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Review Article

Hot button topic in the treatment of locally advanced esophageal carcinoma

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Abstract: Background: Esophageal cancer is a highly malignant carcinoma with poor prognosis. Of note, the treatment of locally advanced esophageal carcinoma remains a huge challenge in clinical and a hot issue in research. Discussion: To obtain the most effective treatment strategy, many clinical studies compared the advantages and disadvantages among different methods for treating locally advanced esophageal carcinoma. Although the triple therapy, including neoadjuvant radiotherapy, chemotherapy and surgery, is a well-established standard treatment for locally advanced esophageal cancer, the prognosis remains very poor. Recently, researches have focused on studying the effectiveness and safety of neoadjuvant chemoradiotherapy, neoadjuvant chemotherapy and adjuvant chemotherapy. Targeted therapy is another hot topic in the treatment of esophageal carcinoma. Summary: This article will focus on discussing the above hot topics in the treatment of locally advanced esophageal carcinoma and gastroesophageal junction cancer.

Keywords: Esophageal cancer, neoadjuvant chemoradiotherapy, targeted therapy, gastroesophageal junction cancer

Introduction

Esophageal cancer is a malignant carcinoma with a high incidence in China [1]. In the United States, there were 16980 new cases and 15590 deaths attributable to esophageal cancer in 2015 [2]. Thus, the therapy strategy for treating locally advanced esophageal carcinoma (T1-4aN1-3M0) has always been a hot issue in clinical research. Although neoadjuvant chemoradiotherapy has become a traditional method in treating esophageal cancer in the United States, the prognosis is still poor and the death risk from surgery increases. In contrast, neoadjuvant chemotherapy is more secure at the point. This article will make a comprehensive analysis of the clinical researches on locally advanced esophageal cancer therapy during the past two decades, focusing on the advantages and disadvantages of neoadjuvant chemoradiotherapy and neoadjuvant chemotherapy. In addition, the current hotspots of targeted therapy for gastroesophageal junction cancer are also reviewed.

Neoadjuvant and adjuvant therapy for locally advanced esophageal carcinoma

Neoadjuvant chemotherapy

To evaluate the effect of neoadjuvant chemotherapy on locally advanced esophageal carcinoma, a number of randomized clinical studies compared the efficacy between neoadjuvant chemotherapy combined with surgery and surgery alone. Among seven early researches, four showed no survival benefit but three displayed an improved survival. In 2002, the MRC study revealed that neoadjuvant chemotherapy (2 cycles of preoperative chemotherapy with cisplatin and 5-FU) improved the patients' 2-year survival rate from 34% to 43% [3]. The median survival time of patients undergoing neoadjuvant chemotherapy was 16.8 months, while that was only 13.3 months in patients with surgery alone. Updated survival data showed that the survival benefit of neoadjuvant chemotherapy remained stable, and the 5-year survival rate was 23%, which was significantly higher than 17.1% in the surgery group (HR: 0.84, P =

0.03). The efficacy was basically the same in adenocarcinoma group and squamous cell carcinoma group [4]. In 2006, a MAGIC study of 503 participants also demonstrated that perioperative chemotherapy (3 cycles of neoadjuvant chemotherapy and 3 cycles of postoperative adjuvant chemotherapy) improved the patients' overall survival rate from 23% to 36% [5]. A meta-analysis about the effect of neoadjuvant chemotherapy or chemoradiotherapy for locally advanced esophageal carcinoma was updated in 2011. The neoadjuvant chemotherapy group included 9 studies, 1981 patients, and the data revealed that the neoadjuvant chemotherapy had a 5.1% advantage over chemoradiotherapy in 2-year survival rate (HR: 0.87, 95% CI: 0.79-0.96, $P = 0.005$). The statistical significance was positive in the subgroups of patients with adenocarcinoma ($P = 0.01$), but was negative in the squamous cell carcinoma subgroup ($P = 0.18$) [6]. Taken together, neoadjuvant chemotherapy for locally advanced resectable esophageal carcinoma is safe and effective, but the best neoadjuvant chemotherapeutic scheme requires further validation in clinical researches. Besides, whether neoadjuvant chemotherapy has different clinical significance of esophageal cancer with different pathological types or different locations needs further investigation.

