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Advances in translational therapy for locally advanced gastric cancer

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Abstract

Translational therapy refers to a combination of chemotherapy, radiotherapy, targeted therapy, and immunotherapy for patients with advanced gastric cancer who are initially unable to undergo R0 resection. This treatment can achieve partial or complete remission of the unresectable tumors to meet the criteria for R0 resection, thus enabling the patients to prolong their survival time and improve their quality of life. In gastric cancer, translational therapy has been tried and improved. At present, there are a large number of patients with locally advanced gastric cancer in China, and the selection of suitable patients for translational therapy to prolong objective survival and improve survival quality is one of the hot spots in the field of gastric cancer research.

Key Words: Translational therapy; Locally advanced; Gastric cancer; Chemotherapy; Radiotherapy treatment; Targeted therapy

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Core Tip: In general, for patients with locally advanced gastric cancer, translational therapy can achieve different levels of survival benefit. Immunohistochemistry and genetic testing should be performed before treatment to select a more optimal comprehensive treatment strategy. For patients with locally advanced gastric cancer that is difficult to be resected at the initial stage, translational therapy followed by surgery can improve the survival benefit of patients.

INTRODUCTION

The incidence and mortality rates of gastric cancer are among the highest in China and around the world[1]. As early gastroenteroscopy is not performed in all medical centers, the proportion of patients with advanced gastric cancer is high, and locally advanced gastric cancer accounts for 10%-35%. R0 resection cannot be performed due to severe

invasion by the tumor, which cannot be separated from surrounding normal tissues or may be wrapped around large vessels, metastasized to regional lymph nodes, and fused into clusters. Yoshida *et al*[2] proposed that advanced gastric cancer can be divided into four categories: Class I, metastases are technically resectable, including single liver metastases, and 16a2, b1 lymph node metastases; Class II, patients with resectable metastases, accompanied by multiple liver metastases, intrahepatic metastases larger than 5 cm, or accompanied by No. 16a1, b2, or mediastinal lymph node metastases; Class III is only peritoneal metastases visible to the naked eye; Class IV refers to the combination of other distant metastases in addition to peritoneal metastases[2]. Several national and international studies[3-5] have shown that D2 Lymph node dissection should be the first treatment option for advanced gastric cancer, and there is little difference between open surgery and laparoscopic surgery[6]. The treatment model has changed from a single D2 lymph node dissection to a multidisciplinary and comprehensive treatment based on surgery for patients with locally advanced cancer. The integrated treatment model can further improve the survival quality of patients compared to traditional radical surgery combined with postoperative chemotherapy. For patients with locally advanced cancer, attention is focused on the examination of comprehensive treatment options and reducing the proportion of perioperative recurrence and achieving partial or full remission of unresectable factors by translational therapy, which has become one of the hot spots of research. Based on existing national and international research results[7,8], the current translational therapy for locally advanced gastric cancer generally includes the following: postoperative adjuvant chemotherapy and chemoradiotherapy, targeted therapy and immunotherapy. Neoadjuvant therapy refers to the preoperative administration of chemotherapy or radiotherapy to lower tumor stage, increase R0 resection rate and pathological remission, and improve patient prognosis. Neoadjuvant chemotherapy has potential advantages such as elimination of small metastases and reduction of postoperative recurrence. Preoperative tumor vessels are more abundant, and the drug can enter the tumor *via* blood vessels more easily, which increases the sensitivity of radiotherapy. A

series of studies have been conducted on preoperative neoadjuvant chemoradiotherapy[9].

POSTOPERATIVE ADJUVANT CHEMOTHERAPY

The ACTS-GC study in Japan in 2011 included a total of 1059 patients with stage II and III gastric cancer after radical D2 surgery in a controlled study, with the experimental group (n = 529) given S-1 monotherapy postoperatively and the control group (n = 530) undergoing surgery only. The results showed that the 5-year progression-free survival (PFS) rate of patients in the experimental group (65.4% *vs* 53.1%, HR = 0.65, 95%CI: 0.54-0.80) was significantly higher, and the analysis showed that postoperative S-1 monotherapy provided benefit in patients with stage II and IIIA gastric cancer, but did not improve the survival of patients with stage IIIB disease[10]. Due to the difference in pharmacokinetics between Caucasians and Xanthoderms, and the fact that D0-D1 surgery for gastric cancer was mostly performed in Europe and America at that time, while D2 surgery was performed in Japan, the ACTS-GC study was not directly extended to the postoperative adjuvant treatment of gastric cancer in Europe and America. Furthermore, the JACCRO GC- 07 study conducted in Japan treated advanced gastric cancer patients with either S-1 monotherapy or S-1 combined with docetaxel chemotherapy. The 3-year disease recurrence-free survival (RFS) rate (67.7% *vs* 57.4%, P = 0.0008) and 3-year overall survival (OS) rate (77.7% *vs* 71.2%, P = 0.007) were significantly improved in the combination treatment group[11]. In order to determine the optimal adjuvant treatment protocol for advanced gastric cancer, the CLASSIC study by Korean and Chinese researchers included 1035 patients with gastric cancer who underwent stage II-IIIb radical D2 surgery, and were randomly divided into the experimental group (520 cases) and the observational group (515 cases), and the experimental group was treated with the XELOX regimen (oxaliplatin and capecitabine) for 6 mo. The 5-year follow-up results showed that the XELOX regimen improved disease-free survival (DFS) (68% *vs* 53%, P < 0.0001) and OS (78% *vs* 69%, P < 0.0015), suggesting that the XELOX regimen can be used as the standard adjuvant

chemotherapy regimen after D2 radical surgery for stage II-IIIb gastric cancer[12,13]. Based on the ACTS-GC and CLASSIC studies, it was determined that postoperative adjuvant chemotherapy may be the standard treatment strategy after radical D2 surgery for gastric cancer.

