

Use of immunotherapy in the treatment of gastric cancer (Review)

LUHONG YANG^{1,2}, YANXIA WANG² and HUAFENG WANG^{1,2}

¹Modern College of Humanities and Science, and ²School of Life Science,
Shanxi Normal University, Linfen, Shanxi 041004, P.R. China

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Abstract. Gastric cancer (GC) is a malignant tumor that negatively impacts human health, which typically presents in the advanced stages of disease in the majority of patients. Despite the development of combination chemotherapy, only a modest survival advantage is gained in patients with GC treated by this method. Recently, cancer immunotherapies have received considerable attention as a viable therapeutic option for GC. Specifically, the immune checkpoint inhibitors, chimeric antigen rector (CAR)-T cells and tumor vaccines, represent immunotherapies that have exhibited promising effects in the treatment of GC. A number of clinical trials have employed either immuno-oncology monotherapies or combination therapies to improve the overall survival time (OS) and objective response rate (ORR) of patients with GC. The current review presents a summary of the clinical effects of checkpoint inhibitors, including CAR-T and tumor vaccines, in the treatment of GC.

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1. Introduction

Gastric cancer (GC) is a malignant tumor type, with wide-reaching impacts on human health. In 2016, there were ~834,000 GC-associated mortalities worldwide (1). GC is the sixth most common type of cancer worldwide in

terms of incidence, with the second highest mortality rate among all types of cancer worldwide (1). In China, it has been estimated that there were 67,910 new cases of GC and 49,800 GC-associated mortalities in 2015 (2); therefore, GC is one of the most common types of cancer ranking second following lung cancer in terms of morbidity and mortality, and the 5-year survival rate of GC is only 28% (2). As the majority of patients with GC are primarily diagnosed at the advanced stages of disease, the potential for successful treatment is limited to a few patients where early detection and comprehensive treatment were achieved (3,4). Even with use of combination chemotherapy, consisting of platinum and 5-fluorouracil (5-FU), only a modest survival advantage is obtained for patients with advanced GC (5-8). Therefore, the identification of novel therapeutics for the treatment of advanced GC represents an important area of investigation.

Immunotherapy is the treatment of disease by inducing, enhancing or suppressing an immune response (9). Immunomodulatory regimens often have fewer adverse side effects compared with the presently used drugs and include less potential for creating resistance when treating microbial diseases (10). Two types of cancer immunotherapies exist: Active and passive (11). Active immunotherapies utilize components of the patient's own immune system, in order to boost an immune response against tumors (11). Examples of active immunotherapies include chimeric antigen receptor (CAR)-T cell therapy and cancer vaccines (11). Passive immunotherapies utilize components of the immune system manufactured outside of the body, including monoclonal antibodies (11). Over the past 10 years, cancer immunotherapy has demonstrated to be surprisingly effective in the treatment of melanoma and has subsequently been applied to breast, prostate, kidney and lung cancer (12). Therefore, immunotherapy was designated as the breakthrough treatment of the year in 2013 (12).

The potential use of immunotherapy in GC has received a considerable amount of interest. The molecular features of GC have been analyzed by the Cancer Genome Atlas Research Network and four classes of tumor subtypes have been identified, including Epstein-Barr (EB) virus-positive tumors, microsatellite instability tumors, genomically stable tumors and tumors with chromosomal instability (13). In the EB virus subgroup, which accounts for 15% of GC tumors, the expression of programmed death-ligand-1 (PD-L1) is increased (13), which is indicative of the presence of stable immune cells and supports the use of an immune checkpoint inhibitor for the treatment of this GC subtype (13).

Correspondence to: Dr Huafeng Wang, School of Life Science, Shanxi Normal University, 1 Gongyuan Street, Linfen, Shanxi 041004, P.R. China
E-mail: wanghf@sxnu.edu.cn

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In the present review, three principal types of cancer immunotherapies for GC were evaluated, including immune checkpoint inhibitors, adoptive cell therapy, including CAR-T cells, and tumor vaccines.

