(PF465) GM-CSF NEUTRALISATION EFFECTIVE IN VENETOCLAX RESISTANT AML WITH RAS MUTATIONS

Topic: 03. Acute myeloid leukemia - Biology & translational research

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Background

Venetoclax (VEN) plus azacitidine (AZA) is the current standard-of-care for acute myeloid leukaemia (AML); however, outcomes remain poor in AML arising from antecedent myelodysplastic syndromes (MDS), particularly chronic myelomonocytic leukaemia (CMML). Data from published reports and our South Australian MDS/AML Registry revealed inferior median overall survival (OS) in CMML-transformed AML (3.5-3.7 months) and lower CR/CRi rates (0-33%) compared with newly-diagnosed, previously untreated AML receiving VEN/AZA (median OS 14.7 months; CR/CRi 66.4%). Granulocyte-macrophage colony stimulating factor (GM-CSF) hypersensitivity is a hallmark of CMML, and augmented spontaneous myeloid colony formation in semisolid medium has been proposed as a surrogate parameter for RAS pathway hyperactivation in CMML. We recently observed durable responses to the humanised anti-GM-CSF antibody, Lenzilumab (LENZ) in high blast, RAS pathway mutant CMML at increased risk of AML transformation in the PREcision Approach to CHronic Myelomonocytic Leukaemia (PREACH-M; ACTRN 1262100022383) clinical trial.

Aims

To investigate the cytokine dependency of RAS-mutant CMML-transformed AML and evaluate sensitivity to antibody-directed GM-CSF neutralisation, alone and in combination with VEN/AZA.

Methods

Mononuclear cells from RAS-mutant CMML-transformed AML were assayed for viability, colony formation and drug sensitivity in the presence of receptor-blocking or ligand-neutralising antibodies and VEN/AZA.

Results

In the absence of exogenous cytokines, CMML-transformed AML (CD45+ myeloid cells) demonstrated robust spontaneous growth in vitro. Receptor blockade and cytokine neutralisation established that this spontaneous growth was uniquely dependent on GM-CSF. In colony-forming assays, spontaneous colonies were inhibited by 20 µg/mL LENZ (mean 67.1 ± 7.8% reduction *vs.* IgG control, P=0.003), indicative of an autocrine GM-CSF loop amenable to antibody blockade.
CMML-transformed AML exhibited marked resistance to VEN (IC_{50} >500 nM), consistent with clinical experience. Notably, VEN-resistant colonies were significantly suppressed by LENZ, alone and in combination with VEN/AZA. Preliminary mechanistic data suggest that GM-CSF neutralisation downregulates MCL-1 protein expression but not Bcl-2.
Clinically, a patient with CMML-transformed AML refractory to 8 cycles of VEN/AZA was treated with VEN/AZA/LENZ triple therapy (100 mg PO VEN D1-D28, AZA 75 mg/m^2 D1-D7, LENZ 552 mg D1 and D15; 35-day cycle). The patient achieved a durable response following 15 cycles of triple therapy, with bone marrow blasts <20%, improved haemoglobin and platelet counts. Triple therapy was well-tolerated and the patient remained transfusion-independent with no acute admissions and reported meaningful improvements in weight and quality of life.

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Summary/Conclusion

Spontaneous growth in VEN-resistant RAS mutant, CMML-transformed AML may be driven by autocrine production of the pro-inflammatory cytokine, GM-CSF, revealing a therapeutically targetable vulnerability. GM-CSF neutralisation with LENZ limited MCL-1 expression and suppressed VEN-resistant colonies. LENZ/VEN/AZA triple therapy in a VEN-refractory AML patient produced a well-tolerated and durable response, supporting further clinical investigation.

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