**ABSTRACT**

**Introduction:** Diffuse large B-cell lymphoma (DLBCL) is a heterogeneous subtype of non-Hodgkin lymphoma varied with clinical, immunophenotypic and genetic features. Anthracycline is considered as the key cytotoxic agent of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone). However, whether anthracycline dose intensification can improve the prognosis needs to be addressed.

**Methods:** In this phase III randomized trial, we assigned 400 patients with untreated DLBCL between the age of 16 and 60 years to receive six courses of regimen on a 21-day basis, at either the standard dose (doxorubicin 50 mg/m², R-CHOP50 or epirubicin 70 mg/m², R-CEOP70) or a high dose (epirubicin 90 mg/m², R-CEOP90), followed by additional two cycles of rituximab consolidation. The primary end point was progression-free survival. Moreover, whole genomic sequencing (WGS) and whole exome sequencing (WES) were performed on tumor samples of 28 and 63 patients, respectively.

**Results:** In the intention-to-treat analysis, R-CEOP90 resulted in higher 2-year progression-free survival rate than R-CHOP50/R-CEOP70 (90.3% vs 82.2%, P = 0.016). The rates of serious adverse events were similar among the three groups. Median follow-up was 24.2 months. In subgroup analysis, good R-IPI and germinal center B-cell origin benefited from intensified anthracycline dose. As revealed by WGS/WES, frequent mutated genes (>5%) were enriched in pathways as previously reported by Western population (ASH abstract. Blood 2016 128:152): NOTCH (CTBP2, MAML2, DTX1, NOTCH2, SGK1, NCOA2), TP53 (TP53, FAS, TP73), JAK-STAT (PIM1, SOCS1, STAT3), epigenetic (KMT2D, ARID1A, TET2, CREBBP/EP300, TAF1), BCR (CD79B/CD79A, NFKBIE, CARD11, LYN), toll-like/TFN receptor (MYD88, TNFAIP3, TRAF2), PI3K (KLF2, MTOR, RAG1, FoxO1, BCL2L11, GNA13), MAPK (FGFR3, DUSP2, ETS1), B-cell differentiation (PRDM1 and IRF4), immune surveillance (B2M, HLA-B, CIITA, CD58) and cell cycle (ATM, MYC, CCND3). Two novel pathways were identified: TCR/NK-mediated cytotoxicity (NFATC1 and KIR2DL1) and EBV/HHV infection (DDX3X and HSPG2). Pathway-specific genes less frequently observed than Western population (<5%) were NOTCH (NOTCH1, NOTCH3, FBXW7), JAK-STAT (STAT6), epigenetic (EZH2 and MEF2B), BCR (BCL10, PRKCB, MALT1), PI3K (ID3, TCF3, PTEN, PIK3CD, PIK3R1, PIK3CA), MAPK (BRAF, MAP4K1, KRAS, MAP3K7), B-cell differentiation (BCL6 and IRF8) and cell cycle (CDKN2A, CDK6, RB1). Clinical relevance study on gene mutations was ongoing.

**Conclusions:** This is the first prospective study on anthracycline dose intensification in Chinese DLBCL cohort. High-dose epirubicin improved progression-free survival in young adults with DLBCL. Significant difference in gene mutation pattern was observed between Chinese and Western population. (ClinicalTrials.gov number: NCT00049517).

**Keywords:** anthracycline; diffuse large B-cell lymphoma (DLBCL)

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**189 PHASE 2 RANDOMIZED TRIAL COMPARING STANDARD RCHOP VERSUS BRCAP AS FIRST LINE TREATMENT IN YOUNG PATIENTS WITH HIGH-RISK DLBCL. A STUDY FROM SPANISH GROUP GELTAMO**


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**Introduction:** Survival of DLBCL patients with high IPI treated with RCHOP is poor. Combination of RCHOP with new drugs is an attractive approach, along with performing an evaluation with PET/CT after 2-4 cycles to change therapy if an early CR is not achieved.
Methods: Clinical trial comparing 6 cycles of RCHOP vs BRCAP, a modified RCHOP changing vincristine by bortezomib 1.3 mg/m2 sc days 1, 8, and 15 of a 21-day cycle (ClinicalTrials.gov Identifier: NCT01848132). Inclusion criteria: ≤70 years, DLBCL, aaIPI 2-3 or 1 with increased beta2microglobulin. Primary end point: proportion of patients who survives free of event at 2 years. Centralized pathology review was performed in all cases; samples were classified as germinal center B-cell-like (GCB) vs non-GCB by immunohistochemistry (Hans algorithm). PET/CTs were performed at baseline, after 2, 4, and 6 cycles, and were reviewed at real time by at least 3 experts of a central panel. Response at the end of therapy was analyzed following the visual method (Deauville scale), and PET2/PET4 were evaluated using the semiquantitative method. Persistent disease at PET4 was considered failure of therapy, and patients were withdrawn from trial treatment.