2. Immune checkpoint inhibitors

Introduction to immune checkpoint inhibitors. In tumor immunity, the immune system recognizes and eliminates tumor cells in order to inhibit tumor development (14). However, tumors can escape recognition and destruction by the immune system, thereby achieving a malignant reproduction regime (15). As the primary participant in the tumor immune response, the regulation of T lymphocyte activity can exert coordinated effects upon stimulatory and inhibitory molecules, with these inhibitory molecules serving as an immune checkpoint (16). The capacity for malignant tumors to escape immune surveillance involves the suppression of T cell activity and can occur through immune checkpoint pathways (Fig. 1A) (17,18). As shown in Fig. 1A, the activity of T cells is inhibited by cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) and programmed death 1 (PD-1)/PD-L1. Checkpoint inhibitor signaling pathways contribute to the anti-tumor effects of T cells, which achieve their goal of destroying tumor cells by inhibiting the capacity for tumor immune escape. As shown in Fig. 1B, checkpoint inhibitors combine with CTLA-4, PD-1 and PD-L1 to activate the immune response. Immune checkpoint inhibitors have previously been demonstrated to be effective in the treatment of a variety of malignant tumor types. As a result, utilization of immune intervention checkpoint signaling pathways has become a novel cancer treatment strategy (19,20). In the past decade, three main types of checkpoint inhibitor immunotherapy drugs have been developed for use in preclinical and clinical studies. These drugs target CTLA-4, PD-1 or PD-L1 (21).

Anti-CTLA-4 antibodies. Ipilimumab is a monoclonal antibody that targets CTLA-4, which was approved by the USA Food and Drug Administration (FDA) for the treatment of advanced melanoma in 2011 (22). However, Ipilimumab has also been used in the treatment of numerous other types of cancer, including small-cell lung cancer (23). In a stage II clinical trial (NCT01585987) comparing Ipilimumab with that of standard care as administered immediately following first line chemotherapy in 114 patients with locally advanced (unresectable) or metastatic gastric and gastroesophageal junction cancer, no beneficial effects of Ipilimumab were observed (Table I) (24).

Tremelimumab is a monoclonal antibody that targets CTLA-4, which was approved as an orphan drug treatment for malignant mesothelioma on April 15, 2015 (25). The remission rate was 5% for 18 patients with gastric/gastroesophageal junction adenocarcinoma included in a phase II clinical trial (26); a rate that was below the second-line chemotherapy curative effect of cytotoxic drugs. Although the test of tremelimumab failed to achieve a pre-set remission rate in the final analysis, 4 patients achieved a stable condition and there was one case of partial relief, thereby demonstrating a continuing curative effect in remission, and such findings are promising with regard to the treatment of advanced GC.

Anti-PD-1 antibodies. Pembrolizumab, an IgG4 antibody, was the first monoclonal antibody to be developed that targets PD-1 (27). Pembrolizumab was approved by the USA FDA for the treatment of advanced non-small cell lung cancer in 2017 (28). The safety, tolerability and anti-tumor activity of pembrolizumab (also referred to as MK-3475) were assessed in patients with advanced triple negative breast cancer (TNBC), advanced head and neck cancer, advanced urothelial cancer and advanced GC in a phase I clinical trial (KEYNOTE-012/NCT01848834) (29). Of the 162 patients with advanced GC screened, 39 PD-L1⁺ patients were enrolled in order to evaluate pembrolizumab. The results revealed that the overall response rate (ORR) was 33% (95% CI, 19-50) (29), the 6-month progression-free survival (PFS) and OS rates were 24 and 69%, respectively. These results indicate that pembrolizumab exhibits a manageable degree of toxicity and promising antitumor activity in patients with advanced GC, with PD-L1 expression levels associated with the ORR.