Adjuvant chemotherapy

Clinical studies on postoperative adjuvant chemotherapy for locally advanced esophageal carcinoma are relatively few. A randomized clinical study of 242 squamous cell carcinoma patients with adjuvant chemotherapy (cisplatin and 5-FU) was carried out in Japan in 2003. The findings showed that adjuvant chemotherapy prolonged the disease-free survival (DFS) of patients, but not the overall survival (OS). However, the findings remained controversial, because they were restricted to patients with squamous cell carcinoma, and 25% of them had not accepted complete adjuvant chemotherapy. The intervals to start adjuvant chemotherapy were not unified as well [7]. Macdonald et al. found that postoperative application of radiotherapy and chemotherapy with 5-FU extended the survival time of patients with gastric cancer and gastroesophageal junction carcinoma [8]. Unfortunately, there were only 20% of patients diagnosed with gastroesophageal junction carcinoma in the research. Therefore, the reference value of their results is not clear. In conclusion, due to the lack of large sample, multicentered and randomized controlled studies, the significance of postoperative adjuvant chemotherapy remains still inexplicit.

Neoadjuvant chemoradiotherapy

For locally advanced esophageal cancer treatment, surgery alone does not appear to be effective for a low R0 resection rate, high local recurrence rate and short survival time. Neoadjuvant chemoradiotherapy can theoretically increase the R0 resection rate and reduce micro-metastasis to improve the survival rate. Recently, there have been at least 10 randomized clinical trials comparing the efficacy between neoadjuvant chemoradiotherapy plus surgery and surgery alone [9, 10]. In 2006, a reasonable-designed small-group study reported that neoadjuvant chemoradiotherapy plus surgery significantly benefited the esophageal cancer patients [11].

A landmark CROSS clinical study was carried out in 2012, where the patients were randomly divided into surgery group and neoadjuvant chemoradiotherapy-plus-surgery group [9]. Patients in neoadjuvant chemoradiotherapy group had been treated with carboplatin plus paclitaxel chemotherapy and concurrent radiotherapy for 5 weeks before surgery. The results showed that 92% of the patients in neoadjuvant chemoradiotherapy group achieved R0 resection, while that was only 69% in the operation group ($P < 0.001$); 29% of the patients with neoadjuvant chemoradiotherapy achieved a complete pathological remission and the median survival time reached up to 49.4 months, whereas was only 24 months in the surgical-alone group (HR: 0.657; 95% CI: 0.495-0.871; $P = 0.003$). This study fundamentally laid the status of neoadjuvant chemoradiotherapy in locally advanced esophageal cancer treatment. In 2011, an updated meta-analysis of employing neoadjuvant chemotherapy or chemoradiotherapy for treating locally advanced esophageal cancer put 24 randomized-controlled studies in the chemotherapy subgroup, including a total of 4188 patients. And the HR turned out to be 0.78 (95% CI: 0.7-0.88; $P < 0.0001$). The data suggested that patients treated with neoadjuvant chemotherapy reduced the death risk by 22%, relative to those with surgical therapy alone, and both subgroups of squamous cell

carcinoma (HR: 0.8, $P = 0.004$) and adenocarcinoma (HR: 0.75, $P = 0.02$) possessed statistically significance. In 2013, a phase II clinical study which evaluated the therapuetic effect of neoadjuvant chemoradiotherapy (docetaxel + cisplatin + 5-FU + radiotherapy) also presented a good outcome. The complete pathological remission rate was 47%, and the 3-year and 5-year survival rate were 83% and 77%, respectively [12]. Together, the above researches demonstrated the superiority of neoadjuvant chemoradiotherapy in the therapy of locally advanced esophageal carcinoma. However, neoadjuvant chemoradiotherapy increased the death risk after surgery by contrast to neoadjuvant chemotherapy [13, 14].

