



Is phosphatidylinositol 3-kinase/AKT/mammalian target of rapamycin pathway therapeutic target for esophageal adenocarcinoma

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Provenance: This is an invited Editorial commissioned by Editor-in-Chief Changqing Pan (Shanghai Chest Hospital Affiliated to Shanghai Jiao Tong University, Shanghai, China).

Comment on: Zaidi AH, Kosovec JE, Matsui D, *et al.* PI3K/mTOR Dual Inhibitor, LY3023414, Demonstrates Potent Antitumor Efficacy Against Esophageal Adenocarcinoma in a Rat Model. *Ann Surg* 2017;266:91-8.

Received: 10 October 2017; Accepted: 17 October 2017; Published: 08 November 2017.

doi: 10.21037/shc.2017.10.07

View this article at: <http://dx.doi.org/10.21037/shc.2017.10.07>

Introduction

Esophageal cancer (EC) is the eleventh most common cause of cancer worldwide (459,299 cases) and the sixth most common cause of cancer mortality (439,000 deaths) (1). Esophageal adenocarcinoma (EAC) is one of the major histological types of EC with the rapidly rising incidence in the West. Molecularly targeted drugs that have produced modest advantage in EAC patients include trastuzumab (for patients with HER2 positive EAC) but VEGFR2 inhibitor, ramucirumab in combination with paclitaxel in the second-line setting (2,3). Other molecular biomarkers to select therapy are PD-L-1 and MSI status. However, data are preliminary and need to be pursued.

Zaidi and colleagues recently published a report in which they assessed the efficacy of a phosphatidylinositol 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) dual inhibitor, LY3023414, on established EAC *in vivo* model (4). They used the Levrat's surgical model of esophagojejunostomy in rats, which leads to gastroduodenal esophageal reflux and subsequent development of reproducible EAC in 70% of rats at 28 weeks. Thirty two weeks after Levrat's surgery, rats were randomized to one of the two groups; LY3023414 treatment cohort and control cohort. Tumors volume evaluation by magnetic resonance imaging (MRI) 8

weeks after randomization showed that tumor in control group increased 109.2%, and tumor in LY3023414 group decrease 56.8%. Moreover, 5 of the 13 treatment cohort achieved complete tumor response by MRI. Other 8 tumors had histological evaluation, which showed that 3 achieved complete histological response and 3 had more than 50% histological response. In addition, PI3K/v-AKT murine thymoma viral oncogene homolog (AKT)/mTOR pathway and Ki67 (proliferation maker) was significantly decreased in the treated tumors, while cleaved caspase-3 (apoptosis maker) was significantly increased in the treated tumors compared to control tumors. These preclinical model results suggest that inhibition of PI3K/AKT/mTOR pathway is possibly effective for EAC by impairing proliferation and facilitating apoptosis.

PI3K/AKT/mTOR pathway alternation and clinical outcome

TCGA recently reported an integrated genomic landscape in EAC and show that EAC were similar with chromosomal instability (CIN) subtype for gastric cancer characterized by TP53 mutation, ERBB2 amplification, and VEGFA amplification (5). This result is consistent with clinical benefit of HER2 inhibitor and VEGFR2 inhibitor for EAC.

TCGA research also showed that 13% EAC have PI3K/AKT/MTOR pathway alteration with PIK3CA activation (3%), PIK3R1 inactivation (3%), and phosphatase and tensin homolog (PTEN) inactivation (7%) (5). Another study of whole-exome sequencing with 149 EACs also showed that the PI3K pathway was altered in 13% by *PIK3CA* (6%), *PIK3R1* (4%) and *PTEN* (3%) mutation (6). Moreover, Prins *et al.* performed Immunohistochemistry assay and showed that p-mTOR overexpression was detected in 19.7% and correlated with poor survival (7). These results suggest that approximately 20% EAC might be driven primarily by the PI3K/AKT/MTOR pathway. However, the relationship between PIK3CA mutation and survival remains unclear for EAC. Shigaki *et al.* showed that PIK3CA mutation was associated with better survival in esophageal squamous cell carcinoma (8), while Harada *et al.* showed that PIK3CA mutation was not associated with survival in gastric cancer (9). In addition, the PI3K/AKT/mTOR pathway activation confers treatment resistance. Hildebrandt *et al.* demonstrated that genetic variations in genes which were related to PI3K/AKT/MTOR pathway correlated with increased recurrence risk in EAC patient who underwent therapy (10). Saeed *et al.* demonstrated that AKT expression level involved in pathologic response to preoperative chemoradiation for EAC; non-responders had higher expressions of AKT compared to complete responders (11). Therefore, the PI3K/AKT/mTOR pathway inhibition might be effective for EAC activating PI3K/AKT/mTOR pathway.