Due to the encouraging results of the KEYNOTE-012 trial, numerous clinical trials involving inhibitory treatment of PD-1 for GC were initiated. The first study (30) was a phase II clinical trial of pembrolizumab as monotherapy and in combination with cisplatin + 5-FU in subjects with recurrent or metastatic gastric or gastroesophageal junction (G/GEJ) adenocarcinoma (KEYNOTE-059/NCT02335411) (31). Based on this research, pembrolizumab was approved as a third-line therapy for recurrent or metastatic G/GEJ cancer by the FDA in September 2017. In addition, there has been a phase III, randomized, open-label clinical trial (32) of pembrolizumab compared with paclitaxel in subjects with advanced gastric or gastroesophageal junction adenocarcinoma that progressed following first-line therapy with platinum and fluoropyrimidine (KEYNOTE-061) (33). Finally, a randomized, active-controlled, partially blinded, biomarker select, phase III clinical trial of pembrolizumab + cisplatin + 5-FU as a first-line treatment in subjects with advanced G/GEJ adenocarcinoma is ongoing (KEYNOTE-062) (34).

Currently in progress is a study involving a phase I dose escalation trial (NCT02268825) to assess the mean tolerated dose (MTD) of MK-3475 (pembrolizumab) in combination with mFOLFOX6, followed by a phase II expansion open label, nonrandomized trial with MK-3475 at the MTD in combination with mFOLFOX6 and supplemental celecoxib in patients with advanced gastrointestinal cancer. In this study, 128 cases of late-stage colorectal, stomach, esophagus, pancreas and biliary tract cancer are being assessed, which will be completed in 2020.

In 2014, the FDA approved nivolumab, sold under the name Opdivo, which is a monoclonal antibody that targets PD-1 and is used for the treatment of advanced melanoma and lung squamous carcinoma (35). In 59 patients with advanced GC, nivolumab monotherapy was tested in the clinical trial Checkmate-032 (NCT02267343); the ORR was 17%, and the 6-month PFS and OS rates were 18 and 49%, respectively (36).

A study with 480 patients is in progress for a phase III trial (NCT02267343) to evaluate the efficacy and safety of ONO-4538 (nivolumab) in the standard treatment failure of unresectable advanced or recurrent GC, including esophago-gastric junction cancer, which are refractory to or intolerant of standard therapy. Preliminary results revealed an improvement

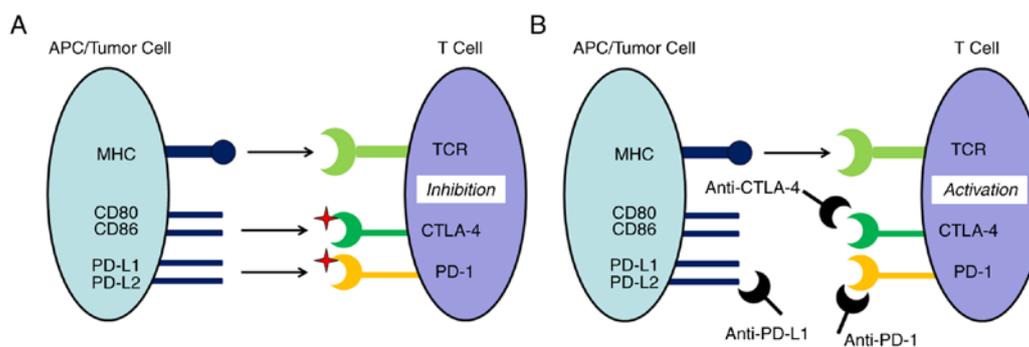


Figure 1. Principle of immune checkpoints and checkpoint inhibitors. (A) Tumor immune escape, which is the activity of T cells inhibited by the immune checkpoint signaling pathways, including CTLA-4 and PD-1/PD-L1. (B) Immune checkpoint inhibitors, which are monoclonal antibodies against immune system inhibitors, including CTLA-4 and PD-1, and its ligand PD-L1, activate an immune response. MHC, major histocompatibility complex; PD-L, programmed death-ligand; CTLA-4, cytotoxic T lymphocyte-associated antigen-4; PD-1, programmed death 1; TCR, T cell receptor; APC, antigen-presenting cell.

in survival with nivolumab treatment in advanced G/GEJ adenocarcinoma compared with placebo treatment (37).

