3. Aggressive Lymphomas

E. National Lymphoma Study Group: Interim Results and Accumulated Experience Of The First National Cooperative Study For The Management Of Aggressive NHL.

**Purpose:** In Egypt, there exists a different clinicopathologic profile of adult NHL compared to western countries. Would this discrepancy have any impact on treatment results? Therefore, the primary objective of this national multicentric randomized study is to evaluate the clinical benefit of standard CHOP regimen in the management of high-risk NHL adult patients in Egypt, as well as whether more aggressive 3rd generation regimens (CEOP/MT) with HD Etoposide, and BECO (Epirubicin) can improve the therapeutic outcome. The second objective is to evaluate the role of Rituximab in consolidation of remission.

**Patients and Methods:** Inclusion criteria are: previously untreated adult patients with histologically confirmed intermelod, and high-gr NHL, in clinical stage I-Iv, exhibiting one or more risk factor (Age >60 yrs, PS >2, LDH >26/ids, disease 3cm & more than one extranodal site). 123 pts were randomized to either 1-Standard CHOP (Doxorubicin 50 mg/m2 d1, etoposide 50mg/m2 d1-2); 2-CEOP/MTs (HD Etoposide 100mg/m2 on day 21) or 3-BECO (Epirubicin 40mg/m2 d1 & 8). Recycle on D21 for a total of 8 cycles. Pts with original bulky disease and those who achieve delayed CR are to be randomized weekly to receive Rituximab or not. Revival of the 2nd line for refractory.

**Results:** 123 pts were recruited from 3 centers: NEMROCK a=55, Ain SHAMS Univ a=41, ASSUFT Univ a=27. Male/female: 57% to 43% (mean age: 43.5. The risk factors were well balanced (P>0.05). CR was obtained in 66.6% of CHOP, 71% and 84% respectively (P>0.05). Relapse rates within 6 months of treatment were 5%, 7.3% and 4%. Disease progression was 20% in both CHOP and CEOP arms. Grades 3-4 leucopenia were reported in 13% and 15% for both CHOP and BECO/CEOP groups compared to 5% for CHOP groups. Gr 2-4 infections were observed mainly among the BECO group (9%) compared to 2% and 1.3% for the other groups. Therefore, antibiotics were used in 9% of the BECO pts for an average of 10 days.

**Conclusion:** The preliminary results of the trial seem encouraging as regards objective responses and acceptable toxicity profile. We continue to recruit patients till achieving a total of 500.

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Serum IL-10 And Soluble IL-2 Receptor Measurement: Prognostic Indicator In Egyptian Patients With Aggressive Non-Hodgkin’s Lymphoma.

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**Background:** Recently, the measurement of initial cytokine and soluble receptor levels has been suggested as an additional tool for the clinical assessment of patients with NHL. In The present study, The combined detection of serum levels of soluble interleukin-2 receptor (sIL-2R) and interleukin-10 (IL-10) was tried to investigate their prognostic significance and their abilities to predict treatment outcome as reflected by the identification of a subset of patients at high risk of failing treatment.

**Methods:** Between March 1997 to March 1998, serum IL-10 and IL-2r were measured in two groups of Egyptian patients with aggressive NHL. Group A (n=25) included newly diagnosed patients, and group B(n=10), patients with relapsing disease. The mean age was 46.5 years (range=20-70), 16 males and 19 females. In group A, serial evaluation was done before and after treatment with 3 cycles of combination chemotherapy regimens, either standard CHOP (n=16), or CEOP/MT (n=9) with high dose Epirubicin, intermediate dose methotrexate and leucovorin rescue.

**Results:** There was a significant elevation in the serum - IL-2r and IL-10 levels among both the newly diagnosed as well as the relapsing NHL Egyptian patients, compared to control healthy subjects (p <0.0001), with lower values among the latter group. sIL-2r was detected in all the patients, while IL-10 was detected in the sera of 94% of the patients at diagnosis and 66% of relapsing cases. Cytokine and receptor levels remarkably declined in patients who achieved complete remission, compared to partial or non-responders (p<0.002). sIL-2r correlated significantly with sIL-2R levels (r=0.72) as well as late stage, B symptoms and poor performance status (p<0.004). Pretreatment sIL-2 -3r levels >140 pg/mL was associated with a higher incidence of failure to achieve CR (P<0.01). IL-10 did not correlate with any of the studied prognostic factors neither with response to treatment.

**Conclusion:** Combined sIL-2r and IL-10 measurements showed that sIL-2r can be a prognostic factor of value, also it may be a reliable indicator for better therapeutic outcome in Egyptian patients with aggressive NHL.

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TREATMENT OUTCOME OF ADVANCED STAGE AGGRESSIVE LYMPHOMA WITH CAMBO-VIP AND ITS MODIFICATIONS: 10 YEAR FOLLOW-UP RESULTS IN A SINGLE INSTITUTE.


**Patients and Methods:** Between October 1987 and September 1997 ninety-seven patients (pts) with advanced stage (stage ≥1 bulky) aggressive lymphoma, age ≤65 years were treated with one of three 12 week regimens: CAMBO-VIP (N=29, Oct ’87 – May ’90); CAMBO-VIP II (N=16, June ‘90–June ’92) or CAMBO-VIP III(N=52, July ‘92–Sept. 97). CAMBO-VIP regimen consisted of gemcitabine 40mg/m2 given in combination with either cyclophosphamide 500mg/m2, etoposide 70mg/m2 qd x 4 or ifosfamide 1000mg/m2 qd x 4 by turns on weeks 1, 3, 5, 7, 9 and 11, and vincristine 1mg/m2 given with either methotrexate 200mg/m2 or bleomycin 10mg/m2 on week 2, 4, 6, 8, 10 and 12. Prednisolone 40mg/m2/day was administered for the first and the last 4 weeks. In CAMBO-VIP II and CAMBO-VIP III, doses of doxovibin, cyclophosphamide and ifosfamide were intensified to 50mg/m2, 600mg/m2 and 1.200mg/m2, respectively by using G-CSF support. The sites of bulky mass received 40 Gy irradiation after chemotherapy.

**Results:** Eighty-eight of 97 pts completed one of 3 regimens with maximal delay of 3 weeks. All the pts were evaluated. 88 (91%) achieved a CR (including 17 CR), 4 PR, 3 showed NR and 2 died of sepsis. Among 7 pts with PR and NR, 2 were salvaged and are alive. With a median follow up of 71 months 20 have died (17 of lymphoma). 18 pts (20%) achieved a CR, 6 are alive in subsequent CR. At 5 years overall survival (OS) is 82% and disease-free survival (DFS) is 71%. Within the subgroups defined by the International Prognostic Index (IPI) low risk group showed better OS and DFS, but they did not differ significantly from those of other risk groups.

**CR % OAS % DFS %**

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As of Dec ‘98

**Conclusions:** Although these results are obtained from a single institutional study, CAMBO-VIP shows high effectiveness for advanced stage aggressive lymphoma with more than 70% of pts alive disease-free at 5 years.
SALVAGE CHEMOTHERAPY WITH MITOXANTRONE, FLUDARABINE, CYTARABINE AND CISPLATIN (MIFAP) IN RELAPSING AND REFRACTORY LYMPHOMA

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Introduction: The aim of the study was to evaluate the feasibility and efficacy of the combination of mitoxantrone, fludarabine, cytarabine (Ara-C) and cisplatin (DDP) in patients with refractory or multiply relapsed Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL).

Methods: Twenty intensively pretreated patients (median age 39 years, range 23-63) with relapsed (n=9) or refractory (n=11) malignant lymphomas were enrolled. The MIFAP protocol consisted of fludarabine (15 mg/m², q2-12 h, day 1-4), cytarabine (50 mg/m² by continuous infusion (CI) over 22 hours, day 1-4), cisplatin (25 mg/m² by CI over 24 hours, day 1-4) and mitoxantrone (4 mg/m², day 2-5).

Results: Nine patients achieved complete remission (CR) and 5 patients partial remission (PR) for an overall response rate of 70%. Progressive disease (PD) developed in 6 patients. Ten patients responding to MIFAP (7 CR, 3 PR) have been consolidated by high-dose therapy (HDT) with subsequent autologous stem cell transplantation (ASCT). After a median follow-up of 25 months 7 patients are in continuous CR (CCR), 3 patients are in a very good PR without any evidence of disease progression. Six patients died of their lymphoma (5 non-responders as well as one patient with a new relapse of a Ki-NHL). The major toxicity was myelosuppression, thrombocytopenia and neutropenia. World Health Organization (WHO) grade IV in all 35 courses (median over 8 and 12 days). In contrast, non-hematological side effects were moderate, predominantly reaching WHO grades I and II. No treatment-related death was observed.

Conclusion: Our preliminary results with MIFAP in 20 heavily pretreated patients with prognostically unfavourable HD and NHL are encouraging. Further investigations of the MIFAP protocol in a larger number of patients with poor prognosis lymphomas are planned.

MANTLE CELL LYMPHOMA: BIOLOGICAL AND CLINICAL FEATURES


Mantle cell lymphoma (MCL) is generally accepted as clinically important separate entity and incorporated in the REAL and WHO classifications. The disease represents some 4-9% of all non-Hodgkin's lymphomas (NHL) and is its incidence rises with age and male gender. Cell morphology is variable, but the immunophenotype is characteristic – slg, CD5, CD20, CD3, CD10. The distinct cytogenetic abnormality is t(11;14)(q13;q32) involving bcl-1 locus on the long arm of chromosome 11.

We analyzed a group of 29 patients (16 females, 14 males) with median age of 57 years (39 - 87 years). Bone marrow involvement was documented in 93% of patients, one fourth of them had the blast variant of the disease. The elevation of serum LDH, B lymphoblasts and thymidine kinase levels was found in 3/4 of the cases. Most patients were classified as high-intermediate- or high-risk according to the International Prognostic Index (IPI) value, median being 2 (1-5) points. 15 patients (52%) had IPI value higher or to equal to 4 points. Immunophenotype, cytogenetic and molecular-biology findings will be discussed.

26 MCL pts. were treated (4x chlorambucil monotherapy, 4x COP, 12x CHO, 5x ProMACE-CytaBOM, 1x intensive ALL-therapy). Only 2 pts. (8%) reached a CR (including histological remission in bone marrow) and 8 pts. (31%) obtained a PR. 16 pts. (61%) didn't respond to the first-line therapy. No response to chlorambucil and COP was observed. 4 PR's were achieved by CHOPE chemotherapy, the effect of ProMACE-CytaBOM was PR in 3pts. and CR in 2 pts.

High dose chemotherapy (BEAM) followed by autologous peripheral blood stem cells (PBSC) support was given to 5 MCL pts. Only 1 pts. is in CR 4 pts. had evidences of their disease at day +100 evaluation. 1 pt. progressed rapidly and died 15 months after high-dose chemotherapy; 20 pts. died, their median overall survival is 16 months.

Our analysis shows poor outcome MCL's patients and the requirement of intensive first-line chemotherapy followed by high-dose chemotherapy with autologous stem cells support or allogeneic transplantation in younger patients.

The work is supported by grant GA CR No.2215/042 and grant IGA No.752/52-3.

ANAPLASTIC LARGE CELL LYMPHOMA (ALCL): CLINICAL PRESENTATION AND OUTCOME OF 40 PATIENTS

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ALCL is a distinct entity of high grade non-Hodgkin lymphoma. Large pleomorphic blasts infiltrate the lymph node sinus as well as extranodal sites and have abundant cyttoplasm and multiple nucleoli. Forty cases of ALCL has been identified in the last five years in our three centers. The median age was 42.5 years (range 16-79) 24 were males. Ann Arbor stages were I in 7, II in 11, III in 9 and IV in 13 cases. B symptoms were present in 30 patients (75%). According to the international prognostic index 20 patients were in low, 8 in low-intermediate, 2 in high-intermediate and 5 in high risk group. Initial transfusions involved bone marrow in 2 (5%), skin in 12 (30%) lung in 4 (10%), pleural in 4 (10%), bone in 2 (5%), stomach, pericardium and gut in 1-1 cases. Laboratory characteristics included anaemia in 16 (40%), high serum lactate dehydrogenase level (≥ 1x normal) in 20 (50%), low serum albumin level (<1x normal) in 10 (25) and high β2-microglobulin (≥ 1x normal) in 21/33 (65%) cases. Immunophenotype of the lymphoma revealed null cell in 26 (65%) T cell in 7 (18%), B cell in 4 (10%) and unknown in 3 (7%) cases. Among the 15 samples that were subjected to immunostaining 2 reacted with anti-CD8 antibody. Seventeen patients received CHOP or CHOP-like therapy, 3 ProMACE-CytaBOM, 4 VEP, 1 ABVD as first choice therapy. Twenty eight patients died before starting of any treatment, one patient underwent radiotherapy alone and 2 surgical treatment (1 splenectomy). Twenty four patients achieved complete remission (CR). 5 partial remission (PR) after first line or salvage therapy (CR+PR rate 93%). Twelve patients died (7 C, 4 PD, 1 CR without disease progression), 3 in cardiac failures and one in septicaemia. We lost contact with two patients in the follow up period. The median follow up of 26 survivors is 25 months (7-35). The incidence of null cell phenotype was relatively high. We are planning to repeat the immunohistochemistry with ALK1 antibody, evaluate molecular biological examinations and collect data from more Hungarian centers.

