Mucinous gastric adenocarcinoma: A good candidate for immune therapy?

Ming-Huang Chen[a,b,*], Wen-Liang Fang[b,c], Yi-Ping Hung[a,b], Yee Chao[a,b]

[a]Center for Immuno-Oncology, Department of Oncology, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [b]School of Medicine, National Yang-Ming University, Taipei, Taiwan, ROC; [c]Division of General Surgery, Department of Surgery, Taipei Veterans General Hospital, Taipei, Taiwan, ROC

Tseng et al[1] authored a valuable article published in the recent issue of the *Journal of the Chinese Medical Association*.

This retrospective cohort study enrolled 2637 patients with gastric cancer (GC) between 1992 and 2013. Among these, 92 (3.5%) were in the mucinous GC (MGC) group and others in the nonmucinous GC (NMGC) group. The authors compared the clinicopathological features and genetic alterations between the two groups. We recognize the probity of this publication.

MGC is a rare subtype of GC, accounting for 2%-6% of cases.[2] The prognosis of MGC is controversial. However, the study performed by Tseng et al[1] demonstrated that MGC is diagnosed at a more advanced stage, resulting in a worse prognosis. This study found MGC itself is not an independent prognostic factor, which is the similar finding of other studies. In their analysis of the genomic profile of MGC, identified no difference between MGC and NMGC (non-MGC). The most novelty finding in their study was MGC correlated with higher programmed death-ligand 1 (PD-L1) expression than NMGC.[1]

Programmed death 1 (PD-1) is a cell surface receptor expressed on immune cells, such as cytotoxic T cells. Under normal physiologic conditions, the PD-1 binds to its ligands PD-L1 or PD-L2; protect normal cells from immune recognition; and inhibits subsequent destruction by cytotoxic T cells. (Note: several cancers typically develop these similar mechanisms of evading this immune surveillance by upregulating PD-L1 expression on the surface of cancer cells.)[3] In recent years, immune checkpoint inhibitors, which block the PD-1 or PD-L1, have been developed. It is believed that PD-L1 expression is a potential predictive biomarker of immune therapy.[4] Indeed, in several cancer types, including GC, PD-L1 expression plays a partial predictive role of immune therapy.

Two PD-L1 studies have given meaningful information; the KEYNOTE-059 study and the ATTRACTION 2.[5,6] In the KEYNOTE-059 study, the anti-PD-1 antibody treatment pembrolizumab demonstrated promising activity in patients with advanced GC who had previously received, at minimum, second-line therapy. The objective response rate and median response duration were 15.5% and 16.3 months and 6.4% and 6.9 months in patients with PD-L1-positive and PD-L1-negative tumors, respectively.[5] Therefore, the Food and Drug Administration (FDA) granted accelerated approval to pembrolizumab for PD-L1 positive GC. In the ATTRACTION 2 study, nivolumab, which is also an anti-PD-1 antibody, also resulted in clinically meaningful long-term improvements in overall survival for patients with previously treated GC.[6] In contrast, the benefit of the nivolumab antibody did not impact expression of a PD-L1 tumor.

The significant difference between these two studies is they used different PD-L1 antibodies; different analytic platforms; and distinctive methods of scoring. In the KEYNOTE-059, they used anti-PD-L1 antibody with 22C3 (Dako, Carpinteria, CA, USA), whereas the ATTRACTION-2 study, they used 288 (Dako, Carpinteria, CA, USA). Scoring methodology differed by the combined positive score (CPS) in the KEYNOTE-059 study and the tumor proportion score (TPS) in the ATTRACTION-2 study. The CPS is given by summing the number of PD-L1 stained cells, including tumors cells, lymphocytes, and macrophages; and dividing the result by the number of total viable tumor cells. The TPS is the percentage of viable tumor cells showing membrane staining, relative to all viable tumor cells. The CPS method predict response to pembrolizumab in patients with GC and was adapted in the current study.[7]

