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Modern Immunotherapy for Gastric Cancer

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Abstract

Gastric cancer is one of the most common malignant diseases in the world. Although its prognosis has improved markedly due to developments in surgical techniques and several perioperative treatments, only a few patients survive. Recently, immunotherapy has been recognized as a novel type of therapy for gastric cancer. In contrast to conventional therapies, immunotherapies produce anti-tumor effects by strengthening the immune functions of tumor cells. Immune checkpoint blockade therapy is a novel immunotherapy. The most important immune checkpoint molecules are cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) and programmed cell death-1 (PD-1). Antibodies against these molecules are currently approved for use as treatments for gastric cancer. Clinicians should use both immune checkpoint blockade therapy and conventional treatments to treat gastric cancer.

Keywords: CTLA-4; PD-1; Gastric Cancer; Immunotherapy

Introduction

Gastric cancer is one of the most common malignant diseases in the world, especially in Eastern Asia, Central and Eastern Europe, and South America. The lowest frequencies of the disease are seen in Northern America and Africa [1]. Although the prognosis of gastric cancer has improved significantly due to developments in surgical techniques and perioperative treatments, including chemotherapy, the 5-year overall survival rate of gastric cancer patients is only 10-15% [2]. Until quite recently, the conventional treatments for malignant disease included surgical therapy, chemotherapy, and radiotherapy. However, immunotherapy has since been recognized as a fourth type of treatment for various forms of cancer around the world. Immunotherapy is different from conventional therapy because it produces anti-tumor effects by strengthening the immune functions of tumor cells. Cancer peptide vaccines, dendritic cell vaccines, the adoptive transfer of cytotoxic T lymphocytes, tumor-infiltrating lymphocyte (TIL) therapy, and chimeric antigen receptor (CAR) T-cell therapy, etc., are all immunotherapies [3].

Immune Checkpoint Blockade Therapy

A novel type of immunotherapy, called immune checkpoint blockade therapy, has recently been established. In contrast to previous treatments, immune

checkpoint blockade therapy aims to induce therapeutic benefits by "cancelling the immunosuppressive machineries generated in the tumor microenvironment" [3]. The most important immune checkpoint molecules for tumor-associated immunosuppression are cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) and programmed cell death-1 (PD-1).

Anti-CTLA-4 Therapy

CTLA-4 is a co-inhibitory molecule expressed on activated T-cells and T regulatory (Treg) cells. The interaction of the CTLA-4 receptor on T-cells with B7 family ligands on antigen-presenting cells inhibits T-cell stimulatory signaling [2,4]. So, the inhibition of this interaction using an anti- CTLA-4 antibody leads to the reactivation and proliferation of T-cells and a reduction in the number of immunosuppressive Tregs in the tumor microenvironment. The anti-CTLA-4 antibody ipilimumab is currently approved for use as a treatment for gastric cancer [4].

Anti-PD-1/PD-L1 Therapy

PD-1 is a typical co-inhibitory receptor that is expressed on T-cells and other immune cells. Programmed cell death ligand-1 (PD-L1) is one of the ligands for PD-1. The binding of PD-L1 to PD-1 can downregulate the immune responses of T-cells [5]. The presence of PD-1 and PD-L1 plays a major role in the inhibition of effector T-cell functions. Several clinical studies have demonstrated that anti-PD-1 and -PD-L1 antibody therapy has reliable effects on many advanced malignancies [6]. Additionally this therapy may also function through a direct on macrophages, with substantial implications for the treatment of malignancy with this therapy [7]. The anti-PD-1 antibodies nivolumab and pembrolizumab are currently approved for use as treatments for gastric cancer. In addition, the use of atezolizumab, an anti-PD-L1 antibody, in combination with the anti-PD-1 antibody nivolumab was confirmed to be effective against gastroesophageal cancer.

The targeting of T-cell regulatory proteins, such as CTLA-4 and PD-1, by checkpoint blocking antibodies has been strengthened by research into cancer immunology. Combination therapy with anti-CTLA-4 and anti-PD-1 antibodies exhibits clinical activity against a wide variety of solid tumors [6]. Further potentially targetable checkpoints, such as OX40, YIM3, and LAG3, are also being evaluated in ongoing preclinical and clinical studies [4].

Unlike conventional anti-cancer therapies, the adverse effects of immunotherapies vary. The onset of autoimmune diseases, like thyroid disease, autoimmune pancreatitis, hepatitis, and various skin disorders, etc., which can affect the whole body, due to hyperimmunization is a representative potential complication of immunotherapy. However, immunotherapy is relatively safe to use because myelosuppression is not required.

Conclusions

Various therapies for gastric cancer have become established around the world, and novel immunotherapies have recently been developed. In cases of gastric cancer, clinicians should not only perform conventional therapy as a last resort, but also as part of modern multidisciplinary treatment including immune checkpoint blockade therapy.

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortrt-Tieulent J, et al. (2015) Global cancer statistics, 2012. CA Cancer J Clin 65(2): 87-108.

2. Abozeid M, Rosato A, Sommaggio R (2017) Immunotherapeutic Strategies for Gastric Carcinoma: A Review of Preclinical and Clinical Recent Development. Biomed Res Int 2017: 5791262.

3. Adachi K, Tamada T (2015) Immune checkpoint blockade opens an avenue of cancer immunotherapy with a potent clinical efficacy. Cancer Sci 106(8): 945-950.

4. Myint ZW, Goel G (2017) Role of modern immunotherapy in gastrointestinal malignancies: a review of current clinical progress. J Hematol Oncol 10(1): 86.

5. Liu X, Yang Z, Latchoumanin O, Qiao L (2016) Antagonizing programmed death-1 and programmed death ligand-1 as a therapeutic approach for gastric cancer. Therap Adv Gastroenterol 9(6): 853-860.

6. Alsaab HO, Sau S, Alzhrani R, Tatiparti K, Bhise K, et al. (2017) PD-1 and PD-L1 Checkpoint Signaling Inhibition for Cancer Immunotherapy: Mechanism, Combination, and Clinical Outcome. Front Pharmacol 8: 561.

7. Gordon SR, Maute RL, Dulken BW, Hutter G, George BM, et al. (2017) PD-1 expression by tumor-associated macrophages inhibits phagocytosis and tumour immunity. Nature 545(7655): 495-499.