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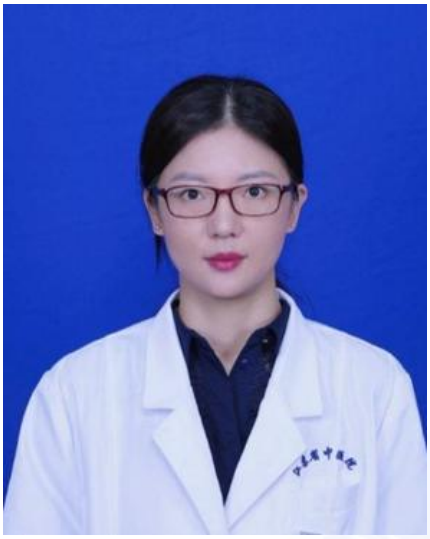

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Research progress in targeted therapy for gastric cancer

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Abstract: Gastric cancer is a common malignant tumor worldwide, and its incidence and mortality have always been in the forefront. Most gastric cancer patients in China are diagnosed in the middle and late stages, with an unsatisfactory 5-year survival rate and poor prognosis. Prior to the emergence of targeted therapy, chemotherapy using the combination of fluorouracil and platinum-based drugs was considered a first-line treatment option, but the clinical benefits were limited. Targeted therapy, as a current research hotspot and new approach in the field of cancer treatment, has been proved to significantly improve the survival rate of gastric cancer patients, especially those in the middle and late stages by practice, clinical trials, and basic research. This article introduces the latest research progress in targeted therapy for gastric cancer, including human epidermal growth factor receptor-2 (HER2), epidermal growth factor receptor (EGFR), fibroblast growth factor receptor (FGFR), etc., aiming to provide new ideas and directions for targeted therapy for gastric cancer.

Keywords: Gastric cancer; Targeted therapy; Human epidermal growth factor receptor-2; Epidermal growth factor receptor; Fibroblast growth factor receptor

Introduction

Gastric cancer (GC) is one of the most common malignant tumors globally, and its mortality accounts for the third highest in terms of tumor-related mortality. There are significant geographic differences in the incidence of gastric cancer, with the highest incidences in Northeast Asia (Japan and Korea), South America, Central America and Eastern Europe [1]. In China, GC has the third highest incidence and mortality among all cancers [2]. In recent years, the incidence of GC has been gradually decreasing, but the incidence of early-onset GC may be increasing. Most patients are diagnosed at an advanced stage because of the insidious symptoms for early-onset GC and the lack of clear clinical indications. For resectable GC, perioperative chemotherapy has become a standard treatment. Systemic treatments for GC include chemotherapy, immunotherapy, and targeted therapy. Current studies are exploring the potential benefits of targeted therapy or immunotherapy in perioperative and adjuvant treatment. This article systematically summarizes the major research advances in targeted therapy for GC, intending to provide new approaches and strategies for the clinical treatment of GC.

1. Human epidermal growth factor receptor-2 (HER2)

The Trastuzumab for GAstric cancer (ToGA) study established the standard treatment regimen that trastuzumab in combination with cisplatin and fluorouracil (5-FU) for patients with HER2-positive advanced gastro-oesophageal junction (GEJ) cancer and the subgroups with high HER2 expression benefited the most [3]. The phase II study (HERXO trial) evaluated the efficacy of trastuzumab in combination with the XELOX

(capecitabine, combined with oxaliplatin) regimen in the first-line treatment of patients with HER2-positive advanced gastric or GEJ cancer. The progression-free survival (PFS) and overall survival (OS) were 7.1 and 13.8 months, while the patients with complete remission, partial remission and stable disease accounted for 8.9%, 37.8% and 31.1%, respectively [4]. Compared with the cisplatin combined with 5-FU regimen, trastuzumab in combination with mFOLFOX6 (modified fluorouracil, leucovorin, and oxaliplatin) improved the tolerability of patients with previously untreated HER2-positive GC [overall response rate (ORR) of 41%, median PFS of 9.0 months, and median OS of 17.3 months] [5]. The above data suggests that trastuzumab combined with XELOX or mFOLFOX6 could be an effective and safe regimen for patients with HER2-positive gastric or GEJ cancer.

Trastuzumab deruxtecan is a new antibody-drug conjugate (ADC). The DESTINY-Gastic01 study demonstrated a much higher ORR in the ADC group compared to the standard chemotherapy group (irinotecan/paclitaxel) (51% vs 14%, P<0.001), and the OS was also longer than that of the chemotherapy group (median: 12.5 months vs 8.4 months) [6]. Therefore, ADC was approved by the Food and Drug Administration (FDA) as a second-line or a subsequent treatment option for patients with HER2-positive adenocarcinomas after failure of prior trastuzumab therapy.

The phase I trial CP-MGAH22-01 examined the efficacy of margetuximab in HER2-positive solid tumors, including GC, with 12% of patients assessed as stable and 50% assessed as in partial remission [7]. In addition, current data suggests that synergistic anti-tumor activity and satiefying patient tolerance could be achieved by the combination of margetuximab and retifanlimab/tebotelimab, and corresponding studies are ongoing [8].

The phase III JACOB trial provided some evidence for the therapeutic activity and acceptable safety of pertuzumab in combination with trastuzumab and chemotherapy in previously untreated HER2-positive metastatic gastric or GEJ cancers, but the trial have not reached its endpoint [9]. In addition, some drugs, including trastuzumab emtansine and lapatinib, have shown clinical benefits in relevant studies, but more researches are still required.

2. Vascular endothelial growth factor (VEGF)

VEGF is one of the key regulators in tumor angiogenesis. Ranimorubicin was approved by the FDA in 2014 for the treatment of patients with advanced gastric adenocarcinoma or GEJ adenocarcinoma that was refractory or progressive after first-line treatment with platinum or 5-FU-based therapy. It was further confirmed in trials that ramorubicin combined with paclitaxel could be used as a second-line treatment in a Chinese population with predominantly advanced GC or GEJ adenocarcinoma [10]. Subsequent studies have found that ramucirumab and trifluridine/tipiracil demonstrated clinical benefits in patients with advanced GC who had been priorly treated (including the usage of ramucirumab) [11]. In addition, trastuzumab in combination with ramucirumab and paclitaxel showed promising efficacy and a manageable risk in previously treated patients with HER2-positive GC [12].

Based on a phase I/II study in Asian patients, fruquintinib combined with paclitaxel was effective in GC patients who received substantial pre-treatment (disease control rate of 68%) [13]. A second-line phase III trial is currently underway in Asia, as well as a phase II trial of fruquintinib in combination with SOX [tegafur，gimeracil and oteracil potassium (S-1) and oxaliplatin] as a neoadjuvant therapy for GC (NCT05122091).

