Letter to the Editor

Need for prospective collection of experience and repeated samples in esophageal squamous cell carcinoma

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Provenance: This is an invited Editorial commissioned by the Section Editor Dr. Jianfei Shen (Taizhou Hospital of Zhejiang Province, Wenzhou Medical University, Wenzhou, China).

Response to: Harada K, Mizrak Kaya D, Baba H, *et al.* Immune checkpoint blockade therapy for esophageal squamous cell carcinoma. J Thorac Dis 2018;10:699-702.

Pectasides E. Immune checkpoint blockade in esophageal squamous cell carcinoma: is it ready for prime time? J Thorac Dis 2018;10:1276-9.

Walsh EM, Kelly RJ. Single agent anti PD-1 inhibitors in esophageal cancer-a first step in a new therapeutic direction. J Thorac Dis 2018;10:1308-13.

Submitted Apr 14, 2018. Accepted for publication Apr 24, 2018.

doi: 10.21037/jtd.2018.05.37

View this article at: http://dx.doi.org/10.21037/jtd.2018.05.37

I appreciate the comments by Ajani, Pectasides, and RJ Kelly on our recent report (1). To my knowledge, two studies have evaluated checkpoint inhibitors related to esophageal squamous cell carcinoma (ESCC) (1,2). These two studies reported similar results with an objective response rate of approximately 20%, although selection bias should be considered. Several factors are thought to have influenced these results. As suggested by Ajani *et al.*, previous treatment with radiotherapy resulted in longer progression-free survival and overall survival with immune checkpoint inhibitors (ICIs); these effects were not simply because of the combination of ICIs and radiotherapy. Radiotherapy has been recently identified as a relevant factor for immune oncology (3). Therefore, an analysis of its tentative anti-tumor effect, as well as the whole oncological course, is needed. Conversely, surgery—especially if there are complications such as infection—could have a negative impact on immuno-sensitivity. Esophagectomy for esophageal cancer is one of the most invasive operative procedures. Surgical stress may induce the release of pro-inflammatory cytokines, and cytokine overproduction can result in systemic inflammatory response syndrome, which may lead to acute lung injury and multiple organ dysfunction syndrome. Such surgical stress may cause immuno-suppression, affecting perioperative mortality, survival, and immune response (4).

Post-immunotherapy-induced hyper-chemosensitization has been recently investigated because post-immunotherapy patients show a favorable overall response (5). The immuno-modulatory effects of chemotherapy appear to improve survival when administered prior to chemotherapy. A report on the association of immune-related adverse events (irAEs) with ICIs (6) showed that development of irAEs was associated with better survival. An early onset, irAEs might be predictive of and maximize the therapeutic effect of these agents, although the mechanisms are unknown. Long-lasting shrinkage of tumor masses after the discontinuation of ICIs is another unique phenomenon to be considered as a treatment strategy (7). This immunotherapy-specific phenomenon should be considered for each disease-specific strategy. The results of ICIs for ESCC (overall response rate: 20%) may seem minimal. Anti-tumor effects may be maximized if we set up ICIs at the best sequence; however, we have no definitive data on the best point for immuno-treatment for ESCC (*Figure 1*).

As several recent investigations of immuno-therapy have reported unexpected results, it could be said that, in the immuno-oncology era, classical oncological indicators are not suitable for the early detection for these new strategies (8). Early investigation by objective response is insufficient for surrogacy for identifying promising treatments for immune-oncology. Rather, we need to define the most appropriate

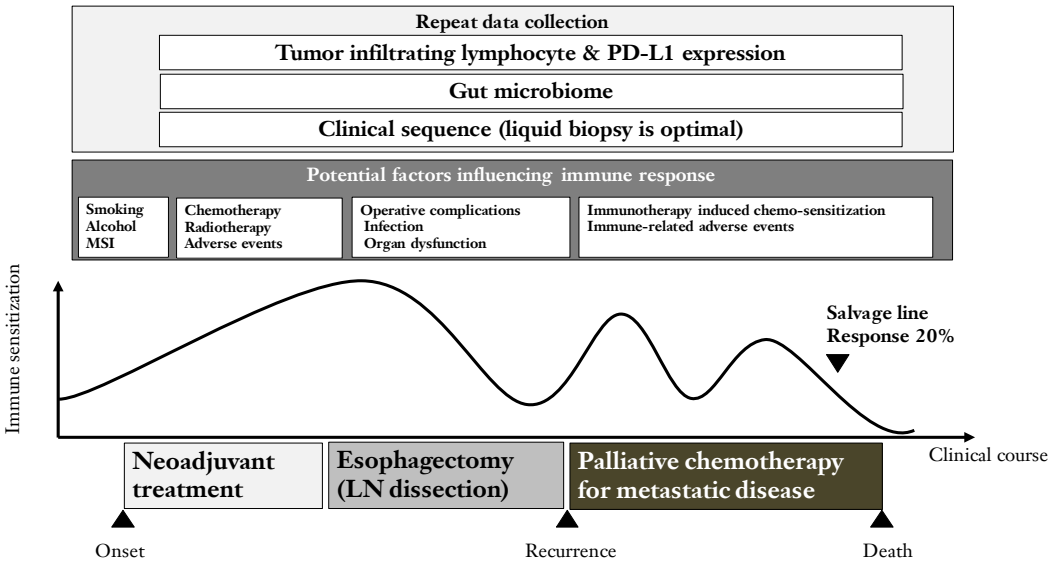

Figure 1 Strategy for investigation of esophageal squamous cell carcinoma.

primary endpoint of ICIs (9).

It could also be said that traditional oncological investigational strategies cannot improve survival. A simple combination of chemotherapy, molecular target agents, and/or radiation is typically used to improve survival. However, these approaches do not lead to immunological specific benefits. Pseudo-progression, hyper-progression, and immunotherapy-induced chemo-sensitization are the typical unexpected and unevaluated results, and these unique new phenomena cannot be evaluated by the standard oncological approach. For evaluation, we need more experience and large cohort data with a variety of samples. In the near future, it may be necessary to redefine the overall strategy and treatment sequence for ESCC in favor of multi-modal treatments.

There are still two important issues that require discussion. One is how to interpret clinical sequence data, which is essential for advancing treatment for ESCC. The other important issue is how to utilize data from fecal samples, as the gut microbiome is known to influence the efficacy of immunotherapy (10). Fecal microbiota transplantation (FMT) from cancer patients who responded to ICIs is one of the most promising immunization strategies. As there are few studies on the role of the microbiota in ESCC, sample collection from prospective cohort trials is needed to gather information that can be used to inform treatment strategies.

In conclusion, there are several suggestions for improving survival in ESCC patients. To overcome ESCC by ICIs, a specific strategy is needed that incorporates experience, clinical sequence, and microbiota data. Prospective cohort trials with repeated collection of biopsy samples, liquids, and feces are thus warranted.

Acknowledgements

I thank Kenta Kawasaki and Akiyoshi Kasuga for their kind suggestion. Research grant from Ono pharm. Bristol-Meyers Squibb, MSD. An advisory board member for BMS and Ono pharma.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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Cite this article as: Hamamoto Y. Need for prospective collection of experience and repeated samples in esophageal squamous cell carcinoma. J Thorac Dis 2018;10(Suppl 17):S2086-S2088. doi: 10.21037/jtd.2018.05.37

