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EDITORIAL

Advancements and challenges in the treatment of esophageal cancer: A comprehensive review

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Abstract

Esophageal cancer (EC) is an aggressive malignancy with a poor prognosis, ranking seventh in incidence and sixth cancer-related deaths globally. EC is classified in two main types, the esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC), with ESCC being more common in Eastern Europe, South Asia, and Africa, while EAC is prevalent in Western Europe and North America. Molecular analysis identifies three subgroups of ESCC, each with distinct genetic mutations and treatment responses. Early-stage EC is often difficult to detect, leading to late-stage diagnoses that necessitate systemic drug therapies, including molecular-targeted therapies and immunotherapies. Immunotherapy, particularly immune checkpoint inhibitor, has shown promising results in improving survival rates for metastatic or persistent EC. It is particularly important to target to multidisciplinary combination therapies, integrating surgery, chemoradiotherapy, targeted therapy and immunotherapy. Additionally, radioimmunotherapy is being explored for its potential to enhance treatment efficacy, especially in advanced and metastatic tumors. However, the pathological complete response rate to neoadjuvant chemoradiotherapy remains suboptimal, highlighting the need for novel treatment strategies. Future research should focus on optimizing treatment combinations and identifying predictive biomarkers to improve clinical outcomes for EC patients.

Key Words: Esophageal cancer; Immunotherapy; Treatment; Targeted therapy; Future

aspects

Core Tip: Esophageal cancer remains an aggressive and deadly malignancy, with significant global incidence and mortality rates. The primary histological types, esophageal squamous cell carcinoma and esophageal adenocarcinom, exhibit distinct geographic prevalence and molecular characteristics. Early detection challenges necessitate advanced systemic treatments. Recent advancements in immunotherapy, especially immune checkpoint inhibitors, combined with traditional therapies, have shown promising improvements in survival rates.

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INTRODUCTION

Esophageal cancer (EC) is an aggressive tumor correlated with a poor prognosis. According to GLOBOCAN 2020 data, EC is the seventh most common cancer worldwide and the sixth cause of cancer-related deaths[1,2]. EC is classifying into two main histological types: Esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). Moreover, ESCC is most common in Eastern Europe, South Asia, and Africa, whereas EAC is more prevalent in Western Europe and North America[1,3]. Each type of EC has different patterns of metastasis, occurring at various stages. Analytically, in stages 1a and 1b lymph node metastasis is absent in general, but the possibility of metastasis increases progressively in later stages[4,5].

ESCC can be divided into three distinct molecular subgroups based on gene analysis, as identified by The Cancer Genome Atlas Research Network. The ESCC cases were categorized as ESCC1: Tumors in this subgroup respond poorly to chemoradiotherapy and are correlated to a poor prognosis, the ESCC2 subgroup, which is characterized by mutations in KDM6A, PIK3R1, KDM2DM, NOTCH1, PTEN and ZNF750 as well as the application of CDK6 and is associated with infiltration by white blood cells. Last but not least, is the ESCC3 that has a disruption of the Phosphoinositide 3-kinase pathway[6].

Surgery is the primary approach for the radical treatment of EC. However, early- stage EC is often difficult to detect due to its subtle onset, resulting in most patients being diagnosed at an advanced stage. Consequently, systematic drug therapy is essential for controlling further cancer spread and it has grown significantly with the advent of molecular targeted therapies and immunotherapies[1]. Novel screening methods may be effective in regions with a high incidence of ESCC. The treatment standard involves a multidisciplinary approach to evaluation and treatment. As regards early stage ESCC, endoscopic resection may be a viable option. Additionally, minimally invasive esophagectomy can be performed either as a primary therapy or following induction chemoradiation[2].

Recent studies have demonstrated a survival benefit for immunotherapy for patients that have a metastatic or persistent EC. Multidisciplinary evaluation and multimodal therapy, which includes cytotoxic chemotherapy, surgery, radiation, and immunotherapy, have shown improved survival rates compared to surgery[2,3]. The targeted therapies and immunotherapies have significantly enhanced the survival of EC patients[1]. Patients that have rejectable disease, the standard treatment remains the neoadjuvant chemoradiotherapy (nCRT) combined with esophagectomy. However, the pathological complete response rate to nCRT ranges from 29.2% to 43.2%, with abouts the half of the patients experiencing locoregional recurrence or distant metastasis[7,8].