Apatinib was approved in October 2014 for the third-line and further treatments of advanced GC. A phase II study showed that apatinib was effective and relatively well tolerated in elderly patients with unresectable GC who had received at least first-line chemotherapy [14]. The study confirmed that apatinib with chemotherapy could be a second-line treatment with good clinical efficacy and acceptable side effects, and may provide a new option for patients with advanced GC [15]. Apatinib and S-1 have been approved for second-line treatment of GC, and the combination group's efficacy was superior to using S-1 alone [16]. In contrast, apatinib combined with S-1 is not superior to other chemotherapy regimens for metastatic GC as a first-line treatment option. In addition, patients with lymph node metastases tended to have longer PFS and OS, and better outcomes than patients with liver metastases [17]. This may help with the design of future clinical trials to select patient populations better. The results of the AHEAD study further confirmed the satisfying security and clinical benefits of apatinib as a third- or late-line treatment in patients with advanced GC [18].

The combination of regorafenib and nivolumab had a manageable security profile and promote anti-tumor activity, and a phase III trial is planned in GC [19]. Sunitinib in combination with FOLFIRI (irinotecan/5-fluorouracil/leucovorin) have shown a tendency in improving OS in GC but have not met the primary endpoint [20]. Sorafenib alone or in combination with chemotherapy could improve OS and PFS in patients with advanced GEJ adenocarcinoma [21-22], but results from high-quality trial are still needed to support this idea. In the first-line treatment of metastatic GC, the addition of sorafenib to the XP (capecitabine and cisplatin) regimen was not superior to XP alone [23]. Single use of pazopanib produced sustained efficacy in recurrent and metastatic GEJ adenocarcinoma [24]. The results of a phase II trial revealed that the addition of pazopanib to chemotherapy (5-FU + oxaliplatin) showed signs of benefit but no significant improvement[25].

3. Claudin (CLDN) 18.2

CLDN18.2 is an isoform of claudin protein, which is a tightly linked structural component. Approximately

40% of GCs exhibit overexpression of CLDN 18.2 [26]. The SPOTLIGHT trial illustrated that zolbetuximab in combination with chemotherapy showed better PFS and OS in patients with CLDN 18.2-positive, HER2-negative, unresectable, locally advanced or metastatic GC, and GEJ adenocarcinomas [27]. Two phase III trials (NCT03504397, NCT03653507) are currently investigating the effect of zobetuximab in combination with chemotherapy in the first-line treatment of CLDN 18.2-positive (≥75% expression) gastric and GEJ cancers. In addition, CLDN 18.2 is being studied as a target for autologous chimeric antigen receptor (CAR) -T cells (NCT04467853, NCT04260191) as well as bispecific T-cell engagers (BiTE) (NCT910) in phase I trials.

4. Fibroblast growth factor (FGFR)

Alterations in the FGF receptor gene occur in a variety of cancer entities, with a frequency range of 3%-7% in GC and GEJ cancer. In a patient-derived xenograft model of FGFR2-amplified GC, AZD4547 showed favorable pre-clinical activity but did not improve PFS compared to paclitaxel [28-29]. Frutibatinib (TAS-120) can overcome resistance to ATP-competitive FGFR inhibitors and clinical trials are conducting [30]. Bemarituzumab achieved a partial response rate of 17.9% in a phase I study of patients with advanced solid tumors and FGFR2b overexpressing gastric and GEJ cancers [31]. The phase Ⅱ study (FIGHT) investigated the efficacy of bemarituzumab in combination with FOLFOX6 as first-line therapy in patients with unresectable locally advanced or metastatic HER2-negative GC with FGFR2b overexpression. The results showed that the median PFS was improved further in the Bemarituzumab group, whereas the median OS was not, and the ORR was improved from 40% to 53% [32, 33].

5. Epidermal growth factor receptor (EGFR)

More than 30% of patients with GC have EGFR overexpression and mostly have a poor prognosis [34]. Cetuximab combined with cisplatin can significantly improve clinical efficacy, reduce tumor metastases, enhance immune function, and improve prognosis in GC patients [35]. Adding cetuximab to an NCT regimen for operable GC/GEJ adenocarcinoma is safe, but the study did not meet the primary endpoint yet (NCT01360086) [36]. The addition of panitumumab to standard chemotherapy as first-line treatment for advanced GC/GEJ adenocarcinoma did not improve efficacy outcomes [37]. However, a small clinical study selecting anti-EGFR therapy for EGFR-amplified gastroesophageal cancers showed a high response rate and prolonged survival [38]. This suggests that targeting EGFR may only work in appropriate patient populations.

6. Mesenchymal-epithelial transforming (MET) factor receptor

In GC, MET is a major oncogenic driver [39]. Savolitinib is a potential targeted therapy (ORR=50%) in patients with GC in the VIKTORY trial, which is under further clinical development [40].

7. Combination with immunosuppressants

The phase III KEYNOTE-811 trial indicated that, compared to trastuzumab in combination with chemotherapy, the addition of pembrolizumab would improve survival in patients with advanced HER2-positive GC/GEJ adenocarcinoma [41].

8. Tropomyosim receptor kinase (TRK) fusion proteins

Relevant evidence suggests that neurotrophic tropomyosin-receptor kinase (NTRK) gene fusions occur in gastric adenocarcinoma and may be associated with an aggressive phenotype[42]. Numerous data suggest that entrectinib and larotrectinib result in clinically meaningful changes in patients with NTRK fusion-positive tumors that are durable, safe and controllable [43-44]. Therefore, entrectinib and larotrectinib are recommended as second-line or follow-up treatment options for patients with NTRK fusion-positive GC.

9. Other potential targets

The disease control rate of first-generation oral mammalian target of rapamycin (mTOR) inhibitor, everolimus, was 56%. In contrast, the subsequent phase III GRANITE-1 trial found that everolimus did not improve survival in patients with advanced GC who had failed prior chemotherapy [45-46]. AZD8055, a second-generation mTOR inhibitor, could suppress invasion and migration of tratuzumab resistant HER2-positive GC cells via the PI3K/AKT/mTOR pathway [47]. AZD2014 was used as second-line chemotherapy in a phase Ⅱ trial in patients with TSC1/2 mutated or TSC1/2-null GC (NCT03082833) [48]. Several dual mTORC1/2 inhibitors are currently under clinical experiments for cancer treatment. Olaparib is a poly(ADP-ribose) polymerase (PARP) inhibitor that blocks base excision repair of DNA and induces synthetic lethality in tumors with defects of homologous recombination repair [49]. The GOLD study showed no statistically significant improvement in the survival rate of paclitaxel plus olaparib in cases with overall metastases or ataxia-telangiectasia mutated protein (ATM)-negative metastases [50].

Targeted therapies against CAR-T cells, GC stem cells, tumor-associated macrophages, etc., have potential to become the new inspirations of targeted therapy for GC.

10. Chinese medicine combined with targeted therapy

In recent years, Chinese medicine has been playing an increasingly important role in the treatment of tumors. Including Chinese medicine in the treatment can enhance the effect of targeted drugs and reduce the side effects,such as loss of appetite and fatigue. Researches have revealed that the active ingredients of some specific anti-rheumatic Chinese medicines, such as quercetin, have a mechanism similar to that of trastuzumab and can down-regulate the expression of VEGF-C and VEGFR-3 [51]. Sunitinib combined with astragalus could enhance the anti-tumor effect of the former on GC [52]. In addition, co-administration of curcumin/curcumin analogs, which is present in various Chinese medicines, with chemotherapy can synergistically increase the efficacy of anticancer chemotherapy and attenuate the associated side effects compared to the group treated with chemotherapeutic agents alone [53].

