Int. j. adv. multidisc. res. stud. 2024; 4(1):1241-1248

Received: 29-12-2023
Accepted: 09-02-2024

International Journal of Advanced Multidisciplinary Research and Studies

ISSN: 2583-049X

Immunotherapy in Gastric Cancer: A Review

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DOI: https://doi.org/10.62225/2583049X.2024.4.1.2375
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Abstract

Globally, gastric cancer (GC) ranks fourth in terms of cancer-related mortality. Patients diagnosed with advanced gastric cancer (AGC) frequently have a median survival around 12-15 months, depending to the therapy. Immunotherapy is becoming an essential therapeutic strategy in medical oncology, and it is projected to make major advances to the way gastric cancer cure. The phase III ATTRACTION-2 showed that nivolumab, a monoclonal antibody targeting programmed cell death 1 (PD-1), substantially increased overall survival (OS) in patients with advanced gastric cancer (AGC) when given as a third- or later-line treatment, as compared to a placebo. Furthermore, nivolumab in combination with 5-fluorouracil and platinum as a first-line treatment increased OS in patients with human epidermal growth factor receptor-2 (HER2)-negative AGC in the international phase III CheckMate-649 investigation. Pembrolizumab, an additional anti PD-1 antibody, when used with trastuzumab and cytotoxic chemotherapy as first line treatment, demonstrated a substantial enhancement in the overall response rate among patients diagnosed with HER2-positive AGC. Hence, immune checkpoint inhibitors (ICIs) are crucial in the present management of GC. Current research is actively investigating alternative treatment following ICI combination therapy, including ICI rechallenge or combination therapy with drugs that have distinct mechanisms of action. Several clinical trials are presently being done to employ immunotherapy as a treatment option in the perioperative and postoperative settings for patients with early gastric cancer, based on the success of immunotherapy in treating advanced gastric cancer (AGC). This article gives an overview of the recent breakthroughs in immunotherapy.

Keywords: Gastric Cancer, Immunotherapy, Immune Checkpoint Inhibitors, Chemotherapy, PD-L1

Introduction

Globally, gastric cancer (GC) ranks fourth in terms of cancer-related mortality and is the malignant tumour with the fifth highest diagnostic rate [1]. The incidence of GC is larger in eastern Asia, notably Korea, than in Western countries [1, 2]. Curative treatment comprises surgical excision followed by adjuvant chemotherapy according to pathologic stage. Although Korea has a high prevalence of early detection of GC employing endoscopy via a nationwide cancer surveillance program [2], some individuals are however detected in advanced stage. Patients with initially unresectable or recurrent GC have an unfortunate prognosis, with an overall survival (OS) of 12–15 months [3, 4]. Thus, patients with advanced GC (AGC) have unmet medical needs.

Immunotherapy is deemed an effective therapeutic approach in medical oncology. Targeting pathways involved in immune regulation, immune checkpoint inhibitors (ICIs) help to breaking the immunological tolerance and allow T-cell identification against tumour cells, increasing immune cell response to cancer and preventing immune evasion induced by cancer cells [5, 6]. GC is a malignancy connected with a high somatic mutational burden [7], which is a potential marker for predicting response to ICIs. Moreover, positive expression of programmed cell death ligand 1 (PD-L1) has been detected in 25%–65% of patients with GC, and genomic abnormalities and epigenetic modifications of the PD-L1 gene have also been reported in GC [8, 9]. Thus, the use of ICIs is crucial to increase survival outcomes in patients with AGC.