Research progress on the targeted therapy for esophageal cancer and gastroesophageal junction cancer

Along with the in-depth understanding on the mechanism of the molecular mechanism in tumor biology, targeted therapy for esophageal cancer has gradually become a new hotspot. But most studies are still preliminary and mainly focused on esophagogastric junction carcinoma and distal esophageal adenocarcinoma. The therapeutic targets used in the studies are always EGFR, HER2, MET, VEGF, and VEGFR, etc.

Anti-EGFR monoclonal antibody

About 50% of gastroesophageal junction cancer showed a high expression of EGFR [15, 16]. Both cetuximab and panitumumab, two earliest anti-EGFR monoclonal antibodies, have been widely examined in gastroesophageal junction cancer. Some studies suggested that the application of anti-EGFR monoclonal antibody alone or combination with chemotherapy was effective in dealing with colorectal cancer metastasis [17, 18]. A number of phase I and II clinical studies, in which the anti-EGFR monoclonal antibody (cetuximab, panitumumab or matuzumab) and chemotherapy were united, displayed good efficacy and acceptable toxicity [19-21]. Safran et al. assessed the therapeutic effect of cetuximab combined with concurrent radiotherapy and chemotherapy in a phase II clinical study, where the esophageal-cancer patients accounted for 57 cases in the total of 60 cases. All were given cetuximab combined with paclitaxel and carboplatin, and radiotherapy (for 6 weeks). And 40/57 (70%) of the cases achieved complete remission finally [22]. Owing to the aforementioned researches, a number of phase III clinical trials have been further carried out in esophagogastric junction carcinoma and gastric cancer.

The REAL-3 study compared the effects between panitumumab combined with EOC chemotherapy and chemotherapy alone on inoperable advanced esophageal gastric junction adenocarcinoma. The OS of the two groups appeared no statistical significance [23]. SCOPE1, a phase II/III randomized-controlled study, compared the efficacy of neoadjuvant chemotherapy with or without cetuximab in 258 patients with locally advanced esophageal cancer. This study was prematurely terminated since combined cetuximab chemotherapy shortened the survival time of the patients. Thus, cetuximab was not recommended to esophageal cancer patients with neoadjuvant chemoradiotherapy adaptation disorder [24]. Another phase III randomized-controlled clinical study (RTOG 0436) revealed that adding cetuximab did not prolong the OS of the locally advanced esophageal cancer patients who had received paclitaxel/cisplatin and radiotherapy [25]. Many related researches such as NCT-11-7639 are still going on. But basing on the results of present large randomized studies, anti-EGFR monoclonal antibody is not a promising drug in the treatment of locally advanced gastroesophageal junction cancer or late palliative treatment.

Anti-HER2 monoclonal antibody

The main monoclonal antibodies against HER2 are trastuzumab and pertuzumab, and a small molecule drug lapatinib. A phase III clinical study (ToGA) tried to disclose the curative effect of adding trastuzumabin to cisplatin/fluorouracil chemotherapy for treating metastatic HER2-positive gastric cancer and gastroesophageal junction cancer [26]. The results showed that employing trastuzumab improved the objective response rate (ORR) (47% vs 35%, $P = 0.002$) and significantly prolonged the PFS (6.7 months vs 5.5 months, $P = 0.0002$) and OS (13.8 months vs 11.1 months, $P = 0.036$). Further analysis showed a significant OS extension in patients of high HER2 expression compared with patients of low HER2 expression. Thus, trastuzumab is the first successful targeted drug in the therapy of advanced gastric and

gastroesophageal junction cancer, and improves the clinical practice. Currently, a noteworthy phase III clinical trial (RTOG 1010), which used trastuzumab combined with cross scheme for treating locally advanced esophageal adenocarcinoma patients with high expression of HER2, is in progress.

