Correspondence

Apatinib: get better application in gastric cancer and other cancers

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Many thanks to Dr. Giandomenico Roviello, Giulia Borsella and Daniele Generali for that they have written the editorial (1) at *Translational Cancer Research* (*TCR*) invitation, e.g., "Expanding treatment options for metastatic gastric cancer", discussing the clinical study (2) evaluating the efficacy and safety of apatinib *vs.* placebo in the treatment of patients with gastric- or gastro-esophageal junction adenocarcinoma for whom at least two lines of prior chemotherapy had failed. Their good suggestions and great expectation about apatinib further treatment and study on gastric cancer (GC) tremendously enlighten and inspired us.

GC is one of the most common malignancies worldwide. Just as Roviello G. *et al*. pointed out in the editorial that the prognosis of metastatic GC is still very poor with a median overall survival that not exceed the year. And there is an urgent need for further active treatments beyond second and further lines of chemotherapy in metastatic/advanced GC mainly because the number of patients suitable and long for a third-line of chemotherapy is growing.

Anti-angiogenesis therapy has been confirmed to exert an antitumor effect on various cancers and plays an important role. Acting as the highly selective and intensive inhibitors of vascular endothelial growth factor receptor 2 (VEGFR-2), there is a high degree of consistency of two trial results of apatinib (1,2) and ramucirumab (3,4) on metastatic GC. Thus those trial results sufficiently prove that anti-angiogenesis agents are very effective and safe in the treatment of metastatic/advanced GC.

Ramucirumab is a humanization monoclonal antibody, specifically inhibiting VEGFR-2 on the cell membrane. However apatinib is an oral, small molecular tyrosine kinase inhibitor (TKI), mainly targeting the intracellular downstream pathways of VEGFR-2 within the cell, and also inhibiting the receptor tyrosine kinase (RTK) such as c-kit, RET, and c-src. Thus there is big difference in each research idea and study protocol design according to their different mechanism.

There were one success and another in ramucirumab trials, e.g., ramucirumab alone or in combination with taxanes in second line treatment for advanced GC as well as non-small cell lung cancer (NSCLC), and available alongside FOLFIRI chemotherapy for metastatic colorectal cancer (CRC). In the similar way, apatinib further development is also on the agenda and gradually realized.

Apatinib's efficacy, tolerability and safety have been evaluated in one phase II and one phase III study in metastatic/advanced GC. And its phase IV study has been conducting and currently recruiting participants (5). There were success examples of small molecular angiogenesis agent nintedanib in combination with chemotherapy treatment for NSCLC (6). A series of preclinical studies (7,8) have also shown that apatinib in combination with taxanes, CPT-11, oxaliplatin and 5-Fu etc. has a certain synergy effect for GC, as well as NSCLC, and CRC. At present, the experimental study and a number of investigator initiate trials (IITs) of apatinib plus chemotherapeutic drugs have been carried out actively, including apatinib in combination with taxanes, S-1 capsule (Tegafur gimeracil oteracil potassium capsule) and others in or after second line treatment for advanced GC.

Moreover, so called anti-tumor maintain therapy is the therapy after completing predefined cycles of inducing chemotherapy, with less side effects and easy to use drugs to

continue treatment, in order to get the best treatment effect and to persistently extend its favorable clinical condition. Two clinical studies using apatinib as maintenance therapy in advanced GC have been launched already. And the exploratory phase II trial of apatinib used in adjuvant treatment of GC is also in synchronized. They are all IITs and explore studies.

It is well known that GC patients in Asia, especially in China, are different from one from European and American countries in their pharmacogenetics feature, etiology, epidemiology, molecular behavior, and clinical treatment strategies. Those obviously affect the patient prognosis and study results. Such as Japan subgroup population in ramucirumab for advanced GC (RAINBOW trial) (2) didn't get overall survival benefit. Therefore it should be paying much attention to those special situations in the future study and clinical practice in GC.

Apatinib may be an option for other cancers after failure of chemotherapy or other targeted therapy. For all we know, the phase II trials (9-12) of apatinib for NSCLC, hepatocellular carcinoma (HCC), advanced breast cancer, and mCRC have been conducted and finished. The phase III trials of apatinib for advanced NSCLC, and HCC registered in CFDA are ongoing smoothly. The phase II trials of apatinib for gastric-intestinal neuroendocrine carcinomas, AFP positive GC (hepatoid gastric adenocarcinoma), thyroid cancer of ^{131}I resistance, and soft tissue sarcoma and so on are also ongoing.

Apatinib is the first generation of oral anti-angiogenesis drug invented in China. Of course, it is understandable that many scholars may pay high attention to a new drug and want to carry out a lot of explore research, just after it advent and coming into the marketing. But it must be emphasized that scholars should follow the medical ethics and scientific principle, emphasize rigorous design, strict quality control and result analysis. The safety and efficacy data finally will decide everything. Continued investigation of apatinib is warranted in future studies, including its mechanism and clinical field (13). We are gladly looking forward to apatinib to get better application in GC and other cancers.

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