ICIs have developed in the treatment of various cancers [5, 10-12]. In GC, ICI monotherapy has been proved to enhance survival in the third- or later-line situation, leading to its inclusion as a standard treatment [13, 14]. Recently, the phase III CheckMate-649 indicated that nivolumab in combination with cytotoxic chemotherapy enhanced OS compared with chemotherapy alone as the first-line treatment for human epidermal growth factor receptor-2 (HER2)-negative AGC [15, 16]. Furthermore, according to a preplanned interim analysis of the KEYNOTE-811 investigation, pembrolizumab in conjunction with trastuzumab and cytotoxic chemotherapy increased the overall response rate (ORR) in patients with HER2-positive AGC [17, 18]. The introduction of ICIs to the present standard first-line treatment has provided a novel systemic therapeutic strategy for AGC. Subsequent treatments after ICI combination therapy, such as ICI rechallenge or combination therapy with drugs with new modes of action, are being actively explored to date [19-21]. On the basis of the success of immunotherapy in the treatment of AGC, numerous clinical investigations are continuing to employ this therapeutic strategy in the perioperative and postoperative settings for patients with early GC [22, 23]. Potential biomarkers for predicting the success of ICIs have been proposed, including Epstein–Barr virus (EBV) positive, microsatellite instability (MSI), and PD-L1 expression. Patients with MSI-high or EBV-positive GC are known to respond successfully to ICIs [24-26]. Another well-known biomarker, PD-L1, positively correlates with the response to pembrolizumab in AGC [14, 27]. In addition, according to the CheckMate-649 research, individuals with increased PD-L1 expression gain improved clinical outcomes with nivolumab [15].

In this review, we focus on recent progress in immunotherapy for GC and putative predictive biomarkers that reflect the effectiveness of ICIs in the treatment of AGC.

Methods

We searched PubMed (www.ncbi.nlm.nih.gov/pubmed) for full-text articles from 2017 to May 31, 2023, using the keywords gastric cancer; Immunotherapy; Immune checkpoint inhibitors; Chemotherapy; PD-L1. The full-text articles found were carefully examined. In addition, all abstracts presented at international conferences between January 2020 and October 2023 were examined.

Immunotherapy in gastric cancer

Table 1 provides a concise overview of the main clinical studies investigating immunotherapy in advanced gastric cancer (AGC). There were six studies that assessed the use of ICI monotherapy, nine trials that examined the combination of ICIs with cytotoxic chemotherapy, three trials that investigated the combination of ICIs with HER2-targeted therapies, two trials that studied the use of dual ICI combination treatment, and two trials that explored the combination of ICIs with anti-angiogenic medicines.

ICI monotherapy

Nivolumab is a humanised anti-PD-1 monoclonal antibody, and the ATTRACTION-2 study was the first randomised, double-blind, placebo-controlled, phase III to prove its safety and efficacy as a third- or later-line treatment for patients with AGC [13]. In this study, 439 patients from Korea, Japan, and Taiwan were recruited without selection based on PD-L1 status and randomly assigned to receive either nivolumab or placebo in a 2:1 ratio. Nivolumab proved an improvement in OS compared with placebo (median OS, 5.26 vs. 4.14 months, hazard ratio [HR] 0.63, P<0.001) [13]. In addition, an OS benefit was shown irrespective of tumor PD-L1 expression [42]. The median OS of patients who had complete or partial response to nivolumab was 26.7 months (95% confidence interval [CI], 21.65–38.57), showing a durable response [42, 43]. In the long-term follow-up in ATTRACTION-2, the advantage was successfully preserved among the responders. In this population, the OS rate at 1, 2, and 3 years was 87.1%, 61.3%, and 35.5%, respectively [42, 43]. In terms of progression-free survival (PFS), nivolumab exhibited superiority compared with placebo (median PFS, 1.61 vs. 1.45 months, HR, 0.60, P<0.001), and the ORR was 11.2% in the nivolumab group and 0% in the placebo group [13]. Because of these results, nivolumab has been authorised for the treatment of AGC in later-line conditions in Asian countries.

In order to prove pembrolizumab monotherapy as a third- or later-line treatment in AGC, 259 patients were recruited in cohort 1 of the KEYNOTE-059 investigation, an open-label, nonrandomized, three-cohort phase II experiment [14]. Pembrolizumab had similar efficacy to nivolumab (ORR, 11.6%; median OS, 5,6 months [95% CI, 4.3–6.9]; median PFS, 2.0 months [95% CI, 2.0–2.1]) [14]. In this study, PD-L1 positivity was defined as a PD-L1 combined positivity score (CPS) of ≥1, as assessed by the 22C3 immunohistochemistry test. The median OS for the PD-L1-positive and PD-L1-negative groups, according to a subgroup analysis, was 4.9 months (95% CI, 3.4–6.5) and 5.8 months (95% CI, 4.5–7.9), respectively. Furthermore, the ORR for patients who received pembrolizumab and were PD-L1-positive or PD-L1-negative was 15.5% (95% CI, 10.1–22.4) and 6.4% (95% CI, 2.6–12.8), respectively. These results show that pembrolizumab is more effective in PD-L1-positive AGC and PD-L1 CPS is a feasible predictive marker for select patients who are likely to respond favourably to pembrolizumab [14]. The most frequent treatment-related adverse effects connected with nivolumab and pembrolizumab include pruritus (9.0% and 8.9%), skin rash (6.0% and 8.5%), weariness (5.0% and 18.9%), and hypothyroidism (3.0% and 7.7%) [13, 14].

