BCL-2 MAY ADVERSELY AFFECT OUTCOME IN HIV-ASSOCIATED DIFFUSE LARGE B CELL LYMPHOMA; RITUXIMAB AND HAART WITH CHEMOTHERAPY MAY ABROGATE THIS EFFECT


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Introduction: BCL-2 expression in diffuse large B cell lymphoma (DLBCL) in HIV-negative patients (pts) is associated with inferior outcome, an effect that at least partially overcome by addition of rituximab to chemotherapy. The effect of BCL-2 expression on DLBCL outcome in HIV-positive pts is less well defined.

Methods: We performed a retrospective clinical-pathological correlation in 141 pts with systemic HIV lymphoma seen at St. Paul’s Hospital between 1982 and 2004; this analysis includes 36 DLBCL since 1992. Clinical DLBCL data were obtained by chart review; HIV-related data from the CPE data base. Stored biopsy material diagnostic of DLBCL was sectioned and stained for BCL-2.

Results: Median age at DLBCL dx (range 20–64), DLBCL stage advanced 27, ECOG PS 1–11; median LDH ratio 1.4 (0.5–8.6); IPJ +2 n = 1; CD4 at DLBCL dx >100 x 21; prior AIDS dx n = 18; hepatitis B/C n = 9; on HAART at DLBCL dx n = 11; BCL-2 + n = 2; HAART with DLBCL tx n = 17; CHOP-R n = 9, CHOP or ACOP n = 18; GCSF n = 10; herpes virus tx n = 10; Pcr polyprolysin n = 35. In univariate analysis, significant for DLBCL-free survival (MS): stage, IPJ, GCSCF, herpes virus tx. Cox analysis, IPJ was significant (HR 10.12 for IPJ 3–5, P=0.001). Though a BCL-2 effect was not apparent, exploratory analysis showed: no HAART prior to DLBCL dx or with tx; MS BCL-2 not reached at (34) months (m) n = 9 and >50m n = 7, BCL-2+9m each n = 6, 3, effect not seen with HAART, MS >50m, >50m, 40m, 40m n = 8, 11, 1, 5, 2; CHOP BCL-2+ MS 9m n = 5, BCL-2 >12m n = 3, BCL-2-16.6m n = 6. Deaths (DLBCL, toxic): CHOP-R 2 (1, 1); CHOP 14 (8, 6).

Conclusions: of pts receiving no HAART, outcome was inferior in BCL-2+ DLBCL, an effect not seen with HAART. BCL-2+ DLBCL had inferior outcome in pts receiving CHOP, an effect not seen with CHOP. These data suggest that optimal treatment of BCL-2+ DLBCL in HIV includes HAART and rituximab with chemotherapy, and awaits confirmation in larger numbers.

TOXICITY RISK GROUPS IN AGGRESSIVE NHL – PROGNOSTIC FACTORS FOR HEMATOOTOXICITY

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Introduction: The German High Grade NHL Study Group recently published the results of the NHL-B1/B2 study (Pfreundschuh et al. 2004), which investigated the effectiveness of moderate dose intensification of standard CHOP regimen for treatment of aggressive NHL. The trial included patients below 60 years with low LDH levels (B1) and patients of any risk group between 60–75 years (B2). Adherence to protocol was extremely high and therefore this dataset is ideally suitable to perform a search for prognostic factors for hematotoxicity.

Methods: The independent impact of prognostic factors (PFs) was assessed and validated for the B1 and B2 study and separately for leukocytopenia (L), thrombocytopenia (T) and anemia (Hb).

Results: The following highly significant adverse PFs were found in the multiv.

NO ADVANTAGE OF CHEMOTHERAPY OVER CHEMOTHERAPY ALONE IN ELDERLY PATIENTS WITH LOCALIZED LOW RISK AGGRESSIVE LYMPHOMA: RESULTS OF THE LN9 93-4 GELA STUDY


Introduction: Chemoradiotherapy is standard treatment for localized aggressive lymphoma (Miller et al. NEJM, 1998). Because previously published series were heterogeneous with regard to prognostic factors such as age, we aimed to determine the optimal therapy for elderly patients with low risk localized lymphoma.

Methods: From March 1993 to June 2002, 576 patients (pts) over 60y of age with aggressive lymphoma and without any adverse factor of the age-adjusted International Prognostic Index were randomly assigned to a chemoradiotherapy arm (299 pts) consisting of 4 cycles of CHOP given
every 3 weeks followed by 40 Gy involved-field radiotherapy or to a chemotherapy-alone arm (277 pts) consisting of 5 cycles of CHOP.

Results: Principal characteristics were: median age, 68y; male gender, 51%; stage I, 66%; bulky disease, 8%; extranodal involvement, 56%; diffuse large B-cell histology, 90%. Complete response at the end of treatment was similar in both groups (90% and 91% respectively). On an intent-to-treat basis and with a median follow-up of 6.6y, the rates of 5 y-event-free survival (EFS) and of 5 y-overall survival (OS) did not differ significantly between the two treatment groups (p = 0.7 and p = 0.6, respectively). EFS rates were 68% for patients treated with chemotherapy alone as compared to 66% for those receiving chemoradiotherapy; OS rates were 72% and 68%, respectively. 78% of the 207 deaths resulted from lymphoma progression. In a multivariate analysis, EFS and OS were affected by stage I (p = 0.001), male gender (p = 0.02), not by tumor bulk.

Conclusion: We conclude that CHOP plus radiotherapy does not provide any advantage over CHOP alone for the treatment of low risk localized aggressive lymphoma in elderly pts.

DOSE INTENSITY (DI), DOSE SIZE (DS) OR DOSE DENSITY (DD): A GISL TEST WITH PROMACE-CYTAROM IN LARGE B-CELL LYMPHOMAS
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Introduction: It is still unclear whether the conventional treatment of aggressive non-Hodgkin lymphomas can be better improved by increasing drug DI or DS.

Methods: A prospective, randomized trial compared the original cyclic schedule of ProMECE-CytA-BOM chemotherapy (c-PC, 5 cycles) with a modified version of it, which administered the same drugs sequentially (s-PC). EFS rates were 71% for patients treated with chemotherapy alone as compared to 68% for those receiving CHOP plus radiotherapy; OS rates were 72% and 68%, respectively. 78% of the 207 deaths resulted from lymphoma progression. In a multivariate analysis, EFS and OS were affected by stage I (p = 0.001), male gender (p = 0.02), not by tumor bulk.

Results: Fifty-six patients received c-PC and 52 s-PC. Clinical and prognostic characteristics were well-balanced in both groups. The actual mean cumulative DI of all the 7 anthracyclur drugs was 0.78 ± 0.15 with c-PC, 0.81 ± 0.14 with s-PC. Clinical response was complete in 59 and 52%, partial in 20 and 21%, null in 5 and 6%, respectively. Progression was recorded in 14 and 13%. Four toxic deaths (2 per arm) were recorded, all due to severe neutropenia. With a median follow-up of 53 months, relapses occurred in 36 and 37% of completely responders, respectively. Toxicity was quite similar in both arms except for higher neutropenia and thrombo-cytopenia with s-PC. Overall, failure-free, progression-free and disease-free survival of the two groups were statistically indistinguishable, with a slight advantage for the c-PC arm, more clear in the overall survival comparison.

Conclusion: The death occurred in 1% of pts in each group. A large study with the current DI actually delivered was the main determinant, much more important than the higher drug DS administered in one arm. It proves that increasing dose size – at least within the limits clinically attainable without stem cell rescue – does not improve results. The slight survival advantage recorded in patients treated with c-PC might be related to its lower toxicity and/or its little higher DD (10 vs. 12 administrations within 113 days).

SURVIVAL IS CORRELATED WITH AVERAGE RELATIVE DOSE INTENSITY IN DIFFUSE LARGE B-CELL LYMPHOMA PATIENTS TREATED BY CHOP: A NATIONAL RETROSPECTIVE STUDY (1995–2000)
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A national retrospective study was performed in a large number of hematological centers in Belgium from 1995–2000 to describe the different regimen of chemotherapy (CT). The average relative dose (ARD) and dose intensity (ARDI) for first line treatment of patients with diffuse large B-cell lymphoma (DLBCL). Three hundred seventy-three adults patients files from 29 centers receiving at least 3 cycles of treatment for DLBCL included or not in a protocol between 1995 and 2000 were retrospectively reviewed. ARD and ARDI analysis (delivered vs planned) was only performed for cyclophosphamide (C) and anthracycline (A) as they are considered to be the most important agents. Three hundred forty-eight patients treated with CHOP like, ACVBp like or CHIvp-Bv were evaluable for the analysis and the results of this analysis were previously presented in EHA meeting in Geneva (2004). In this population, 210 pts were treated with the classical CHOP regimen given every 21 days. Out of these, 150 patients received more than 90% of ARDI; 10 pts received between 90 and more than 85% of ARDI and 46 pts received 85% or less of ARD. Median survival and mean survival (+/- SD) were respectively 7.06 years and 5.38 years (± 0.29), for patients receiving ARDI superior to 90%, 3.14 years and 2.4 years (± 0.31), for patients receiving ARDI between 85% and 90% and a mean survival of 2.15 years (± 0.70) for patients receiving ARDI of 85% or less. Cox regression for effect of ARDI on overall survival was highly significant (P=0.002). Thus, this study presents a large survey of 348 patients on the treatment of diffuse large B-cell lymphoma in academic and non academic hematological departments in Belgium. In patients treated with CHOP-21, overall survival was significantly improved when ARDI was superior to 90%. For the total of the population, only 16.4% did not receive 80% of ARDI and thus the vast majority of lymphoma patients treated in hematological departments in Belgium benefit from optimal chemotherapy treatment with respect to dose intensity.

For the Lymphoma Drug Project from Belgium.

PRELIMINARY RESULTS OF DOSE ADJUSTED-EPOCH PLUS RITUXIMAB (DA-EARP) FOR UNTREATED HIGH- RISK AGGRESSIVE LYMPHOMAS: PILOT STUDY IN A SINGLE CENTRE
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Introduction: Poor risk aggressive non-Hodgkin’s lymphoma have a short EFS and OS when treated with conventional chemotherapy schedules. High dose therapy followed by stem cell rescue has been attempted with disparate results. Based on Wilson et al. schedule, a pilot study has been conducted to assess the efficacy and toxicity of DA-EARP in patients with IPI score diffuse large B-cell (DLBCL) and follicular large (grade 3) B-cell (G3FL) lymphomas.

Methods: Since August 2002 to November 2004, 23 untreated patients (pts) were enrolled in the study. All pts had LDH serum levels over the normal range. The regimen consisted on 6 cycles every 21 days of Rituximab (day 1) followed by DA-EARP as reported by Wilson VH et al. (*).

Results: Characteristics are: median age 62 years (range 26–71), 10 M and 13 F; 16 (70%) DLBCL and 7 (30%) G3FL; 16 (70%) CS IV and 12 (52%) B symptoms; bone marrow involvement 9 (39%); 1 extranodal involvement 18 (78%); PS 2 in 16 (70%); 38% b2microglobulin levels; Hb < 10 g/dl in 11 (48%) and serum albumin < 3 g/dl in 7 (30%); high age adjusted IPI 14 (61%). Of 20 patients evaluated for response 15 achieved CR/CRu (75%) and 5 PR (15%) with an overall response rate of 90%. Additional radiotherapy was given in 5 patients (27.7%); 1 patient died in 14 months (range 1–29) estimated 2-year EFS and OS is 67% and 66% respectively. After 119 cycles administered: grade 3–4 mucositis was observed in 7 courses (6%), grade 3–4 neuropathy in 1 (<1%) and neutropenic fever in 18 (15%).

