(PB3926) COMBINATION OF GOLIDOCITINIB WITH CHIDAMIDE FOR PERIPHERAL T-CELL LYMPHOMA: POSSIBLE MECHANISMS AND THERAPEUTIC POTENTIAL IN INHIBITING TUMOR PROLIFERATION AND MODULATING THE IMMUNE MICROENVIRONMENT

Topic: 21. Lymphoma biology & translational research

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Background

Peripheral T-cell lymphoma (PTCL) is a rare and highly heterogeneous hematologic malignancy. Golidocitinib, a novel highly selective JAK1 inhibitor, has demonstrated promising anti-tumor potential against PTCL. The present study evaluated the direct cytotoxic effects of golidocitinib monotherapy and its combination with chidamide against PTCL, analyzed their anti-inflammatory and immunomodulatory effects on PTCL, and explored whether synergistic multi-mechanistic interactions could enhance anti-tumor efficacy. Subsequently, we performed an exploratory clinical evaluation of this combination strategy in a pilot cohort of four patients with PTCL.

Aims

This study confirmed the pivotal role of golidocitinib in the treatment of PTCL and proposed a combination therapy strategy of golidocitinib and chidamide, providing a novel synergistic treatment approach for PTCL patients.

Methods

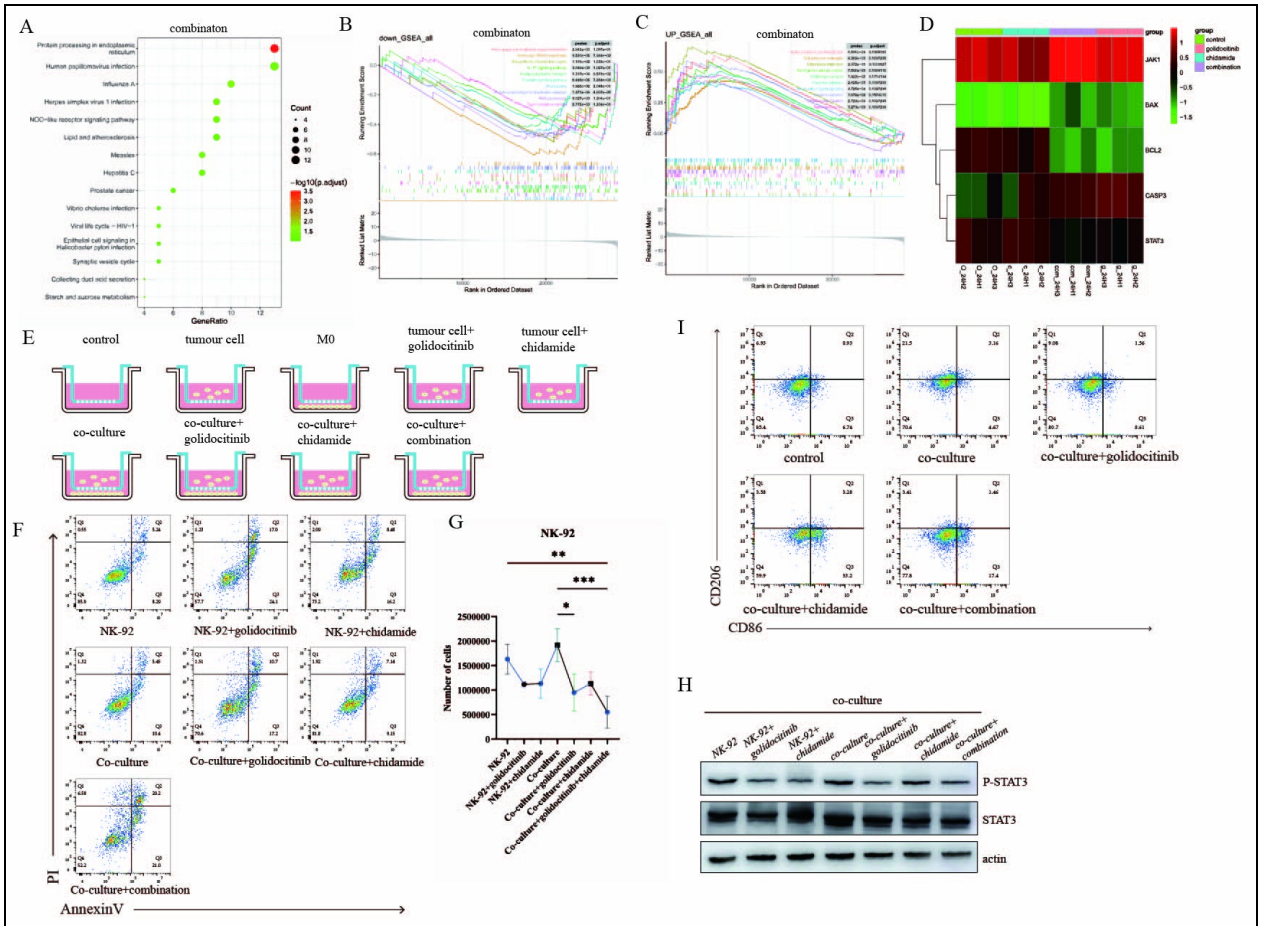
Four classic PTCL cell lines were treated with golidocitinib and chidamide at indicated concentrations and time gradients, either as single agents or in combination, and the combination index (CI) was calculated. Meanwhile, the effects of golidocitinib alone and the combination regimen on the JAK-STAT3 signaling pathway were examined by Western blot analysis, and RNA sequencing was performed to analyze changes in cytokines and signaling pathways. Furthermore, a co-culture model of macrophages and tumor cells was established. Changes in cytokine levels in the supernatant, the number and apoptosis rate of tumor cells in the upper chamber, alterations in related signaling pathways, and the polarization status of macrophages in the lower chamber were detected. Subsequently, we evaluated the clinical efficacy of golidocitinib (150 mg once daily) combined with chidamide (20 mg twice weekly) in four patients with PTCL. The cohort included two chemo-free first-line treatment patients (1 PTCL-NOS, 1 AITL) and two fourth-line treatment patients (1 PTCL-NOS, 1 AITL).