This underscores the need to explore novel and effective treatment strategies to improve clinical outcomes. Systematic drug therapy is crucial for controlling further cancer dissemination and its value in comprehensive EC treatment has become more significant with the advancement of molecular-targeted therapies and immunotherapies[1]. In this editorial we comment on the review "Immunotherapy for esophageal cancer: Where are we now and where can we go" by Shoji *et al*[9].

TREATMENT STRATEGIES TODAY

Manipulation of the host's immune system, allowing tumors to thrive in an otherwise hostile environment is one of the key mechanisms through which cancer cells evade detection, and was proposed by Hannah and Weinberg in their "hallmarks of cancer"[6]. Immune checkpoints play a crucial role in this process by preventing overactivation of the immune response[6]. Significant advances have been made in cancer treatment, including ESCC, through targeted therapies. Immunotherapy, encompassing immune checkpoint inhibitors (ICIs), therapeutic vaccines, immunomodulators, monoclonal antibodies, and adoptive cellular immunotherapy, offers a cutting-edge approach to treating EC[3].

Immunotherapy utilizing ICIs has significantly transformed the treatment landscape for various advanced cancers, including EC. Recent clinical evidence indicate that neoadjuvant immunotherapy may improve survival in patients with rejectable cancers. Additionally, research suggests that chemotherapy and/or radiotherapy can activate the immune system through various mechanisms, resulting in a synergistic antitumor effect when combined with immunotherapy [10]. To date, ICIs are used in cancer treatment by targeting the suppressor immune system, thereby enhancing the ability of immune cells to destroy tumor cells. Alongside, T cells and ICIs engineered to express chimeric antigen receptors, are the most widely used immunotherapies and have been evaluated in various types of cancers. Despite some successes in immunotherapy for EC, many patients do not respond well due to immune resistance[11]. Intrinsic therapy of the immune system resistance involves components, including molecules and normal immune cells that interact during the progression of the immune system and inhibit the antitumor response. Additionally, characteristics of tumor cells contribute to intrinsic immunotherapy resistance, although the exact mechanisms remain unclear[11].

The diversity of ICIs targeting different molecular markers on tumor and immune cells is expanding and is currently being investigated in several clinical trials. These include anti combining programmed cell death 1 (anti-PD-1) antibodies (pembrolizumab, nivolumab, tislelizumab, tebotelimab) targeting T-cells and anti-PD-L-1 antibodies (atezolizumab, durvalumab, avelumab) targeting cancer cells and dendritic cells (DCs), as well as the anti cytotoxic T- lymphocyte associated protein 4 (anti-CTLA-4) antibody ipilimumab targeting T-cells[10]. The connection between infection and malignancy underscores the potential of targeting the immune system to improve outcomes in tumors that are resistant to systematic treatment due to histological, molecular heterogeneity. Research indicates that ICIs are upregulated in tumor tissues with a T cell inflamed phenotype and the presence of T cells in tumors is essential to trigger this. This suggests that targeting the programmed death-1 (PD-1)/programmed death ligeand-1 (PD-L1) axis in EC may be clinically effective primarily in the subgroup of tumors[12].

Preclinical studies have shown that PD-1 inhibitors with chemotherapy can further enhance the host's immune response and inhibit the immune escape mechanisms of cancer cells. Emerging evidence suggests that immunotherapy can improve outcomes in patients with unresectable tumors. Additionally, studies found that first line PD-1 inhibitors combined with chemotherapy significantly improve overall survival (OS) compared to chemotherapy alone[2]. Moreover, the PD-1/PD-L1 axis mediated immune monitoring and has a high tole in tumor progression. Tumors cells that express PD-L1 can evade destruction by cytotoxic T-lymphocytes (CD8 + T cells). When PD-L1 engages with PD-1 on activated T-cells, CD80 is then produced, having the role of a receptor that transport a suppression signal, resulting in endurance of peripheral T-cell. Extensive subjection to tumor antigen causes T cells to enhance negative regulators like PD-1, having as a result to their functional tiredness[11].

In addition to PD-1/PD-L1, another immune checkpoint is cytotoxic T- lymphocyte-Associated protein-4 (CTLA-4), which is often expressed on activated T lymphocytes and regulatory T cells (Tregs). CTLA-4 plays a crucial role in T-cell regulation. It is found by numerous studies hat overexpression of CTLA-4 leads to decreased expression of interleukin-2 T-cell cycle arrest, and arrest of T cells. Consequently, T-cell function is diminished, enabling immune evasion by cancer cells[10].

