MET Overexpression and Amplification Define a Distinct Molecular Subgroup for Targeted Therapies in Gastric Cancer

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ABSTRACT

Background: Gastric cancer is among the leading causes of cancer deaths. Currently, only trastuzumab, ramucirumab, and lapatinib effectively treat gastric cancer. Thus, additional novel targets are required for this disease.

Methods: We investigated the immunohistochemical and fluorescence in situ hybridization expression of MET, ROS1, and ALK in four gastric cell lines and a cohort of 98 gastric cancer patients. Crizotinib response was studied using an in vitro histoculture drug response assay and the patient-derived GC xenograft model in vivo. Gene expression status was also analyzed for association with overall survival.

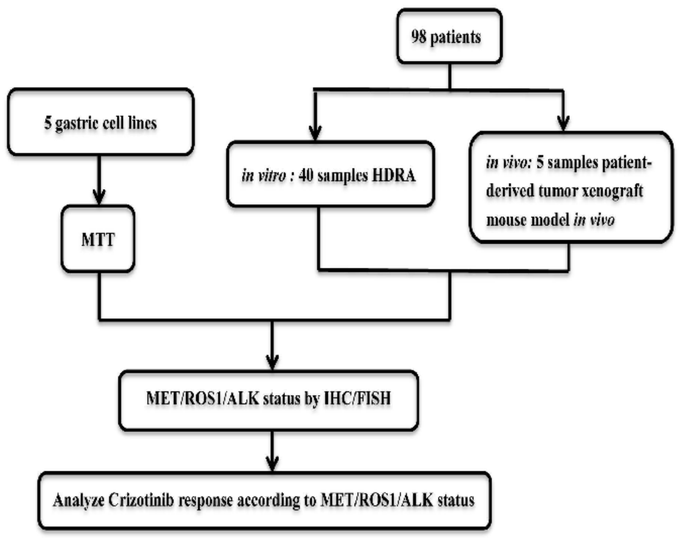
Results: Crizotinib potently inhibited in vitro cell growth in only one cell line, which also showed MET amplification. A positive correlation between crizotinib sensitivity and MET overexpression was observed (P=0.045) in the histoculture drug response assay. Meanwhile, patient-derived tumor xenograft mouse models transplanted with tissues with higher MET protein expression displayed a highly selective sensitivity to crizotinib. In the 98 patients, MET overexpression was found in 42 (42.9%) and MET was amplified in 4 (4.1%). ROS1 and ALK overexpression were found in 25 (25.5%) and 0 patients, respectively. However, none of the patients screened harbored ALK or ROS1 rearrangements. There was no significant association found between overall survival and the MET or ROS1 status. We also observed a case that one advanced GC patient with MET-amplification experienced tumor shrinkage (PR by RECIST) after 3 weeks treated with crizotinib at the time of third-line chemotherapy failure. This patient also showed rapid clinical improvement, with decreased pain and improved performance status.

Conclusions: Crizotinib may induce clinically relevant anticancer effects in MET-overexpressing or -amplified gastric cancer patients.

BACKGROUD

- There is increasing interest in the development of targeted therapies for gastric cancer after the encouraging results of trastuzumab in human epidermal growth factor receptor-2 (HER2)-positive populations.
- Additional aberrantly activated receptors and downstream pathways are now being explored, including epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor 2 (VEGFR-2), fibroblastic growth factor receptor (FGFR), and the MET proto-oncogene (MET), to assess their therapeutic potential in gastric cancer.

PATIENTS AND METHODS



- The cytotoxicity of crizotinib in the gastric cell lines MKN45, N87, AGS, and SNU-1 was determined MTT assays.
- This study included 98 patients who underwent gastrectomy at the General Surgery Department of Drum Tower Hospital between 2010 and 2012. Of these, 40 samples that had sufficient freshly removed tumor tissues were further used for measurement of *in vitro* crizotinib sensitivity by HDRA. In addition, five tumor samples were used to create patient-derived tumor xenograft mouse models for *in vivo* antitumor studies.
- MET, ROS1, and ALK status were examined in all samples and 5 gastric cell lines by IHC and FISH analyses

