Editorial

Immune checkpoint blockade therapy for esophageal squamous cell carcinoma

Kazuto Harada[1,2], Dilsa Mizrak Kaya[1], Hideo Baba[2], Jaffer A. Ajani[1]

[1]Department of Gastrointestinal Medical Oncology, University of Texas M. D. Anderson Cancer Center 1515 Holcombe Blvd, Houston, TX 77030, USA; [2]Department of Gastroenterological Surgery, Graduate School of Medical Science, Kumamoto University, Kumamoto 860-8556, Japan

Correspondence to: Jaffer A. Ajani, MD. Department of Gastrointestinal Medical Oncology, University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030, USA. Email: jajani@mdanderson.org.

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Esophageal cancer (EC) is the eleventh most common cause of cancer worldwide (459,299 cases) and the sixth most common cause of cancer mortality (439,000 deaths) (1). Esophageal squamous cell carcinoma (ESCC) is one of the major histological types, whose incidence has been decreasing in West, but remains the most common type in Asia, Africa, and South America. Prognosis of metastatic ESCC is poor even though it initially sensitive to combination chemotherapy, but resistance emerges rapidly. There has not been an effective targeted agent to treat ESCC. Recently, immune checkpoint blockade has received considerable attention. Programmed death protein 1 (PD-1), together with its ligand (PD-L1) inhibit the response of T cells to tumor cells (2,3). PD-1 expression can be observed on the surface of immune cells, such as T cells, B cells, natural killer cells, and monocytes, and it limits the T-cell activity in a regulatory fashion (2). PD-L1 expression contribute to protect the host against autoimmune activity, but tumor cells and cells in tumor microenvironment express PD-L1 and escape from anti-tumor immunity (2,3). Immune checkpoint blockade has radically changed the treatment of melanoma and lung cancer, and has been applying to gastrointestinal malignancies (4).

Large number of somatic mutations (that can lead to non-sense or missense mutations) can cause neoantigens on surface of tumor cells, leading to the release of proinflammatory cytokines and recruitment of cytotoxic T cells into tumor microenvironment (5). Thus, tumor with high tumor mutational burden (TMB) could potentially response to immune checkpoint blockade therapy (6). TCGA data showed that EC is frequently mutated tumor (7). ESCC commonly have mutations especially in *TP53*, *NFE2L2*, *MLL2*, *ZNF750*, *NOTCH1*, and *TGFBR2* (8). Moreover, previous study showed that PD-L1 overexpression was found in 14.5–63.3% of ESCC (9). Therefore, ESCC is one of the tumor which should be anticipated to response immune checkpoint blockade therapy.

Kudo and colleagues recently conducted an open-label, single-arm, multi-center phase 2 study and assessed the safety and activity of nivolumab (PD-1 inhibitor) monotherapy in metastatic ESCC patients who were refractory or intolerant to standard chemotherapy, such as fluoropyrimidine-based, platinum-based, and taxane-based chemotherapy (10). In 64 patients, 11 (17%) had an objective response (complete or partial response). The median duration of overall survival (OS) was 10.8 months [95% confidential interval (CI), 7.4–13.3], which is particularly longer than previous trial evaluating advanced EC. For example, phase 3 trial evaluating EGFR inhibitor for advanced EC showed that median OS was 3.73 months for the EGFR inhibition group and 3.67 months for placebo (11). Kudo *et al.* also reported that adverse events occurred in 85%, with grade 3–4 events in

26% (grade 3; 23%, grade 4; 3%). Grade 4 dyspnoea and hyponatraemia occurred in one patient each, and common grade 3 adverse events are lung infection in 5 patients, appetite loss in 2 patients, increased blood creatinine phosphokinase in 2 patients, and dehydration in 2 patients. 23% patients resulted in interrupting treatment because of adverse events. 11% patients could not continue treatment. However, there were no treatment-related deaths. Kudo *et al.* concluded that nivolumab could be a potential treatment option in patients with advanced ESCC. To date, a phase 3 trial comparing nivolumab alone and docetaxel or paclitaxel (NCT02569242) is ongoing.

