Review Article

The emerging strategy of comprehensive therapy for esophageal cancer: immunotherapy

Yuandong Wang*, Xinyu Tang*, Hua Min*, Hongcheng Zhu, Qian Lu, Shu Zhang, Xinchen Sun

Department of Radiation Oncology, The First Affiliated Hospital of Nanjing Medical University, Nanjing 210029, China

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*These authors contributed equally to this work.

Correspondence to: Xinchen Sun, MD, PhD. Department of Radiation Oncology, The First Affiliated Hospital of Nanjing Medical University, 300 Guanzhou Road, Nanjing 210029, China. Email: sunxinchen2012@163.com.

Abstract: Esophageal cancer (EC) is a highly malignant tumor, and the overall survival rate remains very low. Traditional treatment is not sufficiently effective, and thus, there is an urgent need for new and effective treatments. The advances in cancer immunotherapy have changed this situation because this type of therapy has a significant potential to eliminate tumors with little damage to normal tissue. This treatment primarily aims to enhance the ability of the immune system to eliminate tumors and prevent tumor immune escape, which is associated with immune surveillance. This review summarizes current cancer therapeutic strategies and immunotherapy studies to demonstrate the potential of immunotherapy for the treatment of EC.

Keywords: Esophageal cancer (EC); tumor immunology; immunotherapy

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Introduction

Esophageal cancer (EC) is the eighth most common cancer worldwide, as it causes almost 400,000 deaths per year (1). Normally, the progression of this disease presents an asymptomatic course, and therefore, EC is diagnosed at advanced stages and is associated with a poor prognosis in many cases. Despite the advancements in therapeutic modalities, the 5-year survival rate remains very low (2). Traditional treatments have not achieved prospective curative effects in patients in an advanced stage of the disease, which raises the need for innovative therapeutic approaches.

In the past several decades, advances in immunology and molecular biology have revolutionized the concept of oncotherapy (3,4). Previous studies have found that the immune system and malignant cells may coexist in a dynamic equilibrium and that the complicated interaction between tumor growth and the immune system may determine the course of the disease (5). The latest theory of immune surveillance has revealed that the immune system initiates the elimination of abnormal cells and prevents cancer formation (6,7). Immunotherapy is aimed at the improvement in the ability of the immune system to find and destroy cancer cells, and it does so by intervening in the immune response to tumors. It is promising that immunotherapy may become an important supplement to tumor comprehensive therapy. Further research will be necessary, and a review of the existing methods may offer new testaments of its effectiveness.

Traditional therapeutic strategies for EC

The traditional treatments of EC include surgery, chemotherapy, and radiotherapy, but surgery is primarily performed in patients who have early- and middle-stage EC. When appropriate, radiotherapy or chemotherapy is used as a supplement to reduce the chances of local recurrence

and distant metastases (8,9). Patients with advanced disease are more likely to receive chemoradiation or comprehensive treatment.

Endoscopic treatment

Patients with early EC that involves the epithelium or the lamina propria are suitable for endoscopic therapies, including endoscopic mucosal resection and endoscopic submucosal dissection. Staging (by the TNM staging system) must be confirmed before endoscopic therapy is started on account of nominal lymph node metastasis, which has been reported even in early-stage disease. Therefore, this type of treatment can lead to good curative effect, and the only disadvantage is the likelihood of relapse (10,11).

Resection

Surgical resection has been the gold standard for localized EC for decades. However, patients who undergo esophagectomy do not experience a significant improvement in their 5-year survival rate, and most patients who are diagnosed with advanced disease have lost the opportunity for surgery; as a result, approximately only 36% of patients undergo esophagectomy (12). The choice of surgical procedure is largely dependent on the location of the tumor and the preference of the surgeons. All of the surgical procedures are highly complicated, and therefore, it is recommended that treatment be given in high-volume centers with experienced surgeons and where postoperative nursing care has been associated with improved outcomes (13). To date, there is still great controversy regarding the best surgical procedure for esophagectomy, particularly in terms of the optimum extent of lymphadenectomy to improve survival and minimize morbidity (14). Unlike the two-field lymphadenectomy that is practiced in western countries, three-field lymphadenectomy (abdomen, chest and neck) is mainly practiced in Asia where the incidence of EC is dominant (15).

Neoadjuvant/adjuvant therapy

Despite the optimization of surgical treatment and the establishment of high-volume centers, the outcome following resection of EC remains unsatisfactory. Therefore, neoadjuvant therapy is applied to decrease the tumor burden (16,17) and to eliminate micro-metastases to improve tumor resectability and reduce the risk of postoperative recurrence. In addition, adjuvant therapy is often used when the pathologic analysis shows positive margins or in lymph node-positive patients to decrease local tumor recurrence (17,18). Several randomized trials compared surgery alone and surgery combined with neoadjuvant therapy or adjuvant therapy, and the addition of adjuvant/neoadjuvant therapy was demonstrated to benefit patients with EC and can thus be recommended for patients with locally advanced cancers.