A COMBINATION OF DEXAMETHASONE, ETOPOSIDE, IFOSFAMIDE, D-cisPLATIN (DVIP) AND HIGH-DOSE METHOTREXATE (MTX) AS SECOND LINE THERAPY FOR PRIMARY REFRACTORY AGGRESSIVE NON-HODGKIN’S LYMPHOMA (NHL)

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Introduction: The survival of patients (pts) with aggressive NHL who fail to achieve CR with first-line chemotherapy or relapse after a short CR (primary refractory NHL) is less than 10%. DVIP is used as our center as a second line therapy in NHL. To improve the therapeutic results we added to DVIP high-dose MTX.

Methods: Patients with aggressive NHL (WF) who developed progressive disease 3 months or less after the onset of a first-line adjuvant-containing regimen were eligible. DVP was given as previously reported (Haim et al. Cancer 80 1980 1997). MTX (initial dose 3.5g/m²) was given at day 8 and Q-CSF was routinely used.

Results: Fourteen pts (age 19-77, median 41 yrs) were treated. Time interval from last chemotherapy was 3-8 mo MTX dose at first cycle was 3g/m² in 5 pts but due to toxicity was subsequently reduced (1.5g/m² in one pt, 1.5g/m² in 4 pts, 3g/m² in 4 pts). Twelve pts were evaluable for response. CR was seen in 2 and PR in 3 (overall response rate 42%) Myelosuppression was the major toxicity. Median hemoglobin, WBC and platelets nadir during the first cycle 8g/dl, 300/mL and 14,000/mL respectively and was more pronounced than in the 56 patients receiving DVIP alone. Two patients died during the first cycle due to severe myelotoxicity.

Conclusions Although high-dose MTX given with leucovorin is considered less-mytotoxic, the addition of high-dose MTX to DVIP markedly increased the toxicity of this regimen. Since DVIP/MTX may be an effective combination in association with primary refractory NHL, we intend to use this regimen with lower doses of MTX (500mg/m²). It is too early to know whether the addition of MTX improves the efficacy over DVIP alone, but the study continues at a lower dose of MTX (500mg/m²).

3. Aggressive Lymphomas
PHASE II STUDY OF PACLITAXEL IN REFRACTORY AND RELAPSED AGGRESSIVE NON HODGKIN’S LYMPHOMAS (NHIL)
R.O. Fenselau, C. Hanke, C. Darmetet, J. Gabrielle, R. Richard, P. Ledez decrypted, C. Gelasbrecht on behalf of the GELA Group d’Etude des Lymphomes de l’Adult, Hopital Le Bougain, CHU Dijon, France.

Introduction: The first clinical studies of paclitaxel as single agent in relapsed or refractory NHIL reported controversial results regarding the response rates observed. These differences were mainly related to the schedule of paclitaxel as a dose of 100 mg/m² was associated with the best response rates reported either in low or intermediate grade NHIL. To obtain additional data concerning the utility of paclitaxel in intermediate or high grade NHIL, we initiated a phase II study using short infusion of high doses of paclitaxel.

Methods: The eligibility criteria included patients (pts) with a relapsed or refractory intermediate or high grade NHIL, a performance status ≤2 (WHO index), a platelet count ≥100,000/μL, a neutrophil count ≥2,000/μL, measurable disease, and adequate hepatic function. Paclitaxel if they were infected with HIV, had a left ventricular ejection fraction ≤50%, or prior peripheral neuropathy. Paclitaxel was administered as a 3 hours infusion at 250 mg/m² dose every 3 weeks with a maximum of 6 courses.

Results: From May 1995 to February 1997, 43 pts received at least one course of paclitaxel and were assessable for toxicity. Of 40 pts assessable for response, 10 (25%) had a primary refractory lymphoma, the remaining had relapsed after either 1 (10%), 2 (27%), or more than 2 (28%) previous chemotherapy regimens. The overall response rate was 15%, including 4 PR (10%) and 2 complete response (CR) (5%). The response was of short duration, with a median time to disease progression of 2 months (range, 2.7 to 11). The response rate was slightly higher in relapsed (17%) than in refractory NHIL (10%) but the difference was not significant.

Overall, the non-hematologic side-effects related to paclitaxel were mild, and none of the 42 pts experienced hypersensitivity reactions or cardiac toxicity. Conversely, the hematologic toxicity related to paclitaxel was frequent. A grade 3/4 neutropenia occurred in 20 patients (48%), and was associated with fever in 17 pts (40%) and sepsis in 3 pts (7%). A grade ≥3 thrombocytopenia or anemia was observed in 14 (33%) and 18 (43%) pts respectively, requiring platelet transfusion in 10 cases (24%) and red blood cells transfusion in 13 cases (31%).

Conclusions: Despite the short infusion of high dose of paclitaxel (250 mg/m²), this phase II showed a modest activity (15% response rate) of this molecule as single therapy in refractory and relapsed aggressive NHIL. The most serious side-effects observed were related to the hematologic toxicity of paclitaxel occurring in about half of the pts.

CHOP THERAPY IN THE ELDERLY NHIL PATIENTS: AN EGYPTIAN EXPERIENCE.
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Introduction: The life expectancy among Egyptian is 58 years. The median age of NHIL patients is 41 years. Considering 55 years as an elderly person, the incidence of NHIL in patients 55 years or more is 29.3% among 3007 cases of NHIL during the years 1985-1994 at the NCICairo.

Methods: Between 1985-1996, 115 cases of NHIL were treated in a study by full doses CHOP therapy for 8 courses. Median age was 46 years (range 19-82). The intermediate grade lymphoma was (90%), stage III and IV was 61%.

Results: Complete response (CR) was attained in 84% of the elderly group, and 75.5% in the younger group, 78.2% in all patients. Under follow up for 30-130 months, the overall survival was 70% for A and 68% for B, the difference was statistically non-significant (NS). Disease free survival for CR patients was 57% for A, and 51% for B, statistically NS. CHOP therapy was well tolerated in both groups with mild to moderate toxicity, and no morbidity.

Ifosfamide, Etoposide And Epirubicin (IVE) For Relapsed And Refractory Lymphomas.
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Introduction: The investigation of alternative chemotherapy combinations in the treatment of relapsed and refractory lymphomas needs pursued in order to improve the current salvage treatment.

Methods: Between 1995 and 1998, 32 patients with relapsed or refractory lymphoma were treated with IVE, comprising Ifosfamide (3-5g/m² days 1-3), Etoposide (100-200 mg/m² daily) days 1-3, and Epirubicin (50 to 60 mg/m² day1). Drug doses were titrated according to performance status, vital organ function and previous treatment.

Results: 32 patients (19 male/13 female; mean age: 47 years) received a total of 112 cycles of IVE. 28 patients had diffuse aggressive non-Hodgkin’s lymphoma, 4 patients had Hodgkin’s disease. 24 patients had stage IV disease, 4 stage III and 4 stage II disease. 18 patients had extranodal disease. ECOG performance status ranged from 0 to 3. The median number of previous treatments was 2 (range 1-6). 21 patients had had 2 or more previous treatments for relapse. 30/32 patients, (94%) had grade IV neutropenia, 7/32 (22%) had grade IV thrombocytopenia. 17 patients, (53%) were admitted to hospital for treatment of neutropenic sepsis. 3 patients developed fully reversible ifosfamide induced encephalopathy. 2 patients died during treatment with IVE: 1 of sepsis, the other of a myocardial infarction. 15 patients had a complete clinical and radiological response, 13 a partial response, with an overall response rate of 87% (28/32). 17 patients underwent peripheral blood stem cell harvesting (PBSC), following IVE. 1 patient underwent PBSC with cyclophosphamide prior to starting IVE. PBSC was successful in all 17 patients after IVE with a mean total CD34 count of 6.2 x 10⁶ cells/kg. 18 patients in CR/GPR went on to receive high dose chemotherapy, (HD-C), and peripheral blood stem cell transplantation, with no transplant related deaths. After a median follow up of 14 months, 17 patients (53%) are still alive, 13 in CR (40%), 2 in PR, and 2 patients have died, of progressive disease.

Conclusions: Despite marked myelosuppression IVE is well tolerated by patients with relapsed and refractory lymphomas and is easily titrated against hematological toxicity. It is very effective in inducing stem cell mobilisation, and has a high overall response rate of 87% in a heavily pretreated group of patients. Further studies with this combination in this setting are warranted.

TWENTY-YEAR EXPERIENCE WITH ADYRMICIN, CYCLOPHOSPHAMIDE, VINCRISTINE AND PREDNSIONE (CHOP) FOR AGGRESSIVE LYMPHOMAS IN A SERVICE OF MEDICAL ONCOLOGY.

Ninety-nine assessable patients (p) with aggressive non-Hodgkin lymphoma has been treated with CHOP as an usual regimen from 1975 to 1997. The median age was 54.5 years (range 8-78) and 37.4% older than 60. There were 61 men and 38 women. The history was diffuse large cell (W.F.) or histiocytic (Rappaport) in 33 cases, diffuse mixed in 8, immunoblastic in 18, anaplastic in 12 and poorly differentiated diffuse lymphocytic histiocytic (Rappaport) in 28. Fifty-five p were in stage III-IV of Ann Arbor and 26 had two or more extranodal sites involved. The median of cycles (c) delivered was 7 (R: 2-15), with the lower number of p that failed (F) and the higher to those who achieved a partial response (PR). Some p received 8-12 c in order to consolidate a complete response (CR). The median of follow up was 177 ± 70 months (m/R: 8-271).

A total of 86 p responded, with 75 in CR and 11 in PR. A 33% (25) of the p in CR relapsed. The median of disease free survival (DFS) was 72 m, with plateau of 41% achieved at 108 m. The median of time to relapse (TRR) of the p in CR was 112m, with a plateau of 44% at 117 m. The median overall survival (OS) has not reached with a plateau of 53% at 107m. The p with stages III and IV and with 2 or more extranodal sites involved did poorly, but not those older than 60.

There is a trend to a poorer DFS(p=0.08) and OS(p=0.08) in the p treated between 1975 and 1985 due to a higher number with poorer prognostic factors, as in the second 12 years these p were referred to more aggressive regimens. However, when the cages were adjusted for stages this poor outcome persisted for stages III and IV, probably because the intensity of dose of adriamycin (ADM) in the regime delivered in the second period of time was a 60% higher. It is to be shown that p with stage I and II, but not III and IV did better when more than 6 c were delivered (p=0.04).

In conclusion, our experience is similar to others already shown, but it could suggest that a decrease of the intensity of dose of ADM must be avoid in stages III and IV. It also might be that to maintain the CHOP for 8-12 c could improve the outcome in stages I and II, but this is a non randomized study and the number of p is too short to draw reliable conclusions.
SIMILAR RESULTS IN PERIPHERAL T CELL NON-HODGKIN'S LYMPHOMA AND B CELL DIFFUSE INTERMEDIATE LYMPHOMAS BY ECHOP-B REGIMEN

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Introduction: The peripheral T cell non-Hodgkin's lymphomas are rare in Europe, but at diagnosis, the disease is almost revealed in advanced stages. The therapy response in T cell lymphomas is considered from many researchers lower than therapy results in B cell lymphomas, with same histology.

Methods: The study contains 28 patients with T cell Lymphomas (that are included in diffuse mixed, diffuse large cell and lymphocytic lymphomas by Working Formulation) and 86 patients with B cell Lymphomas (diffuse intermediate lymphoma). The therapy contained ECHOP-B regimen: Cyclophosphamide 750mg/m² iv day 1; Vincristine 1.4mg/m² iv day 1; Adriamycin 50 mg/m² iv day 1; Prednisone 100mg/m² p.o day 1-5; Bleomycin 10 mg/m² iv day 1; Etoposide 100mg/m² p.o 2-4 days 2-4.

Results: The median age was 54.38 years for the patients with T cell lymphomas and 56.93 years for patients with B cell lymphomas. The two groups showed no difference with regard to median age and sex ratio (by Chi²). 61.5 % patients with T cell lymphomas have 3 or more negative prognostic factors (International Prognostic Index) while only 53.84% of patients with B cell lymphomas presents this conditions.

Complete remission rate was 65.38% for T cell lot and 74.72% for B cell lot. Three years survival was 57.69% vs. 65.30% and disease free survival three years rate was 69.85% vs. 80.88% for included lots. Chi² tests not reveal significant differences between those two lots either on remission rate and three years survival.

Conclusions: the study not make the evidence of significant difference for complete remission rate, three years survival and disease free survival at three years between the lot with peripheral T cell non-Hodgkin's lymphomas and the lot with B cell lymphomas (diffuse intermediate lymphomas), both treated with ECHOP-B regimen.