Conclusion: DA-EARP is a feasible approach and as effective as other more intensive chemotherapy schedules in patients with high or intermediate-high IPI score aggressive lymphomas (DLBCL and G3FL) with acceptable toxicity. Activity and follow up continue.

TREATMENT OF 101 HIGH-RISK AGGRESSIVE B-CELL LYMPHOMA PATIENTS WITH MEGACHOP-BEAM REGIMEN ± RITUXIMAB: THE EVOLUTION OF THE CONCEPT
for the Czech Lymphoma Study Group, Czech Republic
Background: Diffuse large B-cell lymphomas (DLBCLs) and related disorders (medialittal DLBCL, follicular lymphoma grade 3 or composite follicular lymphoma/DLBCL) with high-intermediate to high-risk International Prognostic Index (IPI) score have relatively poor prognosis if treated with CHOP-like chemotherapy. Czech Lymphoma Study Group have treated 101 patients with these characteristics in three consecutive intensive protocols.

Methods: From 1998-1999, patients aged 18-60 years with above specified diagnoses and age-adjusted IPI (aIPI) 2 or 3 were treated with 3-4 cycles of MegaCHOP every 3 weeks (Cyclophosphamide, 3 g/m² d 1, Vincristin 2 mg d 1, Doxorubicin 75 mg/m² d 1, Prednison 60 mg/m² d 1-5, G-CSF 5 μg/kg from day 6) and consolidated with BEAM and ASCT (Protocol 1). From 2000-2002, patients received 3 cycles of MegaCHOP, followed by 3 cycles of ESHAP and BEAM with ASCT (Protocol 2). Since 2002, 4-6 doses of Rituximab 375 mg/m² were added to the previous regimen (Protocol 3).

Results: Fourteen patients were treated with Protocol 1, 25 with Protocol 2 and 62 with Protocol 3. 30 patients enrolled in Protocol 3 before 31st December 2003 were included in outcome analyses. Median age was 41 years, 55% of patients were male, 62% had IPI 2 and 38% had IPI 3. With median follow-up of 29 months, the actuarial 2-year overall survival (OS) is 77% and failure-free survival 71% with no differences between IPI 2 and IPI 3 patients and among the protocols. The PFS was found to be significantly improved by adding rituximab (p=0.03) and the the relative risk of progression was only 0.19 for patients treated with Rituximab (95% CI, 0.05 to 0.78, p = 0.001). However, there were also more toxic deaths in Protocol 3 (p = 0.007).

Conclusions: Dose-intensive chemotherapy with or without Rituximab is feasible and highly effective in younger patients with intermediate-to-high risk aggressive B-cell lymphomas. The addition of Rituximab significantly lowers risk of relapses with MegaCHOP-ESHAP/BEAM regimen while more treatment related toxicity was observed. Further improvement of treatment safety may result in cure of vast majority of these malignancies. This study was sponsored by grants from Czech Ministry of Public Health: NR 823/1.

NON-HODGKIN’S LYMPHOMA IN PATIENTS 80 YEARS OF AGE OR OLDER

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Very elderly patients with NHL frequently suffer from other conditions which can compromise their tolerance to therapy. Therefore, the optimal treatment of these patients is not well defined.

Methods: We reviewed the records of 109 NHL patients 80 years at diagnosis (65 M/44 F; median age: 84 years (range 80–95)) who were diagnosed and treated at 3 hematology centers in Israel between 1984 and 2004.

Results: Seventy-seven patients (70%) had aggressive NHL (66-diffuse large B-cell lymphoma, 9-T-cell lymphoma, 1-burkitt’s like and 1-diffuse large null cell lymphoma) and 24 (24%) indolent NHL (11-follicular, 10-small lymphocytic lymphoma and 3- MALT lymphoma). In 8 the lymphoma was unclassifiable. Forty percent had clinical stage I or II, and 54% advanced stage disease including bone marrow involvement in 26 cases. Fifty-seven patients presented with other extranodal disease (skin, stomach, lung, sinus, tonsil, parotid, orbit, nasopharynx, breast, liver). Forty patients (39%) presented with a poor ECOG performance status, and 49% with intermediate and high risk IPI. Eighty-three of 109 patients were treated with chemotherapy and 38 with radiotherapy-12 as initial therapy. Sixteen patients remained untreated including 3 who refused therapy. Initial chemotherapy consisted of chlorambucil -17 pts, CHOP-33, R-CHOP-3, COP-11, CNO-9, oral etoposide-2, ECV-1, CEPP-1. Only 16% received Rituximab therapy (56% received 70% of the calculated dose) and only 50% completed 6 cycles of combination chemotherapy.

The overall response rate for 69 evaluable patients was 84% (CR:56.5%, PR:27.5%). Five-year survival for the whole group was 39%. It was 31% for patients with aggressive NHL (median 18 months) vs. 63% (median 72 months P=0.016) for the ones with indolent lymphoma. Fifty-one patients (56%) died, 16 from sepsis and 29 from lymphoma. Eight died untreated shortly after diagnosis.

Conclusions: NHL patients 80 years can be treated and probably benefit from aggressive treatment. Although reduced chemotherapy was administered, RR was 84% with 56.5% CR and 5-years survival was 39%. Age alone should not be a contraindication to treatment.

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THE REPLACEMENT OF CONVENTIONAL DOXORUBICIN WITH CAELYX IN CHOP-RI TXUMAB POLICHEMOTHERAPY SEEMS TO IMPROVE THE SAFETY PROFILE IN ELDERLY PATIENTS WITH D-LBCL

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Introduction: To evaluate the efficacy and safety of Caelyx-modified CHOP-Rituximab regimen (COP-Caelyx-R) in elderly patients with diffuse large B-cell lymphoma (DLBCL).

Methods: Thirty unselected patients, age between 60 and 75 years old, stage II-IV or bulky stage I, were enrolled in to the study. Caelyx 30mg/m², was given in combination with standard dosage of Prednison, Vincristine, Cyclophosphamide (according to CHOP- regimen) and Ritux imab every 21 days for 6 courses. Patients with initial bulky disease or localized residual disease received consolidation IF-RT. Cardiac toxicity was evaluated at baseline and during the study period with LVEF determination and serum troponin-I desease.

Results: Twenty-nine patients, median age 69 years (range 60–75 years), are evaluable for response and toxicity. Patients’ distribution according to International Prognostic Index was: low risk 14%, low-intermediate 24%, high-intermediate 38%, high 24%. OR and CR rate were 76% and 49%.

Project’s one year DFS and OS are 65% and 79%. No treatment-related mortality was documented. WHO grade III-IV neutropenia and thrombo cytopenia were 86% and 3.5%. Extra-hematological III-IV toxicity was represented respectively by a single case of infection, mucositis and bleeding. One patient with a previous history of atrial fibrillation experienced a single episode of arrhythmia. None of the patients had other clinical, instrumental and laboratory signs or symptoms of cardiac toxicity; none developed palmar-plantar erythrodysesthesia.

Conclusions: COP-Caelyx-R regimen is an active regimen for the treatment of elderly patients with D-LBCL. The replacement of conventional doxorubicin with Caelyx seems to be associated with a negligible incidence of extra-hematological toxicity, in particular cardiac and infectious complications.

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ADAPTED CHOP PLUS RITUXIMAB IN NON-HODGKIN’S LYMPHOMA PATIENTS OVER 80 YEARS: A FEASIBLE AND EFFECTIVE APPROACH


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Introduction: Very few data are available concerning the optimal treatment in very elderly patients (80 years). Nineteen (79%) patients had large-B-cell lymphoma (DLBCL), 3 (12.5%) mantle-cell lymphoma and 2 (8.5%) follicular lymphoma. Age-adjusted International Prognostic Index was evaluated for all patients: 1 (4.2%) patient had no adverse factor, 11 (45.8%) had one factor, 5 (20.8%) had two factors, and 7 (29.2%) had three factors. Six patients had relapsed and/or refractory disease. All patients but two were treated from the first cycle with adapted doses of doxorubicin (mean 35 mg/m²/cycle, range 25–50 mg/m²/cycle). Cyclophosphamide was dose-reduced too in only three cases. A total of 125 cycles with a mean of 5.2 courses (range 1–8) per patient, were administered. Eight patients (33%) received at least one course of granulocyte colony-stimulating factors. The overall response rate was 79% with 15 patients (62.5%) achieving a complete or unconfirmed complete response and four (16.5%) a partial response. After a median follow-up of 23 months, the 2 year overall survival and event-free survival were 63% and 30%. Considering only newly diagnosed patients with DLBCL (n=15), the 2-year OS and EFS were 76% and 62.5% respectively. The toxicity, mainly hematological, was manageable with febrile neutropenia in 6% of courses and no toxic death.

Conclusion: Addition of rituximab to reduced-dose CHOP chemotherapy seems to be a good compromise between toxicity and efficacy, allowing
clinch**est** to very elderly patients with a curative intent. So, the Groupe d' Etudes des Lymphomes de l' Adulte (GELA) is considering a prospective phase II study of attenuated R-CHOP in patients over 80 years.

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**RITUXIMAB-CHOP-ESHAP VS. CHOP-ESHAP-HIGH-DOSE THERAPY VS. CONVENTIONAL CHOP CHEMOTHERAPY IN HIGH-RISK AGGRESSIVE NON-HODGKIN'S LYMPHOMA**

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**Purpose:** To compare the efficacy of rituximab (R) given in combination with CHOP and ESHAP (arm A) vs CHOP-ESHAP and upfront high-dose therapy (HDT) and autologous stem cell transplantation (arm B) vs standard CHOP (arm C) in patients aged 65 years old newly diagnosed with high and intermediate risk aggressive lymphoma.

**Methods:** Between May 1995 and July 2002, 84 patients, aged 15-65 years, with newly diagnosed aggressive NHL and an age-adjusted international prognostic index (IPI) of 2 or 3 were enrolled. Median age was 38 years (range 15–65). The baseline major prognostic variables were similar between the three groups.

**Results:** The rates of complete remission in arm A, arm B and arm C were 67%, 44% and 36%, respectively (P = 0.043). Median follow-up 44 months (4-756 months). OS was 67% for arm A, 48% for arm B and 24% for arm C (P = 0.117). Failure-free survival (FFS) was 66% for arm A, 34% for arm B, 16% for arm C (P = 0.001) and disease-free survival (DFS) 95% for arm A, 79% for arm B, 44% for arm C (P = 0.028).

Both DFS and FFS were significantly superior for patients in arm A.

**Conclusions:** Rituximab-ESHAP-CHOP is superior over standard CHOP and CHOP-ESHAP-HDT in previously untreated patients, aged 65 years, with aggressive lymphoma of IPI score of 2 and 3. A prospective randomized controlled trial is warranted to confirm the results.

