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[Review]

Immunotherapy for esophageal squamous cell carcinoma : a review

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Abstract

Cancer vaccines and immune checkpoint inhibitors (ICI) have recently been employed as immunotherapies for esophageal squamous cell carcinoma (ESCC). Cancer vaccines for ESCC have yielded several promising results from investigator-initiated phase I and II clinical trials. Furthermore, a Randomized Controlled Trial as an adjuvant setting after curative surgery is in progress in Japan. On the other hand, ICI, anti-CTLA-4 mAb and anti-PD-1 mAb, have demonstrated tumor shrinkage and improved overall survival in patients with multiple cancer types. For ESCC, several clinical trials using anti-PD-1/anti-PD-L1 mAb are underway with several recent promising results. In this review, cancer vaccines and ICI are discussed as novel therapeutic strategies for ESCC.

Key words : esophageal squamous cell carcinoma, immunotherapy, cancer vaccine, immune checkpoint inhibitors

Introduction

A multidisciplinary treatment, including surgery, chemotherapy, and radiotherapy, has been performed for esophageal squamous cell carcinoma (ESCC)[1-3], however, the 5-year global survival is still poor at 30-40 %[4]. Therefore, it is an urgent task to further improve surgical techniques and chemoradiation strategies, and to develop novel therapeutic strategies including molecular target therapy and immunotherapy.

Recent studies have identified several immunogenic cancer antigens (ICA) expressed on ESCC cells[5,6] and clinical trials of cancer vaccines using such ICA have been performed for ESCC. Although results are still challenging as a single agent[7,8], there are several promising results from investigator-initiated phase I and II clinical trials. Furthermore, based on these encouraging results, a Randomized Controlled Trial (RCT) as an adjuvant setting after curative surgery is in progress in Japan[9].

Immune checkpoint inhibitors (ICI) such as anti-CTLA-4 mAb (ipilimumab) and anti-PD-1 mAb (nivolumab and pembrolizumab) have demonstrated tumor shrinkage and improved overall survival in patients with multiple cancer types, leading to renewed enthusiasm for cancer immunotherapy. For ESCC, several clinical trials using anti-PD-1 mAb, nivolumab, are in progress with several recent promising results[9,10]. Furthermore, an RCT has been initiated as a 1st line treatment for ESCC (CheckMate 649).

In this review, cancer vaccines and ICI are discussed as novel therapeutic strategies for ESCC.

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Cancer vaccine

Mechanism of cancer vaccine

Since ICA were identified, translational research for the characterization of cancer antigen-specific cytotoxic T lymphocytes (CTL) in cancer patients has been conducted globally. Cancer vaccine is a strategy that effectively induces cancer antigen-specific CTL using ICA *in vivo* (Fig. 1). Ideal characteristics of ICA for cancer vaccines are : (i) high immunogenicity, (ii) common and specific expression in cancer cells, and (iii) essential molecules for cancer cell survival. There are several types of ICA preparations such as : (i) synthetic tumor-associate antigens (TAA), (ii) whole tumor lysates, and (iii) TAA-encoding vectors. For cancer vaccination, we directly inoculate these ICA alone or dendritic cells (DC) loaded with TAA as well as fusion proteins[11-13].

Although many clinical cancer vaccine trials for malignant tumors including ESCC have been performed[7-9,14-18], unfortunately, only one cell-based vaccine, sipuleucel-T (Provenge®), was clinically approved by FDA for patients with metastatic hormone-refractory prostate cancer in 2010[19]. To enhance the clinical effects of cancer vaccines, it may be necessary to develop new approaches such as the combination therapy with ICI to enhance effect of cancer antigen-specific CTL and the multiple ICA approach derived from the different target molecules to overcome heterogeneity of cancer cells[20,21]. We have recently began the development of a cancer vaccine with DC loaded with multiple TAA, which can simultaneously stimulate CD4- and CD8-positive T cells, since CD4-positive helper T cells enhance the induction and function of cancer antigen-specific CTL (Fig. 1).

