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Anti-Tumour Treatment

Evolution of checkpoint inhibitors for the treatment of metastatic gastric cancers: Current status and future perspectives

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ABSTRACT

Background: Standard treatment options for patients with advanced gastric or gastroesophageal junction cancer (GC/GEJC) are associated with limited efficacy and some toxicity. Recently, immunotherapy with antibodies that inhibit the programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1) interaction has emerged as a new treatment option. This manuscript reviews early-phase and late-phase trials of immunotherapy in advanced GC/GEJC.

Methods: Searches for studies of immunotherapy in GC/GEJC were performed using PubMed, ClinicalTrials.gov, and abstract databases for select annual congresses. Findings were interpreted based on expert opinion.

Results: Monotherapy with anti–PD-1/PD-L1 antibodies, including pembrolizumab, nivolumab, avelumab, durvalumab, and atezolizumab, has shown interesting objective response rates (ORRs; 7–26%) across varying GC/GEJC populations, with ORRs potentially higher in PD-L1 + vs PD-L1 − tumors. Safety profiles compare favorably with chemotherapy, with grade ≥3 treatment-related adverse events occurring in 5–17%. Based on a large phase 2 study, pembrolizumab was approved in the United States for third-line treatment of patients with PD-L1 + GC/GEJC. In a phase 3 trial, third-line or later nivolumab increased overall survival vs placebo in an Asian population, leading to regulatory approval in Japan, although other completed phase 3 trials did not show superiority for pembrolizumab or avelumab monotherapy vs chemotherapy. Other trials in advanced GC/GEJC are assessing various anti–PD-1/PD-L1–based strategies, including administration in first-line and later-line settings and as combination (with chemotherapy or agents targeting other immune checkpoint proteins, eg, CTLA-4, LAG-3, and IDO) or switch-maintenance regimens.

Conclusions: Anti–PD-1/PD-L1 antibodies have shown encouraging clinical activity in advanced GC/GEJC. Results from ongoing phase 3 trials are needed to further evaluate the potential roles of these agents within the continuum of care.

Introduction

Gastric cancer (GC) and gastroesophageal junction cancer (GEJC) are a major global health concern [1]. GC is the fifth most common cancer worldwide and the third leading cause of cancer-related death, with > 700,000 attributed fatalities globally per year, the highest number of which are in Eastern Asia [2]. In countries without active screening programs, GC is mostly diagnosed at an advanced stage due

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to its nonspecific symptoms, which is associated with a poor overall survival (OS) [3,4]. GEJC has historically been considered a distinct disease from GC, although both are genomically very close and have similar recommended treatments for advanced disease [5–8]. There has been a shift in the relative incidence of GC vs GEJC, with GC declining and GEJC increasing, particularly in the Western hemisphere. However, GEJC remains far less common than GC overall. Interpretation of GEJC epidemiology has been complicated historically by a lack of uniform classification [9]. The Cancer Genome Atlas project has identified 4 major genomic subtypes found in both GC and GEJC adenocarcinoma: Epstein-Barr virus (EBV)+, microsatellite instable (MSI), genomically stable, and chromosomally instable [5,6]. In addition, the Asian Cancer Research Group has developed an alternative genomic classification system for GC based on 4 subtypes: MSI, microsatellite stable (MSS)/epithelial-to-mesenchymal transition, MSS/TP53+, and MSS/TP53−; the differential survival durations shown for Asian Cancer Research Group subtypes have been validated in independent cohorts [10].

Cytotoxic chemotherapy is the basis of treatment for most patients with advanced GC/GEJC, with choice of regimen directed by patient performance status, human epidermal growth factor receptor 2 (HER2) expression, and treatment history [7,11–13]. Although various chemotherapy regimens have shown antitumor activity, their toxicity profiles may limit their extended use in a patient population that is often frail and cachectic [11,14]. First-line (1L) chemotherapy for patients with HER2− GC/GEJC varies between countries [7,11,12]; however, combination chemotherapy that includes a fluoropyrimidine and platinum agent is commonly administered and is associated with a median OS of approximately 8–13 months [7]. Fluorouracil (5-FU), leucovorin, and irinotecan (FOLFIRI) and taxane-based regimens have shown similar OS rates [15,16]. It was recently reported in a press release that a phase 3 trial of ramucirumab (an antiangiogenic agent) vs placebo in combination with cisplatin and capecitabine or 5-FU as 1L treatment for patients with HER2– GC/GEJC met its primary endpoint of progression-free survival (PFS) but failed to improve OS [17]. For the 6–30% of patients with HER2+ GC/GEJC [18], trastuzumab in combination with fluoropyrimidine and platinum-based chemotherapy is the standard of care based on a demonstrated OS benefit (median 14 vs 11 months with chemotherapy alone) [19]. In a separate study, adding pertuzumab to the standard trastuzumab/chemotherapy combination did not prolong OS [20]. Other targeted therapies have so far failed to improve clinical outcomes, as seen in trials of epidermal growth factor receptor antibodies (cetuximab or panitumumab) added to platinum-based chemotherapy vs chemotherapy alone in unselected patients with GC/GEJC [21] or esophagogastric cancer [22], and selective MET receptor ligand inhibitors (rilotumumab or onartuzumab) vs placebo added to chemotherapy in patients with MET+ GC/GEJC [23,24]. Across different regions, various second-line (2L) treatments are administered to patients with advanced GC/GEJC [7,11,12], such as FOLFIRI, irinotecan, and taxane-based regimens [16,25], and ramucirumab with or without paclitaxel [26,27]. In randomized trials in the 2L setting, the median OS for ramucirumab vs placebo was 5.2 vs 3.8 months (hazard ratio [HR], 0.776; $P = 0.047$) and for ramucirumab and paclitaxel vs paclitaxel alone was 9.6 vs 7.4 months (HR, 0.807; $P = 0.017$) [26,27]. However, ramucirumab is associated with rates of grade ≥3 treatment-related adverse events (TRAEs) of approximately 60% when administered as monotherapy and ≥80% in combination with paclitaxel [26,27]. Following recent approvals of anti–programmed death 1 (PD-1) antibodies pembrolizumab, in the United States for programmed death ligand 1 (PD-L1)+ tumors, and nivolumab, in Japan, third-line (3L) treatment has evolved to include immunotherapy regimens [28,29], and patients with adequate performance status may otherwise receive chemotherapy regimens not previously received [25]. Because existing treatments generally do not result in durable antitumor responses in any line and OS remains short, novel strategies with the potential to extend treatment response and benefit a wider range of patients are needed.

