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Research Progress in Targeted Therapy for Esophageal Cancer

Jinming Hu, Yanhua Xu*

Oncology Department, Jingzhou Hospital Affiliated to Yangtze University, Jingzhou, China
Email: *1099203229@qq.com

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Abstract

Esophageal cancer (EC) is a prevalent malignant tumor that affects the digestive system and is often linked to a poor prognosis. The absence of effective early screening methods results in the diagnosis of esophageal cancer (EC) patients at advanced or metastatic stages. While historically considered incurable, ongoing advancements in medical research have led to the integration of various treatment modalities as primary approaches for managing advanced endometrial cancer. These modalities include surgery, chemotherapy, radiotherapy, targeted therapy, and immunotherapy. Notably, the introduction of targeted therapy and immunotherapy has significantly enhanced the survival rates of individuals with EC. Immunotherapy has appeared as the predominant treatment for advanced esophageal cancer, while targeted therapy faces certain obstacles. Consequently, this review primarily focuses on the advancements in targeted therapy for esophageal cancer (EC), evaluating the effectiveness and safety of relevant medications, and aiming to provide guidance for the comprehensive management of EC based on current research findings.

Keywords

Immunotherapy, Targeted Therapy, Epidermal Growth Factor Receptor, Vascular Endothelial Growth Factor

1. Introduction

As a malignant tumor, esophageal cancer has a poor prognosis and threatens the health of human beings. According to GLOBOCAN 2020 data, the incidence of esophageal cancer is the seventh highest worldwide, and the overall mortality rate is the sixth, with more than 540,000 deaths [1]. Esophageal cancer is broadly classified into esophageal squamous cell carcinoma (ESCC) and esophageal ade-

*Corresponding author.

nocarcinoma (EAC) based on histologic classification [2]. Notably, EAC appears to be the predominant type of onset in developed countries, while ESCC is endemic in Western Europe and North America, and ESCC is the predominant type in Eastern Europe, Southeast Asia, and Africa, especially in northern and central China [3] [4] [5]. The geographic differences in the incidence of EC may be related to the superior physical environment, and in developed countries, the main risk factors for EC development include smoking, alcohol consumption, obesity, and chronic gastroesophageal reflux disease (GERD). However, the prevailing view is that surgery is the main cornerstone of radical EC curation [6] [7] [8]. However, the onset of EC in the early stages is insidious, and most cases are found at an advanced stage [9]. Therefore, as the key to controlling the further spread of the disease, anti-tumor drug therapy has gradually revealed its value in the comprehensive treatment of EC with the emergence and development of molecular targeted therapy and immunotherapy. Traditional chemotherapy treatments, which block tumor development by acting on DNA replication or other processes of cell division, are less selective and less specific, and can also cause damage to normal cells while being anti-tumor [10]. Unlike conventional chemotherapy for extensive toxicity, targeted therapy aims to block characteristically and precisely the proliferation mechanisms in cancer cells while preserving normal cells [11]. Therefore, compared with chemotherapy drugs, targeted drugs have stronger targeting, a narrower toxicity spectrum, and fewer side effects, and targeted therapy brings survival benefits to cancer patients. Immunotherapy is based on activating the patient's immune system to fight the cancer, rather than directly killing cancer cells [12]. The advent of cancer immunotherapy has revolutionized the comprehensive treatment of cancer, bringing hope to more cancer patients, and has become a new treatment revolution after surgery, chemotherapy, radiotherapy, and targeted therapy. After decades of chemotherapy dominance, targeted therapy is challenged, and the efficacy and safety of EC immunotherapy have been reported. The purpose of this review is to describe the relevant clinical trials of EC-targeted drugs, summarize the latest research progress and prospects, and provide a reference for the comprehensive treatment of EC with targeted drugs.