Current status of cancer vaccine for ESCC

Clinical trials of cancer vaccines using peptides for esophageal cancer are summarized in Table 1. No cancer vaccine has been approved for clinical use for ESCC. Recently we have shown novel ICA including TTK protein kinase (TTK), lymphocyte antigen 6 complex locus K (LY6K), insulin-like growth factor (IGF)-II mRNA binding protein 3 (IMP-3), cell division cycle-associated protein 1 (CDCA1), and KH domain-containing protein overexpressed in cancer 1 (KOC1)[7,8]. Since these ICA, which are derived from different Cancer-Testis antigens, are highly and frequently expressed, and are essential molecules for survival and proliferation in ESCC, we thought that they would be promising targets for cancer vaccine against ESCC[7,8]. We therefore identified three HLA-A24-restricted immunodominant peptides that were derived from TTK, LY6K, and IMP3. We then performed phase I and II clinical trials of the cancer vaccine with a combination of these three peptides in *HLA-A*2402*

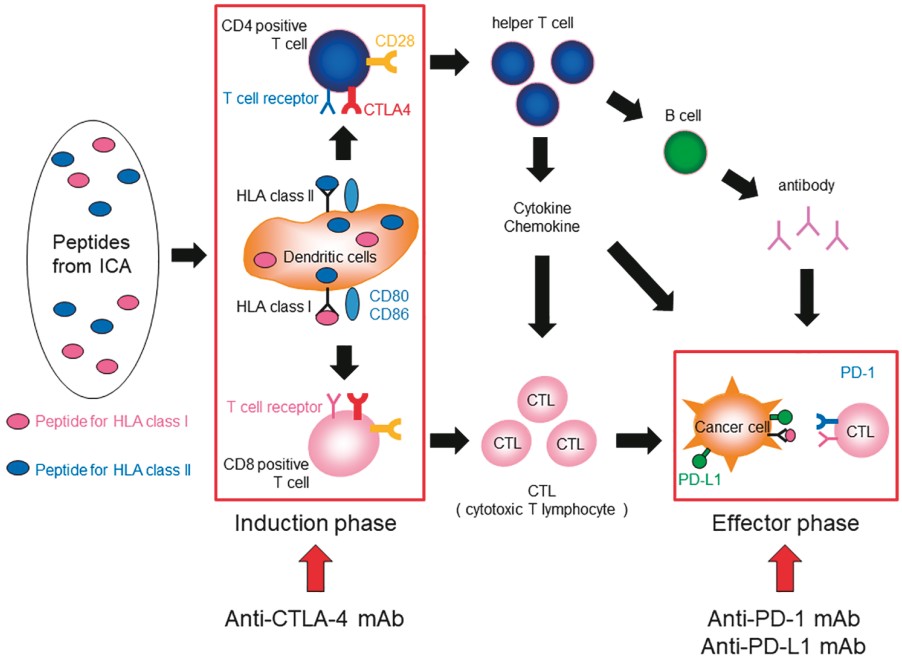

Fig 1. Schematic tumor immune response and mechanisms of ICI. Figure modified from Mimura K *et al.*[48] with permission from Japanese Journal of Cancer and Chemotherapy.

