Gastroesophageal Adenocarcinoma

Subjects: Oncology
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Keywords: Advanced Gastroesophageal cancer ; Precision Medicine ; New Drug development

1. Introduction

Gastroesophageal adenocarcinoma (GEA) represents the fifth most frequent tumor and the third leading cause of cancer-related deaths worldwide. In 2018 GEA was diagnosed in about 1,000,000 people, causing death in 783,000 patients. Historically, Lauren classified gastric cancers into intestinal, diffuse, and indeterminate/mixed histology. The most common type is intestinal, which tends to form glandular structures and is often associated with intestinal metaplasia and H. pylori infection. Conversely, diffuse-type tumors are characterized by non-cohesive scattered cells, sometimes associated with the presence of signet-ring cells. These tumors trends to be locally aggressive with a higher rate of peritoneum invasion and a lower response rate in neoadjuvant studies, when treated with platinum-based therapies without taxanes. The World Health Organization (WHO) further classified gastric cancer into tubular, papillary, mucinous, poorly cohesive (including Lauren diffuse type), and mixed variants. Nevertheless, neither stratification has helped characterize patient outcomes or guide treatment approach. Further research focus has been directed at analyzing predictive biomarkers and targetable drivers. Molecular studies have been led by The Cancer Genome Atlas (TCGA), which studied both adenocarcinoma and squamous cell carcinoma spanning the stomach and esophagus. TCGA proposed a comprehensive molecular classification of GEA according to genomic, transcriptomic and proteomic data into four different subgroups, respectively, named as chromosomally instability (CIN), genomically stable (GS), Epstein–Barr Virus (EBV) and microsatellite instability (MSI). More than 50% of tumors belong to the CIN subgroup, which is mainly characterized by receptor tyrosine kinase (RTK) alterations. Despite this, apart from epidermal growth factor receptor (HER)2 amplification, MSI and EBV, no other molecular alterations have been used in the clinic as effective predictors for treatment decision-making.

2. Treatment of GEA

Despite concerted efforts to develop comprehensive molecular classifications for GEA aimed at offering a precision approach to patients, only a few drugs have been approved, and also the epidermal growth factor receptor 2 (HER2) and microsatellite instability have been recognized as predictive biomarkers, thus far. A randomized multicenter trial (ToGA) assessed the addition of trastuzumab to platinum-based chemotherapy in HER2-amplified patients with locally advanced or metastatic GEA. Patients were randomized to receive trastuzumab plus platinum-based chemotherapy (capecitabine or 5-fluorouracilplus cisplatin) versus chemotherapy alone. In the experimental arm, patients experienced a substantial improvement in all outcomes and particularly in overall survival, which was increased by 2.7 months in the trastuzumab-containing arm (13.8 versus 11.1 months, Hazard ratio 0.74, P: 0.0046). Based on these results, the combination of trastuzumab plus platinum-based chemotherapy represents the gold standard for advanced HER2-amplified GEA. The extent of improvement was related to the degree of amplification, as demonstrated in an exploratory post-hoc analysis. The subset of tumors with HER2 immunohistochemistry (IHC) 3 or IHC2/FISH+ reached a median overall survival of 16 months in the trastuzumab group versus only 11.8 months in the chemotherapy control arm (HR 0.68, 95% CI 0.5–0.83). These results indicated that trastuzumab provides the best therapeutic benefit in strongly HER2-amplified patients. Other HER2 blocking drugs were successively tested to evaluate their potential in HER2-amplified and advanced GEA patients. Disappointingly, no benefit in overall survival was achieved in patients diagnosed with locally advanced or metastatic GEA when treated with lapatinib, either as a single agent or in combination with platinum-based chemotherapy, pertuzumab or TDM-1.

Interesting results have recently been achieved with another antibody-drug conjugate. Trastuzumab deruxtecan (DS-8201) consists of a humanized, monoclonal, anti-HER2 antibody binding a cytotoxic topoisomerase I inhibitor by means of a cleavable, tetrapeptide-based linker. Probably owing to this dynamic feature, trastuzumab deruxtecan represents a good strategy for heterogeneous tumors, such as gastric cancer in which HER2 overexpression may vary from cell to cell or even across different metastatic locations within the same patient In a phase II trial design, patients diagnosed with advanced GEA who had received at least two previous lines were randomized to trastuzumab deruxtecan versus the treating physician's choice of irinotecan or paclitaxel. Objective response was higher in the experimental group than with chemotherapy (51% versus 14%). Patients on trastuzumab deruxtecan gained significantly in median overall survival (12.5 months versus 8.4 months. HR=0.59; p=0.01). Greater efficacy of trastuzumab deruxtecan over chemotherapy was confirmed in patients with the highest level of HER2 expression (Response Rate 58% versus 29%).

The improvement in the molecular analysis due to the application of high throughput technologies based on DNA and RNA sequencing has opened a novel scenario leading to the personalization of treatment. However, several compounds, such as anti-EGFR or MET monoclonal antibodies, as well as tyrosine kinase inhibitors, were no longer able to improve clinical outcomes. Moreover, among the anti-HER2 agents, only trastuzumab when combined to platinum-based chemotherapy was able to improve progression-free survival and overall survival in HER2 amplified tumors, suggesting that tumor characteristics, such as heterogeneity and the co-presence of further molecular alterations could negatively impact a precision medicine approach. Nevertheless, the possibility to target with novel more specific agents, the HER2, Claudine, Fibroblast Growth Factor Receptors (FGFR), and other alterations with a molecular matched novel therapy could significantly improve clinical outcomes over advanced gastric cancer patients. On the other hand, the development of immunotherapy could also represent a promising strategy in a selected population.

3. Conclusions

GEA presents as a very heterogeneous disease. The high number of molecular alterations, as reflected in the percentage of tumors belonging to the CIN subtype, makes a precision approach complicated. Nevertheless, the possibility of identifying certain drivers due to the implementation of omics in recent years has opened up novel opportunities in cancer patients. Among HER2-amplified tumors, more active molecules are leading to significantly improved benefits in these patients. The growing interest in the tumor microenvironment, together with the development of novel immunotherapies and combinations could also herald new approaches. The road towards a personalized approach is long, requiring further studies and breakthroughs in current knowledge.