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Intensive chemotherapy improves the outcome in adolescents and young adults (AYA) with germinal center B-cell-like type diffuse large B-cell lymphoma (DLBCL)

S. Semochkin[1]*, M. Bobkova[1], V. Ivanova[2], T. Perestoronina[1], V. Ptushkin[1]. [1]*Federal Scientific Clinical Center of Pediatric Hematology, Oncology and Immunology, Department of Adolescent and Adult Hematology, Moscow, Russia,* [2]*City Clinical Hospital n.a. S.P. Botkin, Department of Hematology, Moscow, Russia*

DLBCL is a biologically heterogeneous disease. Depending on a gene expression profiling of DLBCL has revealed a molecular subtypes that include germinal center B cell-like (GCB) and activated B cell-like (ABC or non-GCB). The prognosis of pediatric DLBCL mostly GCB has improved since short intensive multi-agent chemotherapy regimens like NHL-BFM 90 was introduced. We hypothesized that AYA with the GCB DLBCL may benefit of such treatment. The purpose of this study was to determine the efficacy of NHL-BFM 90 protocol for AYA with DLBCL.

Materials and methods: From 10.1998 to 04.2008, 28 (m – 14, f – 14) patients (pts) with de novo DLBCL were treated with 6 chemotherapy cycles similar to those in NHL-BFM 90. Before 2006, 18 pts received a modified treatment cycles with the reduction of methotrexate (1 g/m2/36h instead 5 g/m2/24h). Since 2006, 10 pts received therapy on a national pediatric protocol B-NHL 2004M. This protocol differed from BFM by adding rituximab 375 mg/m2 on the first day of each cycle and reduction of methotrexate doses only in the first 2 cycles (1 g/m2/24h instead 5 g/m2/24h). The cases were classified as GCB or non-GC by immunohistochemistry (Hans, 2004).

Results: Median age pts was 21.0 years (range, 15–38). 24 (86%) pts were diagnosed in advanced (III-IV) stages. The molecular subtypes of DLBCL were evaluated for 16 pts: 8 (50%) classified as GCB and 8 (50%) – non-GCB. Complete response (CR) achieved 8 (100%) pts with GCB and 5 (63%) pts with non-GCB ($p > 0.05$). 5y-EFS was 1.0 (SE 0.0) vs. 0.50 (SE 0.18) respectively ($p = 0.046$). 5y-OS was 1.0 (SE 0.0) vs. 0.50 (SE 0.23) respectively ($p = 0.071$). Median follow-up was 3.4 years. The GCB and non-GCB group did not differ in their international prognostic index scores, presence of bulky disease and frequency of rituximab treatment.

Conclusions: AYA with immunohistochemically determined GCB-type DLBCL have an improved prognosis as a result of intensive BFM-like therapy in contrast to non-GCB.

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177Lu-Anti-CD20 monoclonal antibody: Labeling and biologic evaluation

E. Riva[1]*, P. Audicio[2], M. Tassano[2], M. Fernandez[2], G. Castellanos[3], P. Cabral[2], P. Oliver[2], H. Balter[2]. [1]*Hospital de Clínicas, Department of Hematology, Montevideo, Uruguay,* [2]*Nuclear Investigation Center (CIN), Department of Radiopharmacy, Montevideo, Uruguay,* [3]*Cordoba University, Department of Physics, Cordoba, Argentina*