Combined modality therapy of aggressive non-Hodgkin's lymphomas, stage III-IV: effect of adjuvant radiation therapy

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From 1973 to 1997, 106 previously untreated adult patients with morphologically proven aggressive non-Hodgkin's lymphoma stage III-IV received 4-10 cycles of chemotherapy (CHOP, m-BCOD, ProMACE-CytoBOM, COP). Three of them underwent high dose chemotherapy (M-COAP, M-CED, HOAP-Bleo). Then radiation therapy (RT) was given to the residual lymphatic and extralymphatic tumors. In patients with complete remission (CR) the areas of initial bulky tumors were irradiated. Daily doses were 1.8-2.0 Gy, total doses - 30-55 Gy. Total doses above 45 Gy were given only if residual tumor persisted. After chemotherapy (CT) 17 patients (16,0±3,6%) were in CR and 71 patients (67,0±8,4%) in partial remission (PR). CT was ineffective in 18 patients (17,0±2,6%). After completion of irradiation 56 patients (52,8±2,4%) were in CR and 36 patients (34,0±5,2%) in partial remission (13,2±3,2%) remission hasn't been reached. No radiation related mortality was observed. So the main and statistically proven (P<0,01) short-term effect of adjuvant radiation therapy of advanced aggressive non-Hodgkin's lymphomas was conversion the PR into CR in 39 patients (54,9±4,6%) and all the patients with PR after CT. Five year disease specific survival of patients with CR after CT was 78,1±15,2%, with PR after CT but with CR after RT - 68,1±8,6%, with PR after CT and PR after RT - 71,6±6,4% (P<0,08). Five year freedom from progression survival at the same groups of patients was 81,2±9,7%; 61,0±9,2% (P<0,04); 8,3±5,1% (P<0,1).

Conclusion: in advanced aggressive non-Hodgkin's lymphomas adjuvant radiation therapy given after chemotherapy convert the half of partial remission into complete remissions and survival of this patients is very close to survival of the most favorable group of patients that were in complete remission after chemotherapy.

TREATMENT OF ELDERLY PATIENTS WITH AGGRESSIVE NON-HODGKIN LYMPHOMA

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Introduction: Standard chemotherapy proved more effective than "gentle" regimen for elderly Non-Hodgkin's lymphoma (NHL) patients. The purpose of our study was to analyze the outcome of treatment in this group of elderly patients.

Methods: From a series of 109 patients, 51 older than 60 years were selected. Among them, 16 were treated with doxorubicin-containing regimen, 31 with different "gentle" regimens and 4 were operated and treated with radiotherapy. We compared the first two groups, as well as the whole group of elderly patients with those ≥ 60 years old.

Results: Median age in the group of elderly was 68 (61-84). The complete remission rate was 16.7% (37,25%), the partial remission and no remission in 22 (43,14%) and 10 patients died in the course of therapy (19,0%). CR was achieved in 21,6% of patients treated with doxorubicin-containing regimen and in 46,16% of patients treated with "gentle" chemotherapy (Chi-square=0,008; p < 0,05). In the course of therapy 25% of patients died in the first group and 18,12% in the second (Chi-square=0,12; p > 0,05). According to the age-adjusted international index for older than 60, after a median follow-up of a year, overall survival was significantly higher in the low risk than in the high risk group (p =0,039). There was no difference in the distribution of age-adjusted international index between patients > 60 years and patients ≤ 60 (Chi-square =0,31; p > 0,009). CR was achieved in 46,34% of the elder and in 77,78% of the younger ones (Chi-square=8,7; p < 0,01).

The two age groups differed significantly according to existence of concomitant chronic disease (Chi-square=12,85; p < 0,01). Overall survival proved to be comparable (n = 0,20; p < 0,01). After median follow-up of 16 months, median overall survival was 10 months in the elderly and 21 months in the younger ones.

Conclusions: Achieving of CR in the elderly NHL patients is less frequent than in the younger ones and in our study it was not dependent on the regimen given. Overall survival is dependent on age. The elder patients frequently have other diseases and are more likely to die during the therapy. After the short follow-up, their survival is depended on the age-adjusted international index only partially.

AGGRESSIVE HEAD AND NECK NON-HODGKIN LymphOMA: 126 patients TREATED by 29 TWO-GOLEAM5 (5%) and 28 TOTAL (14)

B. Besadolj, Ch. Foucher, Ch. La Manjou, A. Le Mevel, Ph. Colombat, J.-F. Abgrall, Ch. Gendebath, T. Lamy, M.-F. Guittier and S. Tabuteau for the GOELAM group.
Médecins du sud - Sion-CHU Annemasse - France

We report on 136 patients (pts) suffering from an 'aggressive', i.e. intermediate- or high-grade head and neck (HN) non-Hodgkin's lymphomas (NHL) and compare them with 103 cervical nodal NHL, treated by the same two GOELAM 02 & 03 trials.

Initial data were as follows without any statistical difference except for stage (p=3.10^-6)

<table>
<thead>
<tr>
<th>M</th>
<th>F</th>
<th>Median Age</th>
<th>B/I</th>
<th>Age ≥ 60</th>
<th>NED1</th>
<th>NED2</th>
<th>NED3</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>1</td>
<td>71</td>
<td>1/1</td>
<td>0/1</td>
<td>0/1</td>
<td>0/1</td>
<td>0/1</td>
</tr>
</tbody>
</table>

Bulky was defined as ≥ T3 or T4 tumor according to TNM classification among HN NHL and as lymph nodes ≥ 5 cm among nodal NHL. Distributions according to the sites was the following: tonsil 54 pts, nasopharynx 18, paranasal sinuses 15, salivary glands 10, base of tongue 8, oral cavity 7, nasal cavity 7, larynx or hypopharynx 2 and multiple sites 15.

The 93 HN NHL aged less than 60-65 years received DFO (a double CHOP like regimen) and the 43 more aged pts 3-line-VTEP (a CHOP like regimen) before a 40 GY localized irradiation according to the GOELAM 02 & 03 trials. Initial results were:

<table>
<thead>
<tr>
<th>n</th>
<th>pts</th>
<th>Toxic</th>
<th>Failure</th>
<th>CR</th>
<th>Surg</th>
<th>CNO</th>
<th>CT</th>
<th>Radio</th>
</tr>
</thead>
<tbody>
<tr>
<td>163</td>
<td>93</td>
<td>1</td>
<td>11</td>
<td>20</td>
<td>2</td>
<td>2</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>

With a median follow-up time about 8 years, we noted 32 relapses after 5 to 112 months (median 30.5) with only 2 neurological cases. There were 39 deaths of which 8 were 'non-related' (4 due to a solid tumor and 1 due to an AIDS). DFS and specific survival rates (SSS) are also similar among the two groups:

<table>
<thead>
<tr>
<th>3 years</th>
<th>5 years</th>
<th>10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS H &amp; N</td>
<td>Nodal</td>
<td>74%</td>
</tr>
<tr>
<td>SSS H &amp; N</td>
<td>Nodal</td>
<td>80%</td>
</tr>
</tbody>
</table>

A Cox model done on DFS among the 136 HN NHL retained among the 4 prognostic factors (age ≥ 60, PS ≥ 2, L2RH ≥ N, bulky and trial) bulk (p≤0.02) age (p≤0.03). At last the 10-year prognostic of a HN lymphoma without bulk is very excellent: 81 ± 9%.

3. Aggressive Lymphomas
MEDIASTINAL LYMHPHA: ANALYSIS FROM 52 PATIENTS TREATED BY THE GOELAMS 02 TRIAL.


Mélanies du Sang - Hôpital Sud - CHU Amiens - France.

We report on 52 patients (pts) with an 'aggressive,' i.e., intermediate- or high-grade, mediastinal non-Hodgkin’s lymphoma (NHL). There were 19 men and 33 women (sex ratio 0.58) and median age was 40 years (from 20 to 70 years) with only one case more than 60 years. Histology shows a sharp predominance of the G type (42 pts) with often a sclerosing and 5 anaplastic NHL. The B/T cell ratio was 8.25. All pts were staged II with 5 lymphomas in 12 cases (23%). A local extension was seen in 16 cases (31%) (pleura, lung and/or pericardium) and a bulk (mass ≥ 10 cm) in 34 cases (65%). PS was 2 in 7 cases (13%), LDH ≥ 2 in 19/41 cases (46%) and [2m-3] mg/l in 17 cases (65%).<br><br>After initial surgery, no pt was an 'apparent' CR and after 3 courses of VACOP (a double-CICHOP like regimen) we noted 1 toxic death, 3 failures, 9 PR and 39 CR (75%). After ≥ 40 Gray irradiation, we noted 5 failures and 46 CR (88%).<br><br>On January 1999, the median follow-up time is about 9 years and we noted 9 relapses and 13 deaths with only one non-related death due to a drowning accident. The 10-year DFS and 'specific' survival rates (SSR) are 73 ± 6% and 78 ± 6% respectively.<br><br>However, as shown on the figure, the curve of DFS is not usual when looking at other localized 'aggressive' NHL.<br><br>- first point: 6/12 of the 9 relapses occurred very early during the first year of survey and so are rather 'failures' than 'relapses' even if 3 of these 6 pts were in apparent CR after initial chemotherapy. When excluding the 3 late relapses, we found no prognostic value for PS, LDH or bulk.<br>- second point: the 3 other relapses occurred late, at the 78th, 123rd and 160th month of survey. These relapses occurred outside the thorax and were massive.<br><br>3. Aggressive Lymphomas

CONTINUOUS INFUSIONAL CHEMOTHERAPY (EPOCH) FOR PREVIOUSLY UNTREATED AGGRESSIVE NON-HODGKIN’S LYMPHOMA, A PHASE II STUDY.

Mikel Eriksson, Anna Johnsson, Eva Cavallin-Stahl.

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Purpose: Based on in vitro evidence that tumour cells are less resistant to prolonged exposure to low concentrations of certain chemotherapeutic drugs, Wilson and co-workers designed the EPOCH-regimen, which consists of etoposide, vincristine and doxorubicin administered as a 96-hour continuous infusion with intravenous bolus cyclophosphamide and oral prednisone. This regimen was shown to be well tolerated and highly effective in patients (pts) with relapsing non-Hodgkin’s lymphoma (NHLJl Clin Oncol 1999: 11:1573-82). Prompted by this result we have designed a phase II study on EPOCH in previously untreated consecutive pts with aggressive NHL excluding lymphoblastic and Burkitt’s lymphoma.

Patients and methods: Between 1995 and 1998 we included 40 pts, one of which died in liver coma due to aggressive disease twelve days after start of treatment, and one who only received one EPOCH cycle followed by CHOP for technical reasons. In the remaining 38 pts the median age was 54 years (28-81). Three pts had bulky stage I disease, 11 pts stage II, 9 pts stage III and 15 pts stage IV. According to the international prognostic index (IPI), 18 were low risk, 11 low intermediate, 4 high intermediate and 5 high risk. Twenty-five five pts had diffuse large cell B, 9 other aggressive B-cell lymphomas and 4 T-cell lymphomas. In total 35 pts received 4-8 EPOCH cycles, 3 pts less. In a few pts CHOP was given as the first cycle due to technical reasons. Seven pts in CR after EPOCH received consolidating treatment, five localized radiotherapy, one high dose chemotherapy and one other chemotherapy due to toxicity.

Results: Toxicity was manageable with mainly granulocytopenia and neurotoxicity. There was no toxic death. CR was obtained in 84%, which compares favourably with a CR of 50% in 44 pts treated with either CHOP or MACOP-B at our institution within a randomized multicenter trial during the past years. The median follow-up time is 18 months. The 2-year failure-free survival is 55%, and overall survival 79%.

Conclusions: EPOCH is a feasible, although compared with CHOP somewhat more technically complicated, regimen, which in this study produced a high rate of CR in pts with aggressive NHL. Follow-up time is short, and it is too early to assess whether this regimen results in a survival benefit compared to our standard treatment.

3.90

P53 MUTATION AND PROTEIN EXPRESSION, AND ANALYSIS OF OUTCOME IN NODAL DIFFUSE LARGE B CELL LYMPHOMA

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2Department of Haematology, Birmingham Heartlands Hospital.