POSTOPERATIVE ADJUVANT RADIOTHERAPY

As mentioned above, due to the different surgical protocols for gastric cancer used in Europe and America, postoperative chemotherapy is mostly combined with radiotherapy. A total of 559 patients with T3-T4 stage surgically resectable gastric cancer were included in the study by Smalley *et al*[14] in 2012. These patients were randomly assigned to the surgery group or the surgery combined with postoperative radiotherapy group, and the results showed that patients in the surgery combined with postoperative radiotherapy group had a longer 3-year median RFS (27 mo *vs* 19 mo, $P < 0.001$) and 3-year median OS (35 mo *vs* 27 mo, $P = 0.0046$) than those in the surgery-only group[14], which provided the basis for the subsequent NCCN gastric cancer guidelines. The ARTIST and ARTIST-II studies were conducted in Korea to determine whether the addition of radiotherapy to combination chemotherapy after radical surgery for D2 lymph node dissection improves patient survival[15,16]. The studies showed that the addition of radiotherapy to D2 Lymph node dissection plus two-drug adjuvant chemotherapy did not improve patient survival. According to the results of several randomized controlled studies in patients with locally advanced gastric cancer, combination chemotherapy after D2 radical surgery can improve patient survival. For patients with stage III gastric cancer after D2 radical surgery, two-drug combination is more effective than single-drug chemotherapy and the addition of radiotherapy to chemotherapy can improve the survival of patients with D0 or D1 lymph node dissection but cannot improve the survival of patients after D2 radical surgery.

Based on the results of a number of large randomized controlled studies (Table 1), for patients with locally advanced gastric cancer, adjuvant chemotherapy S-1, S-1 + docetaxel, SOX and XELOX are all optional chemotherapy regimens after radical D2

treatment which can significantly improve survival. For stage III gastric cancer patients after D2 radical resection, two-drug chemotherapy is more effective than single-drug chemotherapy. At present, all major guidelines recommend postoperative adjuvant therapy for locally advanced gastric cancer. Adding radiotherapy to postoperative chemotherapy could improve the survival rate of patients in the D1 or D0 clearance range, but could not further improve the survival rate of patients after D2 radical resection.

TARGETED THERAPY

Progress is slow in targeted therapy research for gastric cancer, and overexpression of human epidermal growth factor receptor 2 (HER-2) may be an independent factor in the poor prognosis of gastric cancer. The T0GA study published in 2010 confirmed, for the first time, the effectiveness of trastuzumab in the treatment of advanced gastric cancer, opening the era of targeted therapy for advanced gastric cancer[17]. Currently, there are more drugs and studies targeting HER-2, vascular endothelial growth factor (VEGF), epidermal growth factor receptor (EGFR)-1, the hepatocyte growth factor (HGF)/tyrosine protein kinase Met (c-MET) signaling pathway, immune checkpoints and other related pathways and targets.

Anti-HER-2-targeted drugs

HER-2 is a member of the epidermal growth factor family, which accelerates tumor cell growth and invasion by activating the RAS-RAF-MRK-MAPK pathway, PI3K-AKT and other pathways. The T0GA trial confirmed that trastuzumab combined with cisplatin-based chemotherapy can prolong OS in patients with locally advanced gastric cancer by approximately 1.2 mo[17]. The 2011 NCCN guidelines recommend first-line trastuzumab in combination with platinum-based chemotherapy for eligible patients with advanced gastric cancer, and clinical trials such as JFMC45-1102 showed that in patients with advanced gastric cancer who have not previously been treated with anti-HER2-directed agents, trastuzumab is beneficial as a second- or super-second-line agent[18]. Clinical

trials such as HER-FLOT[19] have also shown that trastuzumab plays a role in the preoperative translational therapy and neoadjuvant therapy of locally advanced gastric cancer.

Anti-angiogenesis-related targeted drugs

The VEGF family accelerates the formation of neovascularization in the tumor through a series of cellular pathways to provide sufficient blood supply and nutrition for tumor cells, and the current anti-angiogenesis-targeted drugs for locally advanced gastric cancer include monoclonal antibodies, tyrosine kinase inhibitors, *etc.* As monoclonal antibodies have more adverse effects and unsatisfactory clinical trial results, most of the drugs have not entered the clinic. Tyrosine kinase inhibitors mainly inhibit tumor angiogenesis by binding to the VEGFR and can selectively inhibit tyrosine kinase activity to exert anti-tumor effects. A phase II clinical trial of apatinib in locally advanced gastric cancer patients after failure of second-line chemotherapy showed that a single agent could improve the survival of patients with locally advanced gastric cancer who had previously received ≥ 2 failed chemotherapy regimens[20]. Currently, it is mainly used in China for third-line and above treatment of locally advanced gastric cancer or esophagogastric junction cancer.