Immuno-monotherapy and cytotoxic chemotherapy

Mainly studies comparing ICI monotherapy with cytotoxic chemotherapy have not shown the superiority of ICI monotherapy. The JAVELIN Gastric 300 was a randomized, open-label, phase III trial that examined avelumab, an anti-PD-L1 monoclonal antibody, with the physician's choice of chemotherapy (e.g., paclitaxel and irinotecan) [28]. A total of 371 patients in third-line setting were included, and 185 and 186 patients were randomly assigned to the avelumab and chemotherapy groups, respectively. Avelumab failed to improve OS (median OS, 4.60 vs. 5.00 months, HR, 1.1 [95% CI, 0.9–1.4]) and PFS (median PFS, 1.40 vs. 2.70 months, HR, 1.73 [95% CI, 1.4–2.2]) compared with cytotoxic therapy [28]. In a subgroup analysis of OS according to tumor PD-L1 expression, no significant differences were detected between the avelumab and therapy groups [28]. In contrast, the PFS subgroup analysis consistently benefitted the chemotherapy arm [28].

Pembrolizumab did not substantially increase OS when compared with paclitaxel as the second-line therapy for AGC in the KEYNOTE-061 trial, a randomised, open-label, phase III trial that included PD-L1-positive patients (PD-L1 CPS ≥1). The median OS was 9.1 months with pembrolizumab vs. 8.3 months with paclitaxel, with an HR of 0.82 [95% CI, 0.66–1.03], P=0.042. Pembrolizumab likewise did not increase PFS compared with paclitaxel (median PFS, 1.5 vs. 4.1 months, HR, 1.27 [95% CI, 1.03–1.57]) [27]. The paclitaxel group outperformed the pembrolizumab arm at the initiation of treatment. However, the Kaplan-Meier curve for OS crossed at 8 months post randomization. The responses to pembrolizumab were more robust than those to paclitaxel (ORR, 16% vs. 14%; median duration of response, 18.0 months in the pembrolizumab arm [95% CI, 8.3–not estimable] vs. 5.2 months in the paclitaxel arm [95% CI, 3.2–15.3]) [27]. This difference continued when the survival curves crossed in favour of pembrolizumab. Notably, in a post-hoc subgroup analysis of patients with a PD-L1 CPS of ≥10, pembrolizumab demonstrated a more efficacy than paclitaxel (HR, 0.64 [95% CI, 0.73–1.32]; median OS, 10.4 months with pembrolizumab vs. 8.0 months with paclitaxel) [27].

The KEYNOTE-062 study was a randomized, blinded, phase III that investigated pembrolizumab monotherapy or pembrolizumab with chemotherapy as a first-line treatment for patients with AGC [29]. Patients with HER2-negative AGC with a PD-L1 CPS of ≥1 were enrolled and randomly randomised to pembrolizumab monotherapy, pembrolizumab plus chemotherapy, or placebo + chemotherapy in a 1:1:1 ratio. Chemotherapy with cisplatin plus 5-fluorouracil and cisplatin plus capecitabine was decided by the treating physician. Regarding overall survival (OS) in patients with a PD-L1 CPS of ≥1, pembrolizumab monotherapy was noninferior but not superior to chemotherapy (median OS, 10.6 months with pembrolizumab vs. 11.1 months with chemotherapy, HR, 0.91 [99.2% CI, 0.69–1.18; noninferiority margin, 1.2]) [29]. Crossing of the OS curves was detected, as in the KEYNOTE-061 experiment. Also analogous to the KEYNOTE-061 research, higher cutoff values of PD-L1 CPS tended to result in stronger responses to pembrolizumab in the first line setting of AGC (CPS ≥1: median OS, 10.6 vs. 11.1 months; CPS ≥10: median OS, 17.4 vs. 10.8 months) [29].