2. Common Targets and Pathways in Esophageal Cancer

2.1. Epidermal Growth Factor Receptor (EGFR), Human Epidermal Growth Factor Receptor 2 (HER-2) Pathway

EGFR, a transmembrane tyrosine kinase receptor with a size of 170 kDa, is also known as ERBB1. EGFR binds to its ligand and is phosphorylated by tyrosine kinase, triggering signaling pathways such as mitogen-activated protein kinase (MAPK), signal transducer and activator of transcription 5 (STAT5), and RAS-RAF-MEK to promote cell proliferation and differentiation, and some studies have shown that approximately 30% - 90% of EC patients develop EGFR overexpression, which is associated with poor prognosis [13] [14] [15]. HER-2 is a

member of the EGFR family of membrane tyrosine kinases, and its activation also induces cell proliferation and differentiation. In particular, the kinase activity of HER-2 differs from EGFR in that it is not ligand binding dependent [16].

2.2. Vascular Endothelial Growth Factor (VEGF)/Vascular Endothelial Growth Factor (VEGFR) Pathway

Vascular formation is a complex process, and the VEGF/VEGFR signaling pathway is considered to be the most potent pro-angiogenic pathway [17]. The excessive proliferation of blood vessels provides a good nutritional environment for the proliferation of tumors. As early as 1971, anti-angiogenic therapy was proposed [18]. The human VEGF family includes VEGFA, B, C, D, E, F, placental growth factor (PlGF), and endocrine adeno-derived vascular endothelial growth factor (EG-VEGF) [19]. VEGFR has been extensively studied as a membrane-bound receptor tyrosine kinase. VEGFR-1 and VEGFR-2 are predominantly expressed on vascular endothelial cells, and VEGFR-3 is predominantly expressed in lymphoid endothelial cells [20] [21].

2.3. Hepatocyte Growth Factor (HGF)/Mesenchymal Epithelial Transition Factor (c-MET) Pathway

c-MET is a receptor tyrosine kinase (RTK) that is predominantly expressed on the surface of epithelial cells, neurons, hepatocytes, and hematopoietic cells. HGF is a 90 kDa glycoprotein that is a specific ligand for c-MET. The binding of HGF to c-MET regulates a variety of cellular functions: differentiation, proliferation, epithelial cell motility, angiogenesis, and epithelial-mesenchymal transition (EMT), a useful molecular target for novel engineered drugs, with several clinical trials underway in various solid tumors [22].

3. Targeted Drugs That Mainly Act on ESCC

3.1. EGFR-Targeted Drugs That Mainly Act on ESCC

Nimotuzumab acts as a fully recombinant humanized immunoglobulin G1 (IgG1) monoclonal antibody that binds to EGFR. Compared to other EGFR-targeting antibodies, Nimotuzumab's inherent bivalent binding ability makes it more effective in targeting EGFR, especially in cells expressing EGFR at high levels, with fewer side effects. In a phase II trial, the combination of nimotuzumab with chemotherapy and radiation therapy appeared to improve the endoscopic complete response (eCR) rate in patients with locally advanced disease [23]. Another phase II trial demonstrated that nimotuzumab plus radiation therapy appears to be an effective option in older or advanced patients [24].

Cetuximab is a human-mouse chimeric antibody that also binds to EGFR, thereby inhibiting the development of tumor cells. In a phase III clinical trial of cetuximab in the neoadjuvant setting of EC, 37 percent of patients with ESCC had no statistically significant difference in progression-free survival (PFS) compared with the control group, but significantly reduced the rate of local recurrence

and prolonged overall survival (OS) [25]. Results from another study, LEOPARD-2, showed that 80.9 percent of those patients had ESCC, and cetuximab in combination with chemoradiotherapy was effective in improving PFS and metastasis-free survival (MFS) in unresectable EC [26]. Therefore, cetuximab can be used as a new strategy for neoadjuvant therapy, with limited benefit for patients with low EGFR expression, and further studies may be needed for patients with high EGFR expression.

Panitumumab is the first fully human monoclonal antibody to be shown to be effective in the treatment of solid tumors. The REAL3 trial was discontinued after an interim analysis showed a significant reduction in median OS (8.8 versus 11.3 months) in patients in the combination with panitumumab [27]. Another phase III trial, POWER, was terminated prematurely because it failed to achieve the desired results [28]. Panitumumab has insignificant effect on EC, and the reasons for its failure must be further studied.

Gefitinib is an oral EGFR inhibitor that has been shown to be highly effective in patients with small cell lung cancer (NSCLC), especially those with EGFR mutations. A phase III randomized controlled trial of COG to investigate the efficacy of gefitinib in patients with advanced EC, 23.7 percent of whom were ESCC, did not alter OS in these patients [29]. Subsequently, the TRANSCOG trial analyzed the molecular profile of participants with COG and concluded that Gefitinib may improve OS in patients with EGFR-amplified EC, but further research is needed [30].

