Enhancing cytotoxic chemotherapy effects by nintedanib in gastric cancer models

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Background

- Gastric Adenocarcinoma (GAC): The 3rd most common cause of cancer-related deaths worldwide
- Five-year survival rate 31%
- Standard treatment: FLOT (5-FU, Leucovorin, Oxaliplatin, Docetaxel)
- Median progression-free survival and overall survival: 5.2 & 11.1 months
- Dismal prognosis factors: late-stage diagnosis, early and aggressive invasion with metastatic disease resistance to conventional chemotherapy
- Post-operative recurrence common
- Second-line therapy: Taxanes and trastuzumab, ramucirumab (targeted agents)
- Angiogenesis:
  - Essential process for tumor growth and metastasis
  - Potential target for cancer therapy
  - Plays an important role in pathogenesis of GAC

Nintedanib (Nil):
  - Potent triple angiokinase inhibitor of VEGFR1/2/3, FGFR1/2/3, PDGFR-alpha
  - Approved therapy for idiopathic pulmonary fibrosis and NSCLC (EU)
  - Currently under clinical investigation for AML, NSCLC and pancreatic cancer

Study Objectives

- Based on the unique targeting profile and high specificity of nintedanib and a crucial role of angiogenesis in the progression and metastasis of GAC, we aimed to evaluate the antitumor activity of nintedanib, and its potency to improve the response of standard chemotherapy agents in diverse preclinical models of GAC.

Methods

- Animal studies were performed following an approved IACUC protocol of Indiana University.
- Animal survival experiments were performed in the peritoneal dissemination xenograft model in NOD-SCID mice using 10x10^6 human gastric cancer MKN-45 or KATO-III cells (n=5-7).
- Tumor growth studies were performed in subcutaneous xenografts in NOD-SCID mice using 7.5x10^6 human GAC MKN-45 or SNU-5 cells (n=5-7).
- In vivo drug doses: nintedanib (25 mg/kg, 5x/wk); 5-FU (50 mg/kg, 2x/wk), epirubicin (1 mg/kg, 2x/wk), oxaliplatin (5 mg/kg, 2x/wk), docetaxel (2 mg/ml, 2x/wk) and irinotecan (10 mg/kg, 1x/wk) were delivered intraperitoneally.
- In vitro cell proliferation was evaluated in three GAC cell lines (MKN-45, KATO-III and SNU-5).
- Mechanistic evaluation: immunoblot and immunohistochemistry analysis in tumor xenografts

Nintedanib and Cytotoxic Therapies: Tumor growth in subcutaneous xenografts

Nintedanib and Cytotoxic Therapies: Animal survival in peritoneal dissemination xenografts

Summary

- Nintedanib increased animal survival by ~33% in GAC peritoneal dissemination xenografts.
- Nintedanib induced survival in KATO-III xenografts carrying FGFR2 gene amplification was much higher (>275%) than MKN-45 xenografts.
- Addition of nintedanib further improved (range 33-61%) animal survival caused by docetaxel and irinotecan.
- Nintedanib exhibited notable tumor growth inhibition (range 64-75%) in GAC subcutaneous xenografts.
- The combinations of nintedanib and cytotoxic agents demonstrated additive response on tumor growth inhibition with maximum benefits in docetaxel plus nintedanib and irinotecan plus nintedanib.
- Nintedanib attenuated tumor cell proliferation and reduced tumor vasculature.
- In vitro cell viability assay demonstrated a dose-dependent growth inhibitory effects of nintedanib on GAC cells.
- Combinations of nintedanib and cytotoxic agents demonstrated additive effects on GAC cell proliferation inhibition.

Conclusion

Nintedanib showed notable antitumor efficacy and significantly improved taxane or irinotecan chemotherapy responses. Combination regimens with nintedanib have the potential for improving clinical GAC therapy.

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