We have used SSCP and streptavidin-biotin immunocytochemistry on formalin-fixed paraffin embedded lymph nodes, to investigate the incidence of p53 mutations and protein expression, and their effect on outcome, in the presentation lymph nodes of a group of nodal diffuse large B cell lymphomas (DLBCL). Primary extranodal DLBCLs and cases with evidence of an underlying low grade tumour were excluded from the study. Using a novel fluorescent SSCP technique which has a sensitivity of 5-10%, band shifts at exons 5-9 have been examined. Analysis of small band shifts was facilitated by Geneescan software. Band shifts were detected in 16% of cases studied (92 to date), 2 cases had a shift at exon 5, 2 at exon 6, 9 at exon 7 and 1 at exon 8. No shifts were detected at exon 9. In all cases in which a mutation was detected >50% of cells were strongly positive for p53 (DOT). In the remainder of cases, 19% had >50% expression of p53 protein despite the absence of a detectable mutation, a further 30% had moderate expression (15-50% cells positive), and 51% were negative (<15% cells positive). The median follow-up time in the group of patients studied was 23 months, overall median survival (OS) was 39 months, and median event free survival (EFS) was 22 months. Patients whose presentation lymph node had a p53 mutation had a worse outcome, 15 months median OS and 19 months median EFS for the p53 mutation group compared to 30 months median OS for the group of patients in which no mutation was detected (p=0.2). The median EFS has not yet been reached. A similar trend was seen when examining the effect of survival on protein over-expression alone, 19 months median OS and 16 months median RFS in the p53 positive group, median OS and EFS have not yet been reached (p=0.1). In the cases in which >50% of cells, but no mutation was detected, it is possible that a mutation was present but undetectable by the method used, or that p53 was stabilised in the nucleus by another mechanism. In conclusion, cases with p53 mutations and protein over-expression, detected at presentation, show a trend towards early relapse and less favourable outcome in nodal DLBCL.
Stage I High-Grade Non-Hodgkin's Lymphoma: Chemoradiotherapy, local control, long-term survival and prognostic factors in 252 patients

Norwegian Radium Hospital, Oslo, Norway

Introduction: Few unselected large patient materials on stage I high-grade non-Hodgkin's lymphoma (H-NHL) have been published. The optimal therapeutic choice of radiotherapy and/or chemotherapy as well as the optimal dose of either modality are disputed and may depend on patient age and disease localization.

Methods: We identified 252 stage I H-NHL patients treated during the years 1980-96. Most patients received 6 CHOP courses followed by involved field radiotherapy to 40 Gy. The SPSS statistical package was used for data presentation and Kaplan-Meier and Cox survival analysis.

Results: Median patient age was 64 years, and 49 % of the patients had extranodal lymphoma. Premonopausal women (n=23) had significantly lower risk of extranodal lymphoma than older women (n=80) or males (p=0.002). Projected disease specific 5, 10, and 15 year's survival in patients <64 years was 83 %, 76 %, and 76 %, respectively; compared to 54 %, 49 %, and 46 % in patients > 64 years of age. Multivariate Cox's analysis identified age, histology different from centroblastic lymphoma, B symptoms, and increased serum LDH as independently negative prognostic factors for disease specific survival ( p < 0.01), while neither extranodal, testicular, or bulky (>6 cm) lymphoma presentation nor increased ESR were of prognostic significance. A radiation dose of 40 Gy in 2 Gy fractions to the primary site retailed in-field failure in 159 of 173 irradiated patients (92 %, 95 % CI 87.6 - 95.9 %), and only 3 of 173 irradiated patients (1.7 %) had local relapse in the absence of systemic dissemination.

Conclusions: Patient age was a salient prognostic factor. Premonopausal females had a low risk of extranodal stage I H-NHL. More than 90 % of treatment failures were due to systemic relapse outside the irradiated site. Better systemic treatment is needed, especially for older stage I patients.

VALUE OF INTERNATIONAL PROGNOSTIC INDEX FOR AGGRESSIVE NON-HODGKIN'S LYMPHOMA (IPI): A RETROSPECTIVE STUDY.
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Dept. of Radiochemotherapy, IRCCS I.Raffelev Hosp. Milan

INTRODUCTION: Although a significant number of patients with intermediate or high-grade NHL classified by the Working Formulation are cured by anthracycline-containing combination chemotherapy, 50 % to 70 % either fail to respond to induction therapy or relapse. All adult patients with aggressive NHL have not the same possibility to cure. It has become quite clear that need to identify some subgroups cannot be compared fairly because they have different chances of benefitting from therapy. It is important to recognize this when making treatment decisions and that clinical trials continue to identify the optimal treatment for each subgroup. The identification of "high" or "low" risk group patients with aggressive NHL modify the therapeutic strategy. Several of the major groups involved in the treatment of this disease have retrospectively analyzed their series of patients trying to identify factors significant for final outcome and several models have been proposed in the medical literature in the last past years. The International Prognostic Index ( IPI ) has been proposed to identify clinical prognostic factors that would form the basis of a new classification for aggressive NHL that would be more reflective of the unique biology of this disease.

PATIENTS AND METHODS: In a retrospective study we have analyzed the value of IPI in 138 patients affected by aggressive (F,G,H) NHL from January 1978 to December 1997.Almost all patients had five prognostic factors necessary to determine IPI (III/IV stage, age>60 years, n of extranodal disease sites, PS according ECOG=1, high serum concentrations of LDH ). We have divided the patients into two groups: 61 pts with an initial score of 0,1 or 2 (low risk) and 77 with a score of 3 or 5 ( high risk ). All patients were treated with combination doxorubicin-containing combination chemotherapy and were evaluated for clinical features predictive of overall survival and relapse survival. RESULTS: Complete remission rate was 93% for low risk group and 66% for other group. The ten-years disease-free survival was respectively of 65% in the first and of 32% in the second group (P< 0.0001).Overall survival rate observed was 72% in low risk group and 29% in the high risk group (P= 0.0001). CONCLUSIONS: Our results confirm that IPI is a valid model to detect high risk group of patients with NHL that obtain only little or non benefits with conventional treatment and should receive more intensive chemotherapy.

AGGRESSIVE CHEMOTHERAPY IN ELDERLY PATIENTS WITH HIGH-GRADE NON-HODGKIN'S LYMPHOMA (H-NHL)

INTRODUCTION: The optimal treatment for elderly patients (pts) with H-NHL remains controversial.

The aim of this study was to analyze the impact of age on response, survival and toxicity in pts with this disease.

METHODS: Between January '84 to August '91,306 evaluable pts. entered in GALTA 3-LNH '83, were analyzed. This protocol included chemotherapy with CAPVE: cyclophosphamide 1000 mg/m2 iv day 1, adrianycin 45 mg/m2 iv day 1, prednisone 100 mg/m2 po day 1 to 5, vincristine 1.4 mg/m2 iv day 1 (maximum 2 mg), etoposide 150 mg/m2 iv day 1, 3, 5. Courses were repeated every 3 to 4 weeks for 8 cycles. Of the 306 pts, 219 were > 60 years (group A) and 87 pts were > 60 years (group B). Both groups are comparable in the distribution of other characteristics with prognostic value.

RESULTS: Although the complete remission rate and toxicity were similar for both groups, the mortality on induction was higher for group B.

The survival probability and event free survival were significantly lower for group B.

AGE # PTS %LTV (%) PS 2 (%) B SYM (%) EXTRAN BULKY
≤ 60 219 145 (66.2) 38 (17.3) 84 (38.5) 37 (19.7) 116 (52.9)
> 60 87 63 (72.4) 16 (18.3) 36 (41.4) 33 (37.9) 41 (47.1)

RESULTS: Age is an independent adverse risk factor.

IN ELDERLY pts with H-NHL showed lower EFS and SV rates, probably related to their poorer tolerance to aggressive CT. Other approaches should be tested in order in improve results in this population.

MODEL BASED DEVELOPMENT AND FIRST CLINICAL EVALUATION OF ECONOMIC G-CSF-SUPPORT IN INTENSIFIED CHOEP-CHEMOTHERAPY FOR AGGRESSIVE NHL.
Institute for Medical Informatics, Statistics and Epidemiology (IMSE), Clinic II of Internal Medicine, University of Leipzig, and Clinic 1 of Internal Medicine, University of Cologne, Germany, in cooperation with the German High Grade NHL Study Group

INTRODUCTION: The German High Grade NHL Study Group is currently conducting a randomized multicenter trial to investigate the effectiveness of moderate-dose intensification of standard CHOP regimen for treatment of aggressive NHL. In a factorial study design, 6 courses of 3-weekly CHOP (CHOEP=21, CHOEP=14), both compared to the addition of Etoposide with 100 mg/m2 q.3 weekly (CHOEP=21, CHOEP=14, G-CSF is given for 10 days in the 2nd weekend). To investigate whether the duration of G-CSF administration can be shortened without jeopardizing the 3-weekly chemotherapy, we developed a computer based quantitative model of human granulopoiesis to stimulate leukocyte time course during the above regimen and thus to identify more economic G-CSF treatment schemes. In a current pilot study, eight patients receiving CHOEP=14 were treated with a shortened G-CSF schedule and evaluated for safety and feasibility.

Methods: Leukocyte counts were available for about 500 pts and 3000 cycles in all regimens. Data were analyzed separately for regimen, cycle number and seventy of hematotoxic response. The model consists of a parametric compartment structure describing the population kinetics of stem cells, granulocyes precursors and mature blood neutrophils, quantitatively being regulated by the circulating G-CSF levels. G-CSF is assumed to dose-dependently enhance activation and differentiation velocity of precursor cells. Chemotherapy damage is described by an acute cell loss and a temporary impairment of the system's G-CSF responsiveness. These damage parameters were adjusted by comparing simulations to clinical trial data. We aimed to determine a shorter G-CSF schedule such that neutropenia would be not worse than with the current standard, as judged by the area under the simulation curve (AUC) under a threshold of 1500 leukocytes/L. Patients with high grade NHL CS-II/IV treated with CHOEP=14 received shortened G-CSF support from day 8-12 in cycles 2-6. For safety, the first cycle was supported with the standard schedule (6-21).

Results: Leukocyte dynamics of all regimens could satisfactorily be described by the respective damage parameters. Based on a model parameter adjustment for the current scheduling, systematic variations of G-CSF scheduling were then simulated (begin and duration at variables). For the CHOEP=14 regimen, the model predicted that neutropenia under G-CSF variations from d8-d12 (5 days) should be worse than with the current schedule (10 days). Leukocyte dynamics of 8 patients treated with CHOEP=14 receiving this shortened schedule showed no major increase in hematotoxicity, though leukocyte nadirs were slightly lower than predicted. However, no delays of the 14-day treatment period occurred due to insufficient hematotoxic recovery.

Conclusions: Our model and first clinical data suggest that G-CSF treatment might considerably be shortened during CHOEP=14. On the basis of our model predicted benefits the no systematic investigation of different G-CSF schedules varying timing, dosing and duration will be initiated in the forthcoming NHL trials.
Vincristine-adriamycine continuous infusion (VAD) in the treatment of elderly patients with aggressive non-hodgkin's lymphoma (NHL).


The aim of this prospective, non-randomized, multicenter trial was to evaluate the efficacy and the tolerance of the VAD followed by an adapted CHOP regimen (ECAP) as first line therapy in elderly patients with intermediate and high grade NHL. Between April 1994 and november 1996, 68 patients (men/f: 35/33) aged from 60 to 78 years (median age: 70 years) were enroled. Histologic sub-types were F or H types. (B/F phenotype: 59/9). Nine pts (13%) were stage II bulky, 11 pts (16%) stage III and 48 pts (71%) stage IV. Performances status (PS) was 2 in 29 pts (43%). HDL level was normal in 41 pts (60%). VAD regimen consisted of Vincristine 0.4 mg/day iv continuous infusion (IVC) DF-1, Adriamycine (ADR) 9 mg/m²/day IVC DF-1 and Dexamethasone 20 mg/12h DF-1. ECAP regimen consisted of Etoposide 100 mg/m² DF, Cyclophosphamide 750 mg/m² DF, ADR 50 mg/m² DF, and Prednisolone 40 mg/m²/day DF-1. Initial treatment design consisted by 4 courses of VAD alternating with 4 courses of ECAP. Forty-seven pts (69%) achieved complete remission (CR). CR rate was significantly lower for pts with poor PS (p=0.02) and T phenotype (p=0.03). At 36 months, the overall survival was 40%. It was significantly lower for pts who did not achieve CR (p=0.0001) and for T phenotype (p<0.01). Relapse occurred in 15 pts between 1 and 18 months after achieving CR. The most frequent relapse sites were central nervous system and bone marrow. Major non-hematologic toxic events occurred in 6 pts. One toxic death was observed. WHO grade III-IV neutropenia and thrombocytopenia were reported in 25% and 2% of the courses respectively. In conclusion, VAD-ECAP regimens appeared as effective and more tolerated than CHOP in the treatment of elderly patients with stage II bulky to IV intermediate- and high-grade NHL. Further prospective controlled randomized trials will be necessary to determine the optimal therapy for these patients.

AGE IS THE MAIN prognostic factor of dose-intensity for intermediate and high grade non-hodgkin's lymphoma.


Patients and methods: We analysed 129 patients with non-Hodgkin's lymphoma diagnosed between 1982 and 1995. Histology was (B)GL(H) in 64 cases and not specified in 11 cases. All were IFI negative. Clinical characteristics were: age >60 (49.5%), PS 2 (11%), stage III/IV (40%), LDH norm (29%), LDH high (25%), unknown (25%), number of extranodal sites (ES): 1 (77%), > 2 (23%), IPI (0.3), LPI (18%), HLI (12%), HLI (12%), unknown (25%). Sevety-four patients received CHOP-CTX, IPI-CHOP-CTX, IA/I-CHIP. For the 15 patients who received CR, the most frequent relapse sites were central nervous system and bone marrow. Major non-hematologic toxic events occurred in 6 pts. A toxic death was observed. WHO grade III-IV neutropenia and thrombocytopenia were reported in 25% and 2% of the courses respectively. In conclusion, VAD-ECAP regimens appeared as effective and more tolerated than CHOP in the treatment of elderly patients with stage II bulky to IV intermediate- and high-grade NHL. Further prospective controlled randomized trials will be necessary to determine the optimal therapy for these patients.

