), 34 pts remain in first complete remission, 34 are alive after 1 or more recurrences, 11 have died of disease and 2 are lost to follow-up. The failure-free survival for all pts is 62% at 3 yrs and overall survival (OS) at 5 yrs is 83%. This compares favorably to a 69% OS for a matched historical control group (130 pts) treated between 1980-85 with an initial plan of observation followed by oral Chlorambucil for symptomatic disease progression (p<0.05). The results are similar to those produced at our institution with aggressive chemotherapy (BP-VACOP) and extensive radiotherapy.

Conclusions: CPF is well tolerated and produces survival outcomes similar to more aggressive combined chemotherapy/radiotherapy strategies. Exploration in combination with targeted novel therapies would be feasible.

A MULTICENTER, RANDOMIZED TRIAL OF FLUDARABINE (FLU) VERSUS FLUDARABINE AND IDARUBICIN (FLU-ID) AS FIRST-LINE TREATMENT IN PATIENTS WITH LOW-GRADE NON-HODGKIN LYMPHOMA (LG-NHL).

P.L. Zinzani on behalf of the Italian Cooperative Study Group on Lymphomas, Institute of Hematology and Medical Oncology “Serafino”, University of Bologna, Italy.

Introduction: FLU has been shown to be an effective agent in the treatment of indolent lymphoma, either used alone or in combination with other drugs. Methods: From 9/95, 185 patients aged 25-76 (median 55) yrs with newly diagnosed stage II bulky IV LG-NHL, standard risk according to the IPI, were enrolled in this multicenter, I:1-randomized study. Of the 173 patients currently evaluable, 88 were allocated to the FLU arm to receive 6 monthly cycles of FLU 25 mg/m²/d on days 1 to 5, while 85 were allocated to the FLU-ID arm to receive 6 monthly cycles of FLU 25 mg/m²/d on days 1 to 3 and ID 12 mg/m²/d on day 1. The two groups were comparable in terms of histological types, stage, extranodal site involvement, age and sex distribution. Clinical response to treatment was evaluated immediately after completion of the chemotherapy schema and defined according to 3 categories: CR, PR and failure. Results: Accordingly, 37 of 88 (42%) patients on the FLU arm and 28 of 85 (33%) on the FLU-ID arm achieved a CR, while on both arms 36 patients (41% and 42%, respectively) achieved a PR. Moreover, an in-depth analysis of the clinical response with respect to histological type showed that FLU treatment appeared to be more effective than FLU-ID against follicular lymphoma (54% vs. 10% CR). No differences were observed for the remaining histological types. Furthermore, no striking differences were observed for any histotype between the 2 protocols in terms of overall response (CR+PR) and toxicity, which was generally mild. However, with a median follow-up of 12 (range: 5-31) mos, only 21 (57%) patients who received FLU alone have maintained their first CR, as compared to 25 (89%) of those who received FLU-ID therapy.

Conclusions: We conclude that although the FLU-ID regimen may not significantly improve the induction of CR in most LG-NHL patients, our preliminary data do suggest that with respect to FLU alone it may be capable of conferring a longer-lasting, and thus better-quality, CR.

PHASE III TRIAL COMPARING FLUDARABINE TO CVP IN PATIENTS WITH RECURRENT LOW-GRADE NON-HODGKIN'S LYMPHOMAS (211-1).

R. Klasa, R. Meyer, C. Shustik, C. Sawka, A. Smith, J.F. Grenier, S. Bérubé. British Columbia Cancer Agency, Vancouver, Canada; Hamilton Regional Cancer Centre, Ontario, Canada; McGill Oncology Group, Montreal, Quebec, Canada; Toronto-Sunnybrook Regional Cancer Centre, Ontario, Canada; London Regional Cancer Centre, Ontario, Canada; Berlex Canada Inc. Montreal, Quebec, Canada.

Objective: The aim of our study was to compare the safety and efficacy of fludarabine (F) to cyclophosphamide-vincristine-prednisone (CVP) in previously treated patients with recurrent aggressive LG-NHL.