In September 2017, based on a phase III study (ATTRACTION-02) of nivolumab in treating advanced gastric or gastroesophageal junction cancer in the Asian population in Japan, nivolumab was approved as a third-line treatment for unresectable or advanced G/GEJ (Table I) (38). This is the first time that a PD-1 monoclonal antibody has been approved for third-line treatment of advanced GC.

In addition, a phase I/II clinical trial (NCT01928394) is currently in progress to investigate the safety and efficacy of nivolumab as a single agent and in combination with ipilimumab in advanced solid tumors (39). The original project was designed to include six tumor types, including TNBC, GC, pancreatic adenocarcinoma, small cell lung cancer, bladder cancer and ovarian cancer; however, as of January 2017 only patients with bladder and pancreatic cancer have been recruited (Table I).

Anti-PD-L1 antibodies. To the best of our knowledge, three checkpoint inhibitor immunotherapy drugs against PD-L1 have been developed, including MDX-11-5, MEDI4736 and Avelumab. MDX-1105 (also known as BMS-936559) is a human monoclonal IgG4 antibody (40), and in a multicenter phase I trial (NCT00729664) (41), a total of 207 patients, including seven with GC, were treated with this anti-PD-L1 antibody. MDX-11-5 mediated the blockade of PD-L1, induced a durable tumor regression and prolonged stabilization of the disease; however, this was only observed in patients with non-small-cell lung cancer, melanoma or renal cell cancer. MDX-1105 was demonstrated to be relatively safe with regard to its use in the treatment of advanced GC (19).

At the 2015 American Society of Clinical Oncology meeting, Segal *et al* (42), reported their results from a phase I/II clinical trial (NCT01693562) with MEDI4736 (also referred to as durvalumab), a type of monoclonal antibody that is resistant to PD-L1. Their preliminary results, as obtained at only a 6-week median follow-up time period, indicated that MEDI4736 was effective against a variety of tumor types, including GC, where the PFS of two cases over a 24-week period was greater compared with that of the median PFS of stomach second-line therapy. The results from this small dataset (42) of patients demonstrated that concurrent palliative radiotherapy

with the anti-PD-L1 durvalumab was well tolerated (43). To follow up on these findings and assess the efficacy and safety of MEDI4736 in combination with tremelimumab, a phase 1b/2 clinical study (NCT02340975) involving MEDI4736 and tremelimumab monotherapy in metastatic or recurrent gastric or gastroesophageal junction adenocarcinoma was initiated in January 2015 and is expected to be completed in 2019 (44).

As an engineered human monoclonal antibody targeting PD-L1, the safety and efficacy of avelumab were evaluated in a phase I, open-label, dose-escalation clinical trial (NCT01772004), which started in 2013 and was conducted in 1,758 cases with solid tumors, including 150 cases of stomach/stomach esophagus carcinoma (45). An additional phase I, open-label, dose-escalation clinical trial (NCT01943461) of avelumab is currently underway in Japanese patients with metastatic or locally advanced solid tumors, with plans to expand the study with the inclusion of Asian patients with GC, and the trial is expected to be completed by the end of June 2019 (46).

3. CAR-T cell therapy

Tumor cells exert an inhibitory effect upon the immune system, which restricts the induction and activation of the patient's autoimmune response (47). As an approach to mitigate this eventuality, immune lymphocytes are usually removed from the patient and trained to activate specific immune cells capable of recognizing cancer cells *in vitro* (48). Following amplification, these engineered cells can be re-infused into the patient to produce a rapid enhancement of the patient's immune function and destroy the tumor cells (49). Immune cells used in such training are primarily derived from lymphokine-activate killer cells, natural killer cells, cytotoxic T cells and tumor infiltrating lymphocytes (TILs), and this immunotherapy is referred to as adoptive cell therapy. Adoptive cell therapy is considered an active immunotherapy (11). CAR-T cell therapy is one of the most effective means for the treatment of malignant tumors (49,50).

