‘‘Focus on…’’ session: lymphoma in the elderly

104 EBV POSITIVE DIFFUSE LARGE B CELL LYMPHOMA OF THE ELDERLY IS AN AGGRESSIVE B CELL NEOPLASM WITH A POST GERMINAL CENTER B CELL PHENOTYPE AND CHARACTERIZED BY NFKB PATHWAY ACTIVATION. EVALUATION OF A WESTERN SERIES OF 47 CASES

S. Montes-Moreno[1], L. Odqvist[1], J. Diaz Perez[1], R. Pajares[1], J. García[1], M. Mollejo[1], C. Ruiz-Marcellan[1], M. Adrados[1], N. Ortiz[1], R. Franco[1], M. Piris[1]
[1]Lymphoma Group, Molecular Pathology Department, Spanish National Cancer Center (CNIO), Madrid, Spain

Background: EBV+ DLBCL of the elderly has been recently recognized as a provisional entity by the WHO. Little data in western countries are available. Here we have performed a retrospective clinical, histological and IHQ study in a series of 47 EBV+ DLBCL in elderly patients (mean age 69 years old (48-91)) retrieved from the consultation files of the CNIO in a period of 6 years.

Material and methods: HE, IHQ and ISH for EBV (EBER) were performed using conventional protocols and antibodies. Cases were classified according to the Cell of Origin (COO) using Choi's and Hans algorithms. Relevant clinical information was retrieved from referral centers.

Results: The series includes 31 male and 16 female. Most cases present at nodal locations (68%) while extranodal cases (32%) appeared in soft tissue, spleen, tonsil and gastrointestinal tract, among others. Morphologically most of the cases here studied show a polymorphic B cell rich population (46 cases) and areas of geographic necrosis (14 cases). All cases were CD20+ and commonly co-expressed CD30 (41/46) and very rarely CD15 (4/42). EBER was always positive and only 4 cases were negative for EBV-LMP1. Most cases belong to the NON-GC/ABC category by Hans (39 NON GC vs 2 GCB, 7 NV) and Choi's algorithms (27 ABC, 8 GCB, 13 NV). When compared to a control series of EBV- DLBCL cases (n 324) it is evident a shift towards a non-GC phenotype in EBV+DLBCL ($P < 0.001$). Overexpression of BCL2 and a high proliferation index (>50%) was found in 94% and 84% of the cases respectively. Both classical and alternative NFkB pathway related proteins p50 and p52 are overexpressed, respectively. 32 out of 37 cases evaluated showed nuclear expression of either p50 only (7/36), p52 only (4/36) or both (21/36) This increased NFkB activation is higher than the observed in the EBV-DLBCL control series ($P < 0.001$). Survival estimates using KM analysis demonstrate a poor OS and PFS for these patients (40% alive at median follow-up of 3 years and 24% without progression/dead at 3 years). When compared with EBV- DLBCL (n 240) these patients show shorter OS and PFS irrespective of age and COO phenotype (p log rank < 0.001).

Conclusions: Our results demonstrate that EBV+ DLBCL of the elderly is an aggressive B cell neoplasm that expresses a post GC B cell phenotype. This differentiation state is related with prominent classical and alternative NFkB activation which in turn is partially driven by EBV.

105 COMPREHENSIVE GERIATRIC ASSESSMENT-ADAPTED CHEMOTHERAPY IN ELDERLY PATIENTS (> 70 YEARS) WITH DIFFUSE LARGE B-CELL NON-HODGKIN'S LYMPHOMA (DLBCL): FINAL RESULTS AND LONG TERM FOLLOW-UP

U. Tirelli[1], L. Fratino[1], M. Balzarotti[2], L. Uziel[3], A. Giacalone[1], A. Ferreri[4], A. Santoro[2], M. Spina[1]
[1]Medical Oncology A, National Cancer Institute, Aviano, Italy, [2]Medical Oncology and Hematology, Humanitas Institute, Rozzano, Italy, [3]Hematology, San Paolo Hospital, Milan, Italy, [4]Oncology, San Raffaele Hospital, Milan, Italy

Background: R-CHOP is the standard treatment for elderly patients (pts) with DLBCL. Many pts aged 70 years (yrs) or more are unable to receive R-CHOP and the majority of them are excluded from clinical trials. Comprehensive geriatric assessment (CGA) is a useful instrument to predict the clinical outcome of elderly pts with cancer. Within the GOL (Gruppo Oncoematologico Linfomi) we started a phase II study aiming to evaluate feasibility and activity of a CGA-driven chemotherapy for elderly pts with DLBCL