Table 1 List of clinical trials with peptide vaccine for Esophageal cancer

Author/Sponsor	Agent	Traget	conditions	HLA type	IFA (incomplete freund's adjuvant)/ combination	Phase	Line	Number : Esophageal cancer (total)	UMIN-CTR ID or ClinicalTrial.gov, number	Recruitment Status
Shionogi & Co., Ltd.	S-588410	DEPDCI, MPHOSPH1, LY6K, CDCA1, KOC1	Esophageal cancer	A*24 : 02	Montanide ISA-51 VG	III	Adjuvant	270	UMIN000016954	Recruiting
Shionogi & Co., Ltd.	S-488410	LY6K, CDCA1, KOC1	Advanced or recurrent ESCC	(−)	?	I/II	Salvage	96	UMIN000005161	Completed
Kono K, *et al.*	(−)	TTK, LY6K, IMP-3	Locally advanced, recurrent or/and metastatic ESCC who had faild for the standard therapy	(−)	Montanide ISA-51	II	Salvage	60	NCT00995358	Recruited
Yasuda T, *et al.*	(−)	LY6K, CDCA1, KOC1	Thoracic ESCC who underwent neoadjuvant therapy followed by curative resection	(−)	Montanide ISA-51	II	Adjuvant	63	UMIN000003557	No longer recruiting
Kinki University Faculty of Medicine	(−)	LY6K, CDCA1, KOC1	LN metastasis positive esophageal cancer without preoperative therapy	(−)	Montanide ISA-52	II	Adjuvant	60	UMIN000003556	Terminated
University of Tokyo	(−)	TTK	Advanced ESCC	A24	?	I	Salvage	6	UMIN000001014	Terminated
Kono K, *et al.*	(−)	TTK, LY6K, IMP-3	Locally advanced, recurrent or metastatic ESCC who had been resistant to the standard therapy	A*24 : 02	Montanide ISA-51	I	Salvage	10	NCT00682227	Recruited
Iinuma H, *et al.*	(−)	TTK, LY6K, KOC1, VEGFR1, VEGFR2	Unresectable chemo-naïve ESCC	A*24 : 02	Montanide ISA-51 radiotherapy : 60 Gy Cisplatin : 40 mg/m^2 5-fluorouracil : 400 mg/m^2	I	Unresectable chemo-naïve	11	NCT00632333	Recruited
Iwahashi M, *et al.*	(−)	TTK, LY6K	Advanced/ metastatic ESCC	A*24 : 02	CpG-7909	I	Salvage	9	NCT00669292	Recruited
Mie University	IMF-001 (CHP-NY-ESO-1)	NY-ESO-1	Curative resected esophageal cancer with NY-ESO-1 antigen expression	(−)	(−)	rII	Adjuvant	70	UMIN000007905	Recruiting
Kageyama S, *et al.*	IMF-001 (CHP-NY-ESO-1)	NY-ESO-1	Advanced/ metastatic esophageal cancer	(−)	(−)	I	Salvage	25	NCT01003808	Recruited
Kakimi K, *et al.*	NY-ESO-1f	NY-ESO-1	Advanced cancer expressed NY-ESO-1 : including six esophageal cancer patients	(−)	Picibanil OK-432, Montanide ISA-51	I	Salvage	6 (10)	UMIN000001260	Recruited
National Cancer Center Hospital East	HSP105-derived peptide vaccnine	HSP105	Advanced esophageal cancer/ colo- rectal cancer	A*24 : 02 or 02 : 01 or 02 : 06 or 02 : 07	(−)	I	Salvage	? (15)	UMIN000017809	No longer recruiting
Saito T, *et al.*	CHP-MAGE-A4	MAGE-A4	Advanced cancer expressed MAGE-4 : including 18 esophageal cancer patients	(−)	(−)	I	Salvage	18 (20)	UMIN000003188	Recruited

(+) patients with advanced ESCC who had failed to standard therapy[7,8]. In our phase II clinical trial, patients with immune response induced by the vaccination showed better prognosis than those with no immune response[7].

Based on the same strategy, two clinical trials of cancer vaccine with three immunodominant peptides derived from LY6K, CDCA1, and KOC1, are in progress as adjuvant setting. Yasuda T *et al.* reported that a group receiving cancer vaccine has a better relapse-free survival in comparison to a group not receiving cancer vaccine[22] Furthermore, Shionogi, a pharmaceutical company in Japan, is performing a phase III clinical trial of cancer vaccine in an adjuvant setting after curative surgery for esophageal cancer to obtain an approval as a drug[9].

ICI

Functional mechanism of ICI

In an interaction between T cells and cancer cells, the T-cell response is regulated by a balance between activating and inhibitory signals in T cells. These signals are currently called the immune checkpoints[23,24]. Two immune checkpoint receptors, cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1), have recently been actively investigated. Both receptors are expressed on T cells where they induce inhibitory signals (Fig. 1).

CTLA-4 counteracts and inhibits CD28, which is an activating T cell co-stimulatory receptor, and fundamentally regulates the induction phase of T cell activation[25]. Although CD28 signaling strongly enhances T cell receptor signaling and leads to activation of T cells, CTLA-4 inhibits the activity of CD28, resulting in inactivation of T cells[25]. In 2010, the FDA approved the anti-CTLA-4 mAb, ipilimumab, as the first ICI for metastatic melanoma[26].

PD-1 interacts with programmed death-ligand 1 (PD-L1) on cancer cells and immune cells. PD-1/PD-L1 signals reduce cytotoxic function of CTL and induce apoptosis of CTL[27,28]. PD-L1 is an inhibitory B7 family member and up-regulation of PD-L1 has been reported in various types of human cancer including ESCC and immune cells[23,29,30]. Currently, two anti-PD1 mAbs, nivolumab and pembrolizumab, are available for clinical use for several types of cancer. They have shown significant and durable responses in several types of refractory tumors including in 31% of patients with melanoma, 29% with kidney cancer and 17% with lung cancer[31-33]. Furthermore, recently, two anti-PD-L1 mAbs, avelumab and atezolizumab, are approved for clinical use in Japan. Avelumab is available for unresectable merkel cell carcinoma and atezolizumab is available for unresectable progressive / recurrent non-small cell lung cancer respectively.