Rationale for maintenance therapy in GC/GEJC

Although 1L chemotherapy for advanced GC/GEJC may be administered until disease progression, duration of combination treatment may be limited by toxicity [7,14,30]. Maintenance therapy, ie, continuation of an agent given as part of the 1L induction regimen or sequential treatment with a different agent until progression in patients with nonprogressive disease (switch maintenance), is an established treatment strategy for several advanced tumors, including colorectal cancer, ovarian cancer, and non-small cell lung cancer, based on studies showing significant prolongation of PFS and OS [31–33]. Unlike combination approaches, switch maintenance avoids the potential for additive toxicity with agents administered concurrently and may limit the overall duration of treatment with cytotoxic chemotherapy while enabling potential synergistic activity between agents with different mechanisms of action [31–33].

Small studies have suggested that fluoropyrimidine-based maintenance therapy is feasible in patients with GC/GEJC, although data are limited [34–36]. Trastuzumab and ramucirumab are administered until disease progression [7]; thus, their clinical efficacy benefits in patients with GC/GEJC may be due in part to maintenance treatment [19]. There is ongoing interest in identifying tolerable agents for maintenance therapy with the aim of prolonging the benefits of systemic chemotherapy in a wider population of patients with GC/GEJC, and initial studies of immunotherapy in this setting are discussed later.

Rationale for checkpoint inhibitors in GC/GEJC

The development and progression of tumors are characterized by evasion of immune responses, including tumor escape mediated through immune checkpoint pathways [37–40]. The etiology of GC/GEJC in some patients has been associated with immunosuppressive treatment for organ transplants and viral infections [41,42], suggesting that the immune system plays an important role in tumor control. Furthermore, key immune checkpoint proteins, including cytotoxic T-lymphocyte antigen 4 (CTLA-4), indoleamine 2,3-dioxygenase (IDO), T-cell immunoglobulin and mucin domain-containing protein 3, lymphocyte activation gene 3 protein (LAG-3), and PD-1, are overexpressed on immune cells in patients with GC/GEJC, suggesting a role for tumor-induced T-cell exhaustion in disease progression [43–45]. PD-1 (expressed on immune cells) and its ligand, PD-L1 (expressed on immune and tumor cells), are expressed on up to 50% of GC/GEJC tumors [46,47]; expression has been associated with a worse prognosis [48,49], although occasional studies have found a reverse correlation [43]. By overexpressing PD-L1 directly or inducing PD-L1 expression on immune cells, cancer cells exploit the PD-1/PD-L1 pathway to promote an immunosuppressive environment and allow immune escape and hence tumor growth [50,51]. Antibodies that block checkpoint proteins can restore and enhance antitumor activity of T cells by blocking inhibitory signals (Fig. 1) [52,53]. Furthermore, some GC/GEJC tumors have a high mutational burden, particularly MSI-high tumors [5], creating tumor neoantigens that can be targeted by immune responses. A high tumor mutational burden has been shown to predict durable clinical benefit with anti–PD-1/PD-L1 treatment in various tumors [54,55]. The potential of immunotherapy for advanced GC/GEJC was initially suggested in preliminary studies showing increased immune activation and antitumor responses following treatment with polysaccharide-K, picibanil, and the bacillus Calmette–Guérin vaccine [42]. Furthermore, it is well established that chemotherapy may increase tumor immunogenicity and potentially increase susceptibility to subsequent checkpoint inhibitor therapy [56], which may be highly relevant to the GC/GEJC treatment landscape.

It has been reported that GC tumors exhibit distinct gene expression signatures related to T-cell function in Asian vs non-Asian patients. Specifically, tumors in non-Asian patients showed higher expression of markers associated with T-cell activity, including CTLA-4, CD3,