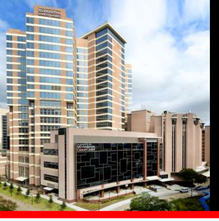


LB097: MET Inhibitor Enhances Efficacies of Gemcitabine and Olaparib in Pancreatic Cancer Cells

Mei-Kuang Chen[1], Yuan Gao[1,2], Dihua Yu[1], Mien-Chie Hung[3,1]

[1]MD Anderson Cancer Center, Houston, TX, USA; [2]Renji Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China; [3]China Medical University, Taichung, Taiwan

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Abstract

Gemcitabine is one of the current first-line chemotherapy agents in pancreatic cancer treatment. However, the response rate of pancreatic cancer patients to gemcitabine treatment is lower than 20%. Among the potential targeted therapies for pancreatic cancer patients, PARP inhibitor (Olaparib) has been approved by the U.S. Food and Drug Administration for maintenance treatment of metastatic pancreatic adenocarcinoma patients with germline BRCA-mutation. Taking advantages of the high oxidative stress in most pancreatic cancer cells, therapeutic agents that enhance the burden of oxidative DNA damages in these cancer cells can be introduced in novel treatment strategies. Because c-MET overexpression positively correlates with poor prognosis in pancreatic cancer, and our previous studies show that oxidative stress induced-nuclear c-MET phosphorylates PARP1 to reduce oxidative DNA damages, we focused on developing novel treatment strategies by combining c-MET inhibitors (crizotinib and tivantinib) with either gemcitabine or olaparib. In this study, we found that gemcitabine induced nuclear accumulation of c-MET, and that tivantinib reduced c-MET mediated PARP1 phosphorylation in both BxPC-3 and L3.6pl pancreatic cancer cell lines. We also found that combination of tivantinib with either gemcitabine or Olaparib induced more DNA damages than the single agent treatments. Further, we demonstrated the synergistic effects of c-MET inhibitors combined with gemcitabine or Olaparib in pancreatic cancer cell lines, suggesting that combining c-MET inhibitor with PARP inhibitor or gemcitabine is a novel and rational therapeutic strategy for pancreatic cancer treatment.

Background

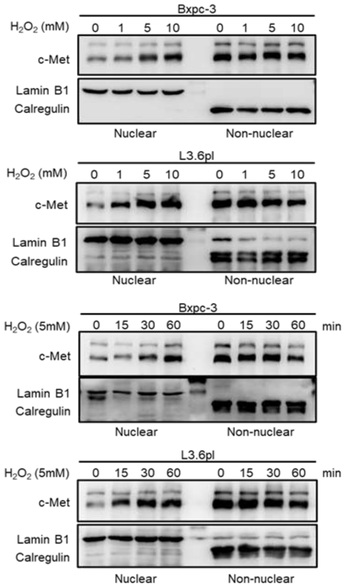
- Pancreatic cancer has become the fourth leading cause of death in the United States [1, 2]. The 5-year relative survival rate is 9%, which is the lowest among all types of cancer [2].
- For patients who are ineligible for surgical interventions due to locally advanced or metastatic PDAC, chemotherapy and targeted therapy are by far the best options to extend survival.
- Treatment with gemcitabine, a first-line chemotherapeutic agent for pancreatic cancer, was effective in less than 20% of patients [3].
- In pancreatic cancer patients, small-molecule inhibitors targeting c-MET tyrosine kinases, such as tivantinib, cabozantinib, and crizotinib, are currently under investigation in clinical trials [4, 5]. However, in a phase 2 trial, treatment with cabozantinib failed to benefit patients with PDAC [6, 7].
- Pancreatic cancer commonly has intratumoral hypoxia and high reactive oxygen species (ROS) production [8].
- PARP inhibitor is one of the targeted therapeutic agents that can stimulate accumulation of ROS and ROS-induced DNA damage [9]. A recent clinical trial showed that treatment with a PARP inhibitor benefited patients with advanced pancreatic cancer and germline breast cancer susceptibility protein (BRCA) mutations [10].