The mechanism of gastric cancer related targets is shown in **Figure 1**.

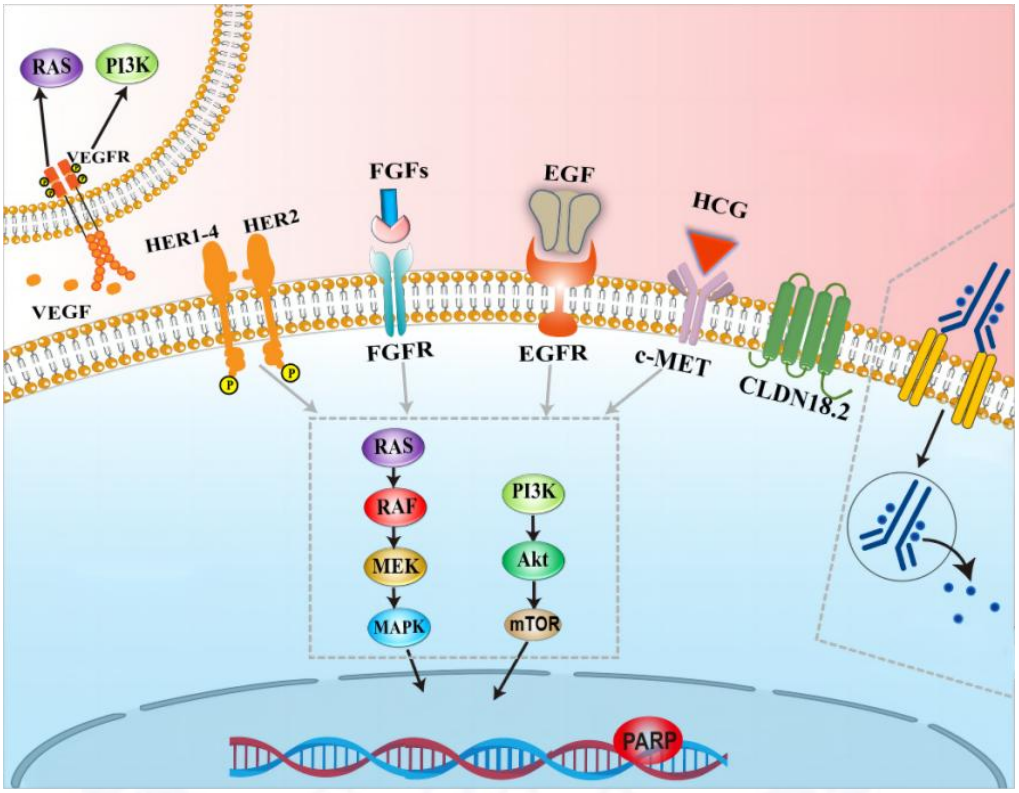

Figure 1 Schematic diagram of the mechanism of GC-related targets

11. Conclusion

Before targeted therapy emerged, chemotherapy was the primary treatment for advanced GC. Now we have entered the era of personalized diagnosis and treatment targeting at specific genes and pathways with the progress of next-generation sequencing (NGS). Various clinical trials for specific targets are in full swing around the world, and precise medical treatment has been gradually accepted and become a consensus. At present, trastuzumab combined with chemotherapy has long been the standard first-line treatment for HER2-positive GC patients in the advanced stage. Guidelines from China and internation have also approved the use of ramucirumab in the second-line treatment of GC. However, the therapeutic efficacy of GC is still mixed. The premise of targeted therapy is to find the corresponding target gene. Therefore, in-depth research on the molecular mechanism of pathogenic signaling pathways, the search for biomarkers, and the understanding of novel immunotherapies in combination with molecularly targeted drugs have become crucial. In the future, the screening of specific populations for particular targets, the combination of multi-targeted drugs with surgery, immunotherapy, radiotherapy, and chemotherapy to improve PFS and OS of patients will be the focus of clinical trials and basic researches.

Conflict of interest None

References

[1] Ajani JA, D' Amico TA, Bentrem DJ, et al. Gastric cancer, version 2.2022, NCCN clinical practice guidelines in oncology[J]. J Natl Compr Cancer Netw, 2022, 20(2): 167-192.

[2] Xia CF, Dong XS, Li H, et al. Cancer statistics in China and United States, 2022: profiles, trends, and determinants[J]. Chin Med J, 2022, 135(5): 584-590.