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**CHOP CHEMOTHERAPY PLUS RITUXIMAB COMPARED WITH CHOP ALONE IN DIFFUSE LARGE B-CELL LYMPHOMA PATIENTS**

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**Objectives:** The standard treatment for patients with diffuse large B-cell lymphoma is CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone). Rituximab, a chimeric anti-CD 20 monoclonal antibody, is effective when given as a single agent in the treatment of relapsed or refractory indolent lymphomas and is active in DLCL.

**Patients and methods:** 39 previously untreated patients with DLCL were included in a retrospective study. 33 patients treated by CHOP (750 mg/m^2 of cyclophosphamide on day 1; 50 mg/m^2 of doxorubicin on day 1; 1.4 mg/m^2 of vincristine on day 1; and 40 mg/m^2 of prednisone per day for 5 days). 26 patients treated with CHOP plus rituximab (R-CHOP; 375 mg/m^2 on day 1 of each cycle of CHOP. Age of patients ranged 16-87 years (median 51.5 years). The median follow-up was 15 months. Compared groups were balanced in all parameters. More than half of patients in each group were referred as high-risk groups: IPI 60 in group CHOP vs 61.5% in group R-CHOP.

**Results/Conclusions:** Complete response was achieved in 73.1% of the patients treated with R-CHOP, as compared to 39.4% of those treated with CHOP alone (P < 0.01). Disease progression during treatment was reported in 30.3% of patients in CHOP group and 15.4% in R-CHOP group. Overall survival was significantly longer in patients treated with R-CHOP than in patients treated with CHOP alone: in 1 year-time, 61.5% of patients treated with R-CHOP were alive, compared to 33.3% treated with CHOP alone (P < 0.01). With a median follow-up of 15 months, 10 (38.5%) events (progression, relapse or death) were observed in the R-CHOP group and 22 (66.7%) in the CHOP group (P < 0.01). In CHOP NON-HODGKIN'S LYMPHOMA

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**RITUXIMAB PLUS DOSE-ENSENSE CHOP (RICHOP14) FOR THE TREATMENT OF PATIENTS WITH AGGRESSIVE LYMPHOMA**

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**Introduction:** Standard first line therapy for aggressive NHL consists of CHOP chemotherapy. The addition of Rituximab to CHOP shows a survival benefit. Moreover the dose dense CHOP recently has shown an improvement in response and survival rate of pts with aggressive NHL.

**Methods:** To evaluate the efficacy and feasibility of dose-dense CHOP plus Rituximab we planned a schedule with Rituximab 375 mg/m^2 and CHOP therapy on day +1 given every 2 weeks, with G-CSF starting from day +7 to +11. We administered prophylaxis with sulfamethoxazole and trimethoprim and (itraconazole). From January 2002, we enrolled 44 patients with aggressive NHL (FL grade III = 13, DLCL = 31). The mean age was 62 years (range 29-76). Two pts were stage I, 8 stage II, 7 stage III and 27 stage IV. Eighteen (41%) pts presented B symptoms, 18 bone marrow involvement, increased LDH value in 28 (64%) pts and 31 pts presented at least one extranodal station involved. According to IPI score 24 pts were Low Risk (IPI = 0-1) and 24 High Risk (IPI = 2-3).

**Results:** All pts completed the programmed 6 cycles and were evaluable for response. Thirteen (29%) pts delayed the treatment (anemia +1, neutropenia +11, thrombocytopenia +1). No remarkable hematological toxicity was observed, in particular we focused our attention on mucositis and cardiotoxicity. Thirty-six (82%) obtained a CR and 8 (18%) a PR (overall response rate was 100%). After a median follow-up of 20 months (range 3-36), 6 (14%) pts relapsed. The 2-rrs OS and DFS were 89% and 78% respectively.

**Conclusions:** R-CHOP-14 was feasible, active and lack of severe toxicity in pts with aggressive NHL.

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**COMBINATION OF CHOP-14 WITH RITUXIMAB FOR NEWLY-DIAGNOSED AGGRESSIVE B CELL LYMPHOMA: PRELIMINARY DATA OF A PROSPECTIVE MULTICENTRIC STUDY**

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**Introduction:** CHOP every 21 days associated with rituximab is the standard treatment for patients over 60 years and low-intermediate risk patients with a diffuse large B cell lymphoma. Moreover, CHOP every 14 days (CHOP-14) is better than three-weekly CHOP. Then, the CHOP-14 associated with rituximab could improve these results.

**Methods:** Patients (pts) 18-75 years old with newly-diagnosed aggressive NHL (diffuse large B cell -DLBCL- or follicular grade 3) diagnosed between April 03 and November 04 received CHOP in combination with rituximab (375 mg/m2) on day 1, and with G-CSF support. A maximum of 8 cycles and radiotherapy for localized or bulky disease were planned.

**Patients characteristics:** Thirty-one pts from five institutions had entered the study and results from 28 evaluable pts are reported. Three had a follicular lymphoma and 25 a DLBCL lymphoma. Median age: 62 years (range 33-73), 11 pts over 65 years. Sex: 12M/18F. Ann Arbor stage: I-II 53.5%, III 14.3%; IV 32.2%. B symptoms: 32.2%. Bulky disease: 25%. International Prognostic Index:low/intermediate-loww 67.9%; intermediate-high/high 32.1%.

**Results:** Response: 25/28 pts (89.3%) obtained CR and 2/28 a partial response. Median n cycles/po: 6 (2-8) and 10 pts received radiotherapy. Toxicity: Hematologic: anemia grade 2 WHO 21.4% and neutropenia grade 4 WHO 14.3%. Infectious: 10%, most of them mild upper respirat- otrary tract infections; one pt died from a bilateral pneumonia without
neutropenia. Survival: 89.3% pts are alive with a median follow-up of 8 months (3–21); only 1 pt has relapsed after 17 months in CR.

Conclusions: Rituximab is associated to two-weekly CHOP chemotherapy is a feasible, safe and effective regimen for newly-diagnosed aggressive B cell lymphomas. These preliminary data show a very high CR rate – almost 90%– and, although follow-up is too short, only one pt has relapsed. Recruitment of more pts and longer follow-up are required to confirm these results and analyze prognostic factors.

In collaboration with Roche Pharma.

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IMMUNOCHEMOTHERAPY (R-CHOP, R-EPOCH) IN THE TREATMENT OF DIFFUSE B-CELL LARGE CELL LYMPHOMAS (DLCLC) – A SINGLE INSTITUTION EXPERIENCE

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Introduction: For over 25 years a principal goal of clinical research in aggressive lymphomas has been to identify therapies that are more effective than standard CHOP. Recently, GELA study confirmed rituximab plus CHOP as a new gold standard for DLCLC. Dose adjusted EPOCH regimen (continuous 96 hours infusion of etoposide/vincristine/doxorubicin/liposomal doxorubicin + rituximab) produced more cell killing than CHOP; dynamic dose adjustment may overcome inadequate drug concentrations and compensate for increased drug clearance over time.

Methods: During 4 years period, 76 patients with newly diagnosed DLCLC were treated at the Institute of hematology with R-CHOP (48 pts) or R-EPOCH regimen (28 pts). Initial evaluation included a history and physical examination, standard blood tests, whole-body computed tomography, and bone marrow biopsies. International Prognostic Index was initially determined for each patient. Sites of disease were restaged every two cycles.

Results: The therapeutic response in both group of patients was very good: in the group of patients treated with R-CHOP regimen, 90% had achieved therapeutic response, with 80% CR and 20% PR. In the group of patients treated with R-EPOCH regimen, 65% had CR and 17% PR, but 6% had stable disease and 12% had progression of disease. Due to IPI score, patients with low, intermediate or high IPI, achieved the same therapeutic answer in the both group of patients: CR were achieved in about 80% of patients, and PR in about 20%. In the median follow up of 32 months, the probability of OS was 100% in the group of patients treated with R-CHOP and 71% in the group of patients treated with R-EPOCH, although this difference was not statistically significant.

Conclusions: This report reflects an interim summary of our single Institution results of R-CHOP vs R-EPOCH regimen in patients with de novo diffuse large B cell lymphoma. Both regimens gave excellent results, although the toxicity was greater with the EPOCH regimen. But, the subgroup of patients with primary mediastinal DKL with sclerosis, who had the bulky form of disease, had better response treated with EPOCH rather than with the standard CHOP regimen.

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RITUXIMAB IMPROVES OUTCOME IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)—SINGLE CENTRE RETROSPECTIVE STUDY

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Background: Several studies (GELA 98.5, MINT) have shown survival benefit for combination of chemotherapy (CHT) plus rituximab (R) in the patients with DLBCL but results of other studies are not so convincing (ECOG 4494 trial).

Aim: retrospective analysis of the 94 patients (pts) with new diagnosed DLBCL treated between January 2001 and November 2004 with evaluation of the efficacy of rituximab.

Methods: 94 pts with DLBCL with median age 58.5 years (range 19–85) were evaluated. Initial stage I/IIf/VB was found in 27/33/17/19 pts, IPI 0–1 in 32 pts (34%), IPI 2–5 in 62 pts (66%). Elevated LDH was observed in 73%, extranodal involvement in 64%, bulky disease>7cm in 36% of cases. The first-line CHT regimen CHOP +/- R was used in 64% of pts, 21 younger pts under 65 years (22%) with high risk (AA IPI 2–3) were consolidated by autologous stem cell transplantation. We compared subgroup of pts treated with CHT only to pts treated with R+CHT. This two subgroups were comparable according to IPI. For statistical analysis Fisher’s exact test and log rank test were used.

Results: 75 pts (80%) finished the planned schedule to December 2004 – 32 pts in R+CHT group (67%) and 43 pts with CHT only (93%). After the first-line therapy uCR + CR were achieved in 84% of pts, in group with R+CHT in 97%, in the group with CHT in 74% (P=0.01). Subsequent relaps or progression were observed in 20 pts—in 39% in CHT group compared to 9% of pts in R+CHT group (P=0.007). Median of time to relaps or progression was 10 months in CHT group (P=0.005). Second line therapy induced 2CR, 2PR (ORR 53%). To December 2004 is alive 80% of pts, 94% in R+CHT group, 67% in CHT group (P=0.001). 78% of pts are in CR, actuarial 2-year survival is 86% and actuarial progression free survival (PFS) is 60%. Pts treated with R+CHT had longer PFS (P=0.007) and EFS (P=0.05) compared to pts with CHT group. Median of follow-up is 15m (range 2–48), in R+CHT group 11.5m (range 2–54m), in CHT group 25m (range 3–48m).

Conclusion: DLBCL in potentially curable disease. 84% of our patients achieved CR after first-line therapy. Rituximab in combination with CHT significantly improved frequency of CR, reduced frequency of relapses (including early relapses) and prolongation PFS and EFS. Response rate in the second line therapy was 53%. These results confirmed that R+CHT is now standard treatment option in all patients with DLBCL.

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CHOP CHEMOTHERAPY WITH RITUXIMAB IN DLBCL NON-HODGKIN’S LYMPHOMA (NH-L-OHR EXPERIENCE)

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Introduction: In this study we have assessed the efficacy and tolerability of rituximab added to standard CHOP regimen in patients with newly diagnosed CD20(+) NHL. Rituximab, the monoclonal hybrid antibody directed against CD20 lymphocyte’s receptor, acts in mixed way: mainly by complement dependent cytotoxicity and antibody dependent cellular toxicity, induction of apoptosis, and as a chemosensitizer.