Immunotherapy with chemotherapy compared to cytotoxic chemotherapy

To improve the response to immunotherapy in distinct cancer types, a combination strategy combining cytotoxic drugs has been devised [19, 44]. Preclinical investigations have indicated that several chemotherapeutic drugs produce immunomodulatory effects via the subsequent mechanisms: 1) improved tumor antigen expression and presentation, 2) downregulation of co-inhibitory molecules and overexpression of co-stimulatory molecules expressed on the surface of tumor cells, and 3) granzyme- and perforin-dependent pathways that boost T-cell-facilitated tumor cell lysis [45, 46]. In GC, chemotherapy alters T-cell populations within the tumor microenvironment and chenge the tumor microenvironment toward an immune-responsive state [47].

Recently, the findings of clinical trials that investigated the addition of ICIs to cytotoxic chemotherapy have led to a change in the current standard of care for patients with HER2-negative AGC [15, 29, 30]. While the ORR with pembrolizumab plus chemotherapy was higher than that with cytotoxic chemotherapy alone (48.6% vs. 37.2%), pembrolizumab plus chemotherapy did not significantly improve OS or PFS when compared to chemotherapy alone in the KEYNOTE-062 trial (median OS, 12.5 vs. 11.1 months, HR, 0.85, P=0.05; median PFS, 6.9 vs. 6.4 months, HR, 0.84, P=0.04) [29].

A randomised, global open-label phase III, CheckMate-649, examined nivolumab in combination with chemotherapy as a first-line treatment for HER2-negative AGC. The original trial design had a 3-arm containing the nivolumab plus chemotherapy, nivolumab plus ipilimumab, and chemotherapy arms, and patients were randomly allocated to each arm in a 1:1:1 ratio. After the enrollment in the nivolumab plus ipilimumab arm was closed, 1,581 patients were recruited regardless of PD-L1 status and randomly randomised to receive nivolumab plus chemotherapy (789 patients) or placebo plus chemotherapy (792 patients) [15]. The dual co-primary end points were OS and PFS, which were evaluated via a blinded independent central review, in patients with a PD-L1 CPS of ≥5. The hierarchically reviewed secondary end point were OS in patients with a PD-L1 CPS of ≥1 and OS in all randomized individuals. In this study, therapy consisted of oxaliplatin plus 5-fluorouracil or oxaliplatin plus capecitabine. The number of patients with a PD-L1 CPS of ≥5 was 955 (60.4%), whereas the numbers of patients with a PD-L1 CPS of 1 to 4 and those negative for PD-L1 were 341 (21.5%) and 285 (18.0%), respectively [15]. The nivolumab plus chemotherapy group fulfilled both end points (OS, 14.4 vs. 11.1 months, HR, 0.71, P<0.001; PFS, 7.7 vs. 6.05 months, HR, 0.68, P<0.001) in patients with a PD-L1 CPS of ≥5 [15, 16]. In patients with a PD-L1 CPS of ≥1, the median OS and PFS of the nivolumab plus chemotherapy and chemotherapy alone groups were 14.0 and 11.3 months (HR, 0.77, P<0.001) and 7.5 and 6.9 months (HR, 0.74), respectively. Moreover, the nivolumab + chemotherapy combination also offered greater OS and PFS than chemotherapy alone in all randomized patients regardless of PD-L1 status (median OS, 13.8 vs. 11.6 months, HR, 0.80, P< 0.001; median PFS, 7.7 vs. 6.9 months, HR, 0.77) [16]. In patients with a PD-L1 CPS of ≥5, the ORR with nivolumab + chemotherapy was 60% (95% CI, 55–65) and that with chemotherapy alone was 45% (95% CI, 54–62). In addition, the median duration of response with nivolumab plus chemotherapy and chemotherapy alone was 9.7 and 7.0 months, respectively, in patients with a PD-L1 CPS of ≥5. The ATTRACTION-4 study was a randomized, double-blind, placebo-controlled, phase II/III trial that enrolled patients with HER2-negative AGC conducted in South Korea, Japan, and Taiwan. A total of 724 patients were recruited irrespective of PD-L1 expression and randomly randomised to the nivolumab plus chemotherapy and placebo plus chemotherapy groups in a 1:1 ratio. The chemotherapy regimen administered in this experiment was oxaliplatin plus capecitabine or S-1. The combination of nivolumab and chemotherapy yielded better outcomes in terms of PFS (median, 10.45 vs. 8.34 months, HR, 0.68, P<0.001) and ORR (57.0% vs. 48.0%) compared with chemotherapy plus placebo; however, no differences were observed in OS (median, 17.45 vs. 17.15 months, HR, 0.90, P=0.260) [30]. Although a caution exists in making direct comparisons across trials, the OS in the control arm of the ATTRACTION-4 trial (17.15 months) was longer than