mTOR inhibitor for EAC

An mTOR inhibitor, everolimus, was evaluated in the GRANITE-1 study, which compared everolimus *vs.* placebo in advanced gastric cancer, and did not benefit overall survival (12). There is another study that compared paclitaxel plus everolimus/placebo but that trial also did not provide advantage (NCT01248403) (13). However, several shortcomings should be considered. Firstly, eligible patients had no evaluation of PI3K/AKT/mTOR pathway activation before treatment. Therefore, efficacy of mTOR inhibitor for GAC with activated PI3K/AKT/mTOR pathway remains unclear. Secondly, mTOR inhibition upregulates phosphorylation of AKT, resulting in resistance for mTOR inhibitor (14). Finally, as everolimus target only complex mTORC1, mTORC2 continue to activate downstream. Thus, dual targeted inhibitor, such as LY3023414, potentially overcomes this

resistant mechanism.

Combination with ERK-MAPK pathway inhibition

The PI3K/AKT/mTOR pathway inhibitor in combination ERK-MAPK pathway inhibitor are found to be more effective rather than single pathway inhibition (15). The two pathways have a complex cross-talk, leading to positive or negative feedback in various contexts (16). MEK inhibition upregulates PI3K pathway signaling, causing resistance to MEK inhibition (17). Tumors harboring RAS or RAF mutation, for example colon cancer, is resistant for single use of growth factor receptor inhibitor (18). The PI3K/AKT pathway was found out to be activated by BRAF inhibitors in BRAF mutated colon cancer, and thus the combination therapy with BRAF inhibitors and PI3K inhibitor has been evaluated in ongoing trial (19). However, EAC rarely have RAS or RAF mutation (5,6).

Potential for trastuzumab resistance

Resistant EAC for current standard treatment is the big issue to be overcome. Deguchi *et al.* showed that PTEN loss were more frequently detected in gastroesophageal adenocarcinoma with HER2-overexpression than that without HER2-overexpression, and PTEN loss caused a poor response to trastuzumab based therapy (20). Given that PTEN loss activates PI3K/AKT/mTOR pathway, this result suggests that HER2 inhibitor in combination with PI3K/AKT/mTOR pathway inhibitor might be effective for tumor with HER2 inhibitor resistance.

Limitations of the mice studies

We congratulate the authors for an excellent study. They have a successful animal model and completed pharmacodynamic studies in addition to efficacy studies. However, all preclinical studies have limitations. The preclinical models have consistently have come up short in predicting benefits in the clinic. The Zaid *et al.*'s paper helps us to move forward. We need better models where human-derived cancer tissue can be evaluated.

Conclusions

In summary, the PI3K/AKT/mTOR pathway involved in promoting cancer cell proliferation for EAC, thus its inhibitor might be effective for selected EAC patients.

PI3K/AKT/mTOR pathway inhibition with multi target or ERK-MAPK pathway inhibition might have a potential. Further study is needed for clinical use.

Acknowledgements

Funding: This research was supported by generous grants from the Caporella, Dallas, Sultan, Park, Smith, Frazier, Oaks, Vanstekelenberg, Planjery, and Cantu families, as well as from the Schecter Private Foundation, Rivercreek Foundation, Kevin Fund, Myer Fund, Dio Fund, Milrod Fund, and The University of Texas MD Anderson Cancer Center (Houston, Texas, USA) multidisciplinary grant program. This research was also supported in part by the National Cancer Institute and Department of Defense awards CA138671, CA172741, CA129926, CA150334 (JA Ajani), and by a grant from the Japan Society for the Promotion of Science Overseas Research Fellowships (K Harada).

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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doi: 10.21037/shc.2017.10.07

Cite this article as: Harada K, Song S, Baba H, Ajani JA. Is phosphatidylinositol 3-kinase/AKT/mammalian target of rapamycin pathway therapeutic target for esophageal adenocarcinoma. *Shanghai Chest* 2017;1:51.