There is another trial regarding PD-1 inhibitor monotherapy in ESCC patients (12). KEYNOTE-028 (NCT02054806) assessed safety and efficacy of pembrolizumab in PD-L1 positive ESCC patients. Thirty-seven (41%) of 90 patients had PD-L1 positive ESCC, and ultimately 23 patients were assessed. Five patients (23%) had an objective response. Six patients (26%) patients experienced adverse events; there were no grade 4 adverse events and no patients died or discontinued because of adverse events. Survival result is not published yet. The CheckMate 032 study showed that PD-1 inhibitor in combination with CTLA-4 inhibitor was active in EC, but most population is adenocarcinoma (13). The KEYNOTE-059 study showed that PD-1 inhibitor in addition to 5-FU and cisplatin is manageable safety as the first line therapy for gastric cancer (14). Further trials evaluating immune checkpoint blockade for EC are expected.

Biomarkers to predict response for immune checkpoint blockade are needed. PD-L1 expression and microsatellite instability (MSI) are considered as potential biomarker so far (13-15). MSI-H being a very reliable biomarker but PD-L1 is a poor predictor of response in GI tumors. TMB is related to MSI status and TMB as a biomarker is under evolution at the moment (6). PD-L1 positive tumor is sensitive to immune checkpoint blockade therapy in upper gastrointestinal cancer, but unclear in ESCC (13,14). One meta-analysis showed that PD-L1 overexpression was found in 559 patients (41.4%) in 1,350 patients and a poor prognostic factor for ESCC (9). We need to evaluate if PD-L1 expression could be a biomarker for immune checkpoint blockade therapy. In terms of MSI, a study for 12 different types of solid tumor with MSI-H showed favorable result; objective responses were detected in 46 of the 86 patients, with 18 patients achieving a complete response, which seem to be more sensitive than other immune checkpoint blockade trial. A small cohort study reported the frequency of MSI in ESCC as 8.1% (16).

Tumor infiltrating lymphocytes (TILs) has a close relationship with PD-L1 expression. Four classification based on PD-L1 and TILs has been proposed (17). PD-L1+/TILs+ type is largely responding to checkpoint blockade because intra tumor T cells are predicted to work when PD-1/PD-L1 pathway are blocked. PD-L1–/TILs– type has lack of detectable immune reaction, therefore PD-1 inhibitor in combination with attracting T-cell into tumors [cytotoxic T-lymphocyte associated antigen 4 (CTLA-4) blockade, vaccination or adoptive transfer] are needed. PD-L1+/TILs- type also need a similar approach for PD-L1-/TILs- type. PD-L1-/TILs+ type might be immune tolerance, or other immune suppressive pathways might be activated. Yagi *et al.* assessed 305 ESCC resected samples and identified 41 patients as PD-L1+/TILs+ type, 91 as PD-L1–/TILs– type, 12 as PD-L1+/TILs– type, and 161 as PD-L1–/TILs+ (18). PD-L1–/TILs+ type has the most favorable prognosis, while PD-L1+/TILs– type has the most unfavorable prognosis. This study suggests that PD-L1 expression and TILs status might predict survival and provide potential personalized immunotherapy strategy for ESCC patients.

Radiation therapy, which is effective treatment for ESCC, in combination with immunotherapy provides the synergistic effects on local and distant tumor (19). Several clinical trials for this approach is ongoing for kinds of tumor. Radiation facilitates MHC class I expression and antigen presentation, subsequently leading to increasing the density of TILs (19). Moreover, radiation increase PD-L1 expression (19). Lim *et al.* assessed 19 pairs of ESCC sample before and after preoperative chemoradiation and demonstrated that PD-L1 expression score increased significantly after chemoradiation from baseline (20). Radiation in combination with checkpoint blockade immunotherapy might be effective for ESCC.

In summary, PD-1 inhibition could be a potential treatment option in ESCC patients. PD-1 inhibitor combination with other therapy, such as CTLA-4, chemotherapy, or radiotherapy, is expected. The Kudo *et al.* paper helps us to understand the benefits and shortcomings of PD-1 inhibition in this difficult disease, however, much more work is needed. MSI is rare in ESCC, therefore, we will need to explore other reliable biomarkers.

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Footnote

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