that in the experimental arm (nivolumab + chemotherapy) of the CheckMate-649 study (14.4 months). The reason for the lack of a difference in OS in the ATTRACTION-4 trial was that ATTRACTION-4 had a higher proportion of patients in the placebo arm who received subsequent systemic chemotherapies, including ICIs, than the CheckMate-649 study (66% of patients in ATTRACTION-4 vs. 39% of patients in CheckMate-649) [16, 30]. In the ATTRACTION-4 study, 131 patients (18.1%) received nivolumab as a second treatment (39 [11%] patients in the nivolumab arm vs. 92 [25%] patients in the placebo arm) [36]. In the CheckMate-649 study, 90 patients (5.7%) underwent immunotherapy as a subsequent treatment (17 [2%] patients in the nivolumab arm vs. 73 [9%] patients in the placebo arm) [16]. Thus, subsequent therapy might be a confusing parameter in the ATTRACTION-4 trial, which did not indicate any difference in OS between the 2 groups. On the basis of these results, the combination of nivolumab and chemotherapy has been universally authorised by several regulatory agencies as a first line treatment for patients with HER2-negative AGC. In the United States, Korea, and Japan, nivolumab plus chemotherapy was authorised for all patients with HER2-negative AGC regardless of PD-L1 expression; however, in Europe, it was allowed only for patients with a PD-L1 CPS of ≥5. In the first-line treatment of AGC, the right PD-L1 criteria for identifying people for whom nivolumab delivers a substantial therapeutic benefit remain disputed.

For the same reason, the global, double-blind, placebo-controlled, randomised, phase III RATIONALE-305 study (NCT03777657) test tislelizumab with platinum-based doublet chemotherapy vs. placebo plus chemotherapy as a first-line treatment for patients with HER2-negative AGC [31]. A total of 997 patients from 13 countries were included irrespective of PD-L1 status. According to the interim analysis, tislelizumab in combination with chemotherapy revealed a survival benefit in patients with PD-L1 expression [48]. The comprehensive efficacy analysis for all randomized patients is planned. Additionally, the KEYNOTE-859 trial (NCT03675737) is a worldwide, randomised, double-blind, placebo-controlled, phase III investigation that intends to evaluate the effectiveness of a pembrolizumab combination approach in contrast with chemotherapy in the first-line treatment of HER2-negative AGC [32]. Patients in this experiment were recruited regardless of their PD-L1 status. The findings of these current studies will offer evidence for the right identification of patients who are likely to obtain a therapeutic benefit from ICIs.

Immunotherapy for HER2-positive Gastric cancer

Trastuzumab in combination with chemotherapy is the traditional first-line treatment for HER2-positive AGC, according to the ToGA trial [4]. Trastuzumab, an anti-HER2 monoclonal antibody, binds to the extracellular domain of HER2 and promotes antibody-dependent cellular cytotoxicity, leading to immunogenic cell death [49]. In addition, trastuzumab upregulates PD-1 and PD-L1 and modifies major histocompatibility complex class II expression [49]. Thus, according to the manner of action of trastuzumab, the addition of ICIs to HER2-targeted therapy may result in an increased anti-tumor effect [33].

