

Taking aim at the genomic diversity of gastrointestinal cancers: a changing landscape

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Submitted Sep 19, 2016. Accepted for publication Sep 20, 2016.

doi: 10.21037/jgo.2016.09.09

View this article at: <http://dx.doi.org/10.21037/jgo.2016.09.09>

Gastrointestinal (GI) cancers are responsible for approximately 1 of every 5 diagnosis with cancer and 1 of every 4 deaths from cancer (1). They encompass a largely heterogeneous and molecularly diverse group of cancers. The process for identifying targets that are “druggable” in this group is only very recent. Back in 2001, the cover of Time magazine featured imatinib as the new generation of revolutionary cancer killing agents that hit their target and spare normal cells. Fifteen years following this historical cover, the revolution towards a “new world order” in the treatment of GI cancers may be finally underway.

Metastatic colorectal cancer (mCRC) has been a hotbed for drug development for several decades with gradual but modest improvements in outcome. Agents targeting VEGF and EGFR have further improved outcome (2,3). However, and for more than a decade now, a largely futile effort was spent in an attempt to define a biomarker for bevacizumab and other anti-angiogenic agents. In parallel, attempts to refine the space for EGFR inhibitors evolved at a relatively slow pace away from the original immunohistochemistry staining for EGFR. Currently, a number of negative genomic predictors for response include expanded RAS (4) and BRAF (5) mutational analysis, and possibly HER2 amplification (6). Unfortunately, there remains a need for a positive predictor for the use of these relatively toxic and costly biologic agents. This obviously is disappointing, especially that twelve years following the approval of the first agents targeting EGFR and VEGF in mCRC, we just learned that anatomic location (left *vs.* right) might allow for “coarse” refinement (7). At first glance, our colleagues that treat lung cancer and melanoma may think GI oncology remains in the prehistoric ages compared to the evolution of the molecular and genetic landscape in their

respective fields. The good news is that it appears that the difference between left *vs.* right is more about molecular and genetic heterogeneity than simply anatomic location (8), and efforts into refining further the value of this observation are underway. Indeed, we have come a long way since the turn of the century where the first pivotal trial in HER2 directed therapy in advanced colorectal cancer was prematurely halted and the low expression of the target was declared a limitation for further development (9). The HERACLES trial and others of the sort have revived the interest into this target in mCRC (10). The same is true about a multitude of low yielding alterations from MSI as a predictor for the efficacy for PD1 inhibitors to BRAF directed therapies and many other efforts in development that will likely move the needle in the treatment of mCRC in a meaningful way.

On the other hand, advancements in non-colorectal cancers, malignancies that tend to have fewer options and generally a worse prognosis, have been slower to evolve until more recently. Uncovering the heterogeneity of cancers involving the stomach and the biliary tract has made it into a target rich and promising area for new drug development. The development of HER2 targeted strategies in gastric cancer helped confirm that there is “life after breast cancer” for trastuzumab (11), with further implications into other GI cancer indications. Furthermore, strategies taking advantage of the molecular heterogeneity of gastro-esophageal cancers have opened the door wide open to promising molecular in this group of disease. The same is true in biliary tract cancer (BTC). Despite their rarity and the lack of a good standard, agents that target FGFR and IDH are feverishly being developed in this small space, based on very promising preliminary data. Additionally, immunotherapeutic strategies

have found promise in almost every GI cancer at different developmental stages with the most advanced being in mCRC and gastric cancers. Unfortunately, adenocarcinoma of the pancreas does not share the same level of genetic diversity or immunogenic potential, thus keeping a “ceiling of tempered glass” on potential advancements in outcomes for patients inflicted with this dreadful disease. Identification of a subtype of pancreatic adenocarcinoma characterized by homologous recombination deficiency may allow us to get closer to breaking this ceiling. Emerging treatment options under development such as the ones targeting PARP (such as Olaparib and Rucaparib) seem to be holding such promise (12).

This special issue titled “Genetic Diversity of Gastrointestinal Malignancies and Emerging Targets: A New World Order”, includes multiple comprehensive reviews that help summarize the current understanding of the molecular, genetic and immunologic landscape of GI malignancies and its potential impact on emerging treatment strategies. The issue will also summarize the promise of “liquid biopsies” into improving selection of patients eligible for targeted approaches and better understand the evolution of resistance to therapy.

Acknowledgements

None.

Footnote

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

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Cite this article as: Bekaii-Saab T, El-Rayes B. Taking aim at the genomic diversity of gastrointestinal cancers: a changing landscape. *J Gastrointest Oncol* 2016;7(5):673-674. doi: 10.21037/jgo.2016.09.09