Tyrosine kinase inhibitors of EGFR and HER2

Several phase I and phase II clinical trials has attempted to explore the efficacy of erlotinib or gefitinib alone, or a combination of them with chemotherapy in treating gastroesophageal junction carcinoma and esophageal cancer, but were all finally failed. In the 2012 ESMO conference, a multicentered phase III randomized-controlled study (COG) in UK was reported. This clinical trial compared the effect of gefitinib and placebo in treating advanced esophageal cancer and gastric esophageal cancer patients who had a failed chemotherapy. 75% of the total 450 patients were diagnosed with adenocarcinoma. The results showed that there was no significant difference (3.7 vs 3.6 months) between the OS of the two groups, but the gefitinib treatment prolonged the PFS (49 days vs 35 days, P = 0.0177) and increased the disease control rate at 8 weeks (25.5% vs 16%. P = 0.014). At the 2014 ASCO meeting, an analysis on the biomarkers of the COG research was announced. It was found that the patients (6.1%) with gene amplification of EGFR benefited from the gefitinib therapy, with HR 0.19 (P = 0.007). The patients with esophageal cancer often possessed a 50-70% of EGFR overexpression, but few of them acquired EGFR mutations. Whether EGFR gene amplification can be used as a biomarker to predict the effect of EGFR tyrosine kinase inhibitors in treating esophageal cancer still needs further exploration.

Lapatinib is a tyrosine kinase inhibitor that against both EGFR and HER2. A study discovered that the single agent response rate of lapatinib in the treatment of esophageal carcinoma was 7% [27]. In the TRIO-013/LOGi clinical research, 487 patients with HER2-positive gastric cancer and gastroesophageal junction cancer were randomly divided into two groups. One group received capecitabine and oxaliplatin chemotherapy, while the other group was treated with additional lapatinib. The OS were 10.5 months vs 12.2 months (P = 0.35), respectively. Further analysis of subgroups showed that the Asian esophageal cancer patients under the age of 60 might have survival benefit from lapatinib therapy [28]. Studies of other new drugs that target HER2 such as TDM-1, MM111 in esophageal cancer therapy are still on the move. Although the above studies indicated that the tyrosine kinase inhibitors of EGFR and HER2 are safer when combined with chemotherapy or radiotherapy, the definite curative effects of these drugs still need to be further confirmed in multi-centered and randomized clinical trials with large samples.

VEGF and VEGFR inhibitors

Tumor angiogenesis is a key process of carcinogenesis, which mainly relies on the function of vascular endothelial growth factor VEGF. About 30% to 60% of patients with esophageal cancer have a VEGF overexpression. Clinical studies on VEGF targeted therapy for esophageal cancer have just started. In the 2008 ASCO meeting, Enzinger and Jhawer et al. announced the effects of using anti-VEGF antibody bevacizumab combined with chemotherapy to treat metastatic gastric esophageal tumors. Their findings showed that with the additive bevacizumab, the disease control rate and PFS significantly improved relative to chemotherapy alone. The sample size of the patients was quite small yet, and many patients were diagnosed with gastric cancer. The patients with esophageal carcinoma or esophagus and gastric junction cancer occupied merely a small proportion. Thus, the efficacy of bevacizumab in treating esophageal cancer should be further investigated with a larger sample. Then a larger phase III clinical study (AVAGAST) including 774 patients were performed, focusing on the curative effect of bevacizumab combined with gemcitabine and cisplatin in treating metastatic gastric and gastroesophageal junction carcinoma. The results revealed that with the addition of bevacizumab, the ORR improved (46% vs 37.4%, P = 0.0315), PFS was prolonged (6.7 months vs 5.3 months, P = 0.0037) and OS had no significant difference (12.1 months vs 10.1 months, P = 0.1002) [29]. Although many related clinical studies are in progress, there is no sufficient data to support the notion that bevacizumab is effective for treating gastroesophageal junction adenocarcinoma or esophageal carcinoma.