Anti-EGFR targeting drugs

The overexpression of EGFR in gastric cancer can reach 50%-63%, and its expression level is positively correlated with tumor aggressiveness and negatively correlated with differentiation degree and survival time, suggesting that EFGR may be a target in gastric cancer treatment. However, the clinical trial results of related targeting drugs have not met the clinical application requirements.

Targeted drugs of the HGF/c-MET signaling pathway

The HGF/c-MET signaling pathway is related to tumor cell migration, invasion and intra-tumor blood vessel formation. Also, 10%-15% of patients with advanced gastric

cancer have amplification of MET, the gene encoding c-MET protein, and 30% of these patients have high expression of MET, and the expression level is negatively correlated with patient prognosis. However, the current clinical trial results of drugs targeting this pathway are unsatisfactory.

IMMUNOTHERAPY

Immune checkpoint inhibitors are used to inhibit tumor growth and invasion by restoring the immunocidal effect of host T cells on tumor cells and weakening the immune escape of tumor cells. KEYNOTE-059 is a global phase II clinical trial of programmed cell death protein (PD)-1 inhibitors for gastric cancer or esophagogastric junction cancer, which has shown that immunosuppressants are effective and safe in the treatment of advanced gastric cancer or esophagogastric junction cancer[21]. The CHECKMATE-649 study showed that chemotherapy combined with nabolutumab significantly improved OS in patients with a PD-ligand 1 (PD-L1) combined positive score (CPS) ≥ 5 compared to chemotherapy alone, and that combination therapy resulted in a statistically significant benefit in PFS in patients with CPS ≥1 and in all randomized patients with CPS ≥ 5[22]. Data analysis in the KEYNOTE-811 study of HER-2 positive patients showed that the experimental group (chemotherapy + trastuzumab + pablizumab) had a significantly improved objective remission rate (74.4% *vs* 51.9% P = 0.00006)[23]. The results of the ongoing ATTRACTION-05 study in Japan which is evaluating the efficacy and safety of adjuvant nabritumomab in combination with SOX or XELOX regimens for stage III gastric or esophagogastric junction cancer after D2 radical surgery have not yet been published. The preliminary data of multiple phase II clinical trials of preoperative immunosuppressive agents combined with chemotherapy in the treatment of locally advanced gastric cancer presented at the 2021 ASCO Congress showed that the pathological complete response rate was 10%-30%[23-25]. At present, a number of multicenter, phase II, randomized controlled clinical trials of preoperative immunotherapy combined with neoadjuvant chemotherapy for the

treatment of advanced gastric cancer (NICE study) are being conducted in China, and the results are expected to be announced.

CONCLUSION

In translational therapy of locally advanced gastric cancer, D2 lymph node dissection is the first standard surgical procedure, and D2 radical surgery + a postoperative adjuvant chemotherapy regimen has long been used as the main treatment regimen. When there is a bottleneck in the therapeutic effect, the emergence of neoadjuvant chemotherapy has improved the survival quality of patients, thus establishing the use of neoadjuvant chemotherapy. D1 radical surgery + postoperative radiotherapy in Europe and America showed improved survival, but the later regimen of D2 radical surgery + postoperative adjuvant chemotherapy + radiotherapy has not further improved survival, and the therapeutic effect of neoadjuvant radiotherapy is still being verified. In recent years, microsatellite instability and high-frequency tumor mutation antigens in Epstein-Barr virus-positive gastric cancer are expected to be potential targets for gastric cancer immunotherapy, and there are several phase III clinical trials underway. We look forward to the announcement of the results. Targeted therapies for gastric cancer are progressing slowly, and the currently available drugs for different targets are not effective in the treatment of locally advanced gastric cancer, but the combination of immunotherapy with targeted therapies is also in progress[26]. Nivolumab in combination with ipilimumab and pablizumab plus trastuzumab[27] can improve the survival of patients to some extent, but the combination of drugs leads to an increase in adverse effects, and further comprehensive assessment of the benefit is thus needed.

Challenges and opportunities

At present, with the continuous development of clinical research on translational therapy, its status in the treatment of locally advanced gastric cancer may be further improved, and immune and targeted therapies are also likely to make breakthroughs. Further refinement of treatment plans and models, identification of the best

combination and treatment opportunities, and even the treatment sequence of immunotherapy and chemoradiotherapy are all future research directions. The heterogeneity of gastric cancer is strong, and the molecular characteristics of tumors are also important factors affecting treatment efficacy and prognosis of locally advanced gastric cancer. Future studies also need to be designed to stratify tumors more accurately. The author believes that with the rapid development of drug research and extensive clinical trials, the survival of patients with locally advanced gastric cancer is expected to be further improved.

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