Methods: Patients who had responded to all prior regimens were stratified according to age (<60, >60), number (1-4) and type of previous chemotherapy (+/− anthracyclines) and randomized to receive F (25mg/m² IV x 5 days every 28 days) or C (75mg/m² IV x 1 day). V (1.2mg/m² IV x 1 day) and P (40mg/m² p.o. x 5 days) every 21 days for 4 to 10 cycles. Response, toxicity, progression-free (PFS), treatment-free (TFS), overall (OS) survival and quality of life (QoL) were assessed.

Results: 91 LG-NHL patients (78% follicular lymphomas) were enrolled (F=47 CVP=44). Overall response rate was 62% (CR+PR%) with F and 52% (CR+PR%) with CVP (p=0.71). Nausea, vomiting, alopecia and neurotoxicity were more frequent with CVP while infections were more frequent with F. No difference in grade 3-4 toxicity was detected. At 2 years, PFS was 32% (median=11 months) with F and 14% (median=6 months) with CVP (p=0.03). TFS was 41% (median=15 months) with F and 70% (median=11 months) with CVP (p=0.03) and OS was 70% with F and 75% with CVP (p=0.74). 19 deaths were reported with F (16 due to lymphoma and 3 due to treatment toxicity) and 17 with CVP (all due to lymphoma). QoL (rated by the EORTC-QLQ-C30 questionnaire) was high in both groups. Similar patterns were obtained between groups during the study except for social function (SF) (p=0.008) which was inferior in the CVP group during treatment.

Conclusion: F and CVP produce similar response rates in previously treated patients with lg-NHL. At 2 years and TFS are superior with F; no difference in OS was observed. QoL is similar with either treatment except for SF which improved with F during treatment, possibly because of lower incidence of nausea, vomiting and alopecia.

Effect of in vitro exposure to interferon alpha (IFNa) on CD20 expression in Chronic Lymphocytic Leukemia Cells (CLL).

S. Sirvakan, P. Venugopala, X. Huang, S. Gregory, A. Jain, H. D. Preider. Rush Cancer Institute & Cook County Hospital, Chicago IL 60612, U.S.A.

Although chimeric CD20 monoclonal antibody is an established therapy in relapsed low-grade non-Hodgkin's lymphomas (NHL), only 50% of patients respond. Augmenting or inducing CD20 expression on CD20 negative tumor cells may improve the cell kill and the effectiveness of antibody therapy.

We have recently reported the upregulation of CD20 expression on peripheral blood mononuclear cells from patients of CLL when exposed to cytokines like TNF, IL-4 and GMCSF.

(Blood Vol. 92, no 10, Suppl, 1, abst 1009, 1998). We present here our preliminary experience of the use of IFNa at 50U/ml and 1000U/ml on CD20 expression in these cells. CD20 expression was studied by flow cytometry at baseline, 24 hours and 72 hours on 10 CLL specimens. The product of MFI and percentage positivity was calculated as a means to represent the protein content corresponding to CD20 antigen on the surface of tumor cells.

Wilcoxon Signed Ranks Test.

At 24 hrs, IFNa at both 500U/ml and 1000U/ml significantly upregulated CD20 expression on the tumor cells. At 72 hrs of the cases evaluable, IFNα at both doses caused upregulation in all the patients, however these values did not attain statistical significance. Lymphocytes from normal donors showed low baseline CD20 expression (33±2 ± 7.88, no Z) incubation with IFNa did not cause any significant upregulation (47±1.07, n=2). Although the number of patients studied is small and insufficient to warrant clearly valid inferences and conclusions to be drawn from the findings, we believe that this is the first report of interferon alpha mediated upregulation of CD20 antigen.

IFNa has been shown to be well tolerated in patients when given along with anti-CD20 antibody therapy. It can have a synergistic effect of not only increasing sites for cell kill but also the mechanism of action of the antibody by augmenting ADC in the cells as has been shown with other cell types. These studies suggest that priming with cytokines/biologic agents may increase effectiveness of anti-CD20 monoclonal antibody therapy.

4. CLL/Indolent Lymphoma/Extranodal Lymphoma

65
RESULTS OF A MULTICENTRIC RANDOMIZED STUDY COMPARING THE EFFICACY OF CYCLOPHOSPHAMIDE, DOXORUBICIN, AND PREDNISONE (CAP) TO THAT OF ANTHEMIC/HYDROCORTISONE IN PATIENTS WITH WALDENSTRÖM’S MACROGLOBULINEMIA (WM) IN FIRST RELAPSE OR PRIMARY REFRACTORY DISEASE.


