ctDNA in Gastric and Gastroesophageal Cancer: Prognostic, Predictive, or Preliminary?

Alexander M. Frankell and Elizabeth C. Smyth

In this issue of *Clinical Cancer Research*, Maron and colleagues describe their analysis of the largest gastric and gastroesophageal cancer circulating tumor (ctDNA) dataset yet published (1). Using a 73-gene ctDNA panel, a large international cohort (n = 1,630 patients) was used to characterize the ctDNA genomic landscape of GEA, whereas a smaller subset of clinically annotated ctDNA samples from two U.S. and Korean cancer centers (n = 369 patients), some with matched somatic tumor next-generation sequencing (NGS) analysis or serial ctDNA collections, was used to study the interaction between ctDNA, prognosis, and treatment effect (Fig. 1; ref. 1). Although there are differences in treatment and outcome for gastroesophageal cancer in Asian and non-Asian countries, these cancers share many fundamental molecular characteristics independent of regional origin (2). The low individual prevalence of individual drivers and high intrapatient heterogeneity has been onerous for developmental therapeutics in gastroesophageal cancer and therefore any tool that can mitigate these challenges is welcome (3, 4).

As a snapshot of gastroesophageal cancer molecular drivers, there were no surprises in the global ctDNA cohort; similar genomic alternations were detected compared with previous large series (1). Although the authors describe differences in Western versus Eastern cohorts, these differences require confirmation in a statistically robust manner. The spatial and temporal heterogeneity of gastroesophageal cancer is reiterated; in a subset of patients with three samples (primary, metastasis, and ctDNA), only 26% of genomic alterations were concordant across triplet sampling. Such high discordance may also derive, in part, from poor sensitivity and specificity of such tumor-naive ctDNA detection approaches in mid-to-low burden disease. This issue would be considerably exacerbated in cohorts not so dominated by stage IV disease. Focusing on HER2, the only routinely targeted amplification in gastroesophageal cancer; of 7 triplet-tested HER2-positive cases, only 2 (28%) were concordant, emphasizing the risk of missed opportunities to target HER2 when using a single site or modality of assessment. Furthermore, in HER2-positive tumors identified using standard clinical testing, ctDNA may refine a more trastuzumab-sensitive population. Using both tissue and ctDNA NGS for HER2 amplification, and considering ctDNA shed, a group of highly sensitive HER2-amplified patients with better survival when treated with trastuzumab were identified [overall survival, 26.3 vs. 7.4 months; HR 0.2–0.6; 95% confidence interval (CI), 0.05–0.6; P = 0.004]. Finally, in patients with putatively sensitive retained tumoral HER2 amplification following trastuzumab, acquired HER2 therapy resistance mechanisms were detected using ctDNA. As the second generation of trials of HER2-targeting drugs in gastroesophageal cancer will be reserved for patients with retained HER2 signaling following trastuzumab, ctDNA may have a role in the early prediction of resistance mechanisms and subsequent treatment for these patients.

Maron and colleagues demonstrate that the incidence of targetable dysregulated genes detected is higher in the ctDNA population than in the sample of matched available tissue–NGS samples. Given the challenges associated with recruitment to low prevalence biomarker trials, this could have important implications. The authors also make an important observation regarding the correction of detected amplifications for overall ctDNA volume; in the context of low ctDNA shed, any measurable ctDNA amplification is likely to represent high-level amplification in tissue and to be predictive of an oncogenically addicted tumor. Drawing a parallel with osimertinib in non-small cell lung cancer, could anti-HER2 therapies be extended to patients with high-level HER2 amplification in plasma who have a HER2-negative biopsy? If ctDNA is to be used in future as an eligibility criterion for trials, standardization of ctDNA amplification assessment and interpretation will be required.

Prognostically, Maron and colleagues confirm that measurement of the largest mutated ctDNA clone (maxVAF) may act as a surrogate for disease burden in patients with metastatic gastroesophageal cancer. Indeed, maxVAF as a crude measure of disease burden also appeared to be prognostic in a small group of patients with resectable GEA. However, in patients with metastatic cancer, it is not clear how much value a one-time static ctDNA measurement adds to conventional imaging. In patients with metastatic gastroesophageal cancer, baseline ctDNA may be more helpful as a steer toward molecularly targeted treatment than as a prognostic tool. In contrast, the results of dynamic measurements of
ctDNA during treatment signposts potential future therapeutic usefulness. In the cohort of patients who had pretreatment and follow-up ctDNA assessment, a decline in variant allele fraction (VAF) of >50% was prognostic for superior survival. However, such assay cutoffs should also be applied to negative control samples (e.g., healthy bloods) to accurately calculate specificity. In addition, the large number of death endpoints in the <50% reduction cohort suggests this cutoff would have an unacceptably low specificity for clinical applicability. Finally, small size of the cohort ($n = 35$) and the wide variation in time from pretreatment test to postanalysis (28–108 days) limit the generalizability of this result. Criticisms aside, these findings do raise the possibility that early measurement of ctDNA could predict for lack of treatment efficacy in gastroesophageal cancer. To systematically validate these findings and determine an optimal cutoff correlating with treatment outcome, large-scale prospective measurement of ctDNA in the context of clinical trials are required, similar to what has recently been achieved in the PALOMA-3 breast cancer study [5].

Although ctDNA-driven changes in treatment are attractive, this approach is predicated on multiple active treatments options, which unfortunately is not true for GEA, a disease in which most non-Asian patients receive between one and three lines of therapy. Where ctDNA could be truly transformative for gastroesophageal cancer is in the perioperative setting. In colon cancer, the presence of mutation-specific DNA following surgery is a clear indicator of relapse, and international clinical trials are currently evaluating ctDNA as a risk stratification marker for treatment deescalation or intensification following surgical resection. A small but intriguing group of patients in the current dataset suggests that the same may be true in gastroesophageal cancer; patients who were ctDNA positive after surgery had worse disease-free survival compared with those who were ctDNA positive [median disease free survival of 12.5 months, vs. unreached ($P = 0.03$; HR = 0.1; 95% CI, 0.01–1.1)]. These findings come with a caveat; three apparently ctDNA-positive patients did not relapse following surgery. These patients had characteristics that suggest clonal hematopoiesis may have been the culprit for these false positive results. If postresection ctDNA results are to provide credible evidence to drive decision making postoperatively, then consideration of more bespoke tumor-based ctDNA panels rather than off-the-shelf kit may be required.

Critically, Maron and colleagues use a tumor-naive approach to detect tumor-derived mutations in cell free DNA (ctDNA), which requires no additional testing and analysis of tumor tissue. However, this requires careful analysis to rule out infiltration of mutations derived from other tissues in the body and the non-reference germline sequences. Maron and colleagues were unable to sequence buffy-coat or matched germline samples in this study to rule out false identification of clonal hematopoiesis, as acknowledged, or uncommon heterozygous SNPs as tumor-derived somatic mutations. Possible infiltration of germline heterozygous SNPs is evidenced by mild clustering at 50% VAF in one figure, despite careful attempts to remove signal from the germline, highlighting this challenge.
In conclusion, Maron and colleagues have shown the possibilities for ctDNA in gastroesophageal cancer; however large-scale prospective confirmatory studies are required before integrating ctDNA assessment into gastroesophageal cancer treatments as a standard of care. To achieve this, at the very least, prospective serial ctDNA collection should be adopted in gastroesophageal cancer clinical trials.

References

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E.C. Smyth is a paid consultant for Astellas, Bristol-Myers Squibb, Gritstone Oncology, Celgene, and Servier. No potential conflicts of interest were disclosed by the other author.

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