[3] Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled

trial[J]. Lancet, 2010, 376(9742): 687-697.
[4] Rivera F, Romero C, Jimenez-Fonseca P, et al. Phase II study to evaluate the efficacy of Trastuzumab in combination with Capecitabine and Oxaliplatin in first-line treatment of HER2-positive advanced gastric cancer: HERXO trial[J]. Cancer Chemother Pharmacol, 2019, 83(6): 1175-1181.
[5] Soularue É, Cohen R, Tournigand C, et al. Efficacy and safety of trastuzumab in combination with oxaliplatin and fluorouracil-based chemotherapy for patients with HER2-positive metastatic gastric and gastro-oesophageal junction adenocarcinoma patients: a retrospective study[J]. Bull Cancer, 2015, 102(4): 324-331.
[6] Shitara K, Bang YJ, Iwasa S, et al. Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer[J]. N Engl J Med, 2020, 382(25): 2419-2430.
[7] Bang YJ, Giaccone G, Im SA, et al. First-in-human phase 1 study of margetuximab (MGAH22), an Fc-modified chimeric monoclonal antibody, in patients with HER2-positive advanced solid tumors[J]. Ann Oncol, 2017, 28(4): 855-861.
[8] Catenacci DV, Rosales M, Chung HC, et al. MAHOGANY: margetuximab combination in HER2+ unresectable/metastatic gastric/gastroesophageal junction adenocarcinoma[J]. Future Oncol, 2021, 17(10): 1155-1164.
[9] Tabernero J, Hoff PM, Shen L, et al. Pertuzumab, trastuzumab, and chemotherapy in HER2-positive gastric/gastroesophageal junction cancer: end-of-study analysis of the JACOB phase III randomized clinical trial[J]. Gastric Cancer, 2023, 26(1): 123-131.
[10] Xu RH, Zhang YQ, Pan HM, et al. Efficacy and safety of weekly paclitaxel with or without ramucirumab as second-line therapy for the treatment of advanced gastric or gastroesophageal junction adenocarcinoma (RAINBOW-Asia): a randomised, multicentre, double-blind, phase 3 trial[J]. Lancet Gastroenterol Hepatol, 2021, 6(12): 1015-1024.
[11] Kawazoe A, Ando T, Hosaka H, et al. Safety and activity of trifluridine/tipiracil and ramucirumab in previously treated advanced gastric cancer: an open-label, single-arm, phase 2 trial[J]. Lancet Gastroenterol Hepatol, 2021, 6(3): 209-217.
[12] Kim CG, Jung M, Kim HS, et al. Trastuzumab combined with ramucirumab and paclitaxel in patients with previously treated human epidermal growth factor receptor 2-positive advanced gastric or gastroesophageal junction cancer[J]. J Clin Oncol, 2023, 41(27): 4394-4405.
[13] Xu RH, Zhang DS, Shen L, et al. A Phase I/II trial of fruquintinib in combination with paclitaxel for second-line treatment in patients with advanced gastric cancer[J]. J Clin Oncol, 2017, 35(4_suppl): 128.
[14] Ren DF, Wang GX, Zhang Y, et al. Efficacy and safety of apatinib for elderly patients with advanced or metastatic gastric cancer after failure of at least first-line chemotherapy: a multi-center, single-arm, phase II study[J]. OncoTargets Ther, 2021, 14: 4499-4508.
[15] Zhang Y, Xu JY, Wang Q, et al. Efficacy and safety of second-line therapy with apatinib combined with chemotherapy as second-line therapy in advanced gastric cancer: a single-arm, open-label, prospective, multicenter study[J]. Ann Transl Med, 2022, 10(11): 641.
[16] Wu QJ, Fu YC, Wen WL, et al. Efficacy and prognosis analyses of apatinib combined with S-1 in third-line chemotherapy for advanced gastric cancer[J]. J BUON, 2020, 25(2): 987-994.
[17] Zhou N, Zhang CT, Liu D, et al. Apatinib in combination with S-1 as first-line treatment in patients with advanced metastatic gastric cancer: results from an open, exploratory, single-arm, phase II trial[J]. Oncol, 2021, 26(3): e374-e381.
[18] Li J, Qin S, Wen L, et al. Safety and efficacy of apatinib in patients with advanced gastric or gastroesophageal junction adenocarcinoma after the failure of two or more lines of chemotherapy (AHEAD): a prospective, single-arm, multicenter, phase IV study[J]. BMC Med, 2023, 21(1):173.
[19] Cytryn SL, Moy RH, Cowzer D, et al. First-line regorafenib with nivolumab and chemotherapy in advanced oesophageal, gastric, or gastro-oesophageal junction cancer in the USA: a single-arm, single-centre, phase 2 trial[J]. Lancet Oncol, 2023, 24(10): 1073-1082.
[20] Mukherjee S, Fountzilas C, Boland PM, et al. Phase I study of irinotecan/5-fluorouracil/leucovorin (FOLFIRI) with sunitinib for advanced gastric or gastroesophageal junction adenocarcinoma[J]. Target Oncol, 2020, 15(1): 85-92.
[21] Janjigian YY, Vakiani E, Ku GY, et al. Phase II trial of sorafenib in patients with chemotherapy refractory metastatic esophageal and gastroesophageal (GE) junction cancer[J]. PLoS One, 2015, 10(8): e0134731.
[22] Sun WJ, Powell M, O'Dwyer PJ, et al. Phase II study of sorafenib in combination with docetaxel and cisplatin in the treatment of metastatic or advanced gastric and gastroesophageal junction adenocarcinoma: ECOG 5203[J]. J Clin Oncol, 2010, 28(18): 2947-2951.
[23] Ryu MH, Lee KH, Shen L, et al. Randomized phase II study of capecitabine plus cisplatin with or without sorafenib in patients with metastatic gastric cancer (STARGATE)[J]. Cancer Med, 2023, 12(7): 7784-7794.
[24] Gupta VG, Rangaraju RR, Saha R, et al. Pazopanib monotherapy is active in relapsed and refractory metastatic gastroesophageal adenocarcinoma and can produce durable response[J]. J Gastrointest Cancer, 2019, 50(4): 943-946.
[25] Högner A, Al-Batran SE, Siveke JT, et al. Pazopanib with 5-FU and oxaliplatin as first line therapy in advanced gastric cancer: a randomized phase-II study-The PaFLO trial. A study of the Arbeitsgemeinschaft Internistische Onkologie AIO-STO-0510[J]. Int J Cancer, 2022, 150(6): 1007-1017.
[26] Dottermusch M, Krüger S, Behrens HM, et al. Expression of the potential therapeutic target claudin-18.2 is frequently decreased in gastric cancer: results from a large Caucasian cohort study[J]. Virchows Arch, 2019, 475(5): 563-571.
[27] Shitara K, Lordick F, Bang YJ, et al. Zolbetuximab plus mFOLFOX6 in patients with CLDN18.2-positive, HER2-negative, untreated, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma (SPOTLIGHT): a multicentre, randomised, double-blind, phase 3 trial[J]. Lancet, 2023, 401(10389): 1655-1668.
[28] Jang J, Kim HK, Bang H, et al. Antitumor effect of AZD4547 in a fibroblast growth factor receptor 2-amplified gastric cancer patient-derived cell model[J]. Transl Oncol, 2017, 10(4): 469-475.
[29] Van Cutsem E, Bang YJ, Mansoor W, et al. A randomized, open-label study of the efficacy and safety of AZD4547 monotherapy versus paclitaxel for the treatment of advanced gastric adenocarcinoma with FGFR2 polysomy or gene amplification[J]. Ann Oncol, 2017, 28(6): 1316-1324.
[30] Hollebecque A, Doi T, Saavedra O, et al. A phase II study of futibatinib (TAS-120) in patients (pts) with advanced (adv) solid tumors harboring fibroblast growth factor receptor (FGFR) genomic aberrations[J]. J Clin Oncol, 2020, 38(4_suppl): TPS470.
[31] Catenacci DVT, Rasco D, Lee J, et al. Phase I escalation and expansion study of bemarituzumab (FPA144) in patients with advanced solid tumors and FGFR2b-selected gastroesophageal adenocarcinoma[J]. J Clin Oncol, 2020, 38(21): 2418-2426.
[32] Catenacci DV, Tesfaye A, Tejani M, et al. Bemarituzumab with modified FOLFOX6 for advanced FGFR2-positive gastroesophageal cancer: fight Phase III study design[J]. Future Oncol, 2019, 15(18): 2073-2082.
[33] Wainberg ZA, Enzinger PC, Kang YK, et al. Randomized double-blind placebo-controlled phase 2 study of bemarituzumab combined with modified FOLFOX6 (mFOLFOX6) in first-line (1L) treatment of advanced gastric/gastroesophageal junction adenocarcinoma (FIGHT)[J]. J Clin Oncol, 2021, 39(3_suppl): 160.
[34] Network CGAR. Comprehensive molecular characterization of gastric adenocarcinoma[J]. Nature, 2014, 513(7517): 202-209.
[35] Chen Q, Shen L, Chen C, et al. Cetuximab combined with cisplatin improves the prognosis of gastric cancer patients and its effect on P38 MAPK expression[J]. J BUON, 2019, 24(6):2490-2498.
[36] Gronnier C, Mariette C, Lepage C, et al. Perioperative cetuximab with cisplatin and 5-fluorouracil in esogastric adenocarcinoma: a phase II study[J]. Cancers, 2023, 15(7): 2188.
[37] Aldana GQ, Salgado M, Candamio S, et al. First-line panitumumab plus docetaxel and cisplatin in advanced gastric and gastro-oesophageal junction adenocarcinoma: results of a phase II trial[J]. Clin Transl Oncol, 2020, 22(4): 495-502.
[38] Maron SB, Alpert L, Kwak HA, et al. Targeted therapies for targeted