Hôpital Pitié-Salpêtrière, Paris, France.

Introduction: We have reported the response to FAMP in 71 patients (pts) with resistant WM and shown that 30% of patients had a good response (JCO,1996,20:2064). We report the results of a randomized study in 92 patients with WM comparing the efficacy of CAP to that of FAMP.

Patients and methods: From December 1993 through December 1997, 92 patients with WM resistant to first-line therapy (42 pts) or in first relapse (40 pts) after allogeneic agents were randomized to receive CAP (cyclophosphamide 750 mg/m² for D1, doxorubicin 25 mg/m² for D1, prednisone 40 mg/m² for D1-D5) (arm A) or FAMP (25 mg/m² for D1-D5) (arm B). Response was evaluated after 6 courses. Response was defined as a sustained decrease in the production rate of IgM greater than 50%, with a greater than 50% reduction in all other involved organs.

Results: No statistical difference was observed between both groups concerning age, sex, PS, IgM level, tumor mass and blood counts. 45 patients received CAP and 45 patients received FAMP. 5 pts (11%) responded in the arm A and 13 pts (28%) in the arm B (p=0.019). The time to progression of the responders was significantly lower in the arm B (p=0.08). 12 (arm A) and 17 (arm B) pts died during the follow-up respectively. The time to treatment failure was statistically lower in arm B (p=0.04). No statistical difference was observed between both arms for the overall median survival time. The median follow-up time of patients treated with CAP were still alive at the date of analysis was 771 days.

Conclusions: FAMP is more active than CAP as salvage therapy in macroglobulinemia and should be proposed as first-line therapy in a randomized comparison with alkylating agents.


Clinic for Internal Medicine, University of Cologne, Cologne, Germany.

Introduction: Low toxicity and high efficacy with 6% complete and 44% partial remissions have been exhibited after administration of 4x375mg/m² of the chimeric monoclonal anti-CD20 antibody rituximab to patients with relapsed advanced low-grade follicular non-Hodgkin’s lymphoma (NHL). Since the CD20-antigen is also expressed on circulating tumor cells in chronic lymphocytic leukemia (CLL), we treated 11 patients with fludarabine-resistant CLL or leukemic variants of other low-grade NHL with 375mg/m² rituximab once weekly for 4 weeks.

Results: Median age of patients was 58 years (range 26-79 years). All patients were in second or higher relapse with a median of three prior chemotherapy regimens (range 2-5). Peripheral lymphocyte counts at baseline varied from 0.2x10⁹/L to 294.3x10⁹/L. During the first antibody infusion patients with lymphocyte counts exceeding 50x10⁹/L experienced a massive cytokine release syndrome. Ninety minutes after onset of infusion mean serum levels of tumor necrosis factor-α and interleukin-6 peaked at 500ng/ml (baseline 20pg/ml) and 280ng/ml (baseline 25pg/ml), respectively. Serum interferon-γ concentrations were not elevated. Peak cytokine levels were associated with clinical symptoms of NCI toxicity grade I-IV, including fever, chills, nausea, and vomiting. During the first rituximab infusion lymphocytes as well as lymphocyte counts were reduced for 50-75% compared to baseline. At the same time there was a 5-10-fold raise of liver enzymes and d-dimers as well as a decrease of coagulation parameters without detection of disseminated intravascular coagulation. Frequency and severity of adverse events upon the first antibody infusion were significantly less pronounced in patients with less than 50x10⁹/L peripheral lymphocytes (p=0.009). While one patient with a leukemic variant of the mantle-cell NHL is in continuous complete remission 6 months after treatment with 4x375mg/m² rituximab, response rates in patients with relapsed CLL were poor with one partial remission, eight cases of stable disease, and one case of progressive disease.

Conclusion: Further clinical studies in patients with CLL are necessary in order to evaluate toxicity and efficacy of higher doses of rituximab administered over a longer period of time or of combination regimens with chemotherapeutic agents.

CLINICAL VALIDATION OF A NEW SCORING SYSTEM FOR THE DIAGNOSIS OF CHRONIC B-CELL LYMPHOMA LEUKEMIAS.

