The Current Status of Immunotherapies in Esophagogastric Cancer

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KEYWORDS

• Adenocarcinoma • Squamous cell carcinoma • Gastric • Esophageal
• Immunotherapy • Immune checkpoint • PD-1 • PD-L1

KEY POINTS

- Immune checkpoint inhibitors that target cytotoxic T lymphocyte antigen-4 or the programmed death-1/programmed death–ligand 1 axis have transformed the treatment of many solid tumors.
- Initial phase I/II studies in esophagogastric cancer suggest significant activity for these drugs.
- Ongoing phase III studies will determine if there is a role for these drugs in the next several years.
- Correlative analyses are ongoing to identify the group of patients most likely to benefit from these therapies.

INTRODUCTION

Outcomes for patients with advanced esophagogastric cancer (EGC) are poor.[1] Approximately 50% of patients with EGC present with overt metastatic disease, and chemotherapy is the mainstay of palliation in this setting. With the high likelihood that patients with initial locoregional disease will eventually have metastatic disease, palliative chemotherapy will ultimately be used in most patients. In recent years, the incorporation of targeted agents—trastuzumab with first-line chemotherapy for Her2-positive disease[2] and ramucirumab as monotherapy[3] or with paclitaxel chemotherapy[4] in the second-line setting—has incrementally improved outcomes, but median overall survival (OS) remains at best only 1 year.

In this gloomy context, excitement is growing among oncologists and patients alike for the use of immunotherapy or, more specifically, immune checkpoint inhibitors. Since the landmark approval by the US Food and Drug Administration (FDA) of

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the anti–cytotoxic T-lymphocyte antigen-4 (CTLA-4) antibody ipilimumab in advanced melanoma,[5,6] these and other antibodies (namely, antagonists of the programmed death [PD]-1/PD-ligand 1 pathway) that de-repress the immune system have undergone extensive evaluation in multiple other solid tumors, including EGC. These studies have led to the FDA approval of additional immune checkpoint inhibitors in several solid tumor malignancies and, in EGC, have culminated in ongoing phase III studies.

This review focuses on the role of the immune system in cancer, a brief history of immunotherapy, the role of immune checkpoint molecules in normal immune homeostasis and, the rapidly accumulating data in EGC.

THE IMMUNE SYSTEM

The immune system protects us from external threats (infectious diseases) and also from internal ones (cancers) while not attacking healthy tissue (which would lead to the development of autoimmune diseases). To fulfill these critical and synchronous roles, it must recognize self from non–self-antigens with unerring accuracy.

The immune system consists of an innate and an adaptive component.[7] The innate immune system involves rapid immune responses, which are mediated by macrophages, neutrophils, dendritic cells, and natural killer cells. These cells are hard wired to recognize non–self-antigens, such as those from infectious organisms, but have (1) relatively low potency, (2) limited specificity for the specific microorganism, and (3) no memory (ie, no ability to generate an enhanced response if re-exposed to the same microorganism).

If a microbe or cancer cell is not rapidly eliminated by innate immune mechanisms, adaptive immune responses are then engendered. These responses are produced by B cells (the humoral arm, which produces antibodies that typically target extracellular antigens) and T cells (the cellular arm, which destroys infected cells that harbor intracellular organisms or malignant cells). In contrast to innate immunity, adaptive immunity develops over days to weeks and is (1) much more potent, (2) highly specific for a specific antigen, and (3) leads to a memory response (which results in a much more rapid and potent response upon re-exposure).

Despite these coordinated mechanisms, the development of cancer necessarily implies a failure of immunosurveillance of incipient malignant cells. Dunn and colleagues[8] proposed the concept of immunoediting to explain this phenomenon. They envisaged that this process comprises 3 phases that are collectively denoted as the 3 *E*s of cancer immunoediting: elimination, equilibrium, and escape. The first E refers to the fact that most cancer cells are indeed recognized and successfully killed by the immune system, leading to the second E, where the surviving cancer cells acquire multiple mechanisms that allow them to exist alongside increasingly ineffective immune responses (eg, down-regulating immunogenic molecules on the tumor cell surface or recruiting immunosuppressive mechanisms in the tumor microenvironment). This second E lasts the longest and may occur over many years. Finally, the balance of forces shifts decidedly in the favor of the cancer cells, allowing them to *e*scape from immune control.

COLEY'S TOXINS

The idea of harnessing the immune system to attack cancer is an intuitively appealing concept but not a new one. The attractiveness of such a proposed treatment stems from the belief that recruitment of the immune system to attack cancer cells potentially offers more durable benefit and less toxicity than conventional therapies (akin to