

Invasion-Metastasis by Hepatocyte Growth Factor/c-Met signaling Concomitant with Induction of urokinase Plasminogen Activator in Human Stomach Cancer : Role as Therapeutic Target

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Background: Increased expression of the hepatocytes growth factor (HGF) receptor (c-Met) and urokinase type plasminogen activator (uPA) correlate with the development and metastasis of cancers. However, the mechanisms by which HGF/c-Met signaling mediate cancer progression and metastasis are unclear. Therefore, we investigated the roles of HGF/c-Met in tumor progression and metastasis in stomach cancer cell lines, NUGC-3 and MKN-28

Method and results: To see the functional c-Met protein, we were performed immunoprecipitation for functional c-Met protein. And also performed western blot analysis and gel zymography for the functional uPA protein. To see the inhibition effects of uPAR monoclonal antibody on invasiveness of two stomach cancer cell lines, we were carried out standard two chamber invasion assay. At first, we observed the HGF-mediated c-Met phosphorylation and cell growth. c-Met phosphorylation was increased in the HGF-treated cells in a dose dependent manner. HGF resulted in increments of both cell growth. And also, HGF treatment increased the uPA expression and the uPA activity at NUGC-3 cell lines. A monoclonal antibody 3936, specific to uPAR receptor, inhibited HGF-mediated tumor cell invasion in a dose dependent manner.

Conclusion: These results suggest that NUGC-3 and MKN-28 cells express functional c-Met and may provide a therapeutic basis for interfering with metastases by inhibition of uPA and uPAR-mediated proteolysis.

진행성 위암에서 Genexol[®](paclitaxel)/cisplatin 복합요법의 다기관 2상 임상연구

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Objective: Because of unsatisfactory treatment results with 5 fluorouracil based palliative combination chemotherapy for advanced gastric cancer (AGC), the evaluation of new effective and well-tolerated regimens is needed. We conducted a multi-center, late phase II trial to evaluate the efficacy and safety of Genexol[®] (a paclitaxel formulation)/cisplatin in metastatic or unresectable AGC.

Pateints and Methods: Patients (pts) received 21-day cycles of Genexol (175 mg/m² IV, D1) and cisplatin (75 mg/m² IV, D1). All pts were chemo-naïve (except adjuvant chemotherapy), and had ECOG PS ≤1, measurable lesions, and adequate organ functions.

Results: From Nov 2002 to Apr 2003, 36 pts were enrolled from 7 hospitals. Clinical characteristics were as follows: median age 59 yrs (range, 28-72); PS 0/1=6/29; and M/F=28/7. Among 33 efficacy-evaluable pts, in intent-to-treat analysis, 16 pts (46%) (95% C.I. 29-63%) had partial response, 7 (20%) stable disease, and 10 (29%) progressed. At a median follow up of 12.7 mo (range, 7.1-14.8), the median duration of response was 7.1 mo (95% C.I. 6.3-7.9), and the median time to progression and overall survival were 4.9 mo (95% C.I. 3.2-6.6) and 13.8 mo (95% C.I. 10.8-16.8), respectively. The major toxicity was neutropenia, with grade 3/4 intensity in 10 pts (29%). However, no febrile neutropenia occurred, and non-hematologic toxicity was usually mild. Grade 3/4 toxicities included nausea (9% of the pts), vomiting (9%), peripheral neuropathy (9%), alopecia (9%), and myalgia (6%). There was no treatment-related death.

Conclusion: Genexol/cisplatin regimen is active and relatively well-tolerated as a first line chemotherapy in AGC.