Dexamethasone, BNU, etoposide, ARA-C, and melphalan (DEXA-BAEM) is not effective in patients with relapsed or resistant aggressive NHL.


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Purpose: The aim of the present study was to evaluate the feasibility and response of the DEXA-BAEM regimen as a salvage therapy followed by high-dose chemotherapy (HDC) with peripheral blood stem cell transplantation (PBSC) in responding patients with high-grade relapsed or resistant NHL.

Material and Methods: 16 pretreated patients with relapsed (8) or resistant (8) NHL were treated with 1-4 cycles of DEXA-BAEM (Dexamethasone 3x8mg p.o. d1-10, BNU 60mg/m² i.v. d2, VP-16 200mg/m² i.v. d2-7, ARA-C 100mg/m² i.v. d2-7, Melphalan 20mg/m² i.v. d3), in order to attain maximal response. Patients achieving CR or PR received HDC with PBSC. The conditioning regimen used was BEAM.

Results: 3 patients achieved CR and 1 PR, resulting in an overall response rate of 25%. 3/4 responding patients underwent high-dose chemotherapy and were successfully transplanted with autologous blood stem cells. Progressive disease developed in one patient after transplant. Myelo-suppression (WHO III-IV) was observed in all courses of DEXA-BAEM. Myelo-suppression-related infections WHO IV* occurred in 6 patients, and 1 patient died in septic shock, despite neutropenia. 1 patient developed diarrhea WHO IV°, causing discontinuation of therapy. In 17/30 evaluable cycles patients developed fever WHO III°.

Conclusions: Although being very effective against HD, Dexcel-BAME was only effective in a minority of patients with refractory or relapsed NHL and was not useful as a cytoreductive regimen prior to HDC. The protocol was not well tolerated in this heavily pretreated group of patients with four severe myelo-suppression-related infections WHO IV* and one treatment-related death. The overall response rate in this study is not comparable to other salvage regimens published and led to the discontinuation of the trial.

BLASTOID Variants of mantle cell lymphoma: Clinical-biologic features and prognosis.

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Introduction: Mantle Cell Lymphomas (MCL) represent a heterogeneous cytoplasmic and histological entity. Blastoid variants (BV) represent about 15% of MCL, but their real frequency is probably underestimated. BV of MCL are often associated with t(4;14) and somatic mutations of VH rearrangement gene. We investigated the biological and clinical features of 18 cases of BV of MCL. This is a retrospective analysis from 1993 to 1998.

Patients and Results: There were 12 males and 6 females, with a median age of 61 yr (29 to 80 yr). All but 2 patients had stage IV disease and lymph node involvement. 12 out of 18 had extranodal sites involvements: lung or specific visceral invasion (n=6), liver (n=3), tonsil and bone (n=2) and NSF (n=2). Of the 18 patients, 9 (50%) had splenomegaly, 15 (83%) had bone marrow infiltration, and 10 (55%) had lymphoid blast peripheral cells. Biological parameters were as follows (median, range): WBC 15.6 x 10^9/L (2.3 to 85 x 10^9/L), Hb: 11.9 g/dL, platelets: 164 x 10^9/L (35 to 288 x 10^9/L), LDH > N (13), D2P > N (11). In most cases BV rearrangement (RT-PCR or FISH) was performed and found positive in 17 patients. CD5 (+)/CD10(-)/CD19(+)/CD23(-) phenotype was observed in the 17 patients analyzed. 3/14 cases had tetrapiptide chromosome clones. The diagnosis of BV of MCL was made initially for 15 patients and at relapse for the 3 who were previously diagnosed as having a diffuse large cell NHL. BV was diagnosed according to cytomorphological and histological pattern. Patients received anthracycline-based regimens (n=17) and COP (n=1) as first-line therapy. 7 patients out of 18 are evaluable for response: 4 patients entered CR (41%), and 4 of these underwent autologous BM (6 patients (including the 4 autografted pts) relapsed within 15 months: one had allogenic BMT and is alive in CR 4 years later: 9 out of 11 refractory or partial responders patients died of progressive disease. The median DNR and overall survival (OS) is 6 and 8 months respectively.

Conclusions: Our results suggest that: 1) Histopathological analysis should be completed with immunophenotyping for a better identification of MCL. 2) BV of MCL is one of the forms of NHL with the worst prognostic characterized by an aggressive behaviour (as compared to the other histological subtypes of MCL) and a poor response to anthracycline-based regimen. Alternative therapies should be proposed in such patients.
HIGH GRADE MALIGNANT NON-HODGKIN LYMHPHOMA: IMPACT OF RADIOTHERAPY IN THE COPBLAM/MM/VP-16 TRIAL

Introduction: In advanced high grade malignant Non-Hodgkin's lymphomas (nHNL, Ki67 and corresponding REAL classification entities) stable complete remissions are not the rule but there exists potential cure. The aim of this study was to determine the prognostic relevance of radiotherapy in complete responders in combination trials and to identify patients (a) who are at high risk for relapse (b) who benefit from combinations of chemotherapy and radiotherapy. Methods: From a prospective multicenter trial conducted in Ann Arbor stage II-III-IV disease, the subset of patients (median age 50 years, completing full course COP-BLAM/MM/VP-16 chemotherapy with complete or partial response (CR/PR) followed by radiotherapy (RT) or observation only were analysed (n=400). According to protocol, converting CR patients without bulky disease were randomised to adjuvant RT (CRRT, involved field 40 Gy, n=411) or follow-up observation (CRFU, n=49). In bulky disease (≤ 10 cm) RT was recommended (BDRT, n=25), in partial responders it was optional (PRRT, n=41, PRFU, n=20). Results: Median observation time was 4 years and all 5 years in all surviving patients. In the randomised comparison of complete responders, 5-10 year survivals were 75%/68% in CRFU and 73%/65% in CRRT, relapse-free survival was 64%/55% and 52%/45% (all non-significant) and in relapse-free survival revealed hereafter (both p > 0.05). Smaller results were obtained for CR patients not consenting to randomisation and for those in the BDRT group. In the non-randomised comparison of partial responders, overall survival and relapse-free survival differed significantly (p = 0.02 and 0.09) in favor of the PRRT group. Conclusions: In the present study in advanced nHNL, adjuvant RT did not provide a significant contribution to the stability of CR in complete responders after COP-BLAM/MM/VP-16 chemotherapy. However, consolidating RT may be instrumental in partial responders in achieving CR and thus long-term survival.
HEALTH-RELATED QUALITY OF LIFE MAY BE A SIGNIFICANT PROGNOSTIC FACTOR IN PATIENTS WITH AGGRESSIVE LYMPHOMA.
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1Nordic Lymphoma Group.
2Department of Oncology, University Hospital, Lund, Sweden; 3Palliative Medicine Unit, Department of Oncology, Regional Hospital, Trondheim, Norway.

Background: The clinical course of patients with aggressive lymphoma is very variable, prompting the search for prognostic factors appropriate for use in risk-adapted therapy. However, the possible prognostic impact of health-related quality of life (HRQOL) has not previously been evaluated.

Patients and methods: 95 patients, median age 46 years, with aggressive lymphoma, entering a randomised multi centre trial comparing CHOP and MACOP-B, also entered a quality of life study, using the EORTC QLQ-C30 questionnaires. The prognostic impact of pre treatment HRQOL in relation to the factors of the International Prognostic Index (IPI) was evaluated, including age, Ann Arbor stage, number of extranodal sites, serum lactate dehydrogenase (LDH) level and performance status.

Results: In multivariate analysis, pre treatment overall quality of life turned out to be an independent prognostic marker. In this series, only 7/95 had a performance status above 1.

Conclusion: In a relatively young patient population with aggressive lymphoma, the majority with good performance status, patient-assessed overall quality of life may substitute for performance status as a factor in the IPI, merit further investigation in prospective studies.

PROGNOSTIC IMPLICATIONS OF CYTOGENETIC ABERRATIONS IN DIFFUSE LARGE B-CELL LYMPHOMA
1Departments of Oncology, 2Clinical Genetics, 3Cytology and Pathology, University Hospital, Lund, Sweden.

Purpose: To evaluate the prognostic value of cytogenetic aberrations with proposed prognostic impact in diffuse large B-cell lymphoma (DLBL).

Patients and methods: 81 cytogenetically categorised cases of DLBL from a single institution were retrospectively reviewed. The prognostic impact of the following aberrations were investigated: >10 cytogenetic aberrations; >4 marker chromosomes; >4 breakpoints; trisomy 2, 3, 5, 6, 7 or 18; duplication of 3p or 2p; deletion of 6q or monosomy 6; deletion of 7p or monosomy 7; deletion of 17p or monosomy 17; breakpoints at 1q21-23, 3q27, 8q21-25, 14q11-12 or 18q21; t(8;14)(q24;q32), t(11;14)(q13;q32), and t(14;18)(q32;q21).

Results: In univariate analysis, a breakpoint at 1q21-23 and trisomy 6 were associated with a shorter overall survival. However, when adjusted for age, stage, performance status, and lactate dehydrogenase (LDH) level, the cytogenetic aberrations were of no independent prognostic value.

Conclusion: The present investigation provides no support for any of the above-mentioned abnormalities being of prognostic importance in DLBL.

REPRODUCIBILITY OF TREATMENT RESPONSE EVALUATION IN PATIENTS WITH HIGH-GRADE MALIGNANT NON-HODGKIN'S LYMPHOMA
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In contrast to survival, estimation of complete (CR) and partial response (PR) in non-Hodgkin’s lymphoma (NHL), is associated with a number of potential sources of error. In this report we have studied the reproducibility of response evaluation performed by an independent review committee (REC). The evaluation, which was based on medical records of individual patients, used exactly the same validation materials at the first (REC 1) and second (REC 2) assessment.

Material and methods: In a phase III multicenter Nordic study patients 260 years of age with high-grade malignant NHL were randomised in a bicentric design to four treatment groups: CHOP or CNOP alone or in combination with granulocyte colony-stimulating factor (G-CSF, Neupogen®). In Sweden 35 institutions included patients. Sixty patients who were already evaluated (REC 1) were randomised to three groups and reevaluated (REC 2). The RC consisted of three senior hematologists/oncologists divided into three teams with two in each. Forty patients were reevaluated by each member. The assessment was classified into one of eight mutually exclusive categories, where the important borderline with regard to one of the major end-points of the study, the CR rate, was between CR, "CR uncertain" and PR. Results: A discrepancy between RC 1 and 2 was found in 39/80 patients. The CR evaluation was changed in five of these patients. Two CR and two PR, patients were reclassified as "CR uncertain" and one was regarded as CR "not assessable". Thus, CR was changed in 8.3% of the patients.

Conclusion: In assessment of CR, only minor disagreement was seen between RC 1 and RC 2. We believe, that an independent RC is a major prerequisite for proper response evaluation in clinical phase III trials. However, the good RC reproducibility does not motivate a reevaluation.

SECONDARY NON-HODGKIN’S LYMPHOMA OF THE CENTRAL NERVOUS SYSTEM – A CLINICOPATHOLOGICAL STUDY OF 68 CASES
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Dept. of Haematology, Fundeni Hospital, Bucharest, Romania and 2Saint Louis Hospital, Paris, France.

A retrospective analysis was performed in order to study the incidence, the risk factors and the role of prophylaxis of secondary central nervous system (CNS) relapse in patients (pts) with non-Hodgkin’s lymphoma (NHL). The study was made upon 68 (4%) of 1743 pts with NHL registered between 1984–1996 in Saint Louis Hospital and Fundeni Hospital. Methods: Patients with AIDS and ALL were excluded. Diagnosis of CNS involvement was made on spinal fluid analysis, myelography, CT or MRI or a combination of these. Risk factors assessed were: age, sex, malignancy grade (according to the Working Formulation), clinical stage, localization, bone marrow, response to initial therapy. CNS prophylaxis consisted of MTX i.1., high dose ARA-C and MXT consisting regimens, or both. CNS relapses were treated by MTX and ARA-C i.1. or intra Oraely and whole brain radiotherapy (RT) with dexanethasine in most cases.

Results: CNS relapses were localized leptomeningeal (n=55), parenchymal (n=3), nerve roots (n=5) and extradural (n=3). 11 pts presented at diagnosis simultaneous CNS and systemic NHL; in 31 pts the CNS lymphoma occurred during the systemic progression of lymphoma not responding to therapy; in 15 pts CNS relapses was isolated after therapy and in 11 pts was simultaneous CNS and systemic relapse after therapy. Of these 68 pts, 3 presented initially with high grade lymphoma, 13 with intermediate grade and 52 with high grade. Median time between initial NHL diagnosis and CNS relapse was 7 months (0–53 mo). The risk factors for CNS relapses were: malignancy grade, age <40, male sex, bone marrow disease, combined nodal and extranodal involvement and partial response after initial therapy. In our study 12 pts received prophylaxis for CNS disease – all cases developed CNS lymphoma. The risk of CNS relapse did not differ between those pts who received a form of prophylaxis and those who did not receive any.