Material and Methods: Pts with no comorbidity received CHOP/R-CHOP; pts with mild cardiopathy received epirubicin instead of doxorubicin; in pts with moderate/severe cardiopathy the use of anthracyclines was omitted; pts with diabetes did not receive prednisone; in pts with neuropathy vincristine was omitted. The dosage of chemotherapy was decided according to CGA: pts with a good score (ADL=6 and IADL>6) received full doses of CT; pts with an intermediate score (ADL=5 and IADL>4) received 75% of the dose; pts with a poor score (ADL<5 and IADL<5) received 50% of the dose.

Results: One hundred pts (41 males and 59 females) have been treated. The median age was 75 yrs and stages III-IV were diagnosed in 51% of pts. Sixty-one percent of pts received full doses of CT; 25% received 75% of dose and 14% received 50% reduced dose; 86% of pts received an anthracycline and 54% rituximab. Toxicity was quite acceptable. Grade 3-4 neutropenia was observed in 30% of pts, mucositis in 12%, and peripheral neuropathy in 9%. Four toxic deaths were observed. Overall, 81% of pts achieved complete remission; with a median follow-up of 50 months, 20% of them have relapsed. The 5 yr-OS, DFS, EFS are 58%, 78% and 50%. It is remarkable that the 5-year specific survival is 72%.

Conclusions: Our results demonstrate that a CGA-driven approach is feasible in elderly pts with DLBCL. This strategy allows offering a curative approach to all pts with aggressive NHL, avoiding to under treating pts with a potentially cured disease or over treat pts with severe comorbidities.

106 R-CHOP14 COMPARED TO R-CHOP21 IN ELDERLY PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL): RESULTS OF THE SECOND INTERIM ANALYSIS OF THE LNH03-6B GELA STUDY

R. Delarue[1], H. Tilly[2], G. Salles[3], L. Fornecker[4], N. Mounier[5], M. Fournier[6], T. Molina[7], S. Bologna[8], H. Ghesquieres[9], S. Picard[10], C. Haioun[11], A. Bosly[12]
[1]Hematology, Hopital Necker, Paris, France, [2]Hematology, Centre H. Becquerel, Rouen, France, [3]Hematology, CH Lyon Sud, Pierre Benite, France, [4]Hematology, Hopital Saint Louis, Paris, France, [5]Hematology, CHU, Nice, France, [6]Biostatistics, GELARC, Pierre Benite, France, [7]Pathology, Hotel Dieu, Paris, France, [8]Hematology, CHU, Nancy, France, [9]Hematology, Centre L. Berard, Lyon, France, [10]Clinical Research, GELARC, Pierre Benite, France, [11]Hematology, Hopital H. Mondor, Creteil, France, [12]Hematology, UCL Mont-Godinne, Yvoir, Belgium

Introduction: In 2000, the GELA established a standard for elderly pts with DLBCL, demonstrating survival advantage of R-CHOP21 over CHOP21. Based on RICOVER-60 results, the DSHNHL proposed R-CHOP14 as a standard. We report the results of the second interim analysis of the randomized phase III trial LNH03-6B, comparing both regimens, with a median follow-up of 44 months.

Methods: Pts between 60 and 80 years old with DLBCL and aaIPI≥1 were eligible. They were randomized between R-CHOP14 and R-CHOP21 for 8 cycles. G-CSF prophylaxis was given according to physician decision. Primary objective was to evaluate the efficacy of R-CHOP14 compared to R-CHOP21 as measured by the EFS.