Results

Golidocitinib, alone and in combination, significantly inhibits the proliferation of various human PTCL cell lines. Moreover, the drug targets the JAK-STAT signaling pathway, downregulates proliferation-related pathways, and reduces the expression of key inflammatory cytokines. In the co-culture system, golidocitinib alone and in combination effectively reversed macrophage M2 polarization, markedly decreased the levels of core inflammatory cytokines, and exerted a synergistic pro-apoptotic effect on NK-92 cells. Building on these preclinical findings, we translated this combination regimen into clinical practice. Two chemo-free first-line treatment patients achieved partial responses (PR) after two cycles, while two fourth-line treatment patients attained complete remission (CR) following four cycles.

Summary/Conclusion

Golidocitinib alone and its combination with chidamide exert anti-tumor effects by inhibiting the JAK/STAT3 signaling pathway. The combination synergistically enhances anti-proliferative activity and suppresses pro-inflammatory signaling, promotes macrophage polarization, inhibits M2-driven immune escape, and remodels the tumor immune microenvironment. These findings are reflected in the clinical responses observed across all four types of peripheral T-cell lymphoma (PTCL) patients, including cases of refractory disease achieving complete remission. This laboratory-to-clinical consistency provides evidence supporting the combination therapy as a promising new treatment paradigm for PTCL.



(A)Transcriptome sequencing was performed after 24 hours of combined treatment with golidocitinib and chidamide. KEGG , GSEA (B, C), and gene expression heatmap analyses (D) showed the enrichment of pathway-related genes. A co-culture model was established (E) and cells were treated with golidocitinib (25 μmol/L), chidamide (2.5 μmol/L) alone or in combination for 48 hours. Tumor cells in the upper chamber were collected and counted (G), apoptosis was analyzed by Annexin V-PI double staining (F), and the expression of P-STAT3 protein was detected by Western blot analysis (H). Collect macrophages from the lower chamber and determine the expression of macrophage surface markers by flow cytometry (I).