CTL induction and infiltration in vivo

Since anti-CTLA-4 mAb mainly activates T cells in the induction phase and anti-PD-1/anti-PD-L1 mAb enhances CTL function in the effector phase (Fig. 1), CTL induction and infiltration *in vivo* is very crucial to enhance the clinical effects of ICI. In order to efficiently induce CTL *in vivo*, ICA and activation of DC, which can phagocytize and present ICA, are regarded important.

Neoantigens have recently been proposed as candidates for ICA to efficiently induce CTL *in vivo*[34]. Neoantigens are formed by peptides that are entirely absent from the normal human genome ; they are solely created by cancer specific DNA alterations in cancer cells, resulting in the formation of novel protein sequences. Several ICI clinical trials have been reported confirming the significant correlations between clinical response and burden of mutation-derived neoantigens, suggesting that a part of the cancer was eliminated by neoantigen specific CTL activated by ICI[34].

The concept of immunogenic tumor cell death (ICD) was proposed by Apetoh *et al.*[35]. In ICD, DC were activated by danger signals such as high mobility group box 1 (HMGB1) and calreticulin released by dying cells. The activated DC could then efficiently phagocytize and present cancer antigens, resulting in CTL induction[35]. We showed that chemoradiation could induce up-regulation of local HMGB1 and cancer antigen-specific CTL in ESCC patients[36]. Furthermore, our *in vitro* study showed that HMGB1 was produced following chemoradiation in a panel of ESCC cell lines[36]. The abscopal effect is rare phenomenon where local irradiation on the tumor causes regression of metastases at sites distant from the irradiated area[37]. This effect is a rare phenomenon but has been shown in several types of malignant tumors, including melanoma, lymphoma, hepatocellular carcinoma and renal cell carcinoma[38,39]. Although its mechanism has not been completely elucidated[40], there is a possibility that the abscopal effect is induced by the ICD process.

Current status of ICI for ESCC

The clinical trials of anti-PD-1/anti-PD-L1 mAb for esophageal cancer are summarized in Table 2. Focusing on clinical trials for ESCC, there are phase II and III clinical trials of nivolumab. In the phase II clinical trial, patients with ESCC who were refractory or intolerant to standard chemotherapy were recruited (n=65) and the design was single-arm as a second line setting[10]. As a result of this trial, the objective response rate (complete response [CR] and partial response [PR]) and disease control rate (CR, PR, and stable disease [SD]) were seen in 14% and 42% of the enrolled patients, respectively, and the adverse event profile was acceptable[10].

Following the promising results from the phase II clinical trial of nivolumab for ESCC, a phase III clinical trial as a salvage setting was started. In total, 390 advanced or recurrent ESCC patients, who

Table 2 List of clinical trials with anti-PD-1/anti-PD-L1 mAbs for Esophageal cancer