Additionally, cancer-associated fibroblasts (CAFs) have been closely linked to tumor progression and resistance to therapy. While their role in ESCC has been studied, the comprehensive characteristics of CAFs and their relationship to ESCC prognosis and response to immunotherapy remain incompletely understood[3].

Activated CAFs contribute to tumor growth, angiogenesis, invasion and metastasis through several mechanisms. They play a significant role in remodeling the extracellular matric and developing chemoresistance. CAFs interact with immune cells infiltrating the tumor microenvironment and immunological components by secreting cytokines, growth factors another active molecule. This results to enabling cancer cells to evade immune detection[13].

A study has identified an inverse relationship between WNT2-expressing CAFs and the presence of active CD8+ T cells in primary oral squamous cell carcinoma (OSCC) tumors. Treatment with an anti-WNT2 monoclonal antibody successfully reinstated antitumor T-cell activity and boosted the number of active DCs in both mouse models of OSCC and colorectal cancer, thereby improving the effectiveness of anti-PD-1 therapy. Directly targeting WNT2 in CAFs has proven effective in restoring DC differentiation and enhancing DC-driven antitumor T-cell responses[14].

Future aspects

Targeted therapy directed against genomic drivers of EC represents a prominent area of research. The GA trial established the role of trastuzumab in treating human epidermal growth factor receptor 2 (HER2)-positive gastroesophageal junction adenocarcinoma. Patients with EC who overexpress HER-2 are recommended to receive trastuzumab in combination with chemotherapy. Additionally, therapies using antibody-drug conjugates (ADCs) are under investigation. Trastuzumab deruxtecan, an ADC drug, has shown significant improvements in response rates and OS for patients with HER-2-positive gastric/gastroesophageal junction adenocarcinoma in third line treatment. These advancements underscore the evolving landscape of targeted therapies in enhancing treatment outcomes for patients with EC[1].

A significant focus in cancer treatment has become multidisciplinary combination. When immunotherapy is combined with surgery, chemoradiotherapy, and targeted therapy shows efficacy in tumors. However, the application of immunotherapy in EC is still developing. Common multimodal immune therapies for EC include PD-1 inhibitors combined with chemotherapy. An example that must be noted is the phase 3 clinical trial KEYNOTE-590, led by Sun *et al*[15] which is evaluating the effectiveness of pembrolizumab in combination with chemotherapy in patients with advanced EC. In addition, research by Van Der Kraak *et al*[16] demonstrated that gastrointestinal cells that are treated with 5-fluorouracil (5-FU) chemotherapy typically show rised levels of PD-L1 expression. This suggests that a mechanism, combining 5-FU with a PD-L1 inhibitor can improve clinical results and survival benefits for patients that have this disease[10].

In last years, ICIs have made advances in treating various tumors. Recent results from the CheckMate 648, JUPITER-06, ESCORT-1st study, indicated that the treatment of PD-1 patients with advanced EC with PD-1 inhibitors combined with chemotherapy as first line treatment significantly improved OS compared to chemotherapy alone. These findings suggest that ICIs have promising potential for the treatment of EC[7].

In conclusion, radioimmunotherapy holds significant promise for enhancing the prognosis of EC. Current research is delving into various facets such as optimal radiation dosages, fractionation schedules, targeted irradiation techniques, and the careful selection of immunotherapy agents. The primary goal of these studies is to uncover the underlying anti-tumor mechanisms and identify predictive biomarkers that could improve treatment outcomes. Radioimmunotherapy, particularly when used in conjunction with ICIs and low-dose radiation, may offer a novel therapeutic approach for patients with locally advanced or metastatic EC by potentially triggering a systemic anti-tumor response[17].

CONCLUSION

EC remains an aggressive malignancy with a poor prognosis. EC is classified into two main histological types, the ESCC and EAC. The molecular characterization has revealed subgroups that have different responses to therapies and treatments. Surgery remains the primary treatment for EC, yet early detection is challenging, often leading to diagnoses at advanced stages. Consequently, systemic drug therapy, including molecular-targeted therapies and immunotherapies, is essential for managing the disease. Immunotherapy has shown promising results in improving survival rates, challenges remain due to intrinsic and acquired immune resistance. The integration of multidisciplinary combination therapies, including surgery, chemoradiotherapy, targeted therapy is emerging as an effective strategy. Furthermore, the role of radioimmunotherapy is being explored as a novel treatment for EC. In summary, the landscape of EC treatments is evolving with the advent of targeted therapies and innovative combination approaches. Continued research and clinical trials are essential to improve outcomes and develop more effective strategies for managing EC.

FOOTNOTES

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