Editorial Commentary

Single nucleotide polymorphisms as the new predictors of therapy decisions in gastroesophageal junction and gastric adenocarcinoma?

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We are delighted having caused an editorial with regard to our paper on single nucleotide polymorphisms (SNPs) and neoadjuvant treatment toxicity of FLOT within locally advanced gastric and gastroesophageal junction cancer (1,2).

Perkhofer and Hann point out the lack of outcome prediction for the now widely used FLOT regiment in gastric cancer. With an aging population, the need for biomarkers predicting toxicity, especially life-threatening toxicity such as neutropenia, is markedly increasing and it is important to individualize treatment options and dosage. In the elderly, intensive treatment options such as the FLOT regimen may not be used just because of the age of the patients. SNPs could therefore represent an easy approach to predict toxicity. As pointed out, a prospective validation would be desirable to include such biomarkers for toxicity in everyday clinical practice.

Therapeutic decisions for perioperative chemotherapy are often solely based on tumor histology and stage. Even tumor board decisions just include the results of organ function diagnostic and a subjective assessment of patients' fitness to recommend an intensive or a less intensive therapy. The assessment of Her2 in metastatic gastric or gastroesophageal adenocarcinoma displays the only proposed personalized therapy individualization according to the current German and European guidelines (3,4).

Pretherapeutic clino-pathological parameters may help to predict response and prognosis of preoperative chemotherapy in gastric cancer and represent a first step towards patient tailored therapy (5). The achievement of a complete pathological response after neoadjuvant treatment is of prognostic value in terms of response but can only be obtained after treatment is completed (6).

The use of germline SNPs from peritumoral formalin-fixed paraffin-embedded stroma tissue has the advantage of sufficient availability of tissue after resection in contrast to small samples from gastroscopy during the diagnostic workup where the spare material is often used up for routine histological staining. A workable compromise displays the use of genomic DNA extracted from peripheral blood which can be obtained before the initiation of therapy. For future trials, the use of complementary use of liquid biopsy and tissue bound analysis represents a further step towards therapy individualization.

Despite some data concerning treatment outcome and toxicity of gastric cancer by the analysis of germline polymorphisms, validated evidence concerning SNPs in the neoadjuvant or adjuvant setting is still limited. The transfer of data derived from palliative setting is suggestive but auxiliary. Same applies to pharmacogenetic data of several other GI tumors. There is growing evidence by data from mostly Asian trials implying the impact of SNPs related to susceptibility and prognosis of gastric adenocarcinoma and cancer of the gastroesophageal junction.

Additional to the well-described SNPs of genes playing a role in the metabolism of fluorouracil and platin derivates, i.e., thymidylate synthase (TS), methylenetetrahydrofolate

reductase (MTHFR), xeroderma pigmentosum group D (XPD), excision repair cross-complementing group 1 and 2 (ERCC1, 2), X-ray repair cross-complementing group 1 (XRCC1) and glutathione S-transferases (GSTs), the range must be extended to implement taxans and monoclonal antibodies (7).

With the growing importance of FLOT both in the perioperative and palliative setting, taxan-induced neuropathy and neutropenia may be the cause of severe side-effects. Comparability and reproducibility of SNPs involved in docetaxel metabolism is hampered by sparse data, lacking validation, heterogeneous trials, various treatment lines, different regimens and tumor entities. Taking into account the preliminary data of the PRODIGY trial, the importance of docetaxel could increase in Asian countries in the neoadjuvant setting (8). Particularly in the view of different tumor biology and ethnic differences in chemotherapeutic metabolism, a comprehensive collection of respective SNP data is warranted.

A novel approach to select patients suffering from Her2 positive metastatic gastric cancer for treatment with trastuzumab is followed by Pietrantonio *et al.* (9). Using a panel of candidate genomic alterations and amplifications including EGFR/MET/KRAS/PI3K/PTEN, they could demonstrate that patients without candidate alterations had a significantly longer median PFS and OS. Furthermore, the authors stress the relevance of other potential oncogenic drivers whose co-amplification may lead to a resistance to trastuzumab. In this regard, for future trials a more comprehensive approach and detailed molecular profiling for translational research in treatment studies is demanded. Apart from that, basket trials should help to provide respective numbers of patients to identify mutations putative of treatment response or toxicity regardless of the tumor entity and stage. In Korean patients with advanced gastric cancer receiving second line therapy, high expression of placental growth factor in tumor tissue was found to be a negative predictive biomarker for the treatment with ramucirumab (10). With new therapeutic options beyond classical chemotherapy in second and further line therapy, there will be an increasing demand for tools of treatment individualization as well.

To pick up the title of the comment by Perkhofer and Hann, SNPs are not the new predictors of therapy decisions but should be further advanced as existing and developing and be integral part of patient tailored therapy in gastric and gastroesophageal junction adenocarcinoma.

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