Emerging Therapeutics of Gastroesophageal Cancers

Subjects: Oncology

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Gastroesophageal cancers are a group of aggressive malignancies that are inherently heterogeneous with poor prognosis. Esophageal squamous cell carcinoma, esophageal adenocarcinoma, gastroesophageal junction adenocarcinoma, and gastric adenocarcinoma all have distinct underlying molecular biology, which can impact available targets and treatment response. Novel therapeutic targets are under development and future treatments will be personalized based on molecular profiling.

Keywords: esophageal cancer ; gastric cancer ; immunotherapy

1. Introduction

Gastroesophageal cancers, including cancers of the esophagus, gastroesophageal junction (GEJ), and stomach, represent some of the most common cancers worldwide, with an estimated 1.7 million new cases per year. When combined, they are the third leading cause of cancer-related deaths globally [1]. Esophageal cancers are comprised of two major histologic subtypes: squamous cell carcinoma (ESCC) and adenocarcinoma (EAC). While ESCC is the most common subtype worldwide, EAC is more common in the Western countries [2]. ESCC is mainly found in the upper to mid esophagus and is associated with tobacco and alcohol use, whereas EAC is mostly found in the distal esophagus and is associated with obesity, gastroesophageal reflux, and Barrett's esophagus [3][4]. In addition to differences in risk factors and locations, these two subtypes also have distinct molecular biology and responses to treatment, which should lead to different treatment strategies [5]. In contrast, GEJ and gastric cancers are almost all adenocarcinomas (ACs). Gastric adenocarcinomas (GACs) can be further classified into intestinal and diffuse histologic subtypes based on Lauren classification [6]. The Cancer Genome Atlas Research Network has also defined four molecular subtypes of GAC (Epstein-Barr Virus [EBV]-positive, microsatellite instability [MSI], genomically stable, and chromosomal instability), which may have implications for future therapeutic development [7]. Many exciting potential new molecular targets are being explored in ongoing clinical trials, leading to a future of personalized therapies.

2. Claudin 18.2

Claudin 18 isoform 2 (CLDN 18.2) is a tight junction molecule that is orthotopically expressed in gastric cancers and ectopically activated in multiple other cancer types, including pancreatic, esophageal, ovarian, and lung [8]. Zolbetuximab, a monoclonal antibody against CLDN 18.2, has previously shown activity when added to chemotherapy in the phase 2 FAST trial, where the addition of zolbetuximab to chemotherapy increased survival of patients with advanced gastric/GEJ AC [9]. During the 2023 ASCO Gastrointestinal Cancer Symposium, results from the phase 3 SPOTLIGHT trial were presented. In HER2-negative, CLDN 18.2-positive, advanced gastric or GEJ AC patients, first line treatment with zolbetuximab + FOLFOX (5-fluorouracil + oxaliplatin) (n = 283) significantly improved progression free survival (PFS; 10.6 months vs. 8.7 months, hazard ratio 0.75, p = 0.0066) and overall survival (OS; 18.2 months vs. 15.5 months, hazard ratio 0.75, p = 0.0053) compared to placebo + FOLFOX (n = 282) [10]. GLOW, another phase 3 trial of zolbetuximab + chemotherapy (capecitabine + oxaliplatin) in CLDN 18.2-positive HER2-negative advanced gastric/GEJ AC patients, recently announced that it met its the primary endpoint of PFS and secondary end point of OS [11]. These positive trials could establish CLDN 18.2 as a new predictive biomarker and zolbetuximab + chemotherapy as a new standard of care treatment for CLDN18.2-positive advanced gastric/GEJ cancer patients. It is important to note that in the SPOTLIGHT trial, only 13.2% patients who were CLDN 18.2-positive also had PD-L1 CPS ≥ 5, and all enrolled patients were HER2-negative. The CLDN 18.2-positive population represents a unique subset of patients who were previously mostly considered triple negative and would not have qualified for any targeted therapy options.

There are now multiple ongoing trials of novel monoclonal antibodies, antibody-drug conjugates, bispecific antibodies, and cellular therapies targeting CLDN 18.2 (NCT04856150, NCT04400383, NCT04632108, NCT04805307, NCT04495296, NCT04404595). Zolbetuximab is also being studied in combination with immunotherapy (IO) agents (NCT03505320).

