Context: Antimicrobial resistance is an emerging problem in communities with frequent non-prescription use of antibiotics (Morgan et al., 2011), which may affect the efficacy of anti-infective prophylaxis in developing countries. Moreover, patient management in the general wards (Biswal and Godnaik, 2013) may further impact on the risk of infectious complications. Frequent over-the-counter use of antibiotics (Hovhannisyan et al., 2007), patient treatment in common wards and unjustified fluconazole prophylaxis for uncomplicated infections are observed in Armenian population. **Objective:** The aim of this study is to evaluate the effectiveness of the triple anti-infective prophylaxis (antibacterial, antiviral and antifungal) on the frequency of febrile neutropenia, infectious-related complications, hospitalization and mortality in patients with acute leukemia. Here we present the preliminary data of this ongoing study. **Design:** To pursue our hypothesis we organized a retrospective case-control study among Armenian patients treated for acute leukemia. Cases are presented by patients receiving anti-infective prophylaxis at the beginning of chemotherapy (introduced in clinic in 2017), while controls are presented with patients receiving anti-infective prophylaxis only when absolute neutrophil count $< 500/\mu L$ (before 2017). **Setting:** Study is conducted in Hematology Center after Prof. R. Yeolyan, Ministry of Health, Republic of Armenia (Hematology Center). **Patients:** Patients, referred to Hematology Center before and after 2017 and further diagnosed with AML or ALL, were included in this study. **Main Outcomes Measures:** Febrile neutropenia episodes, documented infections and duration of hospitalizations are compared in this study. **Results:** Febrile neutropenia episodes were registered in 40.0% (4/10) of patients in prophylaxis arm and 71.4% (5/7) in non-prophylaxis arm (p= 0.33). None of the patients in prophylaxis arm (0/10) suffered from infectious complications, while 4/7 patients in non-prophylaxis arm had at least one episode of detected infection (p= 0.02). The median (interquartile ranges) duration of hospitalization was 14.0 (10.0 - 26.5) days in prophylaxis and 14.0 (9.25 - 36.5) days in non-prophylaxis (p= 0.86) arm. **Conclusions:** Our preliminary data suggest that the introduction of triple anti-infective prophylaxis decreased the infection episodes and neutropenia rate, however febrile neutropenia still remains high compared to the published international data. **Keywords:** acute leukemia, prophylaxis, febrile neutropenia

AML-030

GRP94 Rewires and Buffers the FLT3-ITD Signaling Network and Promotes Survival of Acute Myeloid Leukemic Stem Cells

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Context: FLT3-ITD positive AML has a high risk of treatment failure. We found that FLT3-ITD+ cells are particularly sensitive to HSP90-inhibitors. **Methods:** *Patient cohort:* Samples were collected from 41 AML patients and 6 healthy volunteers.

Mouse PDX studies: AML cells from a FLT3-ITD+ AML patient were transplanted into 8-week-old NOD.Cg-Prkdcscid IL2rgtm1Wjl/SzJ mice. After engraftment, mice were treated with either vehicle ($n = 11$) or ganetespib ($n = 11$) for 3 weeks. A group of mice ($n = 8$/group) was followed for survival after discontinuation of treatment. BM cells from primary recipients were used for secondary transplantation into NSG mice ($n = 3$/group) after treatment and analyzed for survival. **Results:** HSP90 inhibitors target FLT3-ITD-positive AML blasts

FLT3-ITD or FLT3-TKD mutations co-clustered with drugs that included HSP90 inhibitors. FLT3-ITD AML cells were significantly more sensitive to ganetespib and luminespib than WT FLT3. BM cells from healthy donors tolerated very high doses of ganetespib and luminespib.

The HSP90 family member GRP94 is required for ER retention of FLT3-ITD

GRP94 inhibition resulted in maturation and cell surface translocation of FLT3-ITD. Ganetespib also induced cell membrane localization of FLT3-ITD in primary AML patient cells.

GRP94 is required for FLT3-ITD signaling competence

GRP94 inhibition resulted in degradation of the downstream AKT signaling pathway component b-catenin, leading to reduced expression of several b-catenin target genes, such as *CCND1*, *MYC* and *CD44*.

HSP90 inhibitors synergize with TKIs and bypass TKI-resistant mutations in FLT3-ITD

Ba/F3 cell lines expressing FLT3-ITD with a D835V, D835Y, D835F or F691L mutation, confer AC220 resistance. Viability of these mutants, especially the highly TKI-resistant FLT3-ITD-D835Y/F mutants was significantly reduced by both PU-WS13 and ganetespib

Inhibition of HSP90 selectively eradicates FLT3-ITD+ LSCs

Ganetespib treatment resulted in almost complete eradication of FLT3-ITD+ LSCs. CD34+CD38-CD123+ cells derived from FLT3-WT AML patients were sensitive to ganetespib, indicating that ganetespib may impair survival of CD34+CD38-CD123+ AML cells. Thus, FLT3-ITD+ LSCs are highly dependent upon HSP90 activity. **Conclusions:** Our data suggest a complex role for HSP90 family proteins in FLT3-ITD signaling. The results provide a rationale for treatment of FLT3-ITD+ AML with HSP90 inhibitors. **Keywords:** AML, FLT3, HSP90