Session 7: aggressive lymphoma

071 MYC + AGGRESSIVE-B-CELL LYMPHOMAS: NOVEL THERAPY OF UNTREATED BURKITT LYMPHOMA (BL) AND MYC + DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) WITH DA-EPOCH-R

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Background: MYC translocations are associated with a high proliferation and poor outcome in B-cell lymphomas treated with CHOP-based regimens. In BL with MYC translocations, multi-agent intensive chemotherapy is effective but associated with significant toxicity and mortality. Recent reports indicate that 10% of DLBCLs also harbor MYC translocations and have a poor outcome with R-CHOP *(Savage et al. Blood 2009; 114: 3533)*. Thus, better treatment is needed for MYC+ lymphomas to improve outcome and reduce toxicity.

Materials and Methods: We hypothesized that DA-EPOCH-R may be effective in MYC+ aggressive lymphomas based on its efficacy in highly proliferative DLBCL *(Wilson et al. JCO 2008; 26:2717)* and prospectively evaluated it in untreated BL. We also did FISH analysis for MYC translocations using a Break Apart probe (Abbott Molecular) in untreated DLBCL treated with DA-EPOCH-R from 1 NCI (PI Wilson) and 1 CALGB study (PI Wilson). Tumors were scored + if >10% of cells had a break apart signal. Outcome of DLBCL was evaluated with respect to MYC status.

Results: Characteristics of 29 BL are median age 35 (16-88); male sex 22 (76%); median ECOG PS 1 (1-3); stage III/IV 17 (59%); LDH>N 15 (52%); extranodal disease 19 (65%); ileocecal disease 15 (52%), CNS disease 1 (3%) and HIV + 10 (34%). At a median follow-up of 57 months, EFS and OS are 97% and 100%, respectively; 1 patient received RT and remains in first remission. MYC translocations were found in 6 of 59 (10%) DLBCL cases. High-risk IPI scores, present in 50% and 36% of MYC+ and MYC- cases respectively, were not different (P=0.47; Cochran-Armitage test). All DLBCL cases were HIV negative. At a median follow-up of 48 months, the EFS of MYC+ and MYC- DLBCL is 83% and 76%, respectively (P=0.46; Exact two-tailed log-rank). Notable toxicities were tumor lysis syndrome (1 pt) and fever/neutropenia in 16% of cycles.

Conclusions: DA-EPOCH-R is a novel well-tolerated regimen that has an excellent outcome in BL. Preliminary analysis suggests that MYC+ does not convey a worse prognosis in DLBCL treated with DA-EPOCH-R; additional cases are being analyzed for MYC translocation. These results suggest DA-EPOCH-R is effective in MYC+ aggressive B-cell lymphomas. A confirmatory multicenter study of risk-adapted DA-EPOCH-R study is underway in BL and MYC+ DLBCL.

072 A RANDOMIZED MULTICENTRE PHASE III STUDY FOR FIRST LINE TREATMENT OF YOUNG PATIENTS WITH HIGH RISK (AAIPI 2-3) DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL): RITUXIMAB (R) PLUS DOSE-DENSE CHEMOTHERAPY CHOP14/MEGACHOP14 WITH OR WITHOUT INTENSIFIED HIGH-DOSE CHEMOTHERAPY (HDC) AND AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT). RESULTS OF DLCL04 TRIAL OF ITALIAN LYMPHOMA FOUNDATION (FIL)

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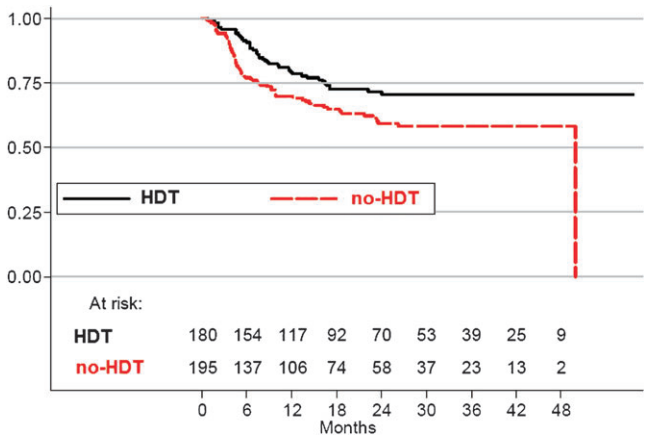
Background: The outcome of young DLBCL patients at high risk is not satisfactory with RCHOP. FIL conducted a multicenter randomized phase III trial, with a 2x2 factorial design, to compare two R-dose-dense chemotherapies, RCHOP14 (RC14) vs RMegaCHOP14 (RMC14), followed or not by HDC+ASCT (HDT).