Traget	Agent	Sponsor / Collaborator	Condition	Arms	Phase	Line	Number	ClinicalTrial.gov, number, UMIN-CTR ID, JapicCTI-No.	Recruitment Status
PD-1	Nivolumab (ONO-4538)	Ono Pharmaceutical Co. Ltd, Bristol-Myers Squibb	Esophageal Cancer	Single-arm : nivolumab	II	Salvage	65	JapicCTI-142422	Recruited
PD-1	Nivolumab (ONO-4538)	Ono Pharmaceutical Co. Ltd / Bristol-Myers Squibb	Esophageal Cancer	Nivolumab Docetaxel or paclitaxel	III	Salvage	390	NCT02569242 JapicCTI-153026	Recruiting
PD-1	Nivolumab (ONO-4538)	Bristol-Myers Squibb / Ono Pharmaceutical Co. Ltd	Stage II/III carcinoma of the esophagus or gastroesophageal junction	Nivolumab Placebo	III	Adjuvant	760	NCT02743494	Recruiting
PD-1	Nivolumab (ONO-4538)	Bristol-Myers Squibb / Ono Pharmaceutical Co. Ltd	Gastric Cancer Gastroesophageal Junction Cancer *Cancer cannot be operated on and is advanced or has spread out.	Nivolumab + ipilimumab XELOX (oxaliplatin + capecitabine) FOLFOX (oxaliplatin + leucovorin + fluorouracil) Nivolumab + XELOX Nivolumab + FOLFOX	III	1st	1266	NCT02872116	Recruiting
PD-1	Nivolumab (ONO-4538)	Sidney Kimmel Comprehensive Cancer Center / Bristol-Myers Squibb	Operable Stage II/III Esophageal/ Gastroesophageal Junction Cancer	Nivolumab + carboplatin/ paclitaxel + radiation Nivolumab + ipilimumab + carboplatin/paclitaxel + radiation	I	Neoadjvant	32	NCT03044613	Recruiting
PD-1	Nivolumab (ONO-4538)	Kyowa Hakko Kirin Co., Ltd / Ono Pharmaceutical Co. Ltd	Locally advanced or metastatic Solid Tumor	Single-arm : mogamulizumab + nivolumab	I	Salvage	108	NCT02476123	Active, not recruiting
PD-1	Nivolumab (ONO-4539)	Osaka University / Kyowa Hakko Kirin Co., Ltd, Ono Pharmaceutical Co. Ltd, Clinical Study Support, Inc., Fiverings Co., Ltd.	Operable Gastric Cancer, Esophageal Cancer, Lung Cancer, Renal Cancer	Single-arm : mogamulizumab + nivolumab	I	Neoadjuvant	18	NCT02946671 UMIN000021480	Recruiting
PD-1	Pembrolizumab (MK-3475)	Merck Sharp & Dohme Corp.	Esophageal Carcinoma Esophagogastric Junction Carcinoma	Single-arm : pembrolizumab	II	3rd	100	NCT02559687	Active, not recruiting
PD-1	Pembrolizumab (MK-3475)	Merck Sharp & Dohme Corp.	Esophageal Carcinoma Esophagogastric Junction Carcinoma	Pembrolizumab Investigator's choice of chemotherapy : paclitaxel, or docetaxel, or irinotecan	III	2nd	720	NCT02564263	Recruiting
PD-1	Pembrolizumab (MK-3475)	City of Hope Medical Center / National Cancer Institute (NCI)	Adenocarcinoma of the Gastroesophageal Junction Gastric Adenocarcinoma Gastric Squamous Cell Carcinoma Metastatic Malignant Neoplasm in the Stomach Stage IV Esophageal Adenocarcinoma Stage IV Esophageal Squamous Cell Carcinoma	Single-arm : pembrolizumab + palliative external beam radiation therapy	II	Salvage	14	NCT02830594	Recruiting
PD-1	Pembrolizumab (MK-3475)	Washington University School of Medicine / Merck Sharp & Dohme Corp.	Untreated metastatic Esophageal Cancer	Single-arm : pembrolizumab + radiation (brachytherapy) *brancytherapy=16 Gy delivered in 2 fractions of 8 Gy per fraction	I	1st	15	NCT02642809	Recruiting
PD-L1	Atezolizumab (MPDL3280A)	Genentech, Inc.	Locally advanced or metastatic solid tumors or hematologic malignancies (including esophageal cancer)	single-arm : atezolizumab	I	Salvage	698	NCT01375842	Active, not recruiting
PD-L1	Atezolizumab (MPDL3280A)	Academisch Medisch Centrum - University van Amsterdam (AMC-UvA) / UMC Utrecht	Stage II/III Esophageal Cancer *adenocarcinoma of the esophagus or gastro esophageal juncion	single-arm : atezolizumab + carboplatin + paclitaxel + radiation (23 × 1.8 Gy)	II	1st	40	NCT03087864	Recruiting
PD-L1	Durvalumab (MEDI4736)	Samsung Medical Center	Esophageal Cancer	Durvalumab Placebo	rII	Adjuvant	84	NCT02520453	Recruiting
PD-L1	Durvalumab (MEDI4736)	Ludwig Institute for Cancer Research / AstraZeneca	Esophageal Cancer	Durvalumab + oxaliplatin + capecitabine Durvalumab + tremelimumab + oxaliplatin + capecitabine Durvalumab + surgery + oxaliplatin + capecitabine Durvalumab + surgery + oxaliplatin + capecitabine + radiotherapy	I/II	1st	75	NCT02735239	Recruiting