L. Cro, MG Grimaldi, M. Monta, C. Patriarca, A. Neri, A. Corteza and AT Mancio.

Servizio di Ematologia, Centro G Marcora, Ospedale Maggiore IRCCS and Istituto di Anatomia Patologica, Ospedale S. Paolo, Milano, Italy.

Introduction: The aim of this study was to investigate a large panel of monoclonal antibodies (MeAbs) in order to identify the most important diagnostic markers in terms of the patients’ clinical-biological characteristics at diagnosis and, if possible, survival in the chronic B-cell lymphoproliferative syndromes.

Methods: 426 patients (M/F: 255/171; median age at diagnosis 66.6 yrs) with B-cell CD 10 negative lymphocytosis were evaluated at diagnosis for the following markers: Sla, CD16, CD5, CD11c, CD19, CD22, CD25, CD45, CD45RO, and FMC7; 260 of whom had an adequate follow-up (median 36.6 mo; 55 deaths). An adequate morphological analysis was possible in 358 cases, and karyotype was available in 315. Results: On the basis of the correlation coefficients between the expression of the markers, their individual impact on survival and the "historical" significance of some, the "strong" markers were: Sla intensity (calculated as the difference between the mean fluorescence of marked cells and negative controls, with a cut-off point of 390 between low – score 2 and high intensity – score 4), and CD5 and CD20 expression: grade 0 < 20% of CD19 positive cells (0 scores for both); grade 1 < 20% and ≤ 60% (scores of 0.5 for CD5 and 1 for CD20); grade 2 ≥ 60% (scores of 2 for CD5 and 1 for CD20). On the basis of this “Maccara Center Scoring System” (MCSS), 4 patient subgroups were identified: group 1 (294 pts with scores of 3.5-5); group 2 (49 pts with scores of 2.5-3); group 3 (12 pts with a score of 2); and group 4 (71 pts with scores of 2). From a clinical point of view, in addition to the significantly different distribution of clinic-laboratory variables at diagnosis (plasmoerythrocytosis and increased serum LDH in groups 2-4 vs group 1: p < 0.001; the presence of serum monoclonal component in group 4 vs groups 1-3: p < 0.001; CLM morphology in group 1 vs groups 2-4: p < 0.001), the most important finding concerned survival. Together with lymphocyte doubling time (p < 0.001), a diffuse bone marrow histological pattern and the presence of cytogenetic anomalies (p < 0.01), the MCSS proved to be prognostically significant: the median survival of the patients in groups 1 and 4 was respectively 64.4 and 21.9 months, as against the 38 and 51.2 months observed in groups 2 and 3 (p < 0.01).

Conclusions: MCSS is a simple phenotype-based diagnostic system capable of distinguishing pathological situations with different prognoses.
FLUDARABINE (FLU) COMBINATION THERAPY IN FRONT LINE AND RELAPSED PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA (CLL). M. Keating, S. O'Brien, W. Flanagan, and H. Kanamaruj UT MD Anderson Cancer Center, Houston, Texas, USA.

FLU has become a major new drug in the management of CLL. Studies in previously treated (PrR) patients (pts) shows a response rate of approximately 50% with 80% in pts receiving FLU as their initial therapy. Subsequent studies have combined FLU with prednisone (FP) or milostatome (FM) or cyclophosphamide (FC). The rationale for the use of FM and FC was the activity of FLU in inhibiting repair of DNA damage due to M and C. FP was not associated with an improved response rate in untreated (UNT) or PrR pts with CLL and was associated with an increased incidence of opportunistic infections. The FM and FC results are illustrated below. In addition, FC is the only combination which has been able to obtain a response rate (25%) in FLU-refractory pts. In UNT pts or PrR pts sensitive to alkylators, neither FM, FP, or FC increased survival compared to FLU. However, FC and FM significantly improved survival of alkylator refractory pts. FM and FC have been well tolerated with no unusual incidence of infections, myelosuppression or other toxicities. No improvement in CR rate has been obtained in UNT pts with combination therapy. However a longer time-to-treatment failure is emerging in FC treated pts. Further development of combination approaches is necessary to improve the CR rate in pts with CLL. A combination of FC and Rituximab is being investigated.