Patients and Methods: The main hypothesis was to test an increase of 2-year Progression-Free-Survival (PFS) from 50% in the standard arm (no-HDT) to 65% in the experimental arm (HDT); secondary comparison was between the two dose-dense regimens. Inclusion criteria were: age 18-65; untreated DLBC; aaIPI 2-3. Patients were stratified according aaIPI and randomized at diagnosis to receive: RC14 x 8; RMC14 x 6 (1200 mg/m2 Cyclophosphamide, 70 mg/m2 Doxorubicin, standard Vincristine/Prednisone); RC14 x 4 + HDT (R + high dose Cytarabine + Mitoxantrone + Dexamethasone + BEAM and ASCT); RMC14 x 4 + the same HDT.

Results: From June 2005 to September 2010, 412 patients were enrolled and 399 were eligible: median age 49 (18-63); stage II/III/IV 6/29/65%; LDH >normal 89%, PS >1 43%, aaIPI 2/3 score 74/26%. At the time of this analysis, 375 are evaluable: 195 no-HDT and 180 HDT arm. Response rates were: CR 74%, PR 6%, NR 12%, toxic deaths 3% and 5% dropped out. Treatment-related deaths in no-HDT and HDT arm were: 2.6% and 3.3%. With a median follow-up of 23 months, 2-year PFS was 65% (95%CI:59-70). Two-year PFS for no-HDT vs HDT was: 59% (95%CI:51-57) vs 72% (95%CI:64-78), p .008 (Fig.1). Two-year PFS rates for RC14 vs RMC14 were superimposable. Two-year OS was 83% (95%CI: 78-87) with no differences between no-HDT and HDT. In a Cox-model, including the four arms, assuming RC14 as reference, the risk of relapse was significantly reduced mainly in RCHOP14+HDT arm (HR=0.47, 95%CI=0.27-0.81, p .007) with minor effect in RMegaCHOP14+HDT (HR=0.69, p .15) arm.

Conclusions: this randomized trial showed that HDT, as first line treatment in young high risk DLBCL, significantly reduced the relapse rate in comparison to standard RCHOP14. A more aggressive dose-dense chemotherapy does not seem to play a significant role. So far, this advantage in PFS does not translate in overall survival differences. A longer follow-up will further clarify the role of HDT as first line treatment in this poor-prognosis DLBCL patients.

072 Figure 1. 2-year PFS for no-HDT vs HDT



073 CONVENTIONAL CHEMOIMMUNOTHERAPY (R-CHOEP-14) OR HIGH-DOSE THERAPY (R-MEGA-CHOEP) FOR YOUNG, HIGH-RISK PATIENTS WITH AGGRESSIVE B-CELL LYMPHOMA: FINAL RESULTS OF THE RANDOMIZED MEGA-CHOEP-TRIAL OF THE GERMAN HIGH-GRADE NON-HODGKIN LYMPHOMA STUDY GROUP (DSHNHL)

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Background: Studies comparing high-dose therapy (HDT) with conventional first-line therapy for younger patients (pts) with aggressive B-cell lymphoma gave conflicting results. None of these studies combined HDT or conventional chemotherapy with Rituximab (R). We wanted to improve outcome for such pts by escalating dose and dose-intensity of drugs with proven efficacy in B-NHL.

Methods: In younger pts (< 61 yrs) with aggressive B-cell lymphoma, the study compared 8 cycles of CHOE(etoposide, 300 mg/m2)P - 14 to 4 courses of MegaCHOEP (cyclophosphamide 1500/4500/4500/6000 mg/m2; doxorubicin 70 mg/m2; vincristine 2 mg/m2; etoposide 600/960/960/1480 mg/m2; prednisone 500 mg) followed by repeated transplantation of autologous blood stem cells. All pts additionally received 6 infusions of R (375/ mg/m^2).

Results: Between 3/ 2003 and 4/ 2009 306 pts with CD 20-positive aggressive B-cell lymphoma were enrolled: 130 pts were randomized to 8 x CHOEP-14 plus 6 x R, 132 pts were randomized to 4 x MegaCHOEP plus 6 x R. 31 pts who did not receive R (non R arms were earlier closed) and 13 patients with missing data/withdrawn informed consent were excluded from this analysis. The median observation time for all patients (median age 47.5 years) with aggressive B-cell lymphoma and aaIPI 2 (73.3%) or 3 (26.7%) was 43 months. Treatment-related mortality was 5.6 % in the R-MegaCHOEP arm and 3.1 % in

the R-CHOEP-14 arm (p = 0.348). The overall response rate was 77.9 % (CR/CRu 75.1%, PR 2.8%). Three-year-progression-free survival (PFS) was 73.7% for pts treated with 8 x CHOEP-14 plus 6 x R compared to 69.8% in pts given 4 x MegaCHOEP plus 6 x R (p = 0.475). Three-year- overall survival (OS) was 84.6% in pts treated with 8 x CHOEP-14 as compared to 77.0 % in pts given 4 x MegaCHOEP plus 6 x R (p = 0.081). OS was significantly better for pts with aaIPI 2 who received conventional chemotherapy plus R (p = 0.013) while survival curves for pts with aaIPI 3 were superimposable.