populations: anti-EGFR treatment for EGFR-amplified gastroesophageal adenocarcinoma[J]. Cancer Discov, 2018, 8(6): 696-713.
[39] El Darsa H, El Sayed R, Abdel-Rahman O. MET inhibitors for the treatment of gastric cancer: what's their potential?[J]. J Exp Pharmacol, 2020, 12: 349-361.
[40] Lee J, Kim ST, Kim K, et al. Tumor genomic profiling guides patients with metastatic gastric cancer to targeted treatment: the VIKTORY umbrella trial[J]. Cancer Discov, 2019, 9(10): 1388-1405.
[41] Chung HC, Bang YJ, S Fuchs C, et al. First-line pembrolizumab/placebo plus trastuzumab and chemotherapy in HER2-positive advanced gastric cancer: keynote-811[J]. Future Oncol, 2021, 17(5): 491-501.
[42] Gatalica Z, Xiu J, Swensen J, et al. Molecular characterization of cancers with NTRK gene fusions[J]. Mod Pathol, 2019, 32(1): 147-153.
[43] U.S. Food and Drug Administration. FDA approves larotrectinib for solid tumors with NTRK gene fusions. 2018. Accessed July 14, 2020. Available at: https://www.fda.gov/drugs/fda-approves-larotrectinib-solid-tumors-ntrk-gene-fusions
[44] Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials[J]. Lancet Oncol, 2020, 21(2): 271-282.
[45] Doi T, Muro K, Boku N, et al. Multicenter phase II study of everolimus in patients with previously treated metastatic gastric cancer[J]. J Clin Oncol, 2010, 28(11): 1904-1910.
[46] Ohtsu A, Ajani JA, Bai YX, et al. Everolimus for previously treated advanced gastric cancer: results of the randomized, double-blind, phase III GRANITE-1 study[J]. J Clin Oncol, 2013, 31(31): 3935-3943.
[47] Liu WH, Chang JX, Liu MW, et al. Quantitative proteomics profiling reveals activation of mTOR pathway in trastuzumab resistance[J]. Oncotarget, 2017, 8(28): 45793-45806.
[48] Kim ST, Kim SY, Klempner SJ, et al. Rapamycin-insensitive companion of mTOR (RICTOR) amplification defines a subset of advanced gastric cancer and is sensitive to AZD2014-mediated mTORC1/2 inhibition[J]. Ann Oncol, 2017, 28(3): 547-554.
[49] O'Connor MJ. Targeting the DNA damage response in cancer[J]. Mol Cell, 2015, 60(4): 547-560.
[50] Bang YJ, Xu RH, Chin K, et al. Olaparib in combination with paclitaxel in patients with advanced gastric cancer who have progressed following first-line therapy (GOLD): a double-blind, randomised, placebo-controlled, phase 3 trial[J]. Lancet Oncol, 2017, 18(12): 1637-1651.
[51] Xu JM, Kang FQ, Wang W, et al. Comparison between heat-clearing medicine and antirheumatic medicine in treatment of gastric cancer based on network pharmacology, molecular docking, and tumor immune infiltration analysis[J]. Evid Based Complementary Altern Med, 2022, 2022: 7490279.
[52] Hojo Y, Kishi S, Mori S, et al. Sunitinib and pterostilbene combination treatment exerts antitumor effects in gastric cancer via suppression of PDZD8[J]. Int J Mol Sci, 2022, 23(7): 4002.
[53] Najafi M, Mortezaee K, Rahimifard M, et al. The role of curcumin/curcuminoids during gastric cancer chemotherapy: a systematic review of non-clinical study[J]. Life Sci, 2020, 257: 118051.

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胃癌靶向治疗研究进展

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摘要：胃癌是全球常见的恶性肿瘤之一，其发病率及死亡率一直位居前列。我国大部分胃癌患者发现时已属中晚期，5 年生存率不理想，预后差。在靶向治疗出现前，氟尿嘧啶和铂类等药物联合化疗作为一线治疗方案，但临床获益有限。靶向治疗作为当前肿瘤治疗领域的研究热点及新型治疗方法，已被实践和临床试验及基础研究证实可以明显改善胃癌患者尤其中晚期患者的生存率。本文介绍了包括人类表皮生长因子受体-2（HER2）、表皮生长因子受体（EGFR）、成纤维细胞生长因子受体（FGFR）等在内的胃癌靶向治疗的最新研究进展，旨在为胃癌的靶向治疗提供新的思考和方向。

关键词：胃癌；靶向治疗；人类表皮生长因子受体-2；表皮生长因子受体；成纤维细胞生长因子受体
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Research progress in targeted therapy for gastric cancer

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Abstract: Gastric cancer is a common malignant tumor worldwide, and its incidence rate and mortality have always been in the forefront. Most gastric cancer patients in China are diagnosed in the middle or late stages, with an unsatisfactory 5-year survival rate and poor prognosis. Prior to the emergence of targeted therapy, the combination chemotherapy of fluorouracil and platinum based drugs was considered a first-line treatment option, but the clinical benefits were limited. Targeted therapy, as a current research hotspot and new treatment method in the field of cancer treatment, has been proven by practice, clinical trials, and basic research to significantly improve the survival rate of gastric cancer patients, especially those in the middle and late stages. This article introduces the latest research progress in targeted therapy for gastric cancer, including human epidermal growth factor receptor-2 (HER2), epidermal growth factor receptor (EGFR), fibroblast growth factor receptor (FGFR), etc., aiming to provide new ideas and directions for targeted therapy for gastric cancer.

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在全球范围内,胃癌是常见的恶性肿瘤之一,位居第五位,其死亡率占肿瘤相关死亡率的第三位。全球的发病率存在明显的地理差异,发病率最高的是东北亚(日本和韩国)、南美洲、中美洲以及东欧[1]。在中国,胃癌的发生率及死亡率均居第三位[2]。近年来,胃癌的发病率逐渐下降,但早发性胃癌的发病率可能正在上升。因其早发症状比较隐匿,缺乏明确的临床指征,大多数患者被确诊时已经是晚期。对于可切除的胃癌,围手术期化疗已成为标准治疗方案。胃癌的全身治疗包括化疗、免疫治疗、靶向治疗,而目前的研究正在探索靶向治疗或免疫治疗在围手术期和辅助治疗中的潜在益处。本文系统总结了胃癌靶向治疗的主要研究进展,以期为胃癌的临床治疗提供新的方法与策略。

1　人类表皮生长因子受体-2(HER2)

