Editorial

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

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Comment on: Schulz C, Zhang W, Lenz HJ, *et al.* Germline polymorphisms (SNPs) to predict toxicity and efficacy in FLOT-treated patients with locally advanced gastroesophageal junction or gastric adenocarcinoma—data from the NeoFLOT study. Transl Cancer Res 2018;7:1393-405.

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Western populations show a remarkable switch in gastroesophageal cancer phenotype with predominance for adenocarcinomas nowadays (1). This contrasts the rest of the world and is mainly caused by lifestyle factors (2). Thereby, obesity and gastroesophageal reflux with Barret's esophagus are the suspected correlates (3,4). Primary diagnosis of gastroesophageal junction (GEC)/gastric cancer (GC) with potentially curatively resectable disease stage is not uncommon (5). Though submucosal infiltration is frequently found with and increased risk of prognostic relevant lymph-node metastases. In line the Magic trial (6) first implemented the concept of perioperative chemotherapy to be superior compared to up front surgery. Therefore, Cunningham *et al.* made use of the palliative established ECF-regimen (epirubicin, cisplatin, 5-fluorouracil). Subsequently the significance of perioperative chemotherapy was underpinned by the ACCORD 07 trial with 5-fluorouracil/cisplatin (7). Moreover, the FLOT (docetaxel, oxaliplatin, 5-fluorouracil/leucovorin) protocol showed promising results in palliative care (8,9) and therefore was transferred to the perioperative setting as well. The recently published FLOT4 study demonstrated superiority of FLOT compared to the ECF/ECX (capecitabine instead of 5-FU) regimen, regarding overall survival (OS) (10). Summarized perioperative chemotherapy established as standard of care in UICC II and III esophageal cancers [≥ cT2 tumors and/or suspect local lymph node status (N)] and entered guideline recommendations (11,12). However, irrespective of the regimen used they all reflect classical chemotherapies and thereby being far from personalized and lacking evidence of individual efficacy and toxicity.

Consequently Schulz *et al.* recently published an interesting novel approach as a spin-off of the NeoFLOT trial. The NeoFLOT trial itself addressed the use of prolonged neoadjuvant chemotherapy (6 cycles of FLOT) in patients with T3 and T4 GEC/GC. The rationale of the trial is the high number of patients that do not receive adjuvant chemotherapy to different reasons (10). The NeoFLOT trial proved effectivity and tolerability of prolonged neoadjuvant FLOT therapy, exposing intestinal type tumors as a subgroup of very good responders. Ideally the trial came along with a translational side project that was now addressed focusing on the need for predictive markers that on the one hand select for therapy responders. On the other hand, select those patients that suffer relevant side effects from therapy. As toxicity is a major hurdle that at worst can postpone resection or negatively influence postoperative outcome caused by e.g., excessive weight loss or remaining side effects. Thereby, Schulz *et al.* took advantage of previously published data on single nucleotide polymorphisms (SNPs) for genes related to pyrimidine and methionine biosynthesis, DNA repair and thymidylate synthase. SNPs represent sequence variations caused by stable substitution of a single base in the DNA. This common phenomenon drives genetic variation among people but mostly not affect health. Nevertheless, SNPs have the potential to act as biological markers and can

affect gene functions, outlined in various publications in GEC/GC (13-17). Within this study DNA was extracted from formalin embedded tumor specimen followed by PCR-based analysis of the candidate SNPs. Results were correlated to the prospectively obtained data and showed significant association with toxicity and less for survival and tumor response.

Predominantly hematotoxicity occurred and was related to SNPs in the nucleotide excision repair proteins ERCC2 (rs1799793 and rs13181) and ERCC1 (rs11615). Interestingly thereby ERCC2 rs1799793 SNPs had a different impact: (I) AA drives thrombocytopenia, (II) A/G and G/G neutropenia. In line, a G/G polymorphism in the methionine synthase (MTR) Rs1805087 was significantly associated with ≥ grade 2 anemia. Polymorphisms in the MTR (rs1805087) were strongly and in ERCC2 (rs1799793 and rs13181) to a lesser extend associated with diarrhea. Selective SNPs related to polyneuropathy development in view of the combined therapy with oxaliplatin and docetaxel in the FLOT protocol were not found. OPRT rs1801019 G/A, an enzyme involved in the pyrimidine biosynthesis, showed best association to overall response rate with increased but statically non-significant prolonged PFS and OS.

Interestingly none of the SNPs were associated with significant survival advantages but much more none of them predicted worse prognosis. Limitations of the trial were given to the small sample size and missing controls. However, data shown was largely in concordance with published findings and thereby strengthens the value and robustness of the approach. The data presented should be the basis for further prospective trials with respect to toxicity stratification that allow timely dose adaption. Therefore, GEC and GC offer the ideal prerequisites as normally being easily and repetitively accessible.

Summarized Schulz *et al.* carried out an approach that could be easy to implement in routine diagnostic with a pre-defined primer set and may help to improve therapy outcome.

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