Nevertheless, the anti-VEGFR2 monoclonal antibody ramucirumab succeeded in a second-line therapy for advanced gastroesophageal

junction adenocarcinoma and gastric cancer therapy. In a phase III randomized-controlled study (REGARD), the advanced gastric esophageal cancer and gastric cancer patients who had failed in first-line chemotherapy were randomly divided into ramucirumab second-line treatment group and placebo group. The survival time of the patients in ramucirumab second-line treatment group was longer than that in placebo group (5.2 months vs 3.8 months, $P = 0.047$). Another phase III randomized and double blind clinical trial (RAINBOW) compared the efficacy between ramucirumab (RAM) combined with paclitaxel and paclitaxel alone in the second-line treatment of metastatic esophageal gastric junction adenocarcinoma and gastric cancer. The data displayed that the OS of RAM combined paclitaxel group was 2 months longer than that of the paclitaxel group (9.63 months vs 7.36 months, $P = 0.0169$), and the median PFS were 4.4 months and 2.86 months, respectively ($P < 0.0001$). In consistent, ramucirumab also achieved positive outcomes in a phase III randomized study in the second-line treatment for advanced esophageal and gastric junction cancer and gastric cancer. But in the first-line treatment, it did not work well. Currently, Ramucirumab has been approved by FDA for the treatment of advanced gastric cancer and the esophagogastric junction adenocarcinoma patients who don't apply to chemotherapy.

MET targeted inhibitors

MET (Mesenchymal Epithelial Transition Factor) is an epithelial mesenchymal epithelial transition factor, with HGF (Hepatocyte Growth Factor) being its ligand. HGF/MET signaling pathway plays an important role in tumor cell migration, invasion and angiogenesis. MET is abnormally expressed in many kinds of tumors [30]. Both the gene amplification and protein expression of MET indicate a poor prognosis. Particularly, MET gene was amplified in 8.8% of esophageal cancer [31].

Many monoclonal antibodies and small molecule inhibitors against MET are applied in the clinical studies on the treatment of gastroesophageal junction carcinoma. Two phase III clinical trials are in progress, aiming to evaluate the curative effect of anti-MET monoclonal antibody combined with onartuzumab and mFOLFOX6 therapy, and rilotumumab combined with ECX chemotherapy in treating advanced HER2-negative, MET positive gastroesophageal junction cancer and distal esophagus cancer. MetGastric (NCT01662869) study enrolled 800 patients, and another RILOMET-1 (NCT01697072) clinical trial recruited 610 patients [32]. Some other early clinical trials also have commenced, but whether they can further enter phase III clinical trial remains unknown. The prospect of MET pathway inhibitors in the esophageal carcinoma therapy is still in exploration.

Discussion

Currently, the triple combination therapy, including radiotherapy, chemotherapy and surgery, is considered to be a standard treatment for locally advanced esophageal cancer. But the best neoadjuvant radio-chemotherapy scheme and the most effective therapy mode remain inexplicit. It is worth consideration that whether treating different pathological types of esophageal cancer requires different therapeutic schemes. Overall, the treatment standard for locally advanced esophageal cancer is yet short of clinical research data of support. It still needs to weigh the benefits and side effects which may arise from the corresponding therapy before designing personalized treatment.

Clinical researches on esophageal cancer targeted therapy are still in infancy. Many of them focused on gastric and gastroesophageal junction adenocarcinoma, and the most patients in the study were diagnosed with gastric cancer. There were only a few patients suffering from gastroesophageal junction carcinoma or distal esophageal cancer. As a result, whether these research findings are applicable to the treatment of different pathological types or tumor sites of esophageal cancer is unclear. Moreover, the efficacy of related targeting drugs remains unknown, only trastuzumab and ramucirumab have showed a survival advantage. Signal transduction in tumor is a complicated and multifactorial network system. Targeting a single molecule may not be sufficient to suppress tumorigenesis. Therefore, for esophageal cancer targeted therapy, combined application of multiple targeting drugs, especially monoclonal antibody drugs combined with new cytotoxic drugs or targeting drugs combined with radiotherapy and chemoradiotherapy will be a hot issue in future researches. Searching for effec-

tive biomarkers that can predict the efficacy of the therapy and identify applicable patients becomes a main goal.

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Disclosure of conflict of interest

None.

Authors' contribution

Yanjun Xu: Writing the article. Yun Fan: Conception and design, critical revision of the article for important intellectual content, administrative, and final approval of the article. All authors read and approved the final manuscript.

Abbreviations

DFS, disease-free survival; OS, overall survival; ORR, objective response rate.

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