ToGA 试验确立了曲妥珠单抗联合顺铂和氟尿嘧啶(5-FU)作为 HER2 过表达阳性的晚期胃食管腺癌患者的标准治疗方案,且 HER2 高表达的亚组受益最多[3]。Ⅱ期 HERXO 试验评估了曲妥珠单抗联合 XELOX 方案用于 HER2 过表达晚期胃癌或胃食管交界处(GEJ)腺癌患者的一线治疗,无病生存期(PFS)和总生存期(OS)分别为 7.1 个月和 13.8 个月,出现完全缓解、部分缓解和疾病稳定的患者分别占 8.9%、37.8%和31.1%[4]。而与顺铂+5-FU 方案相比,曲妥珠单抗联合 mFOLFOX6 改善了既往未经治疗的 HER2 过表达阳性肿瘤患者的耐受性,客观缓解率(ORR) 41%,中位 PFS 为 9.0 个月,OS 为 17.3 个月[5]。以上数据表明,曲妥珠单抗与 XELOX 或 mFOLFOX6 联合治疗是 HER2 过表达阳性胃食管癌患者具有可接受的安全性的有效方案。

曲妥珠单抗德鲁替康(trastuzumab deruxtecan)是一种新型抗体药物偶联物(ADC)。DESTINY-Gastric01 试验研究显示,与标准化疗组(伊立替康/紫杉醇)相比,ADC 组的 ORR 远远高于化疗组(51% *vs* 14%, $P<0.01$),OS 也长于化疗组(中位数:12.5 个月 *vs* 8.4 个月)[6]。ADC 因此被食品药品监督管理局(FDA)批准用于既往曲妥珠单抗治疗失败后 HER2 过表达阳性腺癌患者二线或后续治疗选择。

Ⅰ期试验 CP-MGAH22-01 评估了马吉妥昔单抗(margetuximab)在 HER2 阳性实体瘤(包括胃癌)中的疗效,12%的患者为稳定,50%的患者为部分缓解[7]。另外,目前已有的数据表明,margetuximab 联合瑞替凡利单抗(retifanlimab)/特泊利单抗(tebotelimab)具有协同抗肿瘤活性和良好的耐受性,相关研究正在进行中[8]。

JACOB Ⅲ期试验为帕妥珠单抗联合曲妥珠单抗和化疗在既往未经治疗的 HER2 阳性转移性胃癌或胃食管结合部癌中的治疗活性和可接受的安全性提供了一些证据,但该试验并未达到终点[9]。另外,还有 trastuzumab emtansine、拉帕替尼等,虽在相关研究中见到临床获益,但仍需要大样本的研究去证明。

2　血管内皮生长因子(VEGF)

VEGF 是肿瘤血管生成的关键调节因子之一。2014 年雷莫芦单抗被 FDA 批准用于治疗铂类或氟尿嘧啶类一线治疗后难治性或进展性的晚期胃腺癌或 GEJ 腺癌患者。后又在试验中得到进一步证实,雷莫西尤单抗联合紫杉醇可以作为以晚期胃癌或 GEJ 腺癌为主的中国人群的二线治疗[10]。随后的研究发现,雷莫西尤单抗和曲氟尿苷替匹嘧啶在既往接受过治疗(包括雷莫西尤单抗)的晚期胃癌患者中表现出临床获益[11]。另外,曲妥珠单抗联合雷莫西尤单抗和紫杉醇在既往接受过治疗的 HER2 阳性胃癌患者中显示出可观的疗效和可控的安全性[12]。

在亚洲患者的Ⅰ/Ⅱ期研究中,呋喹替尼(fruquintinib)联合紫杉醇对接受大量预处理(即疾病控制率为 68%)的胃癌患者有效[13]。目前正在亚洲进行二线Ⅲ期试验,以及呋喹替尼联合 SOX 作为胃癌的新辅助治疗的Ⅱ期试验(NCT05122091)也在进行中。

阿帕替尼于 2014 年 10 月获批用于三线及以上晚期胃癌的治疗。一项Ⅱ期研究显示,阿帕替尼对接受过至少一线化疗的不可切除胃癌的老年患者有效且耐受性相对较好[14]。研究证实,阿帕替尼联合化疗作为晚期胃癌的二线治疗具有良好的临床疗效和可接受的副作用,可为晚期胃癌患者提供新的二线治疗选择[15]。阿帕替尼和替吉奥(s-1)已被批准用于胃癌的二线治疗,且联合治疗优于单独使用 s-1[16]。而对于转移性胃癌,阿帕替尼联合 s-1 作为一线治疗

方案并不优于其他化疗方案。另外,与肝转移患者相比,淋巴结转移患者往往 PFS 和 OS 更长,疗效更佳[17]。AHEAD 研究的结果进一步证实了阿帕替尼作为三线或晚线治疗在晚期胃癌患者中具有可接受且可控的安全性和临床益处[18]。

瑞戈非尼加纳武利尤单抗的组合被确定具有可控的安全性,并促进抗肿瘤活性,计划在胃癌中进行Ⅲ期试验[19];舒尼替尼联合 FOLFILI 倾向于改善胃癌的 OS,但没有达到主要终点[20]。索拉非尼单药或与化疗联合使用可改善晚期 GEJ 腺癌患者的 OS 和 PFS[21-22],但需要高质量的试验结果来支持这一观点。在转移性胃癌的一线治疗中,XP 方案中加用索拉非尼的效果并没有优于单独化疗[23]。培唑帕尼单药可对复发性和转移性胃食管腺癌产生持续疗效[24]。一项Ⅱ期试验的结果表明,在化疗(5-FU+奥沙利铂)中加入培唑帕尼显示出疗效改善的趋势,但尚未有统计学差异[25]。

3　Claudin(CLDN)18.2

CLDN18.2 是 claudin 蛋白的亚型,属于紧密连接的结构成分。约 40% 的胃癌表现为过表达[26]。SPOTLIGHT 试验说明:佐贝妥昔单抗(zolbetuximab)联合化疗在 CLDN18.2 阳性、HER2 阴性、局部晚期不可切除或转移性胃癌或 GEJ 腺癌患者中显示出更好的 PFS 和 OS[27]。目前有两项Ⅲ期试验(NCT03504397, NCT03653507)正在研究佐贝妥昔单抗联合化疗在 CLDN 18.2 阳性(肿瘤细胞表达≥75%)胃癌和 GEJ 癌的一线治疗效果。此外,CLDN 18.2 正在Ⅰ期试验中作为嵌合抗原受体 T(CAR-T)细胞(NCT04467853,NCT04260191)以及双特异性 T 细胞接合剂(BiTE)(NCT910)的靶标进行研究。

4　成纤维细胞生长因子受体(FGFR)

FGFR 基因的改变见于多种实体癌症,在胃癌和 GEJ 癌中,频率范围为 3%~7%。在 FGFR2 扩增的胃癌患者衍生的异种移植模型中,AZD4547 显示出良好的临床前活性,但与紫杉醇相比,PFS 并未得到改善[28-29]。福巴替尼(futibatinib, TAS-120)能克服对 ATP 竞争性 FGFR 抑制剂的耐药性,目前正在临床试验中[30]。贝玛妥珠单抗(bemarituzumab)在一项针对晚期实体瘤和 FGFR2b 过表达的胃癌和 GEJ 癌患者的Ⅰ期研究中部分缓解率达到 17.9%[31]。Ⅱ期研究(FIGHT)研究了贝玛妥珠单抗联合 FOLFOX 在不可切除的局部晚期或转移性 HER2 阴性胃癌伴 FGFR2b 过表达的患者中的一线治疗效果。结果表明,贝玛妥珠单抗组的中位 PFS 得到进一步改善,而中位 OS 却未有显著改善,ORR 从 40%提升到 53%[32-33]。