The core of CAR-T cells is the CAR, which includes three domains: i) The single chain fragment variable (scFv, binding tumor-associated antigen); iii) the extracellular hinge and transmembrane domain; and iii) the intracellular signaling domain (51). CARs can be introduced into T cells

Table I. Clinical research of immunotherapy in gastric cancer.

A, Checkpoint inhibitors						
Author/sponsor, year	Antibody	Drug	Trial status	Phase	ClinicalTrials.gov identifier	(Refs.)
Bristol-Myers Squibb, 2012	Anti-CTLA-4	Ipilimumab (Yervoy)	Completed	II	NCT01585987	
Ralph <i>et al.</i> , 2010	Anti-CTLA-4	Tremelimumab	Completed	II		(26)
Merck Sharp & Dohme Corp., 2013	Anti-PD-1	Pembrolizumab (Keytruda)	Ongoing	I	NCT01848834	
Muro <i>et al.</i> , 2016	Anti-PD-1	Pembrolizumab (Keytruda)	Ongoing	I		(29)
Merck Sharp & Dohme Corp., 2015	Anti-PD-1	Pembrolizumab (cisplatin+ 5-fluorouracil + capecitabine)	Ongoing	II	NCT02335411	
Merck Sharp & Dohme Corp., 2015	Anti-PD-1	Pembrolizumab (cisplatin+ 5-fluorouracil + capecitabine)	Ongoing	III	NCT02494583	
Merck Sharp & Dohme Corp., 2015	Anti-PD-1	Pembrolizumab (paclitaxel)	Ongoing	III	NCT02370498	
University of Utah, 2014	Anti-PD-1	Pembrolizumab + mFOLFOX6	Ongoing	I/II	NCT02268825	
Le <i>et al.</i> , 2016	Anti-PD-1	Nivolumab (Opdivo)	Recruiting	II	Checkmate 032	(36)
Boku <i>et al.</i> , 2017	Anti-PD-1	Nivolumab (Opdivo)	Completed	II	ATTRACTION-02	(38)
Ono Pharmaceutical Co. Ltd., 2014	Anti-PD-1	Nivolumab (ONO-4538/Placebo)	Ongoing	III	NCT02267343	(37)
Ono Pharmaceutical Co. Ltd., 2009	Anti-PD-1	Nivolumab (ONO-4538)	Completed	I	NCT00836888	
Bristol-Myers Squibb, 2013	Anti-PD-1+ Anti-CTLA-4	Nivolumab + Ipilimumab + (Cobimetinib)	Recruiting	II	NCT01928394	(40)
Bristol-Myers Squibb, 2008	Anti-PD-L1	MDX-1105	Completed	I	NCT00729664	(41)
Brahmer <i>et al.</i>	Anti-PD-L1	MDX-1105	Completed	I		
MedImmune LLC	Anti-PD-L1	MEDI4736	Ongoing	I/II	NCT01693562	
Segal <i>et al.</i> , 2014	Anti-PD-L1	MEDI4736	Ongoing	I/II		(42)
Levy <i>et al.</i> , 2016	Anti-PD-L1	MEDI4736	Ongoing	I/II		(43)
MedImmune LLC, 2015	Anti-PD-L1	MEDI4736 + Tremelimumab	Recruiting	I/II	NCT02340975	
EMD Serono, 2016	Anti-PD-L1	Avelumab	Recruiting	I	NCT01772004	
Merck KGaA	Anti-PD-L1	Avelumab	Ongoing	I	NCT01772004	
B, CAR-T cell therapies						
Author/sponsor, year	Antibody	CAR generation	Trial status	Phase	ClinicalTrials.gov identifier	(Refs.)
Southwest Hospital, China, 2016	HER2	-	Recruiting	I/II	NCT02713984	
Chinese PLA General Hospital, 2013	HER2	1st and 2nd (CD137)	Recruiting	I/II	NCT01935843	
Baylor College of Medicine, 2009	HER2	2nd (CD28)	Ongoing	I	NCT00889954	
Southwest Hospital, China, 2015	CEA	-	Recruiting	I	NCT02349724	

Table I. Continued.