Results: 602 pts were randomized, 600 were evaluable, 304 with R-CHOP14 and 296 with R-CHOP21. Median age was 70 years. Pts characteristics were similar in both arms. Percentage of pts with baseline IPI3-5 was 72% in R-CHOP14 arm and 78% in R-CHOP21 arm. Median interval between 2 cycles was 14 d in R-CHOP14 arm and 21 d in R-CHOP21 arm. In R-CHOP14 arms, 89% of cycles were administered with G-CSF. Median dose-intensity for R-CHOP14 arm was 88% for cyclophosphamide and doxorubicin. There was no difference in median dose-intensity according to G-CSF administration at first cycle. Response rate (CR+CRu) was 72% in R-CHOP14 arm and 75% in R-CHOP21 arm (p=0.42). The 3-y EFS was 57% in R-CHOP14 arm and 60% in R-CHOP21 (HR 1.03; CI95% 0.81-1.31; p=0.81). Similar trend was observed for 3-y PFS (60% vs 62%; HR 0.98; CI95% 0.77-1.26; p=0.89) and 3-y OS (70% vs 72.6%; HR 0.98; CI95% 0.74-1.30; p=0.89). There was no PFS difference according to dose-intensity. Grade 3-4 toxicities were similar in both arms with the exception of neutrophils and hemoglobin toxicities, more frequent in R-CHOP14 arm leading to higher rate of red cell transfusions (47% vs 32%). In contrast, platelet toxicity was more common in R-CHOP21 arm. Median number of nights of hospitalization was 9 in R-CHOP14 arm and 7 in R-CHOP21 arm.

Conclusion: Results of this second interim analysis did not support the hypothesis of higher efficacy of dose dense R-CHOP14 over R-CHOP21.

107 EFFICACY AND TOLERABILITY OF ABVD AND STANFORD V FOR ELDERLY ADVANCED-STAGE HODGKIN LYMPHOMA (HL): ANALYSIS FROM THE PHASE III RANDOMIZED US INTERGROUP TRIAL E2496

A. M. Evens[1], F. Hong[2], L. I. Gordon[3], R. I. Fisher[4], N. Bartlett[5], J. M. Connors[6], H. Wagner[7], M. Gospodarowicz[8], B. D. Cheson[9], R. Advani[10], B. S. Kahl[11], R. T. Hoppe[12], S. J. Horning[13]
[1]Hematology/Oncology, University of Massachusetts, Worcester, United States, [2]ECOG Statistical Center, Harvard University, Boston, United States, [3]Hematology/Oncology, Northwestern University, Chicago, United States, [4]James P Wilmot Cancer Center, University of Rochester, Rochester, United States, [5]Oncology, Washington University, St. Louis, United States, [6]Centre for Lymphoid Cancer, BC Cancer Agency, Vancouver, Canada, [7]Radiation Oncology, Penn State Cancer Institute, Hershey, United States, [8]Radiation Oncology, Princess Margaret Hospital, Toronto, Canada, [9]Hematology/Oncology, Georgetown University Hospital, Washington DC, United States, [10]Medical Oncology, Stanford University, Stanford, United States, [11]Hematology/Oncology, University of Wisconsin, Madison, United States, [12]Radiation Oncology, Stanford University, Stanford, United States, [13]Clinical Development, Genentech, Inc., San Francisco, United States

Background: Survival rates for elderly patients (pts) (≥60 years) with HL are disproportionately inferior to those achieved by younger pts. Historically, 5-year

failure free survival (FFS) rates for advanced-stage elderly HL pts have ranged from 30-50% versus 70-85% for younger pts. Potential explanations for this discrepancy include inadequate workup/staging, co-morbidities precluding delivery of chemotherapy, treatment-related toxicities, and biology of disease. Notably, there remains a lack of prospective data studying ABVD, or newer regimens such as Stanford V, in advanced-stage elderly HL in the modern era.

Methods: We analyzed the outcomes and tolerability for pts ≥ age 60 years with advanced-stage HL treated in E2496. Pts were randomized to receive chemotherapy (CT) with ABVD x 6–8 cycles with radiotherapy (RT) for bulky mediastinal disease or the Stanford V regimen (12 weeks of CT and RT 36 Gy to sites > 5 cm). The primary endpoint was FFS, defined as time to either progression/relapse or death. The t-test or Fisher's exact test was used to compare pt characteristics and response rates; the stratified log-rank test was used for FFS and overall survival (OS).