5　表皮生长因子受体(EGFR)

超过 30%的胃癌患者会出现 EGFR 过度表达,预后多不良[34]。西妥昔单抗联合顺铂可显著提高胃癌患者的临床疗效,降低肿瘤转移率,增强免疫功能,改善预后[35]。在可手术的胃癌/GEJ 腺癌的 NCT 方案中加入西妥昔单抗是安全的,但研究未达到主要终点(NCT01360086)[36]。在标准化疗中加入帕尼单抗作为晚期胃或 GEJ-ADC 的一线治疗并未改善疗效结局[37]。然而,一项小型临床研究选择 EGFR 扩增的胃食管癌进行抗 EGFR 治疗,结果显示反应率高,生存期延长[38]。这表明,靶向 EGFR 只可能在适当患者群体中发挥作用。

6　间充质—上皮转化(MET)因子受体

在胃癌中,MET 是主要的致癌驱动因素[39]。VIKTORY 试验中,赛沃替尼(savolitinib)在胃癌患者中是一个有希望的潜在靶向治疗药物(ORR 50%),目前正在进一步临床开发中[40]。

7　免疫抑制剂

Ⅲ期试验 KEYNOTE-811 表示,与单独使用曲妥珠单抗联合化疗相比,在曲妥珠单抗+化疗方案中加入帕博利珠单抗将提高晚期 HER2 阳性胃癌或 GEJ 腺癌患者的生存率[41]。

8　原肌球蛋白受体激酶(TRK)融合蛋白

相关证据表明,神经营养因子受体络氨酸激酶(NTRK)基因融合确实发生在胃腺癌中,并且可能与侵袭性表型有关[42]。大量数据表明,恩曲替尼和拉罗替尼在 NTRK 基因融合阳性肿瘤患者中会出现具有临床意义的反应,且持久性强,安全性可控[43-44]。因此,恩曲替尼和拉罗替尼被推荐作为 NTRK 基因融合阳性胃癌患者的二线或后续治疗选择。

9　其他潜在靶点

研究发现,第一代口服 mTOR 抑制剂依维莫司的疾病控制率为 56%,而随后的Ⅲ期试验 GRANITE-1 发现,依维莫司并没有提高先前化疗失败的晚期胃癌患者的生存率[45-46]。AZD8055 是第二代 mTOR 抑制剂,可以通过 PI3K/AKT/mTOR 途径抑制曲妥珠单抗耐药且 HER2 阳性胃癌细胞的侵袭和迁移[47]。

AZD2014 在 TSC1/2 突变或 TSC1/2 无效胃癌患者的Ⅱ期试验中用作二线化疗(NCT03082833)[48]。目前,几种双联 mTORC1/2 抑制剂用于癌症治疗正在临床研究中。奥拉帕尼是一种 PARP 抑制剂,可阻断 DNA 碱基切除修复[49]。GOLD 研究显示在总体转移和 ATM 阴性转移情况下,紫杉醇加用奥拉帕尼对生存率的改善未能显示出统计学差异[50]。

而针对 CAR-T 细胞、胃癌干细胞、肿瘤相关巨噬细胞等的靶向疗法具有一定的潜力,有望成为胃癌靶向治疗的新星。

10　中医药联合靶向治疗

近年来,中医药在肿瘤的治疗中发挥着越来越大的作用。中医药参与治疗不仅可以增强靶向药物的效果,也可以降低包括食欲不振、乏力等相关副反应。研究发现某些抗风湿中药的有效成分如槲皮素与曲妥珠单抗的作用机制类似,可以降低 VEGF-C 和 VEGFR-3 的表达[51]。舒尼替尼联合紫檀芪可以增强其对胃癌的抗肿瘤作用[52]。此外,与单独使用化疗药物治疗相比,存在于多种中药中的姜黄素/姜黄素类化合物与化疗联合给药可协同增加抗癌化疗疗效,并减轻相关副反应[53]。

胃癌相关靶点作用机制见图 1。

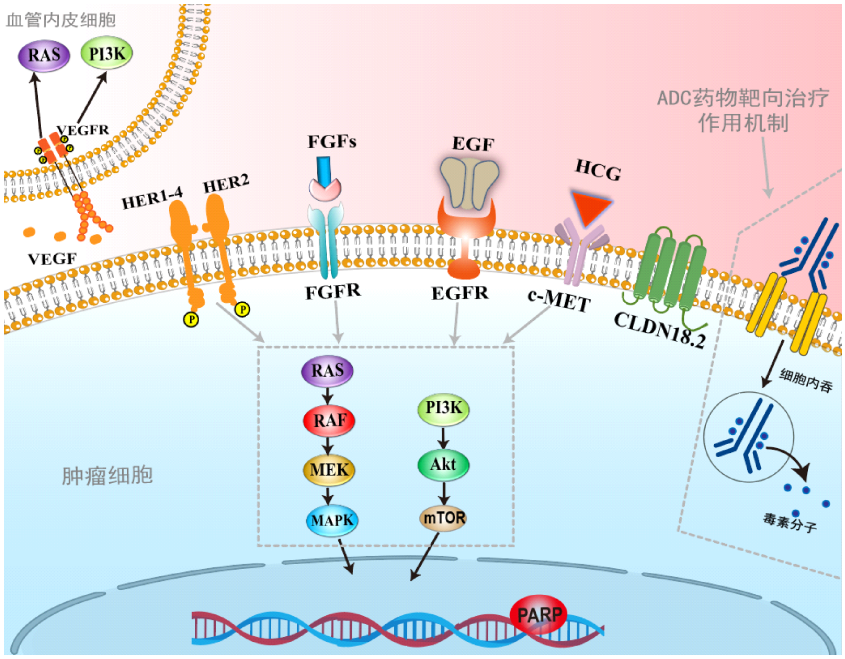

图 1　胃癌相关靶点作用机制示意图

Fig. 1　Schematic diagram of the mechanism of action of gastric cancer related targets

11　结　论

靶向治疗出现前,化疗一直是晚期胃癌的主要治疗手段;随着新一代基因测序(NGS)技术的普及,现已经进入到针对特定基因和信号通路的个体化诊疗时代。各种针对特定靶点的临床试验在全球如火如荼地开展,精准化医疗已逐渐被接受并形成共识。目前曲妥珠单抗联合化疗早已成为 HER2 阳性胃癌晚期患者的标准一线治疗,国内外指南也已将雷莫芦单抗批准用于胃癌二线治疗。然而,胃癌的治疗疗效仍喜忧参半,各种靶向治疗的前提首先是找到相应靶点,即对应靶基因表达阳性。因此,对致病信号通路分子途径的深入研究,探寻生物标志物,以及对新型免疫疗法与分子靶向药物组合的理解都变的至关重要。展望未来,针对特定靶点筛选特异性人群,多靶点药物与手术、免疫、放疗和化疗如何组合提高患者无进展生存期和总生存期将成为未来临床试验和基础研究的焦点。

利益冲突　无

参考文献

[1] Ajani JA, D'Amico TA, Bentrem DJ, et al. Gastric cancer, version 2.2022, NCCN clinical practice guidelines in oncology[J]. J Natl Compr Cancer Netw, 2022, 20(2): 167-192.

