SESSION 7: ADVANCES IN CLL

99 INSIDE-OUT VLA-4 INTEGRIN ACTIVATION IS MAINTAINED IN IBRUTINIB-TREATED CHRONIC LYMPHOCYTIC LEUKEMIA EXPRESSING CD49D: CLINICAL RELEVANCE

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Introduction: VLA-4 (CD49d/CD29), a key molecule for microenvironmental interactions in chronic lymphocytic leukemia (CLL), can be activated via inside-out by BCR triggering in normal B cells. In CLL, nothing has been so far reported regarding these activation mechanisms and their modulation by ibrutinib (IB), a drug known to impair the microenvironmental interactions with consequent shrinkage of tumor masses, and efflux of CLL cells into the blood stream.

Methods: VLA-4 activation was assessed by flow cytometry using conformation sensitive anti-CD29 mAbs (HUTS-21) and LDV-containing VLA-4 ligands, and measured as VLA-4 receptor occupancy (RO) (Chigaev et al. J Biol Chem, 2009). BCR was engaged using goat anti-IgM. In-vitro studies were carried out on purified VLA-4+ CLL cells exposed in-vivo to IB. Clinical assessments of CLL patients treated with IB single agent in the context of name patients program, clinical trials, and real world (n = 97) included: kinetics of absolute lymphocyte count (ALC), reduction of lymphadenopathy measured as sum of products of the diameters (SPD), and clinical outcome defined by progression free survival (PFS).

Results: BCR stimulation (n = 27) induced VLA-4 activation (mean RO control vs stimulated: 0.40 vs 0.52, p = 0.0006), and increased cell adhesion (control vs stimulated: 4.7 vs 7.5; p = 0.0002). Comparison of day 30 (t30) in-vivo IB-treated CLL cells with pre-treatment (t0) showed IB-dependent BCR signaling impairment, reduced constitutive VLA-4 activation (mean RO t0 vs t30: 0.40 vs 0.30; p = 0.02) and CLL cell adhesion (mean adhesion t0 vs t30: 4.7 vs 2.1; p = 0.013), but an unexpected retention of VLA-4 activation upon anti-IgM triggering, with RO values reaching levels similar to those of IB naïve cells (mean RO: 0.49 at t30 vs. 0.52 at t0). From a clinical standpoint, comparison of IB-treated CD49d+ versus CD49d- CLL showed: a) lower % ALC change from baseline at day 30 (-4.4% and 126.8%; p = 0.0002; Figure 1A), and no typical IB-induced ALC peak; b) minor SPD reduction from baseline at 6 months (70.5% vs 83%; p = 0.033) and at 12 months (81.5% vs 92.0%; p = 0.019; Figure 1B); c) inferior PFS (median PFS 39.3 months, vs. not reached; p = 0.004), even considering the concomitant presence of TP53 disruption (Fig.1CD).

A multivariate Cox regression analysis confirmed the relevance of CD49d, along with TP53 disruption and UM IGHV mutational status, as independent predictor of shorter PFS in IB-treated CLL.

Conclusion: During IB treatment CD49d + CLL cells residing in tissue sites keep receiving BCR-mediated BTK-independent stimuli that, by inducing inside-out VLA-4 activation, result in enhanced cell retention, with consequent reduced lymphocytosis, relatively lower and/or slower nodal response, eventually leading to inferior outcome for CD49d + CLL patients.

Keywords: B-cell receptor (BCR); chronic lymphocytic leukemia (CLL); ibrutinib.
Introduction: In phase 3 studies, ibrutinib (ibr) was superior to ofatumumab in relapsed/refractory (R/R) CLL/SLL or chlorambucil in treatment (tx)-naïve (TN) CLL/SLL. Ibr + bendamustine/rituximab (BR) was superior to BR in R/R CLL/SLL. Clinical outcomes of pts in these 3 studies were examined to determine the impact of certain prognostic risk factors other than del17p.

Methods: RESONATE: R/R CLL/SLL, ibr 420 mg/d until progressive disease (PD) or ofatumumab (≤24 wk). RESONATE-2: TN CLL/SLL (no del17p) ≥65 y, ibr 420 mg/d until PD or chlorambucil (≤12 cycles). HELIOS: R/R CLL/SLL (no del17p), BR (≤6 cycles) ± ibr 420 mg/d followed by ibr or placebo until PD. Data from 3 studies (N = 1238) were pooled to analyze outcomes with/without genomic risk factors IGHV, del11q, trisomy 12, or complex karyotype (CK). Covariates for