Methods: We have compared the group of 18 patients (14 female and 4 male, median age 52 years, range 20–73) with diagnosis of DLBCL treated with rituximab added to standard CHOP regimen (R-CHOP) with the group of 20 patients (11female and 9 male, median age 56 years, range 26–76) with the same diagnosis treated with standard CHOP. All patients have been treated in our Center from 2001 to 2004. The groups were well balanced. There was no significant difference between the groups in age, IPI score, stage and time of follow up. Median number of chemotherapy courses was 6 in R-CHOP group vs. 8 in second one. Median time of follow up is 20 months for R-CHOP and 16 for CHOP group.

Results: In R-CHOP group 12 patients (66.6%) achieved CR, 2 (11.1%) PR and there were 4 PD (22.2%). In CHOP group there were 10 CR (50%), 7 PR (35%), 3 PD (15%). There was no significant difference in time to progression (TTP) (P=0.069, median TTP has not been achieved in R-CHOP group yet, in second one is 10 months).The overall survival at one year was 78% vs. 72% respectively. Rituximab was well tolerated, we did not observe WHO grade 3 or 4 toxicity.

Conclusions: We have not observed significant improvement in response rate, time to progression and overall survival in R-CHOP group. This is probably due to small number of patients and short time of follow up.
FEASIBILITY AND TOXICITY OF DOSE-DENSE R-CHOP14 SUPPORTED BY PEGIFLUGASTIN IN DIFFUSE LARGE B CELL LYMPHOMA

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Introduction: Recent studies have shown that CHOP chemotherapy (CT) in a dose-dense setting (CHOP14) or with the addition of rituximab (R-CHOP) may improve response rate and survival of patients with diffuse large B-cell lymphoma (DLBCL). Besides, in dose-dense regimens, G-CSF is instrumental for delivering on time the planned CT dose. This phase II study assessed the feasibility and toxicity of R-CHOP14 supported by pegfilgrastim.

Methods: Eligibility included patients with DLBCL in stage II-IV, aged 18–70. The CHOP regimen was delivered every 14 days (CHOP14), preceded on day 1 by rituximab (375 mg/m²) and followed on day 3 by pegfilgrastim (6 mg per cycle). Fifty patients were enrolled and 42 are evaluable, so far, for a cumulative 219 cycles (177 cycles 2–6). Median age was 55 yrs (range 22–70) and M/F ratio 0.92. Half of the patients were in stage IV (18% with bone marrow involvement); IPI 0–1 accounted for 52% and bulky disease for 40% of total.

Results: Cycles were delivered on day 15 in 162/177 occasions (92%). Delays occurred in 14 instances; 3 cycles (1.7%) were postponed for grade 2 neutropenia and 11 for non-hematological toxicity. Average relative dose intensity was 95% for doxorubicin and cyclophosphamide, and 91% for vincristine. The ANC nadir occurred on day 10, with a median value of 1.5×10⁹/L (range 0.01–23.4). Grade 3 and 4 neutropenia occurred in 36% and 19% of 219 cycles, respectively, with a median duration of grade 4 neutropenia of 2 days. Neutropenic fever developed in six instances (2.7% of cycles), with a median duration of 3 days (range 1–5). Febrile episodes occurred in 11 additional cases who had an ANC above 1×10⁹/L. Thirteen severe adverse events (SAE) were registered (4 of them developed off-therapy) and consisted of interstitial pneumonia in 8 cases (in 3 of them, Pneumocystis carinii was documented), bacterial pneumonia in two, septic shock and GI hemorrhage in one case, each. One patient died of ileal perforation after the first cycle of therapy.

Conclusions: The results of this study indicate that a single dose of cyclosporine successfully supports dose dense R-CHOP14 in DLBCL, allowing the on-time delivery of therapy in 92% of cycles. Incidence of febrile neutropenia was low and average dose intensity was optimal. The rate of interstitial pneumonia (most worrisome, the Pneumocystis carinii pneumonia) was significant and prophylaxis with cotrimoxazole appears mandatory in this setting of patients. Evaluation of immunological status during and after dose-dense immuno-chemotherapy may help understand the mechanism of this unanticipated toxicity.
and clinical background. Quality of life was evaluated serially during treatment using the MOS SF-20 questionnaire.

**Results:** Among 19 CEVO1 and 18 CEVO2 included, no significant difference was observed between the 2 groups according to the main prognostic variables. With 7.5 year median follow-up (range 4.2 to 8.7), we observed lower feasibility (CEVO2 arm stopped because of excess toxicity) but better outcome with CEVO2. 48% dose intensity of d15, significant decrease of quality of life, no difference in CR rates but tendency to improved 5-y OS (65.7% vs 47.4%–12 vs 6 evts- P=0.056) and improved 5-y EFS (66.2% vs 36.8%–14 vs 7 evts- P=0.022). Toxic death rate was equivalent in the two arms (5% and 5.5%).

**Conclusion:** These results tend to show superiority of the d1-d15 CEVO2 schedule, thus confirming the above cited trial conclusions, despite decreased d15 dose intensity and significant decrease of quality of life.

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**STUDY OF SERUM VASCULAR ENDOTHELIAL GROWTH FACTOR AND SERUM BASIC FIBROBLAST GROWTH FACTOR IN RELAPSED AND REFRACTORY AGGRESSIVE B-CELL NHL AND RESPONSE TO ICE PROTOCOL**

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**Introduction:** Tumor growth and metastasis are angiogenesis dependent. Switching from angiogenesis inhibiting to angiogenesis stimulating phenotype is usually accompanied by overexpression of one or more angiogenic factors. SVEGF and ShGF are considered to be the most endothelial specific and relevant of angiogenic growth factors. So we aimed in this study to evaluate the pretreatment levels of SVEGF and ShGF and their correlation with response to ICE protocol.

**Methods:** 40 patients with relapsed / refractory NHL of diffuse large cell type were subjected to complete history taking, physical examination, routine laboratory and radiological investigations for proper staging and evaluation of SVEGF and ShGF by immunoassay method. All patients were treated with ICE protocol “Ilosfamide 1 g/m2 (0–1 h), Etoposide 150 mg/m2 (1–12h), Carboplatin 200 mg/m2 (12–13h), Etoposide 150 mg/m2 (13–24h) D1, D2 with addition of Mesna 333 mg/m2 – 30min, +4h and 8h after ifosfamide over 15 minutes. Evaluation was carried out after two cycles and responding patients continued for 6 cycles.

**Results:** showed that ICE protocol induced complete response in 6 patients (15%), partial response in 10 patients (25%) with overall response rate 40%. High pretreatment levels of SVEGF and ShGF (> median, 229 Pg/ml, 3.3 Pg/ml, respectively) found in 52.5% and 47.5%, respectively, and they were statistically significant in predicting response to chemotherapy (P=0.013, 0.02, respectively). Myelosuppression [neutropenia G (3) in 10%, G (4) 27.5%, anemia G (3,4) in 37.5% and thrombocytopenia G (3,4) in 40%].

**Conclusion:** High pretreatment levels of SVEGF and ShGF were good predictors for poor response to chemotherapy, and ICE protocol was accepted except marked myelosuppression.

**DEXAMETHASONE, HIGH-DOSE CYTARABINE, AND CISPLATIN (DHAP) IN COMBINATION WITH RITUXIMAB AS SALVAGE TREATMENT FOR PATIENTS WITH RELAPSED OR REFRACTORY AGGRESSIVE NON-HODGKIN'S LYMPHOMA**

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**Introduction:** We designed a multicenter phase II trial to evaluate prospectively the safety and efficacy of the combination of rituximab with the DHAP regimen in patients who relapsed after or were resistant to a CHOP-like regimen.

**Methods:** 62 patients with relapsed or resistant aggressive B-cell NHL were included. Median age was 61 years. Treatment consisted of Rituximab (375 mg/m2 per dose) on day 1 followed by dexamethasone 40 mg d3–6 (d 3–5 in first cycle), cytarabine 2 × 2000 mg/m2 d 4, or 2 × 1000 mg/m2 for patients > 60 years of age, respectively, and cisplatin 25 mg/m2 d 3–6 for a maximum of 4 cycles.

**Results:** ORR was 61.8% (34 of 55 patients). 17 patients experienced a CR (30.9%). Median OS was 8.6 months. Patients treated in first relapse had a highly significant better ORR (80.6%) compared to patients with primary refractory disease (21.4%, P <0.001). Subgroup analysis will be presented at the meeting.

**Conclusions:** The combination of Rituximab with the DHAP regimen in the treatment of relapsed or refractory aggressive lymphoma is feasible and effective. Particularly in relapsed patients, high complete remission rates can be achieved. For primary refractory patients, response and survival data are unsatisfactory.
an anthracyclin-containing therapy. Median age was 65, 67% had a 3–5
IPIScore, 20% were refractory.
Results: Median follow up was 7.8 months. ORR was 64%, CR was 36% (respectively 81% and 63% for the 26 relapsing pts). The maximal response was obtained after 3 courses. Among responding pts, EFS rate was 17.5% at 40 m. Retrospective analysis showed 1 case of grade 3 nephrototoxicity, and the absence of acute cardiac or neurologic complications. The main toxicity was neutropenia (61% grade 3–4), as the G-CSF was used for only 15% of delivered cycles.
Conclusions: R-NIMP is an efficient salvage combination. A multicentric phase II trial (GOELAMS R-NIMP) is now open to assess its efficiency (CR rate after 3 courses) and its toxicity in relapse, for 18–75y aged pts. Its reduced toxicity would be of interest before an intensification.

RITUXIMAB, ARA-C, DEXAMETHASONE AND OXALIPITAL (R-ADOX)
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Background and objectives: Patients with relapsed diffuse large B-cell lymphoma who are either not suitable for stem cell transplantation or suffer from relapsed disease after standard second line chemotherapy face a dismal prognosis. Most of them have a reduced performance status and do not tolerate intensive chemotherapy. At the moment, virtually no effective therapy exists for these patients and thus we have investigated a novel chemotherapy regimen.

Design and Methods: We have retrospectively analysed 15 patients with diffuse large B-cell lymphoma relapsing/progressing following at least two prior chemotherapeutic regimens, who were given rituximab 375 mg/m² day 1, Ara-C i.v. 2 × 1000 mg day 2, dexamethasone 40 mg i.v. days 1–4 and oxalipitol 130 mg/m² i.v. over 28 day 3 (R-ADOX).

Results: Three patients (20%) achieved a complete remission (CR), 8 (53%) had a partial response (PR) for an overall objective response rate of 73%; one had stable disease (SD) with disappearance of pleural effusion, while 3 patients (20%) progressed. The median survival was 9 months (range 2–19); and 5 patients are currently alive, while the other 10 patients have died of progressive disease. In spite of extensive pretreatment, side effects were relatively mild and consisted of thrombocytopenia WHO grade III in 5 (33%) and grade IV in 4 (27%) patients, leukocytopenia WHO grade III in 7 (47%) cases and transient peripheral neuropathy in 9 (60%) patients.

Interpretation and conclusion: These data suggest that R-ADOX is well tolerated in heavily pretreated patients with an impaired performance status. In addition, it displays impressive therapeutic activity given the highly unfavourable patients characteristics and should be further investigated for treatment of DLBCL.

