The Evolving Role of Checkpoint Inhibitors in the Management of Gastroesophageal Cancer

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KEYWORDS

• Immune checkpoint • Immunotherapy • Programmed death-1
• Cytotoxic T lymphocyte associated protein −4 • Pembrolizumab • Nivolumab

KEY POINTS

- The connection between inflammation and malignancy has long been recognized in gastric and esophageal cancers.
- Given the considerable success of immune checkpoint inhibitors in other tumor types (eg, lung cancer and melanoma), much attention is being paid to furthering their role in gastric and esophageal cancers.
- The Cancer Genome Atlas has provided further details of the molecular heterogeneity of these tumors, which may help predict responsiveness to immune checkpoint inhibitors.
- This article discusses the rationale for investigating these agents in gastroesophageal (GE) cancer and summarizes the relevant clinical trial data and ongoing studies.

INTRODUCTION

The link between chronic inflammation, infection, and malignancy has long been recognized in both esophageal and gastric cancers. For years, it has been postulated that targeting the immune system in upper gastrointestinal (GI) cancers may lead to improved outcomes in tumors that have proved inherently resistant to novel systemic treatments as a result of histologic, molecular, and etiologic heterogeneity. Although first-line therapy responses of 50% to 60% are typical with systemic chemotherapy in metastatic disease, additional efficacy in the second-line and third-line settings has been limited despite the addition of the targeted agents

Commercial and Financial Conflicts of Interest: Dr R.J. Kelly has received grant funding from Bristol-Myers Squibb.
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Hematol Oncol Clin N Am ■ (2017) ■–■
http://dx.doi.org/10.1016/j.hoc.2017.01.007 **hemonc.theclinics.com**

trastuzumab and ramucirumab.[1,2] Recently, a phase II/III Gatsby study of ado-trastuzumab emtansine (T-DM1) was negative in the second-line setting compared with paclitaxel/docetaxel.[3] This highlights many of the difficulties oncologists have faced in treating upper GI tumors. Continued targeting of HER2 with novel drugs was expected to result in improved overall survival (OS) but it now seems that up to 35% of patients can have down-regulation of initially positive HER2 overexpression/amplification while receiving first-line trastuzumab. This is not a recognized phenomenon in breast cancer, where continued targeting of HER2 is standard of care. In addition, the lack of identifiable common oncogenic driver mutations in upper GI tumors has led to the hope that the use of checkpoint inhibitors, notably programmed death (PD)-1 inhibitors, and future combination studies can lead to substantial benefits, as seen in other common tumors, such as melanoma, non–small cell lung cancer (NSCLC), and renal cell and bladder carcinomas. This article describes the rationale for investigating checkpoint inhibitors in GE cancer, explores some of the current understandings of the immune microenvironment in these diverse tumors, and provides a synopsis of both ongoing studies and the clinical trial data published to date.

RATIONALE FOR INVESTIGATING CHECKPOINT INHIBITORS IN GASTROESOPHAGEAL CANCER

Tumors escape immune surveillance by several mechanisms, of which 4 groups have been proposed on the basis of their programmed death ligand (PD-L)-1 status and the presence or absence of tumor infiltrating lymphocytes (TILs). These include type I (PD-L1^{pos} with TILs driving adaptive immune resistance), type II (PD-L1^{neg} with no TIL indicating immune ignorance), type III (PD-L1^{pos} with no TIL indicating intrinsic resistance), and type IV (PD-L1^{neg} with TIL present indicating the role of other suppressor[s] in promoting immune tolerance).[4] The authors have previously reported that in resected gastric cancers, enhanced CD8$^+$ T cell infiltration in tumors and peritumoral interfaces occurs in patients that were also PD-L1$^+$ compared with those who were PD-L$^-$.[5] When CD8$^+$ T-cell densities were categorized into low, mid, and high, 89% of stroma PD-L1$^+$ tumors had high CD8$^+$ densities. This highlights the importance of the linkage between CD8$^+$ T cells, thought to be a source of cytokines, such as IFNγ, and up-regulation of PD-L1 or the so-called adaptive immune-response. Additional work is required in GE cancer to understand which patients are more likely to respond to single-agent checkpoint inhibition and which will require combination strategies. In melanoma, extensive work has been done to demonstrate that a high proportion of type I and type II microenvironments are seen[6] and this can explain the high response rates in this tumor type to PD-1 inhibitors. This information has yet to be defined in GE cancers. At present, there is not a clear understanding of what the early events are that leads to the aberrant expression of PD-1/PD-L1 by tumor cells and/or host immune cells. Genomic aberrations in tumor cells that lead to aberrant PD-L1 expression have been proposed and microsatellite instability (MSI) may have a predictive role as may Epstein Barr Virus (EBV) status.[7,8] Emerging data suggest that negative immune checkpoint proteins are usually up-regulated in tumor tissues with a T-cell inflamed phenotype and that infiltration of tumors by effector T cells is necessary to drive up-regulation of immune checkpoints.[9] These findings suggest that targeting the PD-1/PD-L1 axis in GE cancers may only be clinically effective for the subgroup of tumors that contain tumor-infiltrating immune cells. Additional factors that suggest GE cancers may respond to checkpoint inhibition include