Icotinib is a highly selective EGFR inhibitor, and in a phase II randomized trial, icotinib plus radiation therapy was well tolerated in older patients with ESCC and had longer OS compared with radiation therapy alone [31]. In contrast, another phase II, single-arm, multicenter clinical trial showed that icotinib is safe and has potential efficacy [32]. In conclusion, Icotinib is effective in ESCC patients with high EGFR expression and is expected to be a safe option for combination radiotherapy in elderly patients.

3.2. VEGF/VEGFR Targeted Drugs That Mainly Act on ESCC

Endostar is a soluble, stable recombinant human endostatin that inhibits angiogenesis by inhibiting the expression of VEGF or VEGFR and thus inhibits tumor formation. Two phase II studies have shown the potential for recombinant human endostatin (rh-endostatin) in combination with chemotherapy to be a promising antineoplastic agent in patients with advanced ESCC [33] [34].

Apatinib is an orally administered, small molecule VEGFR-2 tyrosine kinase inhibitor. Clinical trials have shown that apatinib is safe and effective in the treatment of advanced EC alone or in combination with chemotherapy [35]. Apatinib is expected to be an option for the treatment of advanced EC.

Sunitinib is an oral multi-kinase inhibitor that targets VEGFR, platelet-derived growth factor receptor (PDGFR), and others. A phase II trial showed no therapeutic benefit of postoperative adjuvant therapy with sunitinib in combination

with chemoradiotherapy in patients with locally advanced EC [36]. Another phase II trial found a trend toward improved OS with sunitinib in combination with FOLFIRII (irinotecan, 5-fluorouracil [5-FU], and folic acid) in patients with advanced refractory esophageal cancer [37]. The specific efficacy of Sunitinib requires further study.

Anlotinib is a novel multi-targeted tyrosine kinase inhibitor that primarily blocks VEGFR2/3, fibroblast growth factor receptor (FGFR) 1 - 4, PDGFR a/b, c-Kit, and Ret. In a double-blind randomized controlled trial, median progression-free survival (PFS) was improved in the treatment of advanced ESCC (3.02 versus 1.41 months) [38]. At present, anlotinib has been included in the guidelines of the Chinese Society of Clinical Oncology (CSCO) for the treatment of advanced ESCC.

4. Targeted Drugs That Primarily Act on EAC

4.1. HER-2 Targeted Drugs That Mainly Act on EAC

Trastuzumab is a humanized monoclonal antibody against HER-2. Trastuzumab in combination with chemotherapy in HER2-positive advanced gastric/gastric-esophageal junction (G/GEJ) was shown to improve median OS (13.8 versus 11.1 months) in an open-label, international randomized controlled trial of ToGA [39]. Another open-label randomized controlled phase III trial, RTOG-1010, suggests that trastuzumab in combination with chemoradiotherapy or as neoadjuvant therapy does not increase toxicity but does not prolong disease-free survival (DFS) in patients with HER2-overexpressing EAC [40]. ToGA establishes a strong position of trastuzumab in the treatment of HER-2-positive GC or GAC and also provides a treatment option for patients with HER-2-positive EAC.

Pertuzumab is also a humanized monoclonal antibody against HER-2 and differs from Trastuzumab in its binding domain. The JACOB trial, designed to evaluate the efficacy of pertuzumab and trastuzumab in the first-line treatment of adenocarcinoma in G/GEJ, theoretically could work synergistically, ended in failure [41]. Further research is needed on whether pertuzumab is effective in the treatment of Her-2-positive EAC.

Specifically, Lapatinib is an oral, small-molecule inhibitor of EGFR and HER-2 that acts as an antitumor by binding to the adenosine triphosphate (ATP) binding site in the intracellular domain, thereby blocking tyrosine kinase activity. Results from TRIO-013/LOGiC, a phase III randomized trial, showed that Lapatinib in combination with capecitabine + oxaliplatin (CapeOx) did not prolong OS in patients with her2-amplified GEJ, but its efficacy appears to depend on the location and age of the tumor and further studies are needed to explain it [42].