PACLITAXEL AND TOPOTECAN IN Combination WITH RITUXIMAB AS EFFECTIVE SECOND-LINE SALVAGE REGIMEN IN RESISTANT AGGRESSIVE NON-HODGKIN'S LYMPHOMA
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Introduction: Patients with relapsed or refractory aggressive B-cell lymphoma who fail to respond to the most frequently used salvage regimens as cytarabine/platinum or ifosfamide-based regimens have an unfavorable prognosis and limited options for effective reduction in preparation for transplant. In this population alternative strategies are mandatory, with experimental regimens including the monoclonal antibody rituximab. We present our results using the combination of paclitaxel (taxol), topotecan and rituximab (TIR) in patients with relapsed or refractory aggressive B-cell lymphoma.

Patients and methods: The TIR regimen consists of rituximab 375 mg/m² on day 1, followed by paclitaxel 200 mg/m² on day 2 and topotecan 1 mg/m² on days 2 to 6. At present, 10 patients diagnosed with relapsed or refractory diffuse large B-cell lymphoma (5), follicular large cell (2) or transformed B-cell lymphoma (3) have completed the programmed protocol and have enough follow-up. Three of the five patients with diffuse large B-cell lymphoma had primary refractory disease, and all had received ESHAP as salvage regimen. In addition, three patients had followed autologous stem cell transplantation. Patients with transformed B-cell lymphoma had received multiple salvage regimens. Patients received 2 to 4 courses every 21 days according to response.

Results: The overall response rate was of 60% (6 out of 10 patients), with complete response in 3 of them. In two patients the partial response was intensified with high-dose chemotherapy and autologous stem cell transplantation achieving a complete response. It is remarkable that none of the transformed B-cell lymphoma patients responded. Hematological toxicity was observed in all patients, neurological toxicity related to paclitaxel was observed in 2 patients and 3 patients had diarrhea related to topotecan. In none patient was necessary to discontinue the planned treatment because of toxicity.

Conclusion: The combination of paclitaxel, topotecan and rituximab is an effective salvage regimen in heavily treated patients with relapsed or refractory diffuse large B-cell lymphoma, but other alternative approaches are necessary in transformed B-cell lymphoma.
Improvement of the toxicity profile of R-GERMOX regimens in patients with advanced lymphoma has shown promising activity with an acceptable toxicity.

Treatment of patients with aggressive lymphoma and impaired cardiac function with the R-ICE regimen

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Introduction: The first-line therapy for patients with aggressive lymphoma is usually the CHOEP regimen. However, anthracycline use in patients with impaired cardiac function is problematic. We present two patients who were treated with R-ICE protocol as first-line therapy.

Cases: Patient 1: A 58-year-old male presented with abdominal pain. A diagnosis of diffuse large B cell lymphoma with a large (2.6X6.8 cm) mass in the right adrenal was made. The IPI was 1 (LDH elevation). 4 years previously a diagnosis of idiopathic dilated cardiomyopathy with an ejection fraction of 20% was made. The patient was currently treated with Cardivelol, Enalapril and was asymptomatic. Because of the heart failure R-ICE (Rituximab, Ifosfamide, Carboplatin, Etoposide) protocol was used. After 2 courses the PET 18F-FDG scan showed no evidence of disease. Treatment was continued with radiotherapy (3960 Rad) to the adenral mass HE is currently in complete remission for 18 months.

Patient 2: A 72-year-old male presented with abdominal pain. A diagnosis of diffuse large B cell lymphoma with bulky disease 18x13x8 cm in the mesentery with skin, thyroid, pericardium and peritoneal involvement. The IPI was 4. He had an ejection fraction of 30% due to a previous myocardial infarction and subsequent coronary artery bypass surgery. The R-ICE protocol was used. After 2 courses the PET 18F-FDG showed 2 minute foci of uptake. Treatment was continued with 4 R-CHOP and Dezauran courses. He is currently in complete remission.

Conclusions: These cases suggest the feasibility of using the R-ICE protocol as first-line therapy in patients with aggressive lymphoma and cardiac impairment to avoid Anthracycline use or at least reduce the dose.

Cost-effectiveness of high dose chemotherapy followed by autologous stem-cell support versus CHOP therapy for lymphoma patients in front line therapy

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Introduction: Intensive high-dose chemotherapy with autologous stem-cell support has become a common strategy for non-Hodgkin’s lymphoma. A cost-effectiveness analysis was carried out comparing patients autografted with ASC with those treated by conventional chemotherapy (CHOP protocol).

Methods: 207 patients were randomized in a phase III multicenter trial: the GOELAMS 072 [1]. The cost-effectiveness analysis was carried out from the point of view of the payer setting. Efficacy was assessed by 5-year Event Free Survival (EFS), resources used, labor and direct medical costs per patient were identified, and sensitivity analyses performed.

Results: Patient characteristics were similar except in term of age. EFS was significantly higher in the ASC than in the CHOP group (55% vs 37%, P = 0.037). Among patients with a high intermediate risk of death, according to the age-adjusted International Prognostic Index (IPI), the five-year survival rate was significantly higher in high-dose therapy after CHOP (74% vs 44%, P = 0.001). The cost distribution was also different. CHOP chemotherapy was less expensive than ASC, €12,702 and €44,650 respectively. The cost-effectiveness ratio obtained was 168,143 that needed to be used to avoid an event at 5 years.

Conclusion: ASC appeared to be optimal for clinical and economic considerations in NHL patients transplanted in front line therapy.

References
APPLICATION OF BEAM-LIKE CHEMOTHERAPY WITHOUT CRYOPRESERVATION IN NON-HODGKIN LYMPHOMA STEM CELL TRANSPLANTATION

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Introduction: Insufficiency of conditioning regimens to eradicate malignant cells has prompted clinicians to assess modified therapeutic protocols. In this study, an efficient BEAM-LIKE chemotherapy, CCNU-containing (CEAM), is introduced.

Methods: 22 (16 males and 6 females) NHL patients received CEAM regimen followed by infusion of bone marrow (n = 2) or peripheral blood (n = 20) stem cell transplantation. Median age was 52 (ranged 13 to 61). 11 patients were in complete remission (CR), 7 in CR1, 2 in CR2, and 2 patients were in primary induction failure (PIF). No cryopreservation and radiotherapy used. CCNU was administered as 200 mg/m²/IV for 4 days, VP16 as 300 mg/m²/IV for 2 days, Ara-C as 300 mg/m²/IV for 2 days and melphalan as 140 mg/m²/IV for one day. The patients were assessed for toxicities (hematological, gastrointestinal, pulmonary, renal and cardiac) post-treatment, from October 2002 to January 2005.

Results: Median time of ANC recovery was 17 days (1–45 days) and platelet recovery was 19 days (9–130 days). Detected toxicities for 6 in renal, 2 in pulmonary, and 22 in gastrointestinal tracts, respectively. No cardiac toxicity was seen. 3 Out of 4 relapsed patients are still alive; only one died of PIF. Overall survival and disease free survival at 300 days median follow up were 84.2% and 87.7%, respectively.

Conclusion: CEAM chemotherapy seems promising for treatment of non-Hodgkin lymphoma, owing to its reversible toxicities.

COLOGNE HIGH-DOSE SEQUENTIAL CHEMOTHERAPY IN RELAPSED AND REFRACTORY AGGRESSIVE NON-HODGKIN'S LYMPHOMA – RESULTS OF MULTICENTRE PHASE II STUDY

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Introduction: Combination chemotherapy can cure patients with Non-Hodgkin's lymphoma (NHL), but those with treatment failure or relapse still have a poor prognosis. High-dose chemotherapy (HDCT) with autologous stem cell transplantation (ASCT) can improve the outcome of these patients. Thus we evaluated an intensified salvage program with a final ASCT.

Patients and Methods: Inclusion criteria were age 18–65 years, proven primary progressive or relapsed aggressive NHL and eligibility for HDCT. Treatment program consisted of two cycles DHAP; patients with CR or PR received cyclophosphamide (4 g/m²) followed PBSC harvest; methotrexate (8 g/m²) plus vincristine (1.4 mg/m²) and etoposide (2.6 g/m²). The final myeloablative course was BEAM with ASCT.

Results: 51 patients, median aged 43 years (24–65) were enrolled: 23 (40%) patients were refractory to primary therapy and 24 (60%) patients had relapse of NHL. At 22 months of median follow-up (range 1–71) results are as follows: the response rate 100 days after transplantation was 45.6% (31.6% CR, 14% PR). Toxicity was tolerable. The freedom from treatment failure (FFTF) and event-free survival (EFS) were 20% and 40% for all patients, respectively. FFTF and OS for patients with relapse were: 38% and 58%; for progressive disease: 8% and 20%, respectively.

Conclusion: We conclude that this regimen is feasible, tolerable and effective in patients with relapsed NHL. In contrast the results in patients with progressive disease are unsatisfactory. This program is currently being modified by addition of rituximab for patients with relapsed aggressive NHL.

TREATMENT OF HIGH RISK DIFFUSE LARGE B-CELL LYMPHOMA WITH INTENSIFIED INDUCTION THERAPY AND HIGH DOSE SEQUENTIAL THERAPY

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Introduction: Patients (pts) with diagnosis of DLBCL and IPI age adjusted 2 or present a poor prognosis. The results with high dose sequential therapy (HDST) showed a significant improvement of Overall Survival (OS) and Event Free Survival (EFS) in comparison with a standard chemotherapy.

Methods: We decided to use HDST adding an intensified scheme as debulking phase. The phase I was characterized by an intensified CHOP (MegachOP): cyclophosphamide 3 g/m²; doxorubicin 75 mg/m²; oncovin 1.4 mg/m² on day 1 and prednisone 100 mg for 5 days. Stem cells collection was planned after the third cycle. The phase II was the classical HDST. The phase III was the peripheral blood stem cell transplantation (PBSCT) with melphalan 180 mg/m² and mitoxantrone 60 mg/m² as conditioning regimen. From March 2002 until February 2004 we enrolled 11 pts. Median age was 39 years (range 25–49), 6 pts were stage III–IV (73%), 7 presented bulky disease (64%), all but one had an abnormal LDH value. All pts were IPI 2 or 3. Phase one and two were performed on outpatient basis.

Results: Six pts obtained a very good partial remission (VGPR) after first phase, six were in CR unconfirmed after phase II and 4 were in PR. After PBSCT 8 pts were in CR and 2 were in PR. At the end of planned therapy 9 pts obtained a complete remission (CR) (82%), a patient after radiotherapy was alive with disease and one died of progressive disease during phase I. After a median follow-up of 21 months (range 5–55) OS was 81%. With a median follow-up of 19 months 88% of complete remission pts were free from disease and only one patient relapsed after 2 months from CR. We did not find grade III or IV WHO extramedullary toxicity.

Conclusion: We can conclude that this protocol is feasible as outpatient basis in phases I and II. Moreover, this therapy was highly effective (81% OS) in the subset of pts with very high risk characteristics at diagnosis.