Conclusion: The occurrence of CNS relapse seems to be related to the risk of systemic relapse after CR. No subgroup could be discriminated in which prophylactic treatment would be of substantial benefit.
LONG TERM OUTCOME OF ANAPLASTIC LARGE CELL LYMPHOMA CD30+ (ALCL-CD30+) IN 51 CONSECUTIVE PATIENTS: IMPROVED RESULTS WITH THIRD GENERATION THERAPY.

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From 1982 to 1997, 51 consecutive patients (M/F 30/21, m. age 36 yrs. 3-73) affected by primary ALCL-CD30+ were observed at the Verona University School of Medicine. The subtype was common (CT) in 43 cases, Hodgkin’s-like in 8; 7 cases observed before 1986 were identified by subsequent review. In the ALCL-CT the phenotype was Null in 22 cases (51%), B in 11 (26%), T in 10 (23%). Stage: I in 5pts (bulky 2/3), II in 21, III in 13, IV in 14. Bulky disease was present in 16 cases (31%), B symptoms in 27 (53%), Extravascular disease was seen in 29 pts (57%), mostly involving soft tissue(9) and GIT(9), multiple extranodal involvement in 8. 36 pts underwent third generation therapy (MACOP-B, VACOP-B, 10 CHOP or CHOP-like, 2 intensified CHOP-like (MEGACEOP), 3 other regimens. Results:

<table>
<thead>
<tr>
<th>Pt</th>
<th>CR</th>
<th>PR</th>
<th>NR</th>
<th>Rel</th>
<th>EFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACOP-B/VACOP-B</td>
<td>36</td>
<td>25</td>
<td>6</td>
<td>22</td>
<td>61%</td>
</tr>
<tr>
<td>CHOP, CHOP-like</td>
<td>10</td>
<td>9</td>
<td>1</td>
<td>5</td>
<td>30%</td>
</tr>
<tr>
<td>MEGACEOP</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Other regimens</td>
<td>3</td>
<td>2</td>
<td>-</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Fourteen pts treated with third generation therapy received IF RT on bulky disease. Relapses occurred early (64% within 1 year); 3/5 in the irradiated field. With a median follow-up of 61 mo (5-208), 25 yrs (49%) are event free; EFS was 61% with third generation regimen and 30% with CHOP or CHOP-like. EFS was 62.5% in stage I-II and 48% in stage III-V. No differences in outcome were observed between pediatric and adult pts not according to immunophenotype. In ALCL-CD30+, third generation therapy gave better long term outcome than CHOP or CHOP like regimens.

OVERALL SURVIVAL PROGNOSTIC FACTORS ANALYSIS FOR AGGRESSIVE NON-HODGKIN'S LYMPHOMA IN THE ELDERLY.

Centre Antoine-Lacassagne, Nice, France.

A multicenter randomized phase III study was performed in 160 elderly (> 65 years) patients with intermediate/high grade NHL (groups E,F,G,H of the WP), stage II-IV, PS 0-2. This trial compared CEP regimen (cyclophosphamide 750 mg/m² d1, Epirubicin 70 mg/m² d1, vincristine 1 mg/m² d1, prednisone 60 mg/m² d1-5) and MEBID regimen (mitoxantrone 10 mg/m² d1, etoposide 100 mg/m² d1-3, mitoguazone 100 mg/m² d3, ifosfamide 1 g/m² d1-3, dexamethasone 40 mg d1-3). No difference for response and survival were achieved between the two arms. With 14 months of median follow-up (0.5-56); median overall survival (OS) was 18 months (range 0.5-56). An univariate and a multivariate analysis using a Cox proportional hazards regression model was performed to predict the OS. The following parameters were analyzed: age, gender, performance status (PS) (0 vs 1 vs 2), pathologic subgroup, stage, B symptoms, bulky disease, number of extra-nodal sites involved (0 vs 1 vs 2 vs 3), LDH and β2 microglobulin (normal versus high) and international index. Univariate analysis found as significant: gender (p = 0.04), PS (p = 0.02), number of extra-nodal sites involved (p = 0.03), β2 (p = 0.002), LDH (p = 0.01). In the multivariate analysis, remained significant: PS (p = 0.002), number of extra-nodal sites involved (p = 0.01), β2 (p = 0.02) and gender (p = 0.03).

Interestingly, β2 was still highly significant in multivariate analysis, whereas LDH were not. This analysis stress the point that prognostic in elderly NHL patients need to be adapted for design and analysis of future prospective studies. Among elderly patients, age has no impact for OS: this point confirms that all these patients with good PS have to be treated with a standard regimen.


The CHOP regimen remains a standard chemotherapy for diffuse large cell lymphoma (DLCL) in adults, but a majority of patients will subsequently relapse. The LMB8 protocol is a dose intensive chemotherapy regimen which yields very high survival rates in Burkitt's and other B cell lymphomas of children, as well as in primary cerebral DLCL of adults. Here, we report a prospective evaluation of this regimen in series of 22 adult patients with DLCL outside CNS treated between December 1987 and July 1993. There were 15 males, 7 females with a median age of 30 years (range: 20-55). Ten (45 %) patients had an Ann Arbor stages III or IV diseases, 18 (72 %) patients had an age adjusted international Prognostic Index (IP) ≥ 1. Mean treatment duration was 13 weeks (range 13-18). Nineteen patients (90 %) experienced an objective response (14 complete responses and 5 partial responses) at the end of the induction phase. The predominant toxicity was myelosuppression: 89% of evaluable induction courses were followed by grade IV neutropenia and 5% with grade IV infection. One (3 %) toxic death occurred during the treatment. With a median follow-up of 94 months and a minimum follow-up of 6 months, 8-year overall and progression-free survival were 73 % and 70% respectively. The 8 year overall survival was 100 % in patients with an IP1, 78 % in patients with IP1 I, and 42% for patients IP1 2-3. This short intensive regimen yields promising survival rates in this small multicentric prospective study, and could deserve to be tested in a larger multicentric prospective study vs the CHOP regimen.

CNS Prophylaxis in Adult Patients with Mediastinal T-Cell Lymphoblastic Lymphoma.


From 1988 to 1990, 22 patients with T-cell mediastinal lymphoblastic lymphoma (T-LBL) were treated according to one of two protocols. Both included induction (cyclosphamide, anthracycline, vincristine, prednisone and L-asparaginase) and consolidation therapy. The CNS prophylaxis associated intrathecal (IT) MTX with either cranial irradiation (protocol 1) or high-dose MTX (protocol 2).

<table>
<thead>
<tr>
<th>Protocol 1</th>
<th>Protocol 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age</td>
<td>31 (17-58)</td>
</tr>
<tr>
<td>Female</td>
<td>2</td>
</tr>
<tr>
<td>Stage IV</td>
<td>7</td>
</tr>
<tr>
<td>Bone marrow involvement</td>
<td>0</td>
</tr>
<tr>
<td>CNS involvement</td>
<td>1</td>
</tr>
<tr>
<td>CNS prophylaxis</td>
<td></td>
</tr>
<tr>
<td>MTX IT</td>
<td>15mg (13)</td>
</tr>
<tr>
<td>HD MTX</td>
<td>NO</td>
</tr>
<tr>
<td>Cranial Radiation</td>
<td>3 Gy</td>
</tr>
<tr>
<td>Results</td>
<td></td>
</tr>
<tr>
<td>Mean Follow up</td>
<td>38 months</td>
</tr>
<tr>
<td>Response Rate</td>
<td>81% (2 PR, 7 CR)</td>
</tr>
<tr>
<td>extra-CNS Relapse</td>
<td>3</td>
</tr>
<tr>
<td>CNS Relapse</td>
<td>0</td>
</tr>
</tbody>
</table>

The 3-year event-free survival (Event = no CR, relapse or death) for the protocol 1 and 2 were 27% and 54% respectively due to a higher CNS relapse rate in the group without HD MTX (37% vs 0%). High-dose MTX associated with IT MTX seemed to be superior to cranial irradiation with IT MTX as CNS prophylaxis for adult patients with T-cell mediastinal lymphoblastic lymphoma.

PMLCL is a distinguished clinical entity among aggressive NHL, but it is debated if its treatment must differ from that of other diffuse large cell NHL. We analyzed 119 consecutive pts seen between 1987 and 1997 who received an anthracycline-based chemotherapy (CT) with optional radiotherapy (RT) on initially bulky sites or residual masses (RM). All pts had CAT scan before and after CT, and a gallium scan (GS) was done after CT for 33 pts. Pts characteristics: mean age 36 years; PS>1 18%, LDH > N 72%; stage II-II 62%; stage III 11%; stage IV 27% (lung-pleura 13%, liver 8%, bone marrow 23%); > 1 EN site 12%. The mean tumor surface (85 cm2) correlated with LDH (p = 0.01). During CT 17 pts progressed: salvage was unsuccessful and all pts died (median survival 13 mo); 6 achieved a PR; 3 could be salvaged and are in maintained CR. The CR rate was 81%; 11 pts in true radiological CR and 83 with a RM with a mean largest diameter < 5 cm. Of the 83% none of them could achieve a second CR. OS at 5 years was 69% (90%, 72%, 68% and 45% in the L, LI, HI and HI risk groups of the IPPI respectively, p=0.01). Other prognostic factors were: EN site > 1 (p<0.001), stage IV (p<0.001), stage III-IV (p=0.02). LDH and PS had borderline significance; tumor size, RM after CT, OS had no prognostic value. RT was delivered to 42% of the pts in CR: OS were 92% with RT and 76% without (p=0.01): this apparent benefit was present regardless of stage and IPPI group. Conclusion: PMLCL is an intrathoracic disease where adjuvant RT could play a role for pts in CR. Cure must be obtained with first line therapy as the fate of refractory or relapsing pts is dismal.

INTERMEDIATE AND HIGH-GRADE NON-HODGKIN'S LYMPHOMA (IHG NHL) IN THE ELDERLY. PROSPECTIVE REGISTRATION STUDY IN A REGIONAL LYMPHOMA NETWORK.


Aims: To register IHG NHL in patients older than 65 with or without exclusions. To treat patients according to a physiological index rather than to age.

Material and methods: Between 06/05 to 12/98, 108 patients (pts) older than 65 with IGH NHL, were treated in 17 centers. Pts were classified according to a physiological index (PI) that included performance status (PS), cardiac, renal and hematological status, and clinical background. Pts who validated all items of the PI were considered in good status. Remaining pts were classified in the poor status category.

Results: Ninety-eight pts (58%) were in good status and 57 in poor status (34%). Thirteen pts, who were considered as incomplete PI assessment, were registered. Good status pts were eligible for an anthracycline-containing regimen and a prospective phase II study of CEVP combination (cyclophosphamide, vincristine, 4-epiadriamycin and prednisone plus prolonged oral etoposide) was proposed with initial randomized phase II (CEVP1 (19 pts) versus 2 (18 pts)) and further CEVP phase II trial (37 further pts). Twenty-four pts did not participate for various reasons: refusal (10%), previous cancer (4%), compliance (3%) and mainly received CEOP combination. Fifty-seven pts had poor status (34%) for the following reasons: poor PS (35%), low creatinine clearance (28%), anthracycline contra-indication (19%), morbidity (15%) and severe panencephalopa (4%); they were treated cautiously with CVF combination (cyclophosphamide, vincristine and prednisone). Significant differences were observed between good and poor patients ps characteristics: median age (72 vs 73-75-pc0.01); advanced stages (42 vs 60-pc0.04): bulky tumors >7 cm (22 vs 39%-p=0.3). Anthracycline-containing chemotherapy was administered to all good status pts. Treatment was interrupted in 27 pts because of toxicity (27.5%) and in 8 pts because of progression. CVF was proposed to poor status pts but 19% did not receive this treatment for various reasons. Among CVF-treated pts, after one or two cycles, either 4-epiadriamycin or teniposide was added when possible (70%).

Conclusions: Prospective registration showed that 34% of IGH NHL older than 65 have poor physiological status which precludes pts to receive anthracycline-based regimens. Those pts, generally not included in prospective studies, are generally older and have bulkier disease than good status pts. Specific strategies should be designed.

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CEVP COMBINATION (CYCLOPHOSPHAMIDE, C, EPIRUBICIN (E), ORAL ETOPOSIDE (V), VINCRISTINE (O) AND PREDNISONE (P)) IN THE TREATMENT OF INTERMEDIATE AND HIGH-GRADE NON-HODGKIN's LYMPHOMA (IHG NHL) IN THE ELDERLY WITH FAVORABLE PHYSIOLOGIC INDEX. A PHASE II STUDY OF 56 PATIENTS.


Prolonged oral etoposide administration is efficient in many tumor types including lymphomas.