Author/sponsor, year	Antibody	CAR generation	Trial status	Phase	ClinicalTrials.gov identifier	(Refs.)
Roger Williams Medical Center, 2012	CEA	2nd (CD28)	Suspended	II	NCT01723306	
PersonGen BioTherapeutics (Suzhou) Co., Ltd., 2015	MUC1	-	Recruiting	I/II	NCT02617134	
Sinobioway Cell Therapy Co., Ltd., 2016	EpCAM	-	Recruiting	I/II	NCT02725125	
C) Tumor antigen vaccines						
Author/sponsor, year	Vaccine	Dose/target	Trial status	Phase	ClinicalTrials.gov identifier	(Refs.)
Cancer Advances Inc., 2014	G17DT	500 µg	Completed	II	NCT0245003	
Cancer Advances Inc., 2015	G17DT	250 µg/0.2 ml	Completed	II	NCT02518529	
Cancer Advances Inc., 2015	G17DT	10, 100, 250 µg/0.2 ml	Completed	II	NCT02521649	
Cancer Advances Inc., 2002	G17DT	500 µg	Completed	II	NCT00042510	
Cancer Advances Inc., 2014	G17DT	100, 250, 500 µg	Completed	II	NCT00042510	
Masuzawa <i>et al</i> , 2012	VEGFR	VEGFR1, VEGFR2 (+S-1+DDP)	Published	I/II		(95)
Tokyo University, 2008	VEGFR	VEGFR1, VEGFR2, URLC10	Completed	I/II	NCT00681252	
Tokyo University, 2008	VEGFR	VEGFR1, VEGFR2, URLC10, KOC1	Completed	I/II	NCT00681577	
Kinki University, 2009	URLC10	URLC10	Completed	I	NCT00845611	
Ishikawa <i>et al</i> , 2014	LY6K	LY6K	Published	I	NCT00845611	(96)
National University Hospital, Singapore, 2010	OTSGC-A24	FOXM1, DEPDC1, KIF20A, URLC10, VEGFR1	Ongoing	I/II	NCT01227772	

CTLA-4, cytotoxic T-lymphocyte-associated protein 4; PD-L1, programmed death-ligand-1; PD-1, programmed death 1; HER2, human epidermal growth factor receptor 2; CEA, carcinoembryonic antigen; MUC1, mucin 1; EpCAM, epithelial cell adhesion molecule; VEGFR, vascular endothelial growth factor receptor; URLC10, upregulated in lung cancer 10; FOXM1, forkhead box M1; DEPDC1, DEP domain containing 1; KIF20A, kinesin family member 20A.

with high efficiency using viral vectors, and provide a means for recognition of cell surface components not restricted to major histocompatibility complexes (48). Therefore, T cells with CARs have the capacity to identify a broader range of cell surface components compared with the TCRs of natural T cells (Fig. 2). CAR-T technology represents a promising novel approach for the treatment of cancer. In July 2017, the CAR-T therapy CTL019, for use against relapsed/refractory acute lymphoblastic leukemia, was granted breakthrough therapy designation by the USA FDA (52). Currently, numerous biopharmaceutical companies are developing CAR-T technology for cancer therapy (53,54).

CAR-T cell therapies have demonstrated efficacy against hematological malignancies, as demonstrated in a number of clinical trials (Table I). Recent studies have extended the application of CAR-T cell therapies for the treatment of solid tumors (55-59). Over the past decade, research has been directed at examining the efficacy of CAR-T therapy for use in gastrointestinal tumors, and antigens, including human epidermal growth factor receptor 2 (HER2), carcinoembryonic antigen (CEA), mucin 1 (MUC1) and epithelial cell adhesion molecule (EpCAM), have been used as targets in CAR-T therapy for GC (Table I).