INTENSIVE SEQUENTIAL CHEMOTHERAPY (+/- RITUXIMAB) AND FRONT-LINE AUTOTRANSPLANTATION IMPROVES REMISSION RATE AND SURVIVAL IN PATIENTS WITH POOR PROGNOSIS NON-HODGKIN'S LYMPHOMAS

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Background: The combination of well-defined prognostic indicators can accurately identify a subgroup of poor-prognosis patients with advanced non-Hodgkin's lymphomas. The first-line therapeutic intensification can lead to longer overall survival of such selected patients. In addition there is increasing evidence that the addition of rituximab improves remission rates, and can purge circulating lymphoma cells before stem cells collection.

Patients and methods: 92 newly diagnosed patients under the age of 65 with poor prognosis lymphoma (52 pts. with DLBCL, 18 with FL, 13 with MCL and 10 with PTCL) were treated with intensive induction therapy (PACEBO, IVAM, HAM, including HD-MTX and HD-Ara-C), 41 pts. with CD20+ B-NHL received 4–6 infusions of rituximab (375 mg/m²) prior to chemotherapy cycles.

Results: Among the 87 pts. evaluated after the induction therapy, 33 pts. (38%) achieved CR and 50 (57%) obtained partial response (PR), most of them with more than 75% regression of tumor size. 4 pts. (5%) failed to respond. 77/85 pts. (91%) successfully collected PBSC. 64 pts. were evaluated at day +100 after autologous transplantation and 54 pts. (84%) reached CR/CRu, 7 pts. (11%) very good PR, 3 pts. (5%) relapsed or progressed. 25/92 (27%) pts. failed to respond, relapsed or progressed. The 67 pts. are alive without evidence of active disease with a median follow-up of 19 months (range 2–69 months). The probability of overall survival (OS) between pts. achieved CR or PR prior AT was not statistically different. Only aa-IPI and LDH significantly correlated with poorer OS in multivariate analysis.

Conclusions: The intensive sequential induction therapy (+/- rituximab) leads to a significant tumor regression and subsequent autologous transplantation allows very good tumor control and prolongs OS in both the CR or PR pretransplantation groups of patients. Supported by grant MSM 619 959 92 05.
TREATMENT STRATIFICATION ACCORDING TO EARLY RESPONSE TO MEGA-COMP (MC), BASED ON CT AND GALLIUM 67 SCAN (G67S) WITH OR WITHOUT IFE SALVAGE THERAPY AND AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) IN PATIENTS WITH POOR PROGNOSIS PREDICTIVE OF AGGRESSIVE LYMPHOMA (PPAL): A PRELIMINARY REPORT FROM A PROSPECTIVE GEL/TAMO TRIAL

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Background: Patients (Pts) with IPI 2.3 LCL have a poor outcome with survival lower than 50%. Evaluation of response only with CT scan shows often residual masses which can be tumoral or not. G67S discriminate better this two situations and therefore can help to decide further strategies.

Aim: To assess the efficacy of PBSCT in pts with PPAL according to previous early response to Mega-COMP (MC) evaluated with CT & G67S.

Patients & methods: Inclusion criteria were: G67S positive LBLCL with IPI score 2 or IPI <2 with high β2 microglobulin or FTCL, except ALK+ anaplastic lymphoma regardless of IPI. Pts were evaluated after 3 cycles of MC. Those in CR (CT scan, G67S negative) or uCR (CT scan positive, G67S negative) received a 4rd MC followed by BEAM and PBSCT. Those with positive G67S received IFPE or ESHAP (x2) regiments followed by BEAM and PBSCT. Pts with refractory disease (RD) were dropped from the study. Since 2001, 104 patients have been registered and 84 are currently evaluable. Median age was 51 years (20–67 years) and 57% were males. Fifty-nine (70%) had a DBCL, 6 (7%) a grade 3 FL and, 19 (23%) FTCL. Sixty-two (88%) had IPI 2-2, and 12 (12%) IPI 3. Doses were per cycle 100 mg/m2 for ADR, 65 mg/m2 for VCR and 2 mg/m2 for on day 1 and Pred 60 mg/m2 days 1–5) on a 21 day schedule and for IFPE: ifosfamide 10 g/m2 and VP16 900 mg/m2 (days 1–3) with Mesna.

Results: After 3 MC, 34 pts (40%) were considered on CR or uCR due to a negative G67S, 35(42%) were on PR and 13 (15%) were refractory. Two pts were early deaths. After IFPE 12/35 (34%) achieved CR, 15 (43%) PR and 8 (23%) progressed. Overall, 65 pts received PBSCT and 62 were evaluable for response. Seventeen pts (26%) died, 14 due to lymphoma and 6% due to toxicity. With 25 months of median follow-up (8 to 51 months), 67 pts are alive, 56 (67%), disease free. OSI for G67S positive pts after 3 MC was 84% vs. 74% for G67S positive (P=0.14) and EFS 74% vs. 64% (P=0.30). In the univariate analysis, the only significant variable associated with outcome was non CR or PR after MC ± IFPE vs. RD (P=0.0002).

Conclusion: Our preliminary results suggest that early salvage therapy can overcome the poor outcome of pts with PPAL. Moreover, this early evaluation could identify pts with poor prognosis who only need a short treatment.

TANDEM AUTOLOGOUS STEM CELL TRANSPLANTATION FOLLOWING HIGH DOSE CHEMOTHERAPY FOR TRANSFORMED LOW GRADE AND REFRACTORY HIGH GRADE LYMPHOMA

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The results of autologous stem cell transplantation following high dose chemotherapy for transformed low grade, high grade refractory or relapsing early (< 1 year) lymphoma are disappointing. We describe a tandem intensive chemotherapy followed by autologous stem cell transplantation in 37 patients between April 1996 and February 2004. The median age was 49 yo (33–67yo); 19 patients had a transformed low-grade lymphoma, 7 patients a high grade early (< 1 year) relapse and 11 patients had induction failure. Pre transplant therapy consisted of 2 to 4 courses of polychemotherapy with anthracycline or with cisplatin. The first intensive chemotherapy program consisted of mitoxantrone 45 mg/m2 at day 1 and cycytarbaine 1000 mg/m2 at days 1, 2, 3, 4 followed by autologous stem cell transplantation at day 5. The second intensive treatment consisted of fractionated total body irradiation (12 Gy) and cyclophosphamide 60 mg/m2 for two days followed by autologous stem cell transplantation in 35 patients and of BEAM (carmustine 300 mg/m2 at day 1, cytarabine 200 mg/m2/12hours at days 2, 3, 4; etoposide 400 mg/m2 at days 2, 3, 4, melphalan 100 mg/m2 at day 6) followed by autologous stem cell transplantation in 2 patients who previously received radiotherapy. The regimen was well tolerated with no treatment related death. With a median follow-up of 34.4 months from day 0 of the first intensive treatment, 22 patients are alive in complete remission. The 5y Kaplan Meyer probability of survival is 59%; 15 patients relapsed after a median of 10.6 months (1.9–30.1) and died. The 5y OS in each category was: transformed low grade lymphoma: 68%; high grade early relapse: 29%; induction failure: 64%. The tandem intensive chemotherapy is feasible, well tolerated and effective for transformed low grade lymphoma and induction failure but seems to be disappointing for high grade in early relapse and new therapeutic approaches need to be explored for this category.
Results: Median age was 45 yrs (19–60); 53% at IH and 47% at H risk. CR was 77%, PR 3%, NR 15% and toxic deaths 5%. ASCI was not performed in 22%. With a median follow-up of 2 years, 2-year DFS and 2-year OS were 70% and 76%. These results were compared to those achieved in 41 B-DLCL patients with the same eligibility criteria enrolled in the previous trial without Rituximab. These previously reported patients were treated with: MACOP-B × 8 weeks + BEAM (R-HDC group). CR in this group of patients was 71%, NR 22% and toxic deaths 7%.

Conclusions: These results suggest that the addition of Rituximab to intensified and high dose chemotherapy with ASCT support is feasible and effective in B-DLCL at poor prognosis and compare favorably to our historical experience.

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RITUXIMAB AS ADJUVANT TO INTENSIVE SEQUENTIAL CHEMOTHERAPY (R-ISC 96) IN PATIENTS UNDER 60 YEARS WITH UNTREATED POOR-PROGNOSIS DIFFUSE LARGE B CELL LYMPHOMA: A MATCHED CONTROL ANALYSIS

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Background: The potential benefit of rituximab as adjuvant to high-dose therapy (HDT) has been investigated in patients under 60 years with poor-risk (age-adjusted international prognostic index at 2–3) CD20+ diffuse large B-cell lymphoma (DLBCL).

Methods: The treatment consisted of 4 cycles of high-dose CEP0 (cyclophosphamide, etoposide, vincristine, prednisone), plus etoposide and cisplatin during the two last cycles. Peripheral blood stem cells were collected after cycle 1, and reinfused after cycles 3 and 4. Four weekly rituximab infusions were subsequently delivered.

Results: Among the 36 patients included, 30 could complete chemotherapy schedule, and 24/36 received rituximab. A complete response occurred in 20/36 patients (72%). With a median follow-up of 30 months, the estimated 5-year overall survival (OS) and event-free survival (EFS) rates (mean ± SD) were 65% ± 16% and 63% ± 15%, respectively. For the 24 patients who completed the trial, the estimated 5-year OS and EFS rates were 86% ± 14% and 82% ± 15%. These results compare with the 60% ± 13% OS rate and the 63% ± 13% EFS rate observed in 52 CD20+ DLBCL matched-patients who received HDT without rituximab.

Conclusions: These data suggest rituximab after HDT is feasible, and can improve survival.

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PROGNOSTIC SIGNIFICANCE OF MOLECULAR STAGING AND MINIMAL RESIDUAL DISEASE IN HIGH-RISK DIFFUSE LARGE B-CELL LYMPHOMA TREATED WITH AUTOLOGOUS STEM CELL TRANSPLANTATION (MegaCHOEP)

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Introduction: The prognostic value of peripheral blood (PB) and bone marrow (BM) involvement detected by PCR in patients with aggressive lymphomas has been determined. However, data about minimal residual disease (MRD) assessment and its prognostic relevance are lacking. The German Study Group for High-Grade NHL (DSHNHL) investigated the efficacy of a sequential dose escalated high-dose chemotherapy protocol including autologous stem cell transplantation in newly diagnosed patients with aggressive B-NHL, age below 60 and LDH above normal. Sequential MRD analysis including the autologous stem cell graft was performed within this protocol.

Methods: 132 patients entering the MegaCHOEP protocol were analysed in paraffin lymph node, peripheral blood (PB) or bone marrow (BM) for the presence of clonal rearranged tumour cells by consensus IGHH or IGK (14/18) PCR. Subsequently quantitative MRD analysis was performed in a subset of patients by TaqMan RQ-PCR with allele specific primers in combination with consensus reverse primers and probes. Available follow-up samples and autologous stem cell grafts were analysed.

Results: 66/132 B-NHL had a detectable clonal marker at diagnosis (56 IGH, 10 bcl2). PB involvement was detectable in 18 of 35 patients, BM involvement was determined in 18/29 samples. In 17/46 (37%) patients with available stem cell graft, residual disease was detectable at MRD level >10–3 (n = 5) or in a threshold between 10–4 and 10–14 (n = 12). Due to the highly mutated clonal IGVH genes in DLBCL quantitative IGVH RQ-PCR with consensus probes is hampered and an individual primer/probe design turned out to be necessary for this approach.