Anti-CD20 monoclonal antibody (Mab) is used for the treatment of CD20+ NHL. Its labeling with ß-emitters increase therapeutic effectiveness. Lutetium 177 (T1/2 6.7 d), is a ß- and γ-emitter whose properties allow the analysis of in vivo biodistribution. Mab (Mabthera ®) was conjugated with 3 μmol of DOTA-Ossu and incubated 18 hours at 4ºC, then purified by G-25. Conjugated DOTA-Mab were stored at 4 and –20ºC for stability evaluation. Labeling was performed by addition of 7 mCi of 177 Lu and 1 mg of gentisic acid to 500 μg of Mab-DOTA, incubated 30 min at 37ºC and purified by G25. Stability of 177Lu-Mab in human and saline serum was analyzed by 2 chromatographic systems: ITLC-SG and ITLC-SG strips (BSA 5%) with EtOH-NH4OH-H2O (2:1:5) and Sodium acetate 14% as mobile phase, respectively. Biodistribution studies were carried out in normal mice ($n = 3$) at 4, 16 and 24 hours post injection of 1.1 mCi of Mab-DOTA-177Lu. Immunoafinity was tested in leucocyte membranes extracts. Biodistribution studies were done at same conditions using 150 mg/m2 and 250 mg/m2 of unlabelled Mab. Dosimetric studies were done by Monte Carlo Simulation. Labeling yields of 75% and radiochemical purity (Rqp) >97% after purification for up to 24 hours, both in human and saline serum. Rqp and stability of labeled Mab at 4ºC and –20ºC showed no differencies. Immunoafinity assays confirmed that its activity against CD20 was not affected. Biodistribution of cold Mab showed hepatic uptake (40%) and urinary elimination (30%) at 24 hours. Studies with cold Mab showed significant decrease in the uptake of 177Lu-Mab by blood cells and liver tissue. At theoric dosimetric studies, 83% of the total administered dose was deposited in the tumor mass. This methodology is suitable for the labeling of 177Lu-Mab giving reliable results that make it adequate as a therapeutic radiopharmaceutical.

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High-resolution genomic profiling of 533 B-cell lymphomas defines distinct tumor signatures, genomic aberrations correlated with outcome and pathogenetic subgroups

M. Boi[1]*, I. Kwee[1], C.P. Campos[1], T.C. Greiner[2], W.C. Chan[2], G. Gaidano[3], G. Bhagat[4], M. Ponzoni[5], E. Zucca[1], F. Bertoni[1]. [1]*Oncology Institute of Southern Switzerland (IOSI), Laboratory of Experimental Oncology and Lymphoma Unit, Bellinzona, Switzerland,* [2]*University of Nebraska, Department of Pathology and Microbiology, Omaha, NE USA,* [3]*Avogadro University of East. Piedmont, Division of Hematology, Department of Clinical and Experimental Medicine & BRMA, Novara, Italy,* [4]*Columbia University, Departments of Pathology and Genetics & Development, New York, USA,* [5]*San Raffaele H Scientific Institute, Pathology Unit and Unit of Lymphoid Malignancies, Milan, Italy*

High-resolution genomic profiling of 533 B-cell lymphomas defines distinct tumor signatures, genomic aberrations correlated with outcome and pathogenetic subgroups. To identify recurrent patterns of lesions affecting individual genes and/or pathways, we conducted a bioinformatic analysis of recurrent copy number aberrations (CNA) in a large series of B-cell tumors analyzed with high-resolution arrayCGH at our Center. Genomic profiles were obtained, with the Affymetrix Genechip Mapping 250K Array, in 533 B cell tumors, including 167 DLBCL, 134 splenic MZL, 57 MALT lymphomas, 44 post-transplant DLBCL (PT-DLBCL), 25 nodal MZL, 24 HIV-related DLBCL and other histotypes (82). The in-house developed modified mBPCR method was used to estimate the CN. Differences in recurrent minimal common regions (MCR) frequencies between subgroups were evaluated with Fisher's exact test and multiple test correction. Unsupervised clustering was performed with an in-house optimized version of the NMF algorithm. To evaluate the impact of the genetic aberrations on survival, univariate analysis was performed. Interstitial deletions affecting fragile sites were more common in immunodeficiency-related DLBCL, which lacked del(13q14) and had less 18q gains. PT-DLBCL had also less 3q gains and LOH at 6q21-q22 and at 6p21. MALT lymphoma was characterized by gains at 6p25, gains affecting chromosomes 3 and 18, and losses at 6q and 1p. Splenic MZL was associated with losses at 7q, 8p and 17p. Del(8p), alone or associated with del (17p), was identified as the only CNA determining a worse outcome in different diseases (DLBCL, splenic MZL). Unsupervised clustering identified the main lymphoma histotypes. The prognostic relevance of new DLBCL and splenic MZL clusters is being evaluated and will be presented. Distinct genomic profiles characterizing a number of lymphoid malignancies and CNA determining a poor outcome were identified using arrayCGH.