**Results of Fs of CLL with FLU or Combination Regimens**

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ASSOCIATED TREATMENT OF GASTRIC MALT-OMAS. (THE FIRST RUSSIAN EXPERIENCE).

Poddubnaya I, Probatova N, Moscazenko O, Kovygin A, Jazykova M, Sholochova E, Kushtinov U, Osmanov D, Poddubny B.

Cancer Research Center of RAMS, Moscow, Russia.

**Introduction.** NHL of the stomach is the most frequent extranodal lymphoma, majority cases are low grade MALT-omas associated with H. pylori infection. Efficacy of Anti-H. pylori treatment being investigated.

**Method.** For the last 3 years (1995-1998) cases of primary gastric MALT-omas were defined; median follow up is 2 years According to morphological description. All cases were divided into 3 groups: 1-low grade MALT-omas - 22 pts; 2- high grade MALT-omas - 16 pts; 3- high grade MALT-6 pts. In all cases these pan-B-cell antigens were evaluated (CD 20, 20,22) without CD 5, 10, 23 coexpression, CS-1 (Lugano classification). Group: presence of H. pylori in 100%, main clinical symptoms were epigastric pain - 78%, loss of weight - 40%, females/male - 8/6; age: 31-78. All of them had gastritis or ulcer in anamnesis. 14 pts were treated with omeprazole, clarithromycin, amoxicillin for 7-14 days (1-3 cycles till H. pylori - eradication) and then were followed up every 3 mos with endoscopy, mapping gastric biopsies. After H. pylori eradication lymphoma regressed both endoscopically and histologically, proved immunologically (CR) in 11 pts (78%). Duration of CR: 7-40+ mos (median 23+ mos). CR were registred 2,5-5,0 mos after H. pylori eradication. If H. pylori eradication was not registred we started to use Luerken. H. pylori - infection was rarely in 1/6 and highgrade MALT-omas. Anti - H. pylori treatment was ineffective in lgM MALT-omas.

**Results.** Efficacy of Anti - H. pylori treatment is very high (78%) only in 1 stage low grade primary gastric MALT-omas. Whether H. pylori treatment will definitely cure gastric MALT-oma and prevent its relapse is still unknown, whether addition of chlorambucil after H. pylori eradication is of any benefit in lgM MALT.

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**Introduction:** Purine analogs like fludarabine induce higher remission rates than conventional chemotherapy in CLL, in particular in patients (pts) resistant to alkylating agents. However, there remain open questions with regard to the optimal timing of fludarabine (early or late disease? first-line or in relapsec?), the treatment of fludarabine-resistant pts, the value of fludarabine combinations, and the comparison to DIC. To assess these issues and to prepare future phase III trials, the GCLLSG initiated two phase II studies on FC and DIC (GCLLSG protocol) for advanced CLL (Binet stage B and C).

**Methods:** In the FC regimen, fludarabine (30 mg/m²/day IV) and cyclophosphamide (250 mg/m²/day IV) were given from day 1-3 x 28 days, for a maximum of 6 courses. DIC was given continuously at 0.2 mg/kg/d PO over 6 months (max. dose 15 mg/d). 75 pts were included by June 1999. As of January 1999, 57 pts were evaluable; 25 pts (age 59.4 ± 9.1 yrs) in the FC and 32 (63.3 ± 7.4 yrs) in the DIC arm. The number of previous treatments was 1.5 ± 0.8 and 1.7 ± 0.8, respectively.

**Results:** In 22 pts evaluable for response, FC induced 3 and 16 complete and partial remissions (CR and PR; response rate, RR, 86.4%). DIC (15 pts evaluable) induced 1 CR and 8 PR (RR 60%). Both regimens caused considerable side effects, in particular myelotoxicity (Table 1).

**Table 1. CTC grade 3 and 4 toxicity of FC and DIC**

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**Background:** Several lines of evidence suggest that Helicobacter pylori infection is associated with the growth of either low-grade (LG) or high-grade (HG) lymphomas (NHL) of the stomach. Eradication of H. pylori can induce histological remission of the lymphoma in at least 50% of patients with LG-NHL of mucosa-associated lymphoid tissue (MALT) type. However, the role of H. pylori eradication in gastric HG-NHL is poorly documented with only a few anecdotal report of HG-NHL regression after H. pylori eradication.