Conclusion: A significant fraction of patients with high risk aggressive B-NHL, has detectable PB and BM involvement at diagnosis as well as contamination of the stem cell graft. Data show the impact of molecular diagnostics and MRD on prognosis within the Mega CHOEP trial of the DSHNHL will be presented.
REDUCED-INTENSITY CONDITIONING FOLLOWED BY ALLOGENEIC STEM CELL TRANSPLANT FOR PATIENTS WITH MALIGNANT LYMPHOMA — A SINGLE CENTER EXPERIENCE

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Background: Standard chemotherapy (ASCT included) is not effective in some cases of high risk or recurrently relapsed lymphoma. Nonmyeloablative transplants have been reported as hopeful option for such patients because of their immune (GVL) effect. Although having less toxicity than standard allografts, they still pose a risk of life threatening complications.

Methods: All conditioning therapy consisted of fludarabine based regimens. Of overall 18 patients, 7 patients received peripheral blood stem cells (PBPC) from HLA-identical siblings and 11 received graft from unrelated donor. Graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporinA (CSA) or CSA + MMF (mycophenolate mofetil).

Results: We evaluated 18 patients with lymphoma (4 low grade NHL, 1 x high grade NHL, 3 x HL and 10 x CLL). Median age was 52 years. Median of previous therapy lines was 3. Six patients had previously received autografts. Eight were in remission (CR or PR) and ten had resistant or progressive disease. Seven patients developed acute GVHD grade I–II, one patient developed chronic GVHD, no aGVHD gr. III-IV was observed. With a median follow-up of 29 (4–55) months, the actuarial overall survival (OS) rates at 3 years were 60% for all patients and 65% for CLL. The 100-day and 1-year transplant related mortality (TRM) rates were 28% and 33%. Donor lymphocyte infusion (DLI) was used in one patient for relaps and CR was achieved. Of ten patients transplanted at resistant or progressive disease, four patients achieved remission (CR or uCR) and are still alive.

Conclusion: TRM in our group of very heterogeneous patients was high, probably because of highly pretreated patients and high rates of chemoresistant diseases. However RIC-alloSCT probably may be effective even in some patients with chemoresistant disease. Duration of remission and overall survival benefit in high risk patients consolidated in early remission will be evaluated.
8. T-cell Lymphomas/Lymphomas in AIDS

RECURRENT CHROMOSOMAL REARRANGEMENTS AFFECTING T-CELL RECEPTOR p6 and A HOMOZYGOTE DELETION SPANNING LMB REGION AT 10p11.2 IN ADULT T-CELL LEUKEMIA/LYMPHOMA

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Introduction: Molecular-cytogenetic analyses and their correlation with clinical features are still limited in mature T-cell malignancies. Using multicolor spectral karyotyping (SKY), we have previously identified the two major breakpoints, 10p11.13 (47%) and 14q11.2 (36%), frequently involved in structural rearrangements in adult T-cell leukemia/lymphoma (ATLL). In the current paper, cytogenetic studies are focused on these two breakpoints.

Methods and Results: First, using SKY and double-color fluorescence in situ hybridization (DC-FISH), we studied chromosome rearrangements of T-cell receptor (TCR)αβ gene locus on 52 patients with ATLL and 7 established cell lines. SKY and G-banding analyses identified structural abnormalities of chromosome 14q11.2 in 17 (30%) cases. The partner chromosomal breakpoints of 14q11.2 rearrangements were identified as inv(14)(q11.2q32) in 13 cases (76%) and del(14)(q11.2q32) in 11 cases (65%). DC-FISH with a biotinylated artificial chromosome (BAC) clones identified the involvement of TCRαβ gene in 3 cases of an inv(14)(q11.2q32), in one of t(11;14)(q13.3q11.2), and in one of t(3;14)(q21.1q32). Next, using FISH with 37 BAC clones, we analyzed breakpoints at 10p11.2-1.3 in two cell lines (KOB4 and KKI) and one patient by walking a segment ranging from 10p13 to 10p11.2. Large genomic deletions were detected at 10p11.2 on der(10) in two cell lines. In patient PH, a homozygous deletion was identified at 10p11.2-1.3, spanning the region of 4 Mb in size. Chromosome 14q32 translocation was associated with shorter survival (median survival time: 4.2 months vs. 8.0 months), although statistically not significant.

Conclusion: SKY and FISH analysis identified recurrent rearrangements of TCRαβ gene in a significant number of patients with 14q11.2 translocation in ATLL. A homozygous deletion was also detected at 10p11.2, suggesting the existence of tumor suppressor gene. Chromosome rearrangements will become a possible prognostic factor in ATLL patients.

STABLE OVEREXPRESSION OF THE CHEMOKINE RECEPTOR CCR4 IN THE MAJORITY OF T-CELL MALIGNANCIES: A POTENTIAL TARGET FOR IMMUNOTHERAPY

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Introduction: Chemokine receptors represent promising targets for lymphoma immunotherapy given their restricted pattern of expression. CCR4, the chemokine receptor (CCR4) is expressed by a majority of population of non-neoplastic T-cells. To assess the suitability of this receptor as an immunotherapy target, we compared expression of CCR4 in a large series of T-cell malignancies, using an anti-CCR4 monoclonal antibody that has demethylating cytotoxic activity.

Methods: Using Western blot, and immunostaining on microarrays and tissues sections, we assessed CCR4 levels using the KM210 antibody (Kyowa Hakko Kogyo, Tokyo, Japan), in 235 biopsies from 99 patients with cutaneous T-cell lymphoma (CTCL), 51 patients with nodal peripheral T-cell lymphomas and 39 with T-cell ALL/LLB. CCR4 expression was compared with clinical factors (stage, site of involvement, outcome) and expression of tumor progression markers including p65 NF-κB, Bcl-2, CD25, CD30 and granulocyte B but weakly positively correlated with junB expression (R = 0.32, p < 0.05) but not activated p65/NFκB. CCR4 expression was also seen in 63% of nodal PTCL, but only a minority of T-ALL. Discrepancy in variable expression seen in skin homing T-cells in 94% of chronic dermatitis cases (n = 18) and CCR4+ T-cells were rare in 12 biopsies of reactive lymphadenitis.

Conclusions: CCR4 is stably upregulated in the majority of CTCL cases and in nodal T-cell lymphoma. Increased CCR4 expression during transformation in cutaneous lymphomas may be related to elevated AP1 factors, including junB. The association of stably elevated CCR4 levels with transformation may permit selective targeting of T-cell malignancies by anti-CCR4 immunotherapy.

INCIDENCE AND PROGNOSTIC FEATURES OF NKT-NHL: A SINGAPOREAN EXPERIENCE

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Background: Natural Killer T-cell Lymphoma (NKT-NHL) is a rare lymphoma in the west. Reliable prognostic factors are lacking.

Methods: We retrospectively reviewed all NHL cases presenting to our center since January 1999. All cases had routine investigations for stage & IPI risk evaluation. Type of chemotherapy & radiation therapy (RT), CR and survival information was noted and correlated with presentation LDH, low albumin (<35 g/L), low CD8/CD3, low HB (<10 g/dl), neutrophil count, lymphopenia (<0.70/μl), Ann Arbor stage, IPI risk, extra-nodal involvement, performance status (PS), age, sex, type of chemotherapy and introduction of RT before 60-days from diagnosis (early RT).

Results: There were 880 cases of non-Hodgkin’s Lymphoma (NHL) since 1999. 154 (17.5%) had T-cell phenotype, and the single largest T-cell category was NKT-NHL with 48 cases (5.5% of all NHL). Stage wise distribution was 18 (1), 13 (1), 6 (3) & 11 (4). IPI distribution was 26 (low), 6 (low intermediate), 15 (high intermediate) and 1 (high risk). 16 had B symptoms. 7 patients received RT only and 5 could receive no oncologic treatment due to early progression and death. 36 received chemotherapy (26 anthracycline based & 19 received methotrexate aswell) of which 33 also received RT. 24 of all 40 RT recipients had early RT (60%). 28 (59%) cases had CR to primary therapy. With a minimum follow up of 12-36 months, 80% (30/37) were alive. Early Stage (Stage 1&2) NKT-NHL had a 62% CR and 48% 2-yr survival. During same duration the CR and 2-yr survival of early Stage diffuse large B-cell NHL (DLBCL) treated at our institution was 82% and 68% respectively. For NKT-NHL CR or survival was not influenced by type of chemotherapy (bolus Vs Infusion, anthracycline Vs no anthracycline & VP-16 vs. non-VP-16), sex, HB, LDH, PS at presentation. Borderline better survival with Methylthreoxate Vs no methylthreoxate was noted (p = 0.054). When IPI risk staging akin to that for B-NHL was applied median survival did not correlate with risk magnitude (Low-29.2m, Low-Intermediate-15.2m, High-Intermediate-40m and High risk-14m). Absence of low albumin or lymphopenia at presentation and early RT predicted higher CR and lower risk of dying (all p<0.01).

Conclusions: NKT-NHL fares worse than B-NHL. Stage or IPI risk do not correlate with survival but presence of low albumin & lymphopenia predicts poor CR and survival. Early RT (by d-60) improves response and survival, hence this is suggested rather than at end of chemotherapy. Optimum chemotherapy needs further studies.

ALK-NEGATIVE ANAPLASTIC LARGE CELL LYMPHOMA REPRESENT A DISTINCT ENTITY

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Introduction: Overexpression of anaplastic lymphoma kinase (ALK) has defined a clinically homogeneous group of anaplastic large cell lymphoma (ALCL) of T-cell type with good prognosis. It remains unclear whether
ALK-negative ALCCL also represents a distinct entity or solely a morphological variant of unspecified peripheral T cell lymphoma (pTCL-NOS).

Methods: 24 cases of ALK-positive, 22 cases of ALK-negative ALCCL and 18 cases of predominantly large cell-sized pTCLNOS were analyzed by immunohistochemistry for T-cell characteristic antigens, cytokytic molecules and clusterin. The results were compared with prospective survival data.

Results: Tumor cell morphology and a concomitant constant strong CD15 expression and lack of T-cell receptor molecules reliably separated ALCCLs from pTCLNOS, while expression of cytokytic molecules and clusterin were of no discriminative significance. Prospective freedom from relapse and over-all survival data separated ALK-positive ALCCLs while ALK-negative ALCCLs clustered with pTCLNOS.

Conclusion: Morphological and immunophenotypical evidence point out that ALK-negative ALCCLs represent an own disease group not to be lumped with pTCLNOS.

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AGGRESSIVE NK CELL LEUKEMIA IN SHANGHAI, CHINA

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Introduction: Aggressive natural killer cell leukemia (ANKL) is a rare neoplasm of NK cells associated with bone marrow failure and a dismal prognosis. Diagnosis is complicated by the lack of clonal markers and morphologic and immunophenotypic heterogeneity.

Methods: A series of 8 cases of ANKL presented over a 15 month period were diagnosed in a single laboratory analyzing morphologic, immunophenotypic, cytogenetic, fluorescence in situ hybridization (FISH) and molecular data.