3. FGFR2

Fibroblast growth factor receptors (FGFRs) have been found to be therapeutic targets in multiple cancer types, and FGFR2 specifically is a promising target for gastroesophageal cancers [12][13]. Bemarituzumab is a monoclonal antibody that targets FGFR2b [14]. The FIGHT trial, a phase 2 randomized placebo-controlled study, evaluated bemarituzumab + FOLFOX (n = 77) vs. placebo + FOLFOX (n = 78) in patients with FGFR2b overexpressed/amplified advanced gastric or GEJ AC [15]. While the trial did not meet its primary endpoint of PFS, the bemarituzumab group trended toward longer PFS (9.5 months vs. 7.4 months, hazard ratio 0.68, $p = 0.073$), longer OS (not reached vs. 12.9 months, hazard ratio 0.58, $p = 0.027$), and higher objective response rate (ORR; 47% vs. 33%) compared to the placebo group. The FIGHT trial also showed that around 30% patients with HER2-negative advanced gastric cancer had FGFR2b overexpression or FGFR2 amplification, which supports the development of FGFR2 as a therapeutic target. The phase 3 FORTITUDE-101 trial is currently underway to further evaluate bemarituzumab + FOLFOX as first line treatment of FGFR2b-selected advanced gastric/GEJ AC patients (NCT05052801).

4. DKK1

The canonical Wnt/β-catenin signaling pathway plays an important role in cancer cell proliferation, survival, and migration [16][17][18]. Dickkopf-1 protein (DKK1) is an antagonist of the Wnt signaling pathway, and overexpression of DKK1 has been associated with tumor growth, angiogenesis, and a more immunosuppressive tumor microenvironment [19][20][21]. DKN-01 is a monoclonal antibody against DKK1, and it is being studied in combination with tislelizumab (anti-PD-1) and chemotherapy (FOLFOX or CAPOX) in the phase 2 DisTinGuish trial (NCT04363801). Data from this combination as first line therapy for HER2-negative advanced gastric/GEJ cancer patients (n = 25) showed promising activity [22][23]. The ORR for all patients is 68% and the ORR for the DKK1 high group is 90%.

5. Tyrosine Kinase Inhibitors

The combination of multi-kinase inhibitor (MKI) and IO has been successful in the treatment of other tumor types, including endometrial cancer and renal cell carcinoma. This combination is also being actively explored in gastroesophageal cancers. Prior studies have shown that oncogenic kinases have immunomodulatory activity and can lead to an immunosuppressive tumor microenvironment [24]. Inhibition of oncogenic kinases with MKIs have been shown to increase cytotoxic T-cell infiltration and decrease tumor associated macrophages, which leads to a more immune-permissive tumor microenvironment [25]. The impact of MKIs on the tumor microenvironment can synergize with IO use to improve antitumor efficacy [26]. The EPOC1706 trial was a single-arm phase 2 trial that evaluated lenvatinib + pembrolizumab in patients with advanced GAC (n = 29) and ORR was 69% [27]. There are now phase 3 trials to evaluate pembrolizumab + lenvatinib + chemotherapy in advanced ESCC and gastroesophageal AC (LEAP-014, LEAP-015). Similarly, trials to evaluate other combinations of MKIs and IOs are also underway (atezolizumab + cabozantinib, tislelizumab + sitravatinib; NCT05007613, NCT05461794).

6. Others

The EBV-positive molecular subgroup of GAC patients may present a unique opportunity for treatment with IO therapy. A prospective phase 2 trial of pembrolizumab in patients with advanced gastric or GEJ AC who progressed after first line chemotherapy found that EBV-positive patients (n = 6) had an ORR of 100% [28]. Another prospective observational study noted that EBV-positivity is a biomarker for immunotherapy in metastatic gastric cancer [29]. Due to the small sample sizes, larger prospective trials will be needed to fully evaluate the role of IO in EBV-positive patients. Nonetheless, targeting EBV-positive patients with IO therapy may be a novel option for the management of these patients.

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