The international phase III KEYNOTE-811 study was a randomized, double-blind, placebo-controlled trial that attempted to assess the efficacy and safety of adding pembrolizumab to chemotherapy plus trastuzumab combination as a first-line treatment for HER2-positive AGC [18]. The chemotherapy regimens adopted in this study were cisplatin plus 5-fluorouracil and oxaliplatin plus capecitabine. Participants were randomly assigned to receive either pembrolizumab or placebo in a 1:1 ratio. According to the prearranged first interim analysis of the KEYNOTE-811 trial, the ORR for HER2-positive AGC was significantly higher when pembrolizumab was added to trastuzumab plus chemotherapy as opposed to the standard first-line treatment (ORR, 74.4% in the pembrolizumab arm vs. 51.9% in the placebo arm, P<0.001) [18]. On the basis of these findings, the US Food and Drug Administration granted fast track approval for pembrolizumab with trastuzumab and chemotherapy as the first-line treatment for HER2-positive AGC. The findings for additional efficacy endpoints, including OS and PFS, are further expected.

Zanidatamab, another HER2-targeted therapy is a humanized bispecific antibody directed against extracellular domains 2 and 4 of HER2. Zanidatamab is also being studied in combination with tislelizumab, a PD-1 inhibitor, and chemotherapy in HER2-positive AGC [34]. The HERIZON-GEA-01 trial, an ongoing global, randomized, open-label, phase III compares the effectiveness and safety of zanidatamab with chemotherapy with or without tislelizumab as first-line treatment in patients with HER2-positive AGC.

In order to evaluate the safety and effectiveness of margetuximab (a second-generation anti-HER2 monoclonal antibody) plus retifanlimab (an anti-PD-1 monoclonal antibody) with or without chemotherapy, as well as margetuximab plus MGD013 (a bispecific anti-PD-1 and anti-LAG-3 IgG molecule), the MAHOGANY trial was designed as a randomised, open-label, phase II/III study. Interestingly, margetuximab plus retifanlimab, a chemotherapy-free regimen, produced a remarkable ORR of 53% with a median duration of response of 10.3 months (95% CI, 4.6–not evaluable) in a subset of patients with HER2 immunohistochemistry 3+ tumours and a PD-L1 CPS of ≥1 (cohort A of the MAHOGANY trial) [35]. The disease control rate was 73% (29/40; 95% CI, 56.1–85.4).

Induction and maintenance immunotherapy strategy in gastric cancer

Some techniques have been investigated to study the role of ICIs as a maintenance treatment after induction chemotherapy in the first line setting of AGC, with a focus on long-term responses to ICIs. A randomized, open-label, phase II was conducted to examine the efficacy of ipilimumab monotherapy as a maintenance compared to best supportive care (BSC) [36]. Participants in this investigation were randomised to receive either ipilimumab or BSC in a 1:1 ratio after achieving a complete or partial response to induction chemotherapy (oxaliplatin plus capecitabine, cisplatin plus capecitabine, cisplatin plus 5-fluorouracil, and cisplatin plus S-1). The primary end point was immune-related PFS, and patients in the BSC group were authorised to continue maintenance chemotherapy [36]. Ipilimumab maintenance failed to improve immune-related PFS compared with BSC (median immune-related PFS, 2.92 months in the ipilimumab arm vs. 4.90 months in the BSC arm, HR, 1.44, P=0.097) [36].

The JAVELIN Gastric 100 was an open-label, phase III study that examined the efficiency of avelumab maintenance after induction chemotherapy compared with continued chemotherapy or BSC as a first-line for patients with HER2-negative AGC [37]. All patients had induction platinum-based doublet chemotherapy for up to 12 weeks, and patients without disease progression after induction chemotherapy were randomly assigned in a 1:1 ratio to either switch maintenance treatment with avelumab or continued chemotherapy or BSC [37]. In all randomized patients, avelumab maintenance treatment did not improve OS compared with the continuation of chemotherapy (median OS, 10.4 vs. 10.9 months, HR, 0.91, P=0.178) [37]. However, like KEYNOTE-061 and KEYNOTE-062, crossover of OS curves was permitted in this study, and the survival curve of the avelumab maintenance arm plateaued at 20 months post randomization. In the exploratory analysis, patients with a PD-L1 CPS of ≥1 displayed a more continuous response to avelumab maintenance treatment compared to chemotherapy (median OS, 14.9 vs. 11.6 months) [37]. Regarding safety, the avelumab maintenance arm revealed a lower incidence of all grades of treatment-related adverse events and grade ≥3 treatment-related adverse events than the chemotherapy arm [37]. These studies showed the potential effectiveness of avelumab maintenance in chosen people and its acceptable safety profile, which may serve as a platform for building an induction method in patients with AGC.