Results: All cases presented with fever and 7/8 exhibited thrombocytopenia which was often severe. Lymphadenopathy was common. The median age was 41 (SD = 15) with males predominating over females 6 to 2. The tumor immunophenotype was CD2+, CD56+, CD16-, CD57, CD50+ which was accompanied by variable expression of HLA-DR. Complex cytogenetic abnormalities were found in 6/8 cases, including chromosomes 1q-, 3 or 6q- as well as i(7)(q10).

Conclusions: Results of this relatively large series diagnosed in a single laboratory confirm that ANKL is a distinct diagnostic entity and provide an opportunity to study this rare and aggressive neoplasm.

HIGH EFFICACY OF THE VIP / ABVD REGIMENT FOR THE TREATMENT IN FIRST LINE OF NON EPIDERMOTROPIC PERIPHERAL T CELL LYMPHOMA (PTCL). UPDATE OF A RETROSPECTIVE MONOCENTRIC STUDY

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Introduction: Today there is no international consensus for the treatment of PTCL. The estimated 5 years overall survival (OS) with CHOP like regimen is 40%. We present the updating results of a retrospective study reported on the French Haematology Society congress in 2000.

Patients and methods: Patients (pts) with PTCL were treated in first line from 1989 to 1999 with the VIP/ABVD regimen: VIP (Biotopdam 100mg/m²/d 1–3, Ifosfamide 1000mg/m²/d day 1–5, Cisplatin 20mg/m²/d day 1–5) and ABVD (Doxorubicin 50mg/m², Vinblastine 10mg/m², Bleomycin 10mg/m² and Dacarbazaine 375mg/m² at day 1 and day 14). 6 alternating schemes were distributed before an involved field irradiation of 25 Gy on the initial sites > 5 cm.

Results: 58pts were diagnosed as PTCL (20 ALCCL and 38 nonALCCL). Median age was 51 y (22–82), 57% were in st III-IV, 38% with IPT-2. The CR rate is 89% and 85% of patients didn’t relapse. With a median FUP of 7 years, the 5 years OS is 71% (ALCCL = 85%, nonALCCL = 63%) and DFS is 67% (ALCCL = 85%, nonALCCL = 65%). The best predictive factors are histology and age. The IPI score was not.

Conclusion: This study has shown an important efficacy of VIP-ABVD for PTCL. The French GOELAMS group have led from 1996 a prospective randomised trial to compare the CHOEP21 regimen to the VIP/ABVD.

PRELIMINARY RESULTS OF TREATMENT WITH PEGYLATED LIPOSOMAL DOXORUBICIN, BLEOMYCIN, VINCBLASTINE AND DACARBazine IN ADVANCED CUTANEOUS LYMPhomas

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Introduction: The efficacy and low toxicity of PEGylated Liposomal Doxorubicin as a single agent in second-line therapy of Cutaneous T-Cell Lymphoma was recently demonstrated. In our study we tested the safety and efficacy of PEGylated Liposomal Doxorubicin (Caelyx®) in the treatment of advanced Primary Cutaneous Lymphoma (PCL), in association with three drugs of proven effectiveness in nodal lymphoproliferative and other primary cutaneous neoplastic disorders: Bleomycin, Vinblastine and Dacarbazine (CBVD).
Methods: From February 2003 to October 2004 we observed 15 consecutive patients (pts) with advanced PCL (13 cutaneous T-cell lymphomas, 2 cutaneous B-cell lymphomas), who have relapsed or are refractory to previous topic or systemic treatments. Pts received CBVD therapy, Pegylated Liposomal Doxorubicin, Bleomycin (Cycllex®) 12 mg/m², Bleomycin 10 mg/m², Vinblastine 6 mg/m², Dacarbazine 375 mg/m² at days 1 and 15, that was administered intravenously (i.v.) every 4 weeks for 6 cycles.

Results: Three out of 12 evaluated pts (25%) had a PD: two pts with Sezary Syndrome (SS) after two CBVD cycles and one pt with Anaplastic Large-Cell Lymphoma (ALCL) CD30+ evolved from a SS after four cycles. Nine of the 12 pts (75%) obtained a Complete Response (CR) with the disappearance of cutaneous and nodal lesions and systemic symptoms (itching, fever, weight loss). One of the pts in CR presented a relapse at the seventh month. One pt died due to a cerebrovascular accident in the 11th month of CR. Seven out of 9 pts are in CR after a median observation of 9 months (range 4-20 months). Two pts in the 7th month of CR were submitted to allogeneic stem cell transplantation and conserve their CR 8 and 3 months respectively from the transplant. The CBVD therapy was well tolerated. No pt presented cardiac or mucosal toxicity, nor alopecia or palmar-plantar erythrodysesthesia. Two pts presented neutrophils count below 500/μl and 1 of them had a severe bacterial pneumonia which was resolved with i.v. antibiotics.

Conclusions: The CBVD association is an effective and safe therapy for advanced PCL. The CR rate and duration, at this moment, are comparable to that reported in pts with similar characteristics.

FRONT-LINE AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) IMPROVES THE OUTCOME OF PERIPHERAL T-CELL LYMPHOMA (PTCL) IN FIRST REMISSION PATIENTS PRESENTING WITH UNFAVORABLE PROGNOSTIC FACTORS

Introduction: PTCL is a heterogeneous group of aggressive lymphomas associated with a poor prognosis with standard chemotherapy. Moreover, most of pts who achieve a complete response (CR) relapse of their disease. Consolidation with ASCT may decrease the relapse rate and eventually improve the survival. We aim to describe the impact of consolidation with ASCT in 75 pts transplanted in first CR inside the GELTAMO cooperative group.

Methods: Median age was 46 years (15-69), 29% had Anaplastic large cell lymphoma, 88% or pts presented advanced (III-IV) AA stage, 52% had B symptoms, 48% high LDH, 36% bulky disease, 65% had 2 or 3 risk factors of the a-IP; 49% presented a high Tumor Score and 15% more than 2 adverse factors of the PIT (Prognostic Index for PTCL; Gallamini et al., Blood, 2004, 103, 2474). Conditioning regimens were based on BEAM or modified in 73% of the cases.

Results: With a median follow-up of 62 months for alive pts, the 5 year overall survival (OS) and Event free survival (EFS) were 69% and 65% respectively. The Cox proportional hazard regression analysis showed that the only factor associated with a shorter survival and EFS was the presence of ≥2 risk factors of the PIT risk system (P = 0.0027).

Conclusions: In a retrospective study with a prolonged follow-up, consolidation with ASCT in complete responder patients with PTCL who presented unfavorable prognostic factors at diagnosis, increased substantially the Survival and the EFS of these group of pts. The PIT risk system identifies 15% of complete responders pts with poor prognosis who do not benefit from this ASCT consolidation, thus other innovative therapy is warranted.

LASPARAGINASE AND PEG-ASPARAGINASE: ACTIVITY IN REFRACTORY T-CELL LYMPHOMA
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L-Asparaginase has been little tested in non-lymphoblastic lymphomas in adults. Recent case reports from Asia have indicated activity in N/T K cell NHL salvage regimens, but a specific role in T-cell lymphomas has not been established. At this centre, 4 patients with refractory T-cell NHL of varying histology have been treated with L-asparaginase as a single agent. In two there was definite but transient regression of skin lesions before early progression at skin and other sites. In two other patients there have been major responses. Case 1: A 36 y old woman presented with painful ulcerating cutaneous involvement of trunk and limbs. Histology was consistent with high grade peripheral T-cell NHL with focal CD56 positivity. The disease was resistant to CHOP with frank progression in skin and development of new B-symptoms during cycle 5. However complete resolution of skin lesions occurred within 2-3 weeks of l-asparaginase 10MU/m² im daily ×10. She was rechallenged at subsequent relapse with PEG-asparaginase 2MU/m²×4 (day 1,15, 29 &43) achieving rapid and continuing CR. Case 2: A 68 y old woman with extensive N/K T-cell NHL (nasal type) involving palate, skin & lung attained PR to ‘CHOP-like’ weekly chemotherapy (PmiciBEO) but relapsed with progressive disease in lung and skin after only 3 months. 10MU/m²×10 day L-asparaginase led to resolution of skin lesions and improvement of lung infiltrate seen on CT. Stable response still continues at 12 months. These observations suggest that these well tolerated agents may have a role in palliative or maintenance therapy for certain T-cell NHL subtypes and speculative may enhance the activity of radical conventional therapy given with curative intent. The possible predictive value of asparagine synthetase measurement in T-cell NHL tissue is currently being explored.

TEMOZOLOMIDE TREATMENT IN PRETREATED MYCOSIS FUNGOIDES: EXPERIENCE IN 9 PATIENTS
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Introduction: To evaluate the efficacy and toxicity of temozolomide, an oral alkylating agent of the imidazotetrazine derivates with a low-toxicity profile and activity in solid tumors, in patients with relapsed or refractory mycosis fungoides (MF).
Methods: Between July 2003 and March 2004 in our institute, 9 previously treated patients with MF were enrolled into a phase II trial and treated with temozolomide. This drug was given orally every four weeks for a total of three cycles at the following doses: for the first cycle at a dose of 150 mg/m²/day per os for 5 consecutive days, and then for the second and the third course at a dose of 200 mg/m²/day for 5 consecutive days.

Results: Of the 9 patients, one (11%) achieved complete response (CR), 2 (22%) partial responses (PR), 3 (33%) stable disease, and the remaining 3 showed no benefit from the treatment. The duration of response was 4 months (for CR patient) and 3 and 6 months (for PR patients, respectively). Treatment was well tolerated: hematologic toxicity was mild; nausea/vomiting was mild and no organ toxicity was recorded.

Conclusions: The results of the present phase II study show activity of temozolomide as a single agent in patients with heavily pretreated MF. Further studies that use temozolomide alone or in combination with other drugs in earlier stages of the disease are needed.

AIDS-RELATED B-CELL LYMPHOMA (ARL): CORRELATION OF PROGNOSIS WITH DIFFERENTIATION PROFILES ASSESSED BY IMMUNOPHENOTYPING

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Aims: There is limiting data on immunohistochemical expression profiles in ARL and their relation to clinical course.

Methods: Paraffin embedded sections of 89 cases diagnosed with ARL during 1989–2004 were stained immunohistochemically with antibodies for CD3, CD10, CD20, CD38, CD138/Syn-1, MUM1/IRF4, BCL-2, BCL-6, LMP-1 and Ki-67. Results were correlated with clinical course.

Results: Expression of CD10 and CD20 were associated with better overall survival (OS, P = 0.009 and P = 0.04, respectively). Expression of CD20 was associated with better disease-free survival (DFS, P = 0.03), whereas expression of CD138/Syn-1 was associated with worse DFS (P = 0.03). OS and DFS were worse in patients with immunophenotypic profiles indicating a post-germinal center (GC) differentiation when compared to GC differentiation. Controlled for age-adjusted International Prognostic Index, prior AIDS and year of ARL diagnosis, expression of CD20 and CD10 were associated with improved OS (HR 95% CI): 0.3 (0.1–0.8) and 0.6 (0.3–1.2). CD10 expression was associated with a preserved immunocompetence. CD20 expression was less frequent in patients treated with highly active antiretroviral therapy (HAART) compared to patients without HAART (P = 0.04).

Conclusion: Lack of CD20 or CD10 expression and a post-germinal center signature are associated with worse prognosis in ARL.