Aim: To observe safety profile and efficacy of CEVP combination in IGH NHL.

Material and methods: Between 06/05 to 12/98, 108 patients (pts) with IGH NHL, older than 65 were registered in 17 centers. After quality of life (Qol) evaluation, pts were classified according to a physiological index that included performance status (PS), cardiac, renal and hematological status, and clinical background. Finally, 98 pts were classified in the good status group, able to receive anthracycline-based chemotherapy.

After a preliminary randomized phase II study with two different schedules of CEVP combination, the following schedule was selected: C: 750mg/m² IV D1, E: 60mg/m² D1, V: 50mg/m² orally D1 to D9, O: 1.4mg/m² D2, P: 40mg/m² orally D1 to D9. D1 week 4. Hematopoetic growth factors were not proposed routinely.

Results: 56 pts received the CEVP combination. Some pts did not participate for various reasons (other CEVP schedule: 18; refusal: 10; previous cancer: 4; compliance: 3; various causes: 7). Main descriptive factors were as follows: median age 71y (range 65 to 83); 64% advanced stage; 64% elevated LDH; 22% PS 2. Two hundred and seventy four cycles (cy) of CEVP schedule were evaluable. Mean dose intensity was 81%. With 26% grade 4 neutropenia, febrile neutropenia was observed in 14%. Grade 4 thrombocytopenia was observed in 2%. Treatment was stopped because of toxicity in 27% of the patients. We observed 5 toxic deaths (9%). Finally, among 43 pts evaluable for response, 29 attained CR (67%) including 16 of 21 localized stages (76%) and 13 of 22 advanced presentations (59%).

Conclusion: CEVP schedule appears feasible with acceptable toxicity and high response rates. Comparison to CEOP combination in a phase III trial should be proposed.

This work has been supported by the Programme Hospitalier de Recherche Clinique, Comité Départemental des Pyrénées Atlantiques de l'équipe Nationale contre le Cancer, Pharmacia et Rhône-Poulenc Rorer.

3. Aggressive Lymphomas
SYSTEMIC AND CEREBRAL LARGE CELL NON-HODGKIN'S LYMPHOMA IN A HIV-2-SEROPOSITIVE PATIENT

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Beth Israel Deaconess Medical Center, Harvard Medical School, Boston MA, USA

Non-Hodgkin's lymphoma (NHL) represents 6-10% of neoplasms in HIV-1 infected patients and is a common neoplasm in patients with AIDS (Diebold et al. 1997). Most NHLs in HIV-1 infected patients are high-grade B-cell lymphomas and occur late in the course of the disease. HIV-2 has been isolated from AIDS-patients in West Africa (Clavel et al. 1986) and is thought to be less pathogenic than HIV-1. NHL occurs in only 3% of HIV-2 infected patients (Clavel et al. 1987) and only five cases of HIV-2 associated NHLs have been described in the literature. We report the case of a 44-year-old male patient from Cape Verde (West Africa) with HIV-2 infection, C4 lymphocyte count of 4/mm², who presented with dyspnea and B-symptoms. Radiologic examination showed a perihilar and mediastinal mass as well as multiple liver lesions, and biopsy revealed a large cell lymphoma. Complete remission occurred with CHOP chemotherapy. Two months later, he presented with ataxia and dysmetria, and MRI of the brain showed multiple nodular lesions. Brain biopsy demonstrated the presence of an immunoblastic large cell lymphoma of B-cell origin. Whereas almost all CNS lymphomas in HIV-1 infected patients are linked to EBV, EBV RNA (EBER) or antigens (LMP-1) could not be detected in the brain biopsy of our patient. He died shortly thereafter due to progression of his cerebral lymphoma despite chemotherapy.

Although HIV-2 is regarded to be less pathogenic than HIV-1, oncologists should be aware of the presence of high-grade systemic and CNS lymphomas in patients who are HIV-1 seronegative, but HIV-2 seropositive. Individuals from areas with a high prevalence of HIV-2 presenting with lymphoma should be tested specifically for the presence of HIV-2 antibodies.

DIFFUSE LARGE CELL LYMPHOMA: RETROSPECTIVE ANALYSIS OF 450 PATIENTS TREATED IN A SINGLE CENTER.

Rigacci L., Alterini R., In acquenti F., Bernardi F., Longo G., Bellesi G. and Rossi Ferrini P. Department of Haematology University and Careggi Hospital Florence, Italy

Diffuse large cell lymphoma was shown to be a curable malignancy with chemotherapy. First generation regimens (FGR) are considered standard treatment of this disease. We report a retrospective analysis of 450 patients (pts) treated between 1976 and 1996; 176 pts were treated with F2 and a CHOP-like scheme but with a different scheduling. 135 were treated with a third generation regimen (TGR) (MACOP-B 47 and BAVEC-MiMA 88 pts) and 139 over 65 years were treated with a protocol specifically devised for elderly people (MICEP). The CR rate of whole group was 71%; at a median follow-up of 5 years the 10 years OS, DFS and PFS were respectively 54%, 70% and 55%.
Major prognostic variables were sex, stage (IIH vs III-IV), bone marrow positivity and response to therapy. Age was not a variable significantly related to survival in this study. If we divided the group according to age in the younger (under 65 years) we observed a 10 years OS of 56% and we do not have any difference in survival according to therapy but we have found that the group of pts treated with TGRs had a worst clinical behaviour (LDH, bulky disease and advanced stage). Furthermore pts treated with TGRs showed a earlier plateau in overall survival curves in comparison with pts treated with first generation regimen (5 years vs 9 years). The group of patients over 65 years treated with MICEP showed an OS at 10 years of 58% and the only one significant variable was response to therapy. In conclusions we observed that with a long follow-up TGRs offer identical results in a subset of pts with worse clinical characteristics compared to FGRs and a specific protocol in elderly people can influence the outcome in this subset of pts and offer them identical possibility of cure in comparison to younger pts.

F-MACHOP in the Treatment of Aggressive Lymphoma

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Masaryk Memorial Cancer Institute, Brno, Czech Republic

Introduction: The use of third-generation chemotherapeutic regimens in the treatment of aggressive malignant lymphoma remains a frequently discussed question. This strategy appears beneficial especially in patients with negative prognostic factors, since it induces a favorable therapeutic response in terms of response rate, disease-free survival and overall survival, all of which with an acceptable degree of toxicity. The combined chemotherapeutic regimen F-MACHOP meets the criteria required of a third-generation regimen thanks to its short duration time and intensification due to the use of cross-resistance avoiding substances.

Methods: Implementing experience of The Italian Study Group the authors applied the F-MACHOP (5-Fluorouracil, Methotrexate, Ara-C, Cyclophosphamide, Vinocristine, Doxorubicin, Prednisin, Leucovorin) regimen in a total of 25 patients with histologically verified Non-Hodgkin lymphoma of median and high malignity. The group involved 12 male and 13 female patients with an average age of 38.1 and an average of 5 chemotherapy cycles per patient applied. The therapeutic response and toxicity were assessed in accordance with the standard criteria and a retrospective comparison in an equivalent patient sample treated with the customary CHOP (Cyclophosphamid, Vinocristine, Doxorubicin, Prednisin) regimen was performed.

Results: The F-MACHOP application was well tolerated in our patients with acceptable incidence and degree of hematotoxicity and infectious complications. The treatment induced favorable therapeutic response in terms of both the RR (66%, out of which 52% represented CR and 44% PR, respectively) and the overall survival within the 5-year follow-up.

Conclusions: The F-MACHOP regimen appears to be a well tolerated and effective therapeutic strategy in prognostically disadvantageous patients with aggressive lymphoma. Our results support the tendencies to prefer the third-generation chemotherapeutic regimens to the classic CHOP application in the group of patients with poor prognosis.
LOMUSTINE AND PROCARBAZINE IN ORAL REGIMEN FOR CENTRAL NERVOUS SYSTEM (CNS) INFILTRATION BY NON HODGKIN LYMPHOMA (NHL)

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Several schemes exist for treatment of CNS infiltration by NHL, more frequently intrathecal application of methyltrexate alone or cytarabine, but for some patients this administration route is difficult and painful; for that kind of patients, we designed a novel scheme with lomustine and procarbazine, on basis of their higher concentration and effectiveness in CNS. We report here first three cases of open label prospective trial. RESULTS: One male, two female; an average 43yo (20-59), and CNS infiltration by NHL (all of them with diffuse large cell histology); they received (Lomustine 100mg/m² daily 1 and Procarbazine 100mg/m² days 7-14). After a 3 (2-5) cycles performed, they did not had infiltration by tumoral cells, and nowadays they are at 8 th-(6-11) months of follow up and no one after initial cycles has needed more chemotherapy and they are in CR.

We conclude that this scheme can be an alternative to those patients, who for several reasons cannot receive a conventional scheme. Further information is needed and now we are enrolling more patients in this trial.

FOLLICULAR LYMPHOMA REGISTRY IN FRANCE


Follicular lymphoma (FL) is an indolent disease that represents about 30% of non-Hodgkin's lymphomas. Diagnosis and management are widely spread among medical specialties. Consequently, as most published data come either from large institutions or from cooperative trials, the observed characteristics of the patients may be biased.

AIMS OF THE STUDY: To observe diagnostic and therapeutic approaches in previously untreated patients with FL in a 3-year registration study.

METHODS: 103 centers involved in follicular lymphoma management have been individually contacted among which 202 accepted to participate in this registry (hematologists and oncologists' consultations: 85; other specialties: 4). Systematic review of pathologic material was performed by one of us (N.B.) while registered data were regularly monitored by the scientific committee.

RESULTS: Since November 1994, more than 1200 patients have been registered. Data from the first 1000 patients are presented. Median number of patients registered per center was 3 (range: 1 to 55). Median age was 59 (23-95). Sex ratio was 1.05. Main characteristics were as follows: >7 cm tumor mass (33%), spleen (19%) and liver enlargement (7%). B symptoms (16%) and serum erosion (8%). In two third of the cases, FL diagnosis was performed prior to referral, mainly on a lymph node biopsy (90%). Bcl-2 protein expression was detected in 91% of the 63% tested samples. T(14;18) was detected in 52% of the 33% tested samples. Among 540 biopsies reviewed, 7% did not correspond to FL. Levels of LDH, performed in 97% of the cases, was elevated in 21%. Bone marrow biopsy, performed in 95% of the cases, was involved in 44%. Finally, we observed 30% stages I and II and 70% stages III and IV. Twenty three per cent of the patients progressed in cooperative trials, mainly for disseminated disease. For the remaining patients, while considering radiotherapy (RT) a chemotherapy (CT) as standard treatment in localized sig, different options have been observed in 55% (wait-and-see: 25% in stage I and 24% in stage II; CT x alpha-interferon (INF): 16% sig. I and 45% sig. II; bone marrow transplantation (BMT): 1% sig. I and 1% sig. II). If wait-and-see policy, CT x INF are considered as standard treatment in disseminated sig, different options have been observed in 8% (CT: no sig. II, 2% sig. III, 6% sig. IV).

CONCLUSIONS: Preliminary evaluation of the first 1000 cases included in the French FL registry shows adequate diagnostic work-up to according standard with some peculiarities: more localized stages and less bone marrow involvement than expected. Molecular biology does not appear to be part of routine evaluation. Patients' management is performed in various medical specialties and protocol inclusions are low. Treatment modalities are heterogeneous especially in localized presentations.

LONGEVITY AFTER CNS RELAPSE OF LARGE CELL LYMPHOMA

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Introduction: The outlook for patients who relapse in the CNS following initial treatment for large cell lymphoma is generally poor and the optimal therapeutic approach is not known. We report our experience in two long-term survivors treated with targeted CNS therapy and consolidation with high dose systemic chemotherapy.

Case 1. A twenty one year old man presented in 1990 with Stage IIIb large cell lymphoma of peripheral T cell variant (Ki-1 positive). He was treated with CHOP/PMX chemotherapy in standard doses and received two complete remissions. Three months after completion of treatment he was admitted with headache and ataxia and lumbar puncture confirmed a diagnosis of leptomeningeal relapse of NHL. CT Scan of brain was normal and on repeat there was no evidence of relapse outside the CNS. He received systemic reinduction with CHOP and intrathecal chemotherapy with Methotrexate and Cytarabine. He achieved systemic and CNS remission and in June 1991 was consolidated with cranial irradiation (30Gy in 25 fractions) and in September 1991 underwent BEAM conditioning and Autologous Bone Marrow Transplantation. Since that time he has remained well with no significant haematological or neurological sequelae.

Case 2. A forty six year old man presented in 1994 with bulky Stage IVA cervical large B Cell lymphoma. He received CHOP chemotherapy and involved field radiation and achieved complete remission. He represented 8 months later with visual disturbance, tinnitus, headache and personality change. CT/MRI of the brain was consistent with lymphomatous overtump involving both the optic chiasm and the right temporal lobe. Lumbar puncture confirmed additional leptomeningeal involvement with lymphoma. The patient received systemic reinduction with a modified CHOP regime and intrathecal Methotrexate, Cytarabine and Hydrocortisone. Additional CNS therapy was given with high dose Methotrexate and stem cell mobilisation performed after administration of IV cyclophosphamide, etoposide, and procarbazine. The patient achieved remission and underwent consolidation with cranio-spinal irradiation and a BEAM reinduction. The patient remains well in complete remission of his disease. He has mild impairment of short-term memory but no other significant neurological sequelae. He remains mildly paraplegic but is transfusion independent and has returned to full time employment.