Definitive chemotherapy/concurrent chemoradiation

Many patients with EC have distant metastases at diagnosis, and they thus lose the opportunity for surgical resection. For these patients, the goal is to prolong survival and to improve the quality of life. Chemotherapy or chemoradiation is effective, and as approximately 50% of patients can obtain a survival benefit, this has become the primary criterion for the use of this treatment in patients with advanced EC (19,20).

Tumor immunotherapy in EC

In the past several decades, immunotherapy, which involves the stimulation and enhancement of the host immune system so that it can attack tumor cells, has gradually become a matter of interest. Indeed, immunotherapy is associated with a clinical survival benefit, especially in the treatment of patients with melanoma and lung cancer, among other cancer types. Current research is focused on how to apply this treatment to other tumors. With the development of molecular biology and the accumulation of clinical experience, immunotherapy is likely to change the survival of cancer patients, including those with EC.

Cytokines for immunotherapy

Cytokines have been used as part of cancer immunotherapy for decades. Cytokines function through certain general mechanisms, either by exerting a direct antitumor effect or by indirectly enhancing the antitumor immune response (21).

Interleukin 2 (IL-2) was first used as an effective immunotherapy agent for metastatic renal cell carcinoma and melanoma in the 1990s. Moreover, as a key cytokine, IL-2 was applied to the *in vitro* amplification of T cells, which were isolated from tumors, and as a result, IL-2 fostered the development of a novel cancer therapy. This cytokine can also be used to expand peripheral blood T cells

transduced with antigen-specific T-cell receptors (TCRs) and chimeric antigen receptors (CARs), which are then used in adoptive cell therapy.

In addition, we also investigated the cytokine IL-17A, which is mainly produced by $CD4^+$ T cells. Numerous studies have demonstrated that IL-17A has roles in inflammation, autoimmune diseases and tumors, and it can also induce EC cells to produce inflammatory chemokines and enhance the cytotoxic effects of NK cells against tumor cells via the expression of cytotoxic molecules (22). The frequency of IL-17A-producing cells in tumors is positively correlated with the improved prognosis of patients. Other research is ongoing, and we look forward to more promising results (23).

Antibody-based immune checkpoint inhibitors

Antibody therapy has been used in clinical treatment for many years (24). Antibody-dependent cell-mediated cytotoxicity (ADCC) refers to the process by which effector cells are activated by antibodies so that they recognize specific target cells by specific surface antigens; this results in binding and lysis of the target cells by action of the immune system. Immune checkpoints comprise immune system signaling pathways that either increase or abolish the maintenance of the self-tolerance system and the intensity of the immune-mediated response (25). Antibodies target the immune checkpoints on tumor cells, which improves surveillance and recognition for the restoration of tumor immunity. Currently, immune checkpoint inhibitors are widely used in the treatment of solid tumors, including non-small cell lung cancer, melanoma and renal cancer. Although these inhibitors have acquired FDA certification (26,27), some large clinical validations are still ongoing.

Cytotoxic T-lymphocyte antigen 4 (CTLA-4)

CTLA-4, which is a T cell receptor that belongs to the immunoglobulin superfamily, is generally considered an immune checkpoint molecule. The inhibition of CTLA-4 can improve T cell activation and proliferation and can promote an anti-tumor immune response (28). Some humanized monoclonal antibodies have gained FDA approval for the treatment of melanoma and mesothelioma, but recently, when patients were treated for gastroesophageal cancer, the observed response rate was approximately 5%. Moreover, some patients can indeed show a duration in their response, and thus this treatment strategy provides a meaningful reference for EC immunotherapy (29).

Programmed cell death protein 1 and its ligands (PD1/PDL1)

PD1, which is also a T cell receptor that belongs to the immunoglobulin superfamily, can inhibit T cell function by binding to its ligands PDL1 or PDL2 (30). When T cells are activated in the peripheral tissues, the expression of PDL1 and PDL2 is increased significantly. Generally, PD1 is considered to be related to a late immune response, whereas CTLA4 acts during an early immune response (31). A recent study that investigated PDLI expression in gastric cancer and EC by immunohistochemistry and Q-RT-PCR found that approximately 43.9% of the samples demonstrated overexpression to varying degrees. In addition, the overexpression of PDLI and PD1 is usually considered to be associated with advanced tumors and a worse prognosis. Therefore, the inhibition of PD1 signaling pathways in EC immunotherapy may be of value (32). However, the use of PD1 inhibitors and the associated clinical outcomes have not been reported, and only some preliminary studies have suggested that pembrolizumab used in PDL1-positive patients with EC has certain anti-tumor effects. The objective response rate was approximately 30%, but this encouraging result needs to be verified by further research.