Conclusions: Conventional chemotherapy (8 x CHOEP-14 plus 6 x R) resulted in excellent PFS (73.7 %) and OS (84.6%) representing the best results ever reported for young, high-risk pts. with aggressive B-cell lymphoma. Conventional therapy was significantly better than HDT/ ASCT in pts with aaIPI 2; no significant differences were seen overall and in pts with aaIPI 3. In the Rituximab era, HDT/ ASCT should no longer be considered standard first-line therapy for young, high-risk pts with aggressive B-cell lymphoma.

074 RANDOMIZED PHASE II STUDY OF R-CHOP PLUS ENZASTAURIN VERSUS R-CHOP IN THE FIRST-LINE TREATMENT OF PATIENTS WITH INTERMEDIATE AND HIGH-RISK DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) – PRELIMINARY ANALYSIS

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Background: The combination of rituximab plus CHOP chemotherapy (R-CHOP) is widely used as standard of care for DLBCL; however, long-term survival is low in patients (pts) with high International Prognostic Index (IPI) risk scores. Enzastaurin (ENZ) targets protein kinase C-β (PKCβ), an enzyme correlated with poor pt outcomes in DLBCL. In this trial, we compared the results of first-line treatment with R-CHOP + ENZ to standard R-CHOP.

Material and Methods: DLBCL pts were required to have intermediate or high risk IPI scores (2-5). Pts were randomized (3:2 ratio) to receive six 21-day cycles of either R-CHOP + ENZ therapy (Arm A) or R-CHOP alone (Arm B). After 6 cycles, responders in Arm A could continue single agent ENZ. An 1125 mg oral loading dose of ENZ was given on Day 2 followed by 500 mg ENZ daily. Response was evaluated (IWG criteria, 1999) q8 weeks. The primary endpoint was progression-free survival (PFS). Randomization of 100 pts allowed detection of an improvement in the PFS at 2 years from 65% (R-CHOP) to 80% with R-CHOP + ENZ (80% power, 1-sided alpha 0.2). This preliminary analysis was performed after all pts had completed R-CHOP chemotherapy, and had been followed for at least 1 year.

Results: Pt characteristics were comparable in Arm A (N=57) and Arm B (N=43). A total of 65 pts (65%) had either high-intermediate (44%) or high (21%) IPI risk scores. The median PFS has not yet been reached; however, the 1-year PFS rate for Arm A was 71% (CI 0.58, 0.84) and Arm B 52% (CI 0.35, 0.69). Overall response rates for Arms A and B were 80.4% and 83.3%, respectively; complete response rates were 35.7% and 26.2%. Most frequent grade 3/4 adverse events were neutropenia (56.1% vs 51.1%) and thrombocytopenia (17.5% vs 13.9%) (Arm A vs Arm B). In Arm A 23% and in Arm B 9.3% of pts had grade 3/4 infection-related complications. In Arm A 4 pts died (sepsis 2, pulmonary embolism 1, and ARDS 1) and in Arm B 3 pts (sepsis 2, pneumonia 1).

Conclusions: This preliminary analysis suggests an improvement in PFS and complete response rate for pts with intermediate or high risk DLBCL treated with R-CHOP + ENZ when compared to R-CHOP, with comparable toxicity profiles. Final analysis will be conducted after 2-year followup.

075 SALVAGE REGIMEN WITH AUTOLOGOUS STEM CELL TRANSPLANTATION WITH OR WITHOUT RITUXIMAB MAINTENANCE FOR RELAPSED DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL): CORAL FINAL REPORT

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Background: Chemotherapy followed by autologous stem cell transplantation (ASCT) is the standard treatment for relapsed DLBCL. No study has compared salvage therapies and evaluated maintenance post ASCT.