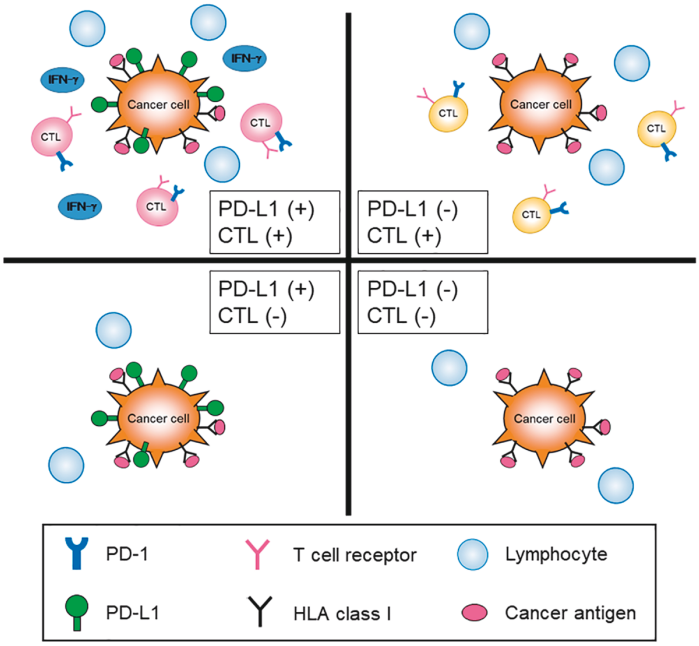

Fig 2. Four subclassifications of tumor microenvironments from the view point of expected clinical effects of anti-PD-1/anti-PD-L1 mAb. Figure modified from Mimura K *et al.*[41] with permission from Japanese Journal of Cancer and Chemotherapy.

were refractory to 5FU + CDDP-based chemotherapy, were enrolled and randomly assigned into either a nivolumab or paclitaxel/docetaxel group (NCT02569242). The primary endpoint of this trial is overall survival (OS) and the results are expected to be released in 2020. Furthermore, enrollment is currently underway for a new RCT as a 1st line setting for ESCC (CheckMate 649). In this trial, inoperable advanced or recurrent ESCC patients will be randomly assigned into three groups : nivolumab + ipilimumab, 5FU + CDDP + nivolumab, and 5FU + CDDP.

Next challenge of cancer immunotherapy for ESCC

It is assumed that anti-PD-1/anti-PD-L1 mAb will be key drugs for immunotherapy for ESCC. As described above, anti-PD-1/anti-PD-L1 mAb enhance CTL function in the effector phase (Fig. 1). If there are tumor infiltrating lymphocytes (TIL) in the tumor microenvironment, CTL should be present. From the view point of expected clinical effects of anti-PD-1/anti-PD-L1 mAb, several articles including ours suggested that the tumor microenvironment can be subclassified into 4 types : CTL(+) and PD-L1(+) on cancer cells, CTL(+) and PD-L1(−), CTL(−) and PD-L1(+), and CTL(−) and PD-L1(−) (Fig. 2)[41,42]. We speculate that optimum clinical effects of anti-PD-1/anti-PD-L1 mAb can be obtained from the tumor microenvironment like as CTL(+) and PD-L1(+). This suggests that it is important to increase CTL infiltration in the tumor microenvironment before administration of anti-PD-1/anti-PD-L1 mAb.

Anti-CTLA-4 mAb, cancer vaccine, and chemoradiation have a potential to induce CTL infiltration *in vivo* because anti-CTLA-4 mAb mainly activates T cells in the induction phase to induce CTL (Fig. 1) and the cancer vaccine induces cancer antigen-specific CTL. Furthermore, we showed that chemoradiation could induce cancer antigen-specific CTL in ESCC patients[36]. Some cytotoxic drugs or molecular target drugs are also thought to induce ICD, resulting in CTL induction[43,44]. In addition, since activated CTL produce IFN-γ, activated CTL in the tumor microenvironment could induce PD-L1 expression on cancer cells through the effect of IFN-γ. Our next challenge is the clinical development of combinatorial approaches, using anti-PD-1/anti-PD-L1 mAb with treatments to induce CTL. In animal models and pre-clinical data, a strong synergy was observed between cancer vaccine and ICI, anti-CTLA-4 mAb and anti-PD-1 mAb[45,46]. Moreover, it was reported that a combination of anti-CTLA-4 mAb with anti-PD-1 mAb led to rapid tumor regression in almost a third of melanoma patients[47].

Collectively, ESCC has biological characteristics suitable for immunotherapy, such as high frequency

of neoantigens, radio-sensitive tumor, and several identification of ICA. We suggest that a combination of anti-PD-1/anti-PD-L1 mAb with treatments to induce CTL including anti-CTLA-4 mAb, cancer vaccine, chemoradiation, and cytotoxic and/or molecular target drugs, may be an ideal and reasonable strategy for ESCC therapy.

Conflict of interest statement and ethical statement

All authors have no conflict of interest in this study. All procedures in this study were in accordance with the ethical standards of the responsible committee on human experimentation at Fukushima Medical University and with the Helsinki Declaration.

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