Therapeutic cancer vaccines

Therapeutic cancer vaccines aim to increase the presentation of tumor-associated antigens (TAAs) to the immune system and improve the activation of tumor-specific T cells and B cells to elicit antitumor responses. In the past several years, the technology of cancer vaccines has resulted in resounding success (33). The classic example of a polyvalent allogeneic cancer vaccine is Cancer Vax, a whole-melanoma cell vaccine used in the treatment of advanced melanoma.

Dendritic cell (DC)-based cancer vaccines

Recently, various DC-based vaccines have been developed because DC cells are considered to be the most potent antigen presenting cells (APCs), which bridge the connection between innate and adaptive immunity. The main role of DCs is to take in antigenic peptides of pathogen-derived or host-derived proteins and present them to native T cells in peripheral tissues (34). Furthermore, DC vaccine-based gene immunotherapy is another effective immunotherapeutic method that applies recombinant DNA or mRNA constructs that encode tumor antigens (TAs) to

significantly improve the efficiency of these vaccines.

Complexes of cholesteryl pullulan (CHP)-based cancer vaccines

Vaccine therapy may also be studied as an adjunctive treatment strategy that can induce antitumor responses through the action of the immune system. Recently, the discovery of CHP, which comprises a new type of cancer vaccine with a novel antigen delivery system, has revealed that it presents multiple epitopes to both MHC class I and class II molecules. It has been shown that CHP-based cancer vaccines, which induce antigen-specific $CD4^+$ and $CD8^+$ T cell immunity and humoral immunity, will efficiently induce immune responses (35). Previous studies have revealed a significant effect of the NY-ESO-1 protein vaccine complexed with CHP on immune responses and survival benefits of EC patients (36). Follow-up studies are currently underway.

Adoptive T cell therapy

Adoptive T cell therapy (ACT) involves the *in vitro* activation and amplification of tumor-specific T cells and the reinfusion of those cells into cancer patients to directly destroy tumors.

Lymphokine-activated killer (LAK) cells

In the past several years, the advent of LAK cells seems to have led to a surge in the study of tumor immunotherapy. However, the activity of LAK cells is dependent on the presence of interleukin-2, and moreover, the efficacy of LAK cells is largely confined to malignant melanoma and renal cell carcinoma, which means that their effects are very limited. Recently, some studies have focused on the mechanism of postoperative immunosuppression in cases of esophagectomy (37). We found that LAK cells that are transferred immediately after surgery overcome postoperative immunosuppression. This process can transfer and restore the appropriate helper and cytotoxic T-cell populations. Moreover, LAK therapy was used to prevent infection after surgery for the treatment of compensatory anti-inflammatory response syndrome in patients with EC, and thus, this therapy may be a new approach for the treatment of tumors (31).

Tumor infiltrating lymphocytes (TILs)

ACT based on TILs, which are derived from autologous fresh tumor tissues, are activated and expanded extensively *ex vivo*; this method has been developed as a novel form of personalized cancer therapy. This treatment has been used clinically on a small scale, especially for the treatment of metastatic melanoma, and it increased the response rate and the proportion of patients with persistent tumor remission. This significant result has stimulated the demand for multicenter phase III clinical trials to demonstrate the effectiveness of this treatment. TILs may be approved as a novel complement treatment that could be combined with immune inhibitors and other forms of therapy in clinical oncology practice.

Conclusions

Although immunotherapy has progressed significantly, surgery remains one of the best therapeutic modalities for early stage EC, especially since the development of minimally invasive surgery, which can effectively reduce mortality and complications. However, for patients with locally advanced EC, comprehensive therapy can significantly reduce the number of micro-metastases as well as tumor burden and thus improve the overall survival of patients.

Immunotherapy has been studied for many years as an important supplement to comprehensive therapy for EC and has gradually become a promising treatment particularly due to its assistance in the reduction of immunosuppression and the improvement of endogenous immunity. Furthermore, the molecular and genetic factors that influence the immune response should be studied further to stratify those patients who are more suitable for immunotherapy.

Future directions

Despite that the treatment of EC remains challenging and the overall survival rate remains low, the main recommendations are based on a survival benefit analysis and treatment side effects. The optimal treatments are discussed by a multidisciplinary team (MDT) to formulate individualized treatments for a better clinical outcome.

In recent years, it is promising that studies have found immune therapy plays an important role in the comprehensive treatment strategy for EC and that checkpoint inhibitors and its preliminary application showed some positive results. However, some issues require further clarification. The first is which patients should be treated to maximize benefits, and the second is how immunotherapy

would be combined with other treatments. The third is to optimize biological dosing, which may be determined by the toxicity of a treatment as well as its cost effectiveness. Although further studies are needed to guide clinical trials, as our understanding of EC increases, new strategies to decrease immune suppression and enhance endogenous immunity in patients with EC are being developed, and prior successes will drive the discovery of more effective strategies.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2016.12.04). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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