HER2 is a proto-oncogene, which serves an important role in the pathogenesis and clinical development of gastric and gastroesophageal cancer (60-63). Investigators have developed anti-HER2 CAR-modified T cells and validated their efficiency in targeting HER2-positive cancers in preclinical studies (64). In order to establish the efficacy and adverse effects, and evaluate CAR-T cells persistence, tumor elimination and disease status following treatment, clinical studies (65-67) have been conducted with GC (Table I).

CEA is generally expressed in GC, and CEA-specific CAR-T cells can contribute to the delay of tumor growth and an extension in the survival of mice with GC (68). The primary purpose of the clinical trial NCT02349724 was to verify the safety of CEA-targeted CAR-T cells and to identify the proper dosage of CAR-T cells that should be infused (69).

MUC1 and EpCAM are transmembrane glycoproteins that are highly expressed in various types of cancer, including advanced prostate cancer, lung cancer and nasopharyngeal carcinoma (70-74). MUC1-specific CAR-T cells have previously been demonstrated to be effective in attacking MUC1-positive tumor cells (75); however, the altered expressions of EpCAM are associated with an aggressive biological response in GC (76). EpCAM-targeted CAR-T cells for stomach cancer will be evaluated in the phase I/II trials NCT02617134 and NCT02725125 starting in 2015 and estimated to be completed in November 2019, to assess the safety and efficacy of anti-MUC1 CAR-T cells for MUC1-positive relapsed or refractory solid tumors (77,78).

4. Tumor antigen vaccines

A tumor antigen vaccine is a vaccine generated from cancer cells, portions of cancer cells or pure tumor antigens, which are isolated from tumor cells. A tumor antigen vaccine may stimulate the body's immune system to locate and destroy cancer cells (79). Sipuleucel-T (developed by Dendreon Corporation) was the first FDA-approved tumor vaccine,

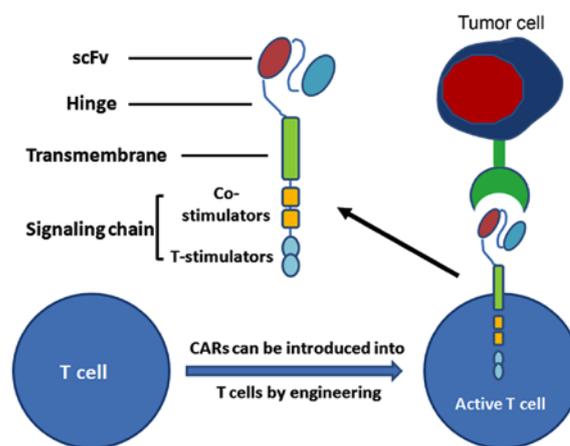


Figure 2. CARs and armoured CAR-T cells for antitumor therapy. T cells from a patient are modified by the introduction of predesigned CARs. When these T cells are re-infused into the patient, they can recognize and destroy malignant cells within the patient. CAR, chimeric antigen receptor.

approved in April 2010 for the treatment of asymptomatic or mild metastatic castration treatment of prostate cancer (80). Tumor vaccines mainly include whole-cell tumor vaccines, gene-modified tumor vaccines, dendritic cell vaccines, peptide vaccines and DNA vaccines (81). At present, thousands of tumor antigens that have been examined to evaluate their efficacy as antitumor agents and the antitumor activity of tumor peptide vaccines, such as G17DT, vascular endothelial growth factor receptor (VEGFR) and OTSGC-A24, have also been utilized in previous studies investigating GC (82-84).

G17DT is a vaccine that neutralizes gastrin-17, which is a hormone required for the growth of a number of cancer types of the gastrointestinal tract. G17DT has previously been demonstrated to be well tolerated and effective in the treatment of patients with advanced cancer (85-87). Previous studies (88,89) and a clinical trial (90) have been designed to investigate antibody responses to G17DT, dose-ranges, tolerability and safety in the treatment of patients with GC (Table I). In addition, results from a clinical phase II/III study (NCT00042510) revealed that following successful inoculation, G17DT induced specific and affinity antgastrin antibody (AGA), and AGA could inhibit proliferation and metastasis of tumors (89); therefore, G17DT combined with cisplatin and 5-FU could contribute to prolonging the median time-to-progression and median survival time for patients with unresectable adenocarcinoma of the stomach or gastroesophageal junction, compared with those without an anti-G17DT immune response (89). A report from the FDA, which designated G17DT as a fast track product on February 21, 2003, suggested that this agent may provide a way to improve the overall survival of stage IV GC when used in combination with cisplatin and 5-FU (91).