4.2. VEGF/VEGFR Targeted Drugs That Mainly Act on EAC

Bevacizumab, a humanized VEGF-A-targeted monoclonal antibody, a multicenter, randomized, open-label phase II-III trial was shown to be suboptimal and more likely to lead to wound healing complications in perioperative patients

with resectable stomach, esophagogastric junction, or low EAC [43]. Based on this trial, bevacizumab is not recommended for the conventional treatment of EAC.

Ramucirumab is a complete human anti-VEGFR-2 IgG1 monoclonal antibody. In a double-blind randomized controlled phase III trial (RAINBOW), ramucirumab in combination with paclitaxel significantly increased OS in patients with advanced G/GEJ adenocarcinoma [44]. Another RAINBOW-modeled bridging study (RAINBOW-Asia) investigated the efficacy of ramucirumab in the Chinese population and supported the use of ramucirumab and paclitaxel as second-line therapy for patients with advanced G/GEJ adenocarcinoma [45]. The efficacy of ramucirumab in patients with advanced G/GEJ adenocarcinoma was further supported in the REGARD trial [46]. In summary, ramucirumab is beneficial in improving survival in patients with advanced G/GEJ adenocarcinoma.

Sorafenib is an oral multikinase inhibitor that targets VEGFR2 and PDGFR as well as RET and RAF1. A phase II trial supported the potential efficacy of sorafenib in combination with chemotherapy in the treatment of advanced G/GEJ adenocarcinoma [47]. Another phase II clinical trial demonstrated that Sorafenib prolonged PFS in patients with esophageal and GEJ cancer [48]. More research evidence is needed to support the efficacy of sorafenib in the treatment of EC.

5. Targeted Drugs for the HGF/c-MET Pathway

Rilotumumab (AMG102), is an anti-HGF-resistant human monoclonal. In a phase II, open-label, randomized, three-arm trial (PRODIGE 17-ACCORD 20-MEGA), rilotumumab in combination with mFOLFOX6 (oxaliplatin, leucovorin, and fluorouracil) chemotherapy did not provide the expected efficacy [49]. Another phase II trial (RILOMET-1) also found that rilotumumab was ineffective in unresectable locally advanced G/GEJ adenocarcinoma [50]. Therefore, further studies are needed to demonstrate its efficacy.

Onartuzumab is a humanized monovalent monoclonal antibody against MET. Studies have shown that the efficacy of onartuzumab in advanced G/GEJ adenocarcinoma is suboptimal [51]. No studies have shown any survival benefit of onartuzumab for EC treatment.

Tivantinib (ARQ 197) is an oral, non-ATP-competitive c-Met tyrosine kinase inhibitor. In first-line phase II trials, tivantinib plus FOLFOX chemotherapy has been shown to be effective in prolonging PFS in G/GEJ adenocarcinoma [52].

6. Immunotherapy for EC

The purpose of this review is to provide a reference for the use of targeted drugs in the combination of EC therapy by describing relevant clinical trials of EC-targeted drugs. Therefore, this review does not focus on the analysis of immunotherapy for EC, but briefly introduces the current representative drugs.

Immune checkpoint molecules are defined as ligand-receptor pairs that regulate immune stimulation or immunosuppression, and tumor cells formally borrow the immune checkpoint molecules they possess to produce immune evasion, theoretically, activating immunostimulatory molecules or blocking immunosuppressive molecules can prevent immune escape of tumor cells, immune checkpoint agonists are immature and most research is in its early stages, and fortunately, immune checkpoint inhibitors (ICIs) have been shown to be highly effective in the treatment of solid tumors [53].