**Patients and results:** 4 cases (2 female and 2 male, median age 65 years, range 44-74 years) with localized (stage I) gastric HG-NHL. (i.e., diffuse large B-cell lymphoma with or without LG-MALT component) and H. pylori infection were treated with antibiotics. Histological regression of the HG component was evident in all cases at the first endoscopic biopsy that documented H. pylori eradication (40-70 days after treatment). One patient then underwent a total gastrectomy that confirmed the absence of HG-NHL, the others were followed without further treatment. At a median follow-up of 16 months all patients are alive and free of lymphoma.

**Conclusion:** This finding confirms that eradication of H. pylori may lead to a regression of some gastric HG-NHL and suggest that -analogous to LG-MALT NHL- an antigen drive can be important in some gastric HG-NHL. At present, however, there is no evidence to recommend antibiotic alone as adequate treatment for HG-NHL.

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4. CLL/Indolent Lymphoma/Extranodal Lymphoma

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THE INTERNATIONAL PROGNOSTIC INDEX (IPI) CORRELATES TO SURVIVAL IN PATIENTS WITH LOCALIZED PRIMARY GASTRIC DIFFUSE LARGE B-CELL LYMPHOMA (PGL).
Etiologico, Ospedali Riuniti, Bergamo; Istituto dei Tumori, Milano; Cattedra Etiologico, Università, Verona; Oncologia, Ospedale “Circolo Fondazione Macchi”, Varese; Etiologico, Azienda Ospedaliera “S. Giovanni Battista”, Torino; Radiationtherapy, Ospedale “Umberto I”, Mestre; Oncologia, Ospedale “Fatebenefratelli”, Rimini; Fondazione Centro S. Raffaele del Monte Tabor, Milano; Istituto Europeo di Oncologia, Milano; Etiologico, Ospedale Maggiore, Milano, Italy; and Servizio Oncologico Cantonalre, Ospedale “San Giovanni”, Bellinzona, Switzerland.

Aims of the study: To assess the value of IPI in predicting the outcome of a large and unselected series of patients with PGL.

Patients and methods: 421 consecutive newly diagnosed patients (median age 61 years, range 14-86 years) with localized PGL (stage I = 267/111 = 0.66, 12/7 = 51, according to Lugano staging system for GI lymphomas) referred from April 1972 to June 1998 to 9 Italian and 1 Swiss centers were reviewed. 416 patients were given single (surgery, SX; Chemo; radiotherapy, RT = 3) or combined (SX+Chemo, RT = 3) therapy with successful front-line therapy. Results: After a median follow-up of 60 months (range 1-300 months), 273 (67%) patients were in 1st CR and OS at 5 years was 75% and 68% respectively. Cox multivariate analysis showed that IPI was the only variable associated with clinical outcome.

Conclusion: This study indicates that IPI is an effective predictive model also in this localized extranodal aggressive NHL.

PRIMARY GASTROINTESTINAL (GI) LYMPHOMA: TREATMENT OUTCOME AND PROGNOSTIC FACTORS: RESULTS OF A PROSPECTIVE MULTICENTRE STUDY
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Introduction: In primary GI NHL biology and appropriate management still are matters of an ongoing part controversial debate. We therefore initiated a prospective multicenter study to evaluate their historical features, sites of involvement and management.

Methods: From 10/92 until 12/96 377 patients are evaluable to date. Standardised diagnostic workup included endoscopic and radiologic evaluation of the complete GI tract as well as a central histologic review. Treatment consisted of primary chemotherapy or conservative management depending on the physician’s decision, followed by standardised radio- chemotherapy. 95 patients had to be excluded according to protocol regulations (age: 31, 2nd malignancies: 18, violation of protocol mostly because of non-conformation of histologic subtype by the reviewed sample). In 15 cases data are not complete yet. Therefore on 29th January 1999 263 patients are evaluable for treatment outcome.