It looks quite reasonable to believe MGC might be a good candidate for immune therapy due to a higher PD-L1 expression. However, the response to immune therapy should also consider several further aspects, such as tumor mutation load, neoantigen load, microsatellite instability (MSI) status, and tumor microenvironment.[8–11] Currently, there is no report to investigate the tumor mutation burden and neoantigen load in MGC. Furthermore, Millar et al[12] had observed of a reduction in host tumor-infiltrating lymphocytes in mucinous colorectal cancer. One possible explanation is that mucus around a tumor microenvironment might mask the tumor antigens to exposing to the immune cells.

All the factors above result in questioning whether MGC is a unique histology suitable for immune therapy—this is still inconclusive. We still need more clinical studies to answer this question.

*Address correspondence. Dr. Ming-Huang Chen, Center for Immuno-Oncology, Department of Oncology, Taipei Veterans General Hospital, 201, Section 2, Shi-Pai Road, Taipei 112, Taiwan, ROC. E-mail address: mhchen9@vghtpe.gov.tw (M.-H. Chen).

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2020) 83: 624-625.

Received April 3, 2020; accepted April 6, 2020.

doi: 10.1097/JCMA.0000000000000329.

REFERENCES

1. Tseng CH, Fang WL, Huang KH, Chen MH, Chao Y, Lo SS, et al. The clinicopathological characteristics and genetic alterations of mucinous carcinoma of the stomach. *J Chin Med Assoc* 2020;83:141–7.

2. Kunisaki C, Akiyama H, Nomura M, Matsuda G, Otsuka Y, Ono HA, et al. Clinicopathologic characteristics and surgical outcomes of mucinous gastric carcinoma. *Ann Surg Oncol* 2006;**13**:836–42.
3. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer* 2012;**12**:252–64.
4. O'Malley DP, Yang Y, Boisot S, Sudarsanam S, Wang JF, Chizhevsky V, et al. Immunohistochemical detection of PD-L1 among diverse human neoplasms in a reference laboratory: observations based upon 62,896 cases. *Mod Pathol* 2019;**32**:929–42.
5. Fuchs CS, Doi T, Jang RW, Muro K, Satoh T, Machado M, et al. Safety and efficacy of pembrolizumab monotherapy in patients with previously treated advanced gastric and gastroesophageal junction cancer: phase 2 clinical KEYNOTE-059 trial. *JAMA Oncol* 2018;**4**:e180013.
6. Kang YK, Boku N, Satoh T, Ryu MH, Chao Y, Kato K, et al. Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2017;**390**:2461–71.
7. Kulangara K, Zhang N, Corigliano E, Guerrero L, Waldroup S, Jaiswal D, et al. Clinical utility of the combined positive score for programmed death ligand-1 expression and the approval of pembrolizumab for treatment of gastric cancer. *Arch Pathol Lab Med* 2019;**143**:330–7.
8. Rizvi NA, Hellmann MD, Snyder A, Kvistborg P, Makarov V, Havel JJ, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science* 2015;**348**:124–8.
9. Dudley JC, Lin MT, Le DT, Eshleman JR. Microsatellite instability as a biomarker for PD-1 blockade. *Clin Cancer Res* 2016;**22**:813–20.
10. Schumacher TN, Schreiber RD. Neoantigens in cancer immunotherapy. *Science* 2015;**348**:69–74.
11. Ji RR, Chasalow SD, Wang L, Hamid O, Schmidt H, Cogswell J, et al. An immune-active tumor microenvironment favors clinical response to ipilimumab. *Cancer Immunol Immunother* 2012;**61**:1019–31.
12. Millar EK, Beretov J, Sarris M, Lee CS. Mucinous differentiation in colonic adenocarcinoma is associated with a reduction in tumour-infiltrating lymphocytes. *Eur J Surg Oncol* 2001;**27**:273–7.