Results: Of 812 eligible pts enrolled, 43 were ≥ 60 years of age (n=23 ABVD and n=20 Stanford V). Pt characteristics between CT arms were balanced; data for the 43 elderly pts included: median age 65 (60-83 years); stage: II 7%, III 69%, IV 23%; B symptoms 47%; and IPS ≥ 4 16%. Several differences were noted comparing pts ≥ 60 vs < 60 years: mixed cellularity cell type (35% vs 13%, respectively, p=0.0004, OR=3.52) and ECOG PS 0 (35% vs 58%, respectively, p=0.004, OR=0.38). CT dose modifications, as required by protocol, were common with 84% of all elderly pts having at least 1 dose reduction. CT was tolerated relatively well; besides neutropenia, there were 11 total grade 4 toxicities (dyspnea n=3, motor and sensory neuropathy n=2 each, hypoxia n=1, constipation n=1, infection n=1, myalgia n=1). The treatment-related mortality rate was 5% (n=1 pulmonary with ABVD and n=1 infection with Stanford V). Among all elderly pts, overall response rate (ORR), complete response (CR), FFS, and OS did not differ between CT arms. Therefore, treatment arms were pooled and stratified for an exploratory analysis comparing outcomes in pts ≥ 60 vs <60 years. The ORR (70% vs 78%, respectively, p=0.19) and CR rates (65% vs 71%, respectively, p=0.49) did not differ for elderly pts compared with non-elderly pts; however, 3- and 5-year FFS and OS were significantly inferior for elderly pts (Table 1).

Conclusions: ABVD and Standford V had comparable efficacy and tolerability among elderly advanced-stage HL pts. When comparing elderly vs non-elderly HL pts in the comtemporary era this trial was conducted, we observed similar ORR and CR rates, but inferior FFS and OS. These observations suggest a potential difference in disease biology, underscoring the continued need for novel therapeutic approaches for elderly HL.

Table 1. Survival comparisons.

Survival	Elderly (≥ 60 years) n=43 %	Non-Elderly (< 60 years) n=769 %	Log rank p
3-year FFS	55	76	0.0014
5-year FFS	46	74	
3-year OS	69	93	<0.0001
5-year OS	56	90	

108 AUTOLOGOUS STEM CELL TRANSPLANT IS FEASIBLE IN VERY ELDERLY PATIENTS WITH LYMPHOMA AND LIMITED COMORBIDITY

R. L. Elstrom[1], P. Martin[1], T. B. Shore[1], R. R. Furman[1], J. Ruan[1], R. N. Pearse[1], M. Coleman[1], T. Mark[1], J. P. Leonard[1], U. Gergis[1]
[1]*Medicine, Weill Cornell Medical College, New York, United States*

Introduction: In patients with lymphoma for whom initial therapy is not curative, high dose therapy followed by autologous stem cell transplant (autoSCT) may offer long term survival. Because of potential toxicities, elderly patients are often not considered candidates for autoSCT, and data regarding feasibility in patients 69 or greater are lacking.

Methods: The stem cell transplant database at Weill Cornell Medical College was reviewed to identify patients with a diagnosis of lymphoma aged 69 or greater who had undergone autoSCT. Baseline Charlson comorbidity index (CCI) and stem cell transplant comorbidity index (HCT-CI) were correlated with outcome.

Results: Twenty-one patients age 69 or greater (range 69-86, median 71) who underwent autoSCT for treatment of lymphoma were identified. Two patients underwent total body irradiation-based conditioning, while 19 patients underwent conditioning with chemotherapy alone. Sixteen patients underwent autoSCT in first relapse with chemotherapy sensitive disease, 2 patients had primary refractory lymphoma, 2 were in 2nd or greater relapse, and one patient was in first complete remission (CR). Sixteen patients (76%) achieved CR following autoSCT, while 3 patients did not achieve CR; 2 patients died before response assessment could be undertaken. With median follow up 23 months, median progression-free survival (PFS) following autoSCT was 8 months and median overall survival (OS) was 18 months. Age was associated with PFS (HR 1.18, p=0.05, 95% C.I. 1.05-1.33) but not OS (HR 1.11, p=0.09, 95% C.I. 0.98-1.25). Time to neutrophil engraftment was not predictive of OS. Eight of 18 patients with adequate follow up (44%) remained in remission for at least 18 months post-transplant. CCI and HCT-CI were calculated for all patients. Two patients died on day 8 of transplant; both were high risk by HCT-CI, while one was high risk and the other intermediate risk by CCI. Two other patients died of treatment-related causes (TRM) at approximately 100 days post-transplant; one was high risk by HCT-CI and intermediate risk by CCI, while the other was low risk by both indices. HCT-CI was a better predictor of OS than CCI, with HR 3.41 (p<0.01) for HCT-CI, and HR 2.12 (p=0.16) for CCI.

Conclusion: Autologous stem cell transplantation is feasible and of potential benefit in selected elderly patients with lymphoma. Age alone need not exclude patients with good functional status and limited comorbidity.