Results: The distribution of GI NHL is as follows: Stomach 73%, small bowled 9%, ileocolic region 9% and other sites 3%. More than one GI site was involved in 6%. Considering all GI NHL site of origin is a significant prognostic factor. When located in the stomach or ileocolic region event free and overall survival (all stages, all histologic subtypes) is significantly better than in the small intestine or in multilocular GI involvement. In gastric lymphoma stage according to Musshoff (II, III, IV) is predictive. In our treatment setting histologic grading does not influence the outcome of therapy. No differences between surgical and organ preserving treatment can be seen.

Conclusions: Primary GI NHL is a heterogeneous disease, which can be divided roughly in 3 groups (located in the stomach, the small intestine and the ileocolic region). They differ in their clinical features and also in response to therapy.
Enteropathy-type intestinal T cell lymphoma: clinical features and management of 31 patients in a single centre
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Between Jan 1979 and Nov 1996, 31 patients (23M, 8F) with enteropathy-type intestinal T cell lymphoma have been managed in the WMOU. The median age at diagnosis was 50yrs (20-80). A past history of coeliac disease was noted in 12 patients, and was biopsy proven in 9. Presenting symptoms were most commonly abdominal pain (26), weight loss (25), diarrhoea (12), and vomiting (9). 7 patients presented with small bowel perforation and 6 with small bowel obstruction. 11 symptoms were a feature in 10. Diagnosis was made at laparotomy in 25 of the 31 patients; surgery was performed as an emergency in 13. Lymphoma was found in a single bowel site in 21, and at multiple sites in 10. Other infiltrated sites were mesenteric nodes (11), omentum (2), liver (2), mesentery (1), colon (1), bone marrow (2). Stage at diagnosis was I (5), II (15), IV (6), not recorded in 5. 7 patients were initially treated with surgery alone, of whom only 1 remains disease free at 49months. 24 patients received combination chemotherapy. Less than 50% completed their planned courses. 10 patients required parenteral feeding and 2 enteral feeding during primary combination chemotherapy. Complications of chemotherapy included gastrointestinal bleeding (1); small bowel perforation (4); development of an enterocele (1). 14 patients responded to chemotherapy (CR10, PR4). 4 showed no response. 1 had obvious PD. The remainder were not evaluable for response. The median time to relapse for those who responded to initial therapy was 4 months (2-61). 26 patients have died (84%). All those who have died have died of progressive disease or complications of the disease and/or treatment. Median survival was 7.5 months (0-83). 5 patients remain alive and disease free 49-219 months from diagnosis. In this disease, late diagnosis, advanced local disease, and poor nutritional status are associated with poor tolerance to chemotherapy. However, patients should receive combination chemotherapy with drugs known to be active in intermediate/high grade lymphomas. Nutritional support should be considered for all patients. The role of salvage treatments or high dose chemotherapy at relapse is unclear.

Evolution of a clinical research programme for extranodal lymphoma - the population based lymphoma group model (Scotland & Newcastle Lymphoma Group) (SNLG). Proctor, SJ; Taylor, PRA; White, J; Prescott, R; Mackie, M; Matheson, L; Lennard, AL; Angus, B; Lessells, A. On behalf of the Scottish & Newcastle Lymphoma Group Therapy and Working Party.

The SNLG has developed a population-based data system, which collects information on population representative lymphoma patients whether on trial or not. We estimate that presently > 90% of incident cases from a population of 8.5 million are prospectively evaluated. The data consists of presentation features, treatment and outcome with detailed annual follow up to death, recorded by the physician in charge of their care.

Extranodal NHL's are an extremely heterogeneous group of disorders which present to different specialty groups and classical trials are rarely attempted on representative populations. The SNLG data base consists of HD 2567, NHL 9337 (Total 11,4904 unselected cases). Current rate of accrual annually using 1996 as example, new cases HD 161, NHL 875 (Total 1036 per annum). For study of common extranodal diseases the data set provides information in order of the decreasing frequency on GI lymphomas 945, skin 288, thyroid 144, bone 114, parotid 89, CNS 77, testicular 71, breast 58, orbit 49, lung 45, maxillary sinus 39. In addition the data provides a vehicle for investigation of rare extranodal sites eg genitourinary - bladder 21, kidney 17, prostate 7, cervix 5, vagina 2, table 2, urethra 2 (Total 56). The approach taken to skin lymphoma and breast lymphoma, will be used to illustrate the value of the system.

4. CLL/Indolent Lymphoma/Extranodal Lymphoma