Significance

- Identifying molecular mechanisms of overcoming ROS-induced stress in pancreatic cancer cells is important for the development of novel therapeutic strategies.
- While most targeted therapies for PDAC are currently in phase 1 clinical trials, identifying effective therapeutic strategies for advanced PDAC is urgently needed.

Results

1. ROS-generating agents promotes nuclear c-MET translocation.



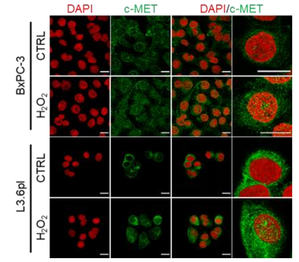


Figure 1. Hydrogen peroxide promotes nuclear c-MET translocation in dose- and time-dependent manner.

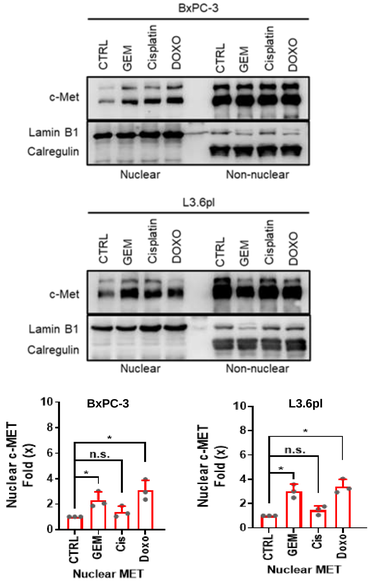
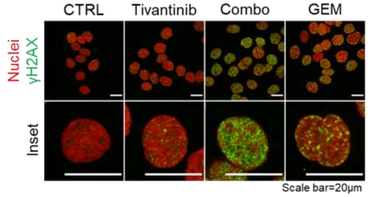


Figure 2. Gemcitabine and doxorubicin induces nuclear c-MET translocation.

2. Combining either gemcitabine or olaparib with tivantinib induces more DNA damages than single agent treatments.



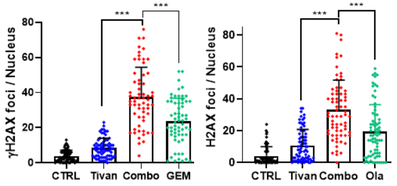


Figure 3. Combinations of gemcitabine/ tivantinib and olaparib/tivantinib induce more γH2AX foci than single agent treatments.

3. Both gemcitabine/tivantinib and olaparib/tivantinib combinations showed synergistic effect in pancreatic cancer cells.

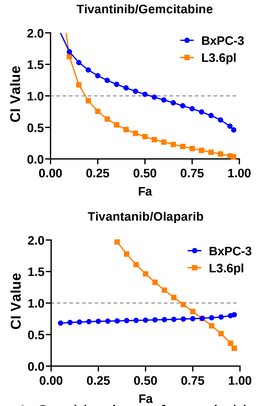


Figure 4. Combinations of gemcitabine/ tivantinib and olaparib/tivantinib showed synergistic effect (Combination index, CI <1) [11] in pancreatic cancer cells.

Conclusion

Our findings suggest that combining c-MET inhibitors with PARP inhibitors or gemcitabine is a novel, rational therapeutic strategy for advanced pancreatic cancer.

References

[1] McGuigan et al. *World J Gastroenterol* 2018; 24: 4846-4861.
[2] Siegel et al. *CA Cancer J Clin* 2020; 70: 7-30.
[3] de Sousa Cavalcante et al. *Eur J Pharmacol* 2014; 741: 8-16.
[4] Yap et al. *J Clin Oncol* 2011; 29: 1271-1279.
[5] Rosen et al. *Clin Cancer Res* 2011; 17: 7754-7764.
[6] Schöffski et al. *European Journal of Cancer* Supplements 2010; 8: 117.
[7] Sharma N and Adjei AA. *Ther Adv Med Oncol* 2011; 3: S37-50.
[8] Koong et al. Pancreatic tumors show high levels of hypoxia.
[9] Slade D. *Genes Dev* 2020; 34: 360-394.
[10] Golan et al. *N Engl J Med* 2019; 381: 317-327.
[11] Chou TC. *Pharmacol Rev* 2006; 58: 621-681.