Discussion: We believe that a phased approach to management offers the best prospect for long-term survival following relapse of large cell lymphoma in the CNS. Although data is limited on which components of therapy are important, therapy based on (1) systemic reinduction with consolidation dose chemotherapy, (2) involved CNS disease with intrathecal chemotherapy and where necessary high dose systemic chemotherapy targeted to the CNS. (3) CNS consolidation with cranial irradiation and (4) systemic consolidation with high dose chemotherapy and autologous marrow rescue may be feasible for patients fit enough to undergo this approach. In carefully selected patients the outcomes may be excellent with minimal or no long-term toxicity.

COMBINED CHemo- radiation therapy in the treatment of intermediate or high grade non hodgkin's lymphoma (NHL) stage I; results of a chemo response adapted radiotherapy dose.

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Introduction: Patients with stage I intermediate or high grade NHL usually receive treatment consisting of a limited number of chemotherapy courses followed by involved field radiotherapy (ifRT). The optimal dosage of ifRT however, is not known at present. We studied in a retrospective non-randomised fashion if patients who are in complete remission (CR) after 4 courses of CHOP and 24 Gy ifRT do as good as patients in partial remission (PR) after 4 courses of CHOP receiving 40 Gy ifRT.

Patients and Methods: Between 1980 and 1993, 136 patients with histological proven intermediate and high grade NHL (working Formulation D-J) were treated with 4 courses of CHOP and ifRT. Ten patients did not respond and were excluded from this analysis. The others were divided in three groups: I: 4 CHOP-CR: 25-30 Gy (N=71); II: 40 CHOP-CR: ≥ 40 Gy (N=20) and III: 4 CHOP-PR: ≥ 40Gy (N=35). The three groups were comparable with respect to age, gender, nodal extra nodal site and bulky disease (2 /cm), only LDH elevation was more frequent in group III. In relapse patients the localization in or outside the radiation field was not distributed between the three groups.

Results: Overall survival at 6 months (se) 100% 6 months (se) 80% 6 months (se) 60% Disease free survival at 6 months (se) 97% (5%) 85% (15%) 74% (21%) Relapse rate at 6 months (se) 7% (9%) 14% (8%) 24% (6%)

Conclusions: Our data show a strong suggestion that if patients with stage I intermediate or high grade NHL, even if they achieve CR after chemotherapy, the dose of 24 Gy ifRT is too low. Also the patients with PR and 40 Gy ifRT do not worse.
10 YEAR FOLLOW UP IN 246 PATIENTS WITH ADVANCED STAGE DIFFUSE LARGE CELL LYMPHOMA (DLCL) TREATED WITH CONVENTIONAL 12 WEEk CHEMOTHERAPY: OUTCOME, LATE RELAPSE AND LATE TOXICITIES

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Introduction: Standard chemotherapy is effective in the treatment of advanced stage DLCL. New intensive approaches give promising results. However these need to be compared with the long term results achievable with prior regimens. Thus long term analysis was performed on a cohort of patients treated with 12 week chemotherapy from 1980 through December 1993 in order to define the cure rate, late toxicities and late relapses.

Methods: 246 patients, aged 15-60, with advanced stage DLCL (B symptoms, bulky, elevated LDH level and/or stage II-IV) were treated with MACOP-B (60) or VAOPB (46) regimen. Patients were retrospectively grouped according to age-adjusted IPI score: low risk, 5-10 low-intermediate risk, 11-15 high-intermediate risk, 16 high risk. Both regimens were equally effective for terms of OS, DFS and FRS rate.

Results: Median follow up was 115 months. 76% achieved a CR, 9% a PR, 11% showed a NR and 4% died of toxicity. 10 year OS is 58% and 10 years DFS is 53% . DFS significantly decreased from low to high IPI groups: 76%, 54%, 39%, 22%. Among 185 CRs, 133 pts are in continuous CR and 52 pts relapsed. Late relapses (> 2 years from the completion of therapy) were recorded in 9 patients. The median time to late relapse was 48 months (range 24-96). Seven patients relapsed with aggressive DLCL, one with low grade follicular lymphoma and one showed a Hodgkin's disease at relapse. Five were alive in second CR and four died of lymphoma. Late toxicities (> 1 year from the completion of therapy) were recorded in 28 patients. The most common toxicity was febrile head orthocinesias that was observed in 7 patients with a median time off chemotherapy 15 months. Six patients had cardiac toxicities: 4 cardiomyopathies, one ischemic disease and one arytenoid (median time off therapy 60 months.). 3 patients suffered from severe peripheral neuropathy. One developed acute renal failure, one pulmonary thrombosis and one vein stasis. A second cancer occurred in 7 patients with a median time off therapy of 70 months, while in CR of lymphoma. Two patients developed secondary acute myelogenous leukemias and died of it. 15 months. Six patients had solid tumors: 2 breast, 2 lung, 1 breast, 1 gastric and one breast and neck cancer. Two of them subsequently died of that. All patients entered a local dissection and one second cancer was diagnosed. A second cancer occurred in 7 patients with a median time off therapy of 70 months, while in CR of lymphoma. Two patients developed secondary acute myelogenous leukemias and died of it. 15 months. Six patients had solid tumors: 2 breast, 2 lung, 1 breast, 1 gastric and one breast and neck cancer. Two of them subsequently died of that. A second cancer occurred in 7 patients. Two of them subsequently died of that. A second cancer occurred in 7 patients. Two of them subsequently died of that. A unique toxicity was the development of a second cancer was 6% at 10 years.

Conclusions: The 10 year follow up data support the need to do long follow up data to know definitive conclusion; the outcome of DLCL patients may be useful as historical comparison with new trials.
TREATMENT OF INTERMEDIATE AND HIGH GRADE NON HODGKIN’S LYMPHOMA IN ELDERLY.

PIPI ET AL.

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BACKGROUND: The incidence of non Hodgkin’s lymphoma (NHL) has increased over the past decade and a further increase can be expected. The median age at diagnosis is over 60. Nowadays 13% of the Dutch population is older than 65 years. This percentage is increasing with 1.3% per year. Therefore in the future NHL will be diagnosed more often in elderly people. A former study from our group has suggested that many elderly patients are treated with suboptimal chemotherapy regimens in order to avoid toxicity, although this can reduce the likelihood of achieving a complete response.

PURPOSE AND METHODS: Data of all patients with newly diagnosed NHL between January 1991 and January 1993 were retrieved from the Comprehensive Cancer Centre Registry Limburg (UKL) and analysed in a retrospective multicentre study to investigate the treatment schedules and results of elderly patients (> 60 years) with advanced NHL (Ann Arbor Staging > IA) of intermediate- and high grade malignancy. Treatment was considered inadequate if deviating from standard NHL therapy.

RESULTS: Sixty eight patients fulfilled the entry criteria. Of these patients 57 (83.8%) were treated, and 11 (16.2%) were not treated. The treatment consisted of CHOP (50 patients), CODOX (5 patients), storing (13 patients) or COP (2 patients). Because “anthracyclines” (CODOX,CHOP) are part of standard therapy, 42 of 68 patients had adequate treatment schedule, however 14 (21%) patients had suboptimal schedule of cycles (>60). Only sixteen of 28 patients had optimal numbers of cycles and dose, resulting in a total of 52(67.5%) treated in a way different as their younger counterparts. The most important reason for treating optimally was high age and/or poor performance status. The appropriately treated patients had a complete response of 10(16.2%).

CONCLUSION: A significant subset (76.5%) of elderly people with intermediate/high grade NHL received suboptimal therapy. Attention for this aspect is needed to improve treatment results.

TREATMENT OF RELAPSED NON-HODGKIN’S LYMPHOMA: DAUNOXOME® IN COMBINATION WITH CYCLOPHOSPHAMIDE, VINCRIStINE AND PREDNISONE (CDAxoP)

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Introduction: The standard therapy for intermediate and high grade NHL is the CHOP regimen which cures 30-50% of patients [1]. Improvements in the efficacy of the CHOP regimen by escalating the dose of Adriamycin, which is the most potent drug in this regimen, are prohibited by its cardiotoxicity. In contrast to Adriamycin the liposomal adriamycin daunoxome® (Daunoxome®; DAX) markedly ablates pharynchotoxic and cardiotoxicity, which seems to result in a favourable toxicity profile and improved antitumor activity against lymphomas. Characteristic anthracyclin toxicities such as alopecia, cardiotoxicity and mucositis are rare or negligible. To evaluate the safety and efficacy of DAX in combination of CPA, VCR and Pred we have initiated a clinical phase II trial of a CDAxoP regimen for pts with relapsed intermediate and high grade NHL. CDAxoP is similar to the standard CHOP regimen except that adriamycin is replaced by DAX.

Study Design: Pts with relapsed intermediate or high grade NHL were included. For pts with previous treatment of CHOP regimen, response to prior treatment with CHOP® is a delay of at least 1 year was required. Exclusion criteria were: lymphoblastic NHL, severe heart failure (NYHA II/III, EF < 40%), prior mediastinal radiation, total given cumulative doxorubicin dose > 600 mg/m² of the recommended dose, and treatment with more than two anthracyclines. The CDAD/XOP regimen consisted of 750 mg/m² cyclophosphamide iv, 6000 mg/m² DAX iv, 1.4 mg/m² (2 mg/m² max) vincristine given on d1, and 100 mg/m² predonison given po d1. The starting dose of DAX was 60 mg/m² for the first 6 pts. Dose escalations of 20 mg/m² DAX for the next 6 pts will be performed if no side limiting toxicity are observed. The maximum planned dose of DAX is 100 mg/m².

Results: So far, 10 pts (6 male/4 female) have been enrolled in this protocol. All pts suffered from relapsed intermediate or high grade NHL (1 MAL; 4 CEC; 4 CHL; 1 ALL). Pts received 60 mg/m² (first 6 pts) and 80 mg/m² (4 pts) DAX respectively. So far 50 cycles of CDAxoP have been completed: 4 pts showed CR, of whom 2 pts have had prior treatment with CHOP®, while 3 pts did not respond and had minor response to CDAD/XOP. No severe toxicities were observed so far. Typical side effects were neutropenia, obstipation, arthalgia, alopecia, mild malaise and appetite loss. Taken together these data suggest that the CDAD/XOP protocol is safe and feasible in pts with relapsed NHL.

ANAPLASTIC LARGE CELL LYMPHOMA: CLINICAL FEATURES AND PROGNOSIS IN A RETROSPECTIVE SERIES OF 72 PATIENTS TREATED IN A SINGLE INSTITUTION

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Anaplastic, CD30+, large-cell lymphoma (ALCL) is now recognized as a specific entity among high grade lymphomas. ALCL represent a heterogeneous group of lymphomas differing in their histology, phenotype, clinical course and even cytogenticity. This entity is uncommon and information about its clinical behaviour and prognosis is limited. Moreover, published data are yielding to many discrepancies. ALCL must be separated in primary or secondary because the latter are often to have a worse prognosis. We report here a series of 72 cases of primary ALCL retrospectively diagnosed and treated in one institution. Clinical, histologic and immunologic features are determined. There was a majority of male and median age was 43. B symptoms were present for 29 patients (40%). There was a predominance of localized stages (60%). Thirty-seven patients had extra nodal localizations (52%). Skin involvement was the most frequent extra nodal site (18%). Among histologic types, common type was the most frequent (65%). Tumour cell phenotype was B, T, and Null in respectively 28%, 28% and 29% of cases. Complete remission rate was 73%. Five and ten years overall survival were 55% and 45% respectively. Nineteen patients relapsed (26%). Five and ten years relapse-free survival were 62% and 58% respectively. Complete remission rate was 74% after salvage treatment. Five years overall survival after relapse was 38%. For overall survival, in multivariate analysis, favourable independent prognostic factors were respectively: negative immunostaining for CD45 (p<0.003), localized stage (p<0.0064), good performance status (p=0.031) and hemoglobin level (Hrb2=12g/dl) (p=0.036). For relapse-free survival, in multivariate analysis, only negative immunostaining for CD45 was a favorable independent prognostic factor (p=0.012).

Regarding our results, we think that ALCL represents a distinct entity with specific clinical characteristics among high grade lymphomas and should be recognized in international classifications as a single entity whatever phenotype or histologic variants could be. In our experience, though this series is limited and with a majority of localized stages, prognosis of ALCL appears sensibly better than diffuse large B cell NHL because this disease occurs mainly in young adults and response to chemotherapy is much satisfactory, particularly in case of relapse. Hemoglobin level and specifically immunostaining for CD45 could be specific independent prognostic factors in ALCL, but this needs to be confirmed in further studies.