Results: 121 patients were included; evaluable population per-protocol consisted of 115 (diagnosis not confirmed in 6). Fifty-six patients were treated in the experimental arm (BRCAP) and 59 in the control arm (RCHOP). Median age: 57.1 years (limits 23-70), 57 (49.6%) males. Characteristics at diagnosis: non-GCB subtype 38/103 (36.9%), immunohistochemical co-expression of MYC/BCL2 49/91 (53.8%), stage III-IV 107 (93.0%), ≥2 extranodal locations 58 (50.4%), ECOG 2-3: 36 (31.3%), increased LDH 90 (78.3%), increased beta2microglobulin 75 (65.2%), aaIPI 3: 31 (27.0%). No differences were found between arms. Thirty-one (27.0%) patients required of pre-phase treatment. The mean relative dose intensity for bortezomib was 88.9%. Thirty (31.3%) patients had ≥3 prior lines of therapy, and patients were withdrawn from trial treatment.

Characteristics at diagnosis: non-GCB type 22/29 (75.9%), ≥4 extranodal locations 30/41 (73.2%), ECOG 2-3: 36 (31.3%), increased LDH 90 (78.3%), increased beta2microglobulin 75 (65.2%), aaIPI 3: 31 (27.0%). No differences were found between arms. Forty-one (17.4%) patients had ≥3 prior lines of therapy, and patients were withdrawn from trial treatment.

Conclusions: No significant differences were found between RCHOP and BRCAP in terms of CR and proportion of patients free of event at 2 years in this very high-risk population of young DLBCL patients.

Keywords: bortezomib; diffuse large B-cell lymphoma (DLBCL)

190

PHASE 1B STUDY OF PEMBROLIZUMAB IN PATIENTS WITH RELAPSED/REFRACTORY PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA (RRPMBCL): UPDATED RESULTS FROM THE KEYNOTE-013 TRIAL

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Introduction: Current treatments for rrPMBCL often yield poor outcomes, but PMBCL’s genetics may make it susceptible to PD-1 blockade. The multicenter, multicohort KEYNOTE-013 (NCT01953692) phase 1b trial evaluates safety, tolerability, and antitumor activity of the anti-PD-1 monoclonal antibody pembrolizumab in patients (pts) with hematologic malignancies.

Methods: An independent cohort of KEYNOTE-013 is enrolling PMBCL pts who relapsed after or are ineligible for autologous stem-cell transplant (SCT). Pts initially received pembrolizumab IV 10 mg/ kg every 2 weeks (Q2W), later changed to an equivalent regimen of 200 mg every 3 weeks (Q3W). Treatment continues for 2 years or until unacceptable toxicity or confirmed disease progression. Treatment response is radiographically evaluated using 2007 response criteria at week 6, 12, and every 9 weeks thereafter. Primary end points were safety and objective response rate (ORR). Safety population: all pts with ≥1 dose of study drug. Efficacy population: all pts who progress prior to or reach the first efficacy evaluation.

Results: By the analysis cutoff date (January 3, 2017), 22 pts had been enrolled in the PMBCL cohort. 21 were treated, and 19 were radiographically evaluable. Overall, 67% of pts had ≥3 prior lines of therapy, and 67% were ineligible for autologous SCT due to chemorefractory disease. Median follow-up duration was 14.3 months (range, 0.6 to 34.7 months). In the safety population, 14 pts (67%) experienced treatment-related adverse events (TRAEs): 4 pts with grade 3 TRAEs (neutropenia n = 2, fatigue n = 1, increased alanine aminotransferase n = 1) and 1 with a grade 4 TRAE (neutropenia). An additional patient had grade 4 venoocclusive liver disease after allogeneic SCT during the follow-up period after pembrolizumab discontinuation. Seven pts had serious AEs. There were no treatment-related deaths. In the efficacy population (19 evaluable pts and 1 with clinical progression before the first efficacy evaluation), ORR was 50%: 5 pts (25%) each achieved partial or complete response (CR). Five others (25%) had stable disease as best response. Of evaluable pts, 15 (79%) had targeted lesion reductions (Figure). Median duration of response (DOR) was not reached (range, 1.4 to 28.9 months); DOR in pts with CR ranged from 1.4 to 27.1 months. There were 8 ongoing responses, including 5 in pts who discontinued treatment. Seventeen pts discontinued treatment due to progressive disease on imaging (n = 7), clinical progression (n = 5), physician decision (n = 2), patient decision, CR, or AE (n = 1 each); 2 pts were discontinued after completing the maximum 2 years of treatment and remain in remission.

Conclusions: In these heavily pretreated rrPMBCL pts, pembrolizumab had a manageable safety profile and promising antitumor activity. A global multi-center phase 2 trial (KEYNOTE-170) is currently further evaluating single agent pembrolizumab in rrPMBCL.

ABSTRACT