There are three main subtypes of VEGFR; 1, 2 and 3 (92). Among them, VEGFR1 and VEGFR2 are two receptors for VEGF-A, and may serve as promising targets for anti-angiogenic immunotherapy against cancer in clinical settings (93,94). In phase I/II studies (NCT00681252 and NCT00681577), the safety and time-to-progression of multiple-vaccine therapy of VEGFR1, VEGFR2 and upregulated in lung cancer 10 (URLC10) or VEGFR1, VEGFR2, URLC10 and KOC1 in treating patients with refractory GC

have been evaluated. Masuzawa *et al* (95) investigated the ability for the peptide vaccine generated from VEGFR1 and VEGFR2 in combination with chemotherapy in one phase I/II study, and identified that a VEGF-specific cytotoxic lymphocyte reaction was induced. In this report, the efficiency reached 55% in 22 patients with advanced GC. In addition, 82% of the patients produced a cytotoxic T cell immune response to the two-peptide vaccines and exhibited an extension in the period of disease progression and increases in overall survival. In addition, in the NCT00845611 trial, the safety, and immunological and clinical responses of the URLC10 peptide vaccine were evaluated in patients with GC (Table I). On the basis of the same clinical trial registered with ClinicalTrials.gov, Ishikawa *et al* (96) demonstrated the immunogenicity of the LY6K-177 peptide vaccine in patients with advanced GC.

To improve the survival of patients with advanced GC, the safety and optimal dosing schedule of a cancer vaccine cocktail was evaluated in a phase I/II study (NCT01227772) with OTSGC-A24 targeting novel specific tumor antigens, including forkhead box M1, DEP domain containing 1, kinesin family member 20A, URLC10 and VEGFR1 (97).

5. Conclusions

Due to the notable success of immunotherapy in the treatment of different tumor types, including melanoma and lung squamous carcinoma (98,99), the investigation of the therapeutic value of immunotherapy has expanded rapidly for application to other cancer types, including GS. However, the overall immunogenicity of gastric carcinoma is relatively weak and the immune treatment efficiency is quite limited in GC (13). Therefore, treatment with an immune checkpoint inhibitor is applicable for only a restrictive group of these patients, such as those with a gastric tumor subtype positive for the EB virus (100,101).

After having established the effectiveness and safety of GC immunotherapy, the next critical issue to address involves selection of the best mode of treatment (102,103). The investigation of targeted immune checkpoints has changed from that of single drug treatment to that involving a combination therapy, and this approach of applying immunotherapy in combination with chemotherapy has been adopted in numerous clinical settings (104). The majority of findings from studies on GC have demonstrated that, compared with chemotherapy alone, the combination of immunotherapy and chemotherapy improves the efficacy of treatment with varying degrees of success (105,106). Nonetheless, due to the side effects associated with chemotherapy, the optimal protocol for combining chemotherapy with immunotherapy requires further investigation.

Immunotherapy was once considered to have little effect in common epithelial cancers with lower mutation rates (107,108); however, a recent study demonstrated that adoptive transfer of autologous lymphocytes can produce widespread lytic activity against cancer cells (109). Zacharakis *et al* (110) reported a patient with breast cancer with adoptive transfer of four mutant-protein-specific TILs in conjunction with interleukin-2 and checkpoint blockade, which mediated the complete durable regression of metastatic breast cancer. The new immunotherapy approach is also expected to be used for the treatment of GC.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

LY collected and analysed the data, and was a major contributor in writing the original draft of the manuscript. YW collected and analysed data. HW reviewed and edited the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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