The current LEAP-015 study is a randomized, open-label, phase III assessing the efficacy and safety of pembrolizumab plus lenvatinib and chemotherapy as a first-line treatment for HER2-negative AGC [38]. Patients were randomly randomised to the pembrolizumab + lenvatinib + chemotherapy arm and the standard-of-care chemotherapy arm in a 1:1 ratio. In the experimental arm, patients got induction treatment with pembrolizumab plus lenvatinib and chemotherapy for 12 weeks and subsequently maintained the pembrolizumab plus lenvatinib combination to evaluate the efficacy of maintenance therapy.

Combination treatment using anti-cytotoxic T lymphocyte-associated protein 4 (CTLA-4) antibodies

The combination of anti-CTLA-4 antibodies with PD-1 or PD-L1 inhibitors has been examined as a dual immunotherapy method for numerous cancer types [11, 50]. CTLA-4 is a well-known therapeutic target. In the CheckMate-032, patients who undergo at the nivolumab 1 mg/kg + ipilimumab 3 mg/kg combination exhibited a better ORR than those who received nivolumab 3 mg/kg monotherapy as a later-line for AGC [51]. However, in the CheckMate-649 study, nivolumab + ipilimumab failed to increase survival, and rather resulted in lower PFS and ORR, compared with chemotherapy as the first-line treatment for patients with HER2-negative AGC [16]. In contrast, responders to nivolumab + ipilimumab dual immunotherapy displayed longer durable responses than responders to chemotherapy (median duration of response, 13.2 vs. 6.9 months) [16]. An ongoing phase III, ATTRACTION-6, which plans to explore dual immunotherapy with a decreased dose of nivolumab (360 mg every 3 weeks) with ipilimumab (1 mg/kg every 6 weeks) in combination with chemotherapy compared with chemotherapy alone, is already underway.

Combination treatment with anti-angiogenic agents

One of the most notable hallmarks of solid tumours is aberrant angiogenesis, which has led to the creation of many angiogenesis inhibitors that directly target vascular endothelial growth factor signalling [52]. Due to the vascular endothelial growth factor's immunomodulatory actions, anti-angiogenic can enhance immunotherapy by promoting the recruitment and induction of immune cell activities, which can change the tumour microenvironment from an immunosuppressive to an immune-supportive state [19, 44]. In the phase Ib REGONIVO trial, nivolumab plus regorafenib resulted in an ORR of 44% (95% CI, 24.4%–65.1%), a PFS of 5.6 months (95% CI, 2.7–10.4), and an OS of 12.3 months (95% CI, 5.3–not reached) in patients with intensively treated AGC [53]. Interestingly, among 7 responders, 3 ICI-exposed patients gained an objective response with nivolumab plus regorafenib, demonstrating that combination treatment with anti-angiogenic can be a therapeutic option to overcome ICI resistance [53]. In addition, the phase II LEAP-005 trial, which investigated the combination of pembrolizumab plus lenvatinib, reported an ORR of only 10% (95% CI, 2–26), a PFS of 2.5 months (95% CI, 1.8–4.2), and an OS of 5.9 months (95% CI, 2.6–8.7) in the AGC group [20]. However, these conclusions are dubious, because the above-mentioned research were nonrandomized trials. The phase III INTEGRATE-IIb research is proceeding and intended to evaluate the combination of nivolumab and regorafenib compared with the investigator's choice of chemotherapy, such as docetaxel, irinotecan, or TAS-102, in the later-line condition [21]. In the first-line the phase III LEAP-015, which attempts to test pembrolizumab with lenvatinib in conjunction with chemotherapy compared with chemotherapy alone, is under progress [38].

Conclusion

Since the ICI combination strategy has been demonstrated to boost OS when employed as a first-line systemic therapy for AGC, immunotherapy has become more prominent in the treatment of AGC. Accumulating research reveals that patients with GC respond to immunotherapy in various situations. Notable clinical trials studying combination approaches with multiple kinase inhibitors or dual ICIs are ongoing, and further research are necessary to optimise patient selection.

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