Currently, ICIs primarily target programmed death 1 (PD-1) and its ligand, programmed cell death ligand 1 (PD-L1), and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) [53] [54]. PD-L1, a member of the CD28 superfamily, acts primarily as a key co-inhibitory receptor on activated T cells, B cells, and natural killer cells (NK), PD-L1 is one of the natural ligands of PD-1, a transmembrane protein expressed on certain tumor cells and antigen-presenting cells (APCs), and PD-L1 binds to PD-1 to inhibit T cell activation and promote cancer growth [54]. CTLA-4 is a membrane glycoprotein expressed on regulatory T (Treg) cells, and it is an important inhibitory checkpoint receptor, and it is worth noting that blocking CTLA-4 is the first successful antitumor immunotherapy in clinical practice [55]. At present, a variety of immunotherapy drugs have been approved for the first- or second-line treatment of EC patients, especially immunotherapy drugs represented by PD-1 and PD-L1 antibodies, such as Pembrolizumab and Nivolumab. Immunotherapy has made important breakthroughs in anti-tumor therapy due to its significant efficacy, especially for patients who cannot use targeted therapy because they are not positive for driver genes.

Based on the results of the KEYNOTE 181 and KEYNOTE-590 studies, Pembrolizumab has been approved in China for the second-line treatment of locally advanced or metastatic ESCC (CPS≥10) and for first-line combination chemotherapy in locally advanced or metastatic E/GEJ cancer [56] [57]. Based on the positive performance of nivolumab in the ATTRACTION 03, CheckMate 648, and CheckMate 577 trials, CSCO guidelines have recommended nivolumab in combination with chemotherapy as first-line therapy for advanced ESCC and her-2-negative EAC, or as a single agent as second-line therapy for ESCC [58] [59] [60]. In addition, more and more trials have demonstrated that ICIs combined with chemotherapy or radiotherapy have significant anti-tumor effects in EC, and they have become the mainstream treatment regimen for EC. ICIs are a potent, long-acting anti-tumor regimen. However, it is less effective in the early stages of treatment, and the reasons for this are not clear. Therefore, for cancers that develop rapidly, it is generally recommended to undergo early chemotherapy treatment. It is important to note that immunotherapy is particularly unique to the toxicity of immunotherapy, called immunotherapy-related adverse reactions (irAEs), including immune dermatitis, pneumonia, hepatitis, and gastrointestinal adverse reactions, and the causes of irAEs are still unclear and need to be further investigated.

7. Conclusions and Outlook

At present, targeted therapy and immunotherapy have become popular research objects for comprehensive anti-tumor therapy, and the quality of life of cancer patients has been significantly improved. However, EC stays a highly aggressive and fatal malignant disease that is difficult to detect early due to its asymptomatic or atypical symptoms, resulting in more than 50 percent of patients with EC being diagnosed at an advanced stage [61]. Treatment of early EC is typically surgical and includes endoscopic resection (ER), including endoscopic mucosal dissection (ESD) and endoscopic mucosal resection (EMR) [62]. ICIs are also becoming one of the main modalities of cancer treatment and can be used for the treatment of perioperative and advanced EC. The CheckMate 577 study showed that adjuvant nivolumab prolonged DFS in patients [1] [6]. Pembrolizumab may provide benefit in the second-line treatment of advanced EC [56] [57]. In addition, there are more immunotherapy regimens that have been used in the combination of EC treatments, in particular, ICIs in combination with targeted drugs and double immunity therapy have attracted attention, and a series of clinical trials are underway, which deserve further research in order to provide more benefits to patients. Targeted therapy for driver gene positivity is another research hotspot in addition to immunotherapy. EGFR is highly expressed in the EC and is a potential therapeutic target. Most of the current evidence for the treatment of EC with anti-EGFR comes from small studies, and there is no clear conclusion. In contrast, for patients with EAC who overexpressing HER-2, trastuzumab plus chemotherapy is recommended [39]. At present, a series of potential therapeutic targets are also being studied, such as HGF/HGF receptor (c-Met), mammalian target of rapamycin (mTOR), fibroblast growth factor receptor-2, etc. Antibody-drug combination therapies (ADCs), and Trastuzumab deruxtecan, an ADC drug that has been shown to significantly improve response and OS in patients with HER2-positive G/GEJ adenocarcinoma in third-line therapy [63].

In conclusion, with the development of targeted therapy and immunotherapy, the treatment of EC has been changed. In particularly, immunotherapy has become the mainstream treatment of advanced EC, changing the treatment guidelines of EC, but there are still many problems to be solved, such as irAE and its slow onset of action. Targeted therapy has unique targeting and fewer side effects than traditional chemotherapy, but we still need further research and exploration to find better therapeutic targets, so that the diagnosis and treatment of EC can be further improved in the future.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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