Methods: DLBCL CD 20+ in first relapse or pts refractory after first therapy were randomized between R ICE (rituximab, ifosfamide, etoposide, carboplatinum) or R DHAP (rituximab dexamethasone cytarabine cisplatinum). Responding patients received BEAM and ASCT then randomized between observation or maintenance with rituximab every 2 m for 1 yr (*Gisselbrecht J Clin Oncol; 2010).*

Results: Analysis was made on 477 pts (R ICE: 243 pts; R DHAP: 234 pts): 255 relapses >12m, 213 refractory/early relapses; 306 pts had prior rituximab; secondary(s) IPI 0-1: 281 pts; s IPI 2-3:181pts. There was no difference in response rate between R ICE 63.6% and R DHAP 64.3%. There was no difference between R ICE and R DHAP at 4 yrs for EFS (26% vs 37% p=0.2) and OS (43% vs 51%, p=0.3). Factors affecting 4 yrs EFS, PFS and OS were: prior treatment with rituximab; early relapse< 12 m; s IPI 2-3. ASCT was performed in 255 pts and 242 randomized for maintenance: 122 pts rituximab (R), 120 pts observation (O). Distribution between R/O arms were respectively: median age 54 /53 yrs, Male 76/83; female 46/37; secondary IPI 0-1: 84/81; sIPI 2-3: 36/36. 89/76 relapses >12m., 33/41 refractory/early relapses. Median follow up was 44 m with 111 events. 4 yrs EFS was 52.8 % (CI 46-59) with 63% (CI 56-69) OS. There was no difference in EFS, PFS and OS between R and O arms. In multivariate analysis, sIPI2-3 significantly affected EFS, PFS, OS (p=0.0004). Women (83pts) had a better 4 yrs EFS 63% than male (159pts) 37% (p=0.01). The difference was only in the R arm (p=0.004). Gender was an independent prognostic factor in the R arm. Toxicity was mild with 12% SAE versus 4% for R /O respectively.

Conclusions: There was no difference between R ICE and R DHAP and between post ASCT maintenance with R or O. Women did significantly better after ASCT with rituximab. Early relapses to upfront rituximab-based chemotherapy have a poor prognosis

076 AUTOLOGOUS STEM CELL TRANSPLANTATION REMAINS BENEFICIAL FOR PATIENTS RELAPSING AFTER R-CHOP AND WHO RESPOND TO SALVAGE CHEMOTHERAPY

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Background: The CORAL study (Gisselbrecht et al) recently demonstrated that salvage of pts with relapsed or refractory diffuse large B cell lymphoma (DLBCL) with 1 of 2 rituximab-containing regimens (R-DHAP or R-ICE) was less successful in those who had received rituximab as part of their 1° therapy, with objective responses in only 51% vs 83% in rituximab-naïve pts, & 3yr EFS of 21% vs 47%. Pts who responded (complete or partial response) proceeded to autologous stem cell transplantation (ASCT). Any possible similar impact of exposure to rituximab during primary therapy on post-transplant outcomes was not explored. We therefore looked to see if pts with relapsed/refractory DLBCL who received R-CHOP as induction chemotherapy & responded to salvage chemotherapy had a poorer outcome following ASCT compared with those who received CHOP alone. If so, alternative treatment strategies such as reduced-intensity allogeneic transplantation may need to be considered for this group of pts.

Materials and Methods: We undertook a retrospective analysis of pts receiving high dose BEAM chemotherapy followed by ASCT for relapsed/refractory DLBCL in our unit since 1994. All pts who received CHOP +/- rituximab as 1st-line therapy & who required ≤ 2 lines of salvage chemotherapy to demonstrate chemosensitivity were analysed.

Results: 105 pts were identified. 72 received CHOP as 1st-line therapy & 33 received R-CHOP. The groups were balanced for the number of refractory pts (35/72 vs 16/33, p= 1.00), the number of pts relapsing >12 months from completion of induction (18/72 vs 5/33, p= 0.32), & disease status at transplantation (CR in 24/72 vs 12/33, p=0.83). The median age at transplant in the CHOP vs R-CHOP group was 49 yrs (range 20-71) & 55 yrs (range 27-67) respectively. R-CHOP induced patients did not fare any worse after ASCT than CHOP induced pts. 5yr PFS & OS following ASCT was 51% & 64% respectively in the CHOP group compared to 72% & 73% in the R-CHOP group (p=0.41 & p=0.10 respectively). Only 8/36 (22%) pts who relapsed following ASCT went on to receive a reduced intensity allogeneic transplant.

Conclusions: Pts with relapsed/refractory DLBCL who received rituximab at induction but respond to salvage chemotherapy should be offered ASCT with the expectation that they fare no worse than patients who did not receive rituximab with their induction chemotherapy. However, it appears that only a small minority of pts who subsequently relapsed following ASCT could be effectively salvaged & efforts should be intensified to identify this group of pts pre-autograft & alternative treatments sought.