RESULTS

Patient characteristics and MET, ROS1 and ALK status

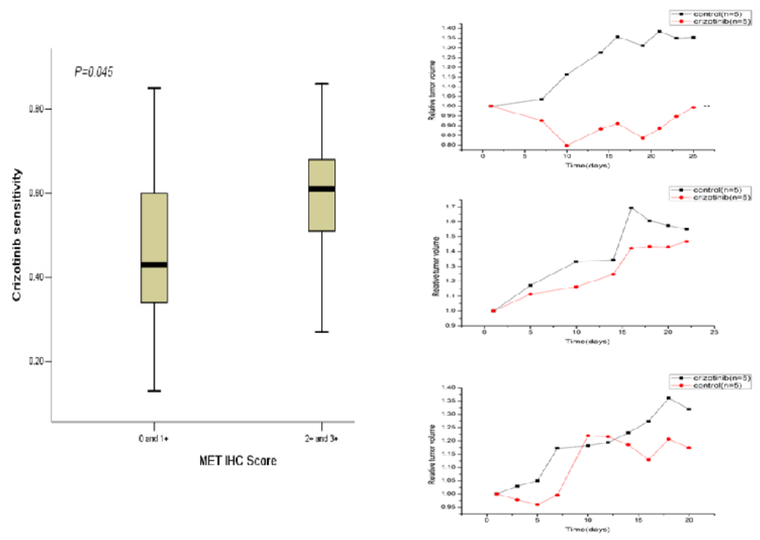
Characteristic	In total (N = 98)	HDRA study cohort (N=40)
Age		
≥ 60	48(49.5%)	19(47.5%)
< 60	49(50.5%)	21(52.5%)
Sex		
Male	71(72.4%)	28 (70.0%)
Female	27(27.6%)	12 (30.0%)
Tumor Site		
Distal stomach	36(37.1%)	15(37.5%)
Proximal stomach	19(19.6%)	8(20.0%)
Whole stomach	42(43.3%)	17(42.5%)
Stage		
I	2(2.0%)	1(2.5%)
II	7(7.1%)	6(15.0%)
III	89(90.8%)	33(82.5%)
Histological grade		
Mixed 1–2	1(1.1%)	1(2.6%)
2	15(16.3%)	7(17.9%)
Mixed 2–3	23(25.0%)	13(33.3%)
3	53(57.6%)	18(46.2%)
MET overexpression		
Yes	42(42.9%)	21(52.5%)
No	66(67.3%)	19(47.5%)
MET amplification		
Yes	4(4.1%)	1(2.5%)
No	94(95.9%)	39(97.5%)
ROS1 overexpression		
Yes	25(25.5%)	14(35.0%)
No	73(74.5%)	26(65.0%)
ROS1 amplification		
Yes	0(0.0%)	0(0.0%)
No	98(100.0%)	40(100.0%)
ALK overexpression		
Yes	0(0.0%)	0(0.0%)
No	98(100.0%)	40(100.0%)
ALK amplification		
Yes	0(0.0%)	0(0.0%)
No	98(100.0%)	40(100.0%)

In vitro sensitivity with respect to biomarker positivity

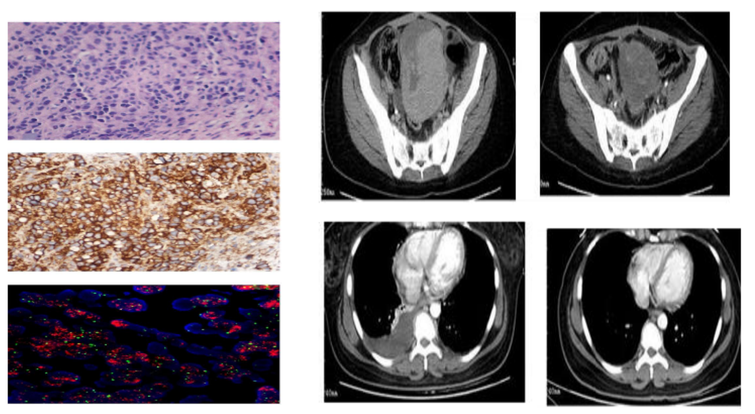
Cell lines	Biomarker positivity by IHC/FISH *MET*	*ROS1*	*ALK*	*In vitro* anti-proliferative IC50(nM) of Crizotinib
MKN45	3+/Positive	0/Negative	0/Negative	40
SNU-1	0/Negative	0/Negative	0/Negative	1400
AGS	0/Negative	1+/Negative	0/Negative	1800
NCI-N87	0/Negative	2+/Negative	0/Negative	7400

MET overexpression and crizotinib sensitivity *in vitro*

Tumor volumes after crizotinib treatment *in vivo*



Diagnostic features and response of MET-amplified gastric cancer patient who response to crizotinib.



CONCLUSIONS

- Crizotinib may induce clinically relevant anticancer effects in MET-overexpressing or -amplified gastric cancer patients.
- ROS1 and ALK rearrangements remain barely detectable in gastrointestinal tumors.

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