[2] Xia CF, Dong XS, Li H, et al. Cancer statistics in China and United States, 2022: profiles, trends, and determinants[J]. Chin Med J, 2022, 135(5): 584-590.

[3] Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (*ToGA*): a phase 3, open-label, randomised controlled trial[J]. Lancet, 2010, 376(9742): 687-697.

[4] Rivera F, Romero C, Jimenez-Fonseca P, et al. Phase Ⅱ study to evaluate the efficacy of Trastuzumab in combination with Capecitabine and Oxaliplatin in first-line treatment of HER2-positive advanced gastric cancer: HERXO trial[J]. Cancer Chemother Pharmacol, 2019, 83(6): 1175-1181.

[5] Soularue É, Cohen R, Tournigand C, et al. Efficacy and safety of trastuzumab in combination with oxaliplatin and fluorouracil-based chemotherapy for patients with HER2-positive metastatic gastric and gastro-oesophageal junction adenocarcinoma patients: a retrospective study[J]. Bull Cancer, 2015, 102(4): 324-331.

[6] Shitara K, Bang YJ, Iwasa S, et al. Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer[J]. N Engl J Med, 2020, 382(25): 2419-2430.

[7] Bang YJ, Giaccone G, Im SA, et al. First-in-human phase 1 study of margetuximab (MGAH22), an Fc-modified chimeric monoclonal antibody, in patients with HER2-positive advanced solid tumors[J]. Ann Oncol, 2017, 28(4): 855-861.

[8] Catenacci DV, Rosales M, Chung HC, et al. MAHOGANY: margetuximab combination in HER2+ unresectable/metastatic gastric/gastroesophageal junction adenocarcinoma[J]. Future Oncol, 2021, 17(10): 1155-1164.

[9] Tabernero J, Hoff PM, Shen L, et al. Pertuzumab, trastuzumab, and chemotherapy in HER2-positive gastric/gastroesophageal junction cancer: end-of-study analysis of the JACOB phase Ⅲ randomized clinical trial[J]. Gastric Cancer, 2023, 26(1): 123-131.

[10] Xu RH, Zhang YQ, Pan HM, et al. Efficacy and safety of weekly paclitaxel with or without ramucirumab as second-line therapy for the treatment of advanced gastric or gastroesophageal junction adenocarcinoma (RAINBOW-Asia): a randomised, multicentre, double-blind, phase 3 trial[J]. Lancet Gastroenterol Hepatol, 2021, 6(12): 1015-1024.

[11] Kawazoe A, Ando T, Hosaka H, et al. Safety and activity of trifluridine/tipiracil and ramucirumab in previously treated advanced gastric cancer: an open-label, single-arm, phase 2 trial[J]. Lancet Gastroenterol Hepatol, 2021, 6(3): 209-217.

[12] Kim CG, Jung M, Kim HS, et al. Trastuzumab combined with ramucirumab and paclitaxel in patients with previously treated human epidermal growth factor receptor 2-positive advanced gastric or gastroesophageal junction cancer[J]. J Clin Oncol, 2023, 41(27): 4394-4405.

[13] Xu RH, Zhang DS, Shen L, et al. A Phase Ⅰ/Ⅱ trial of fruquintinib in combination with paclitaxel for second-line treatment in patients with advanced gastric cancer[J]. J Clin Oncol, 2017, 35(4_suppl): 128.

[14] Ren DF, Wang GX, Zhang Y, et al. Efficacy and safety of apatinib for elderly patients with advanced or metastatic gastric cancer after failure of at least first-line chemotherapy: a multi-center, single-arm, phase Ⅱ study[J]. OncoTargets Ther, 2021, 14: 4499-4508.

[15] Zhang Y, Xu JY, Wang Q, et al. Efficacy and safety of second-line therapy with apatinib combined with chemotherapy as second-line therapy in advanced gastric cancer: a single-arm, open-label, prospective, multicenter study[J]. Ann Transl Med, 2022, 10(11): 641.

[16] Wu QJ, Fu YC, Wen WL, et al. Efficacy and prognosis analyses of apatinib combined with S-1 in third-line chemotherapy for advanced gastric cancer[J]. J BUON, 2020, 25(2): 987-994.

[17] Zhou N, Zhang CT, Liu D, et al. Apatinib in combination with S-1 as first-line treatment in patients with advanced metastatic gastric cancer: results from an open, exploratory, single-arm, phase Ⅱ trial[J]. Oncol, 2021, 26(3): e374-e381.

[18] Li J, Qin S, Wen L, et al. Safety and efficacy of apatinib in patients with advanced gastric or gastroesophageal junction adenocarcinoma after the failure of two or more lines of chemotherapy (AHEAD): a prospective, single-arm, multicenter, phase Ⅳ study[J]. BMC Med, 2023, 21(1):173.

[19] Cytryn SL, Moy RH, Cowzer D, et al. First-line regorafenib with nivolumab and chemotherapy in advanced oesophageal, gastric, or gastro-oesophageal junction cancer in the USA: a single-arm, single-centre, phase 2 trial[J]. Lancet Oncol, 2023, 24(10): 1073-1082.

[20] Mukherjee S, Fountzilas C, Boland PM, et al. Phase I study of irinotecan/5-fluorouracil/leucovorin (FOLFIRI) with sunitinib for advanced gastric or gastroesophageal junction adenocarcinoma[J]. Target Oncol, 2020, 15(1): 85-92.

[21] Janjigian YY, Vakiani E, Ku GY, et al. Phase Ⅱ trial of sorafenib in patients with chemotherapy refractory metastatic esophageal and gastroesophageal (GE) junction cancer[J]. PLoS One, 2015, 10(8): e0134731.

[22] Sun WJ, Powell M, O'Dwyer PJ, et al. Phase Ⅱ study of sorafenib in combination with docetaxel and cisplatin in the treatment of metastatic or advanced gastric and gastroesophageal junction adenocarcinoma: ECOG 5203[J]. J Clin Oncol, 2010, 28(18): 2947-2951.

[23] Ryu MH, Lee KH, Shen L, et al. Randomized phase Ⅱ study of capecitabine plus cisplatin with or without sorafenib in patients with metastatic gastric cancer (STARGATE)[J]. Cancer Med, 2023, 12(7): 7784-7794.

[24] Gupta VG, Rangaraju RR, Saha R, et al. Pazopanib monotherapy is active in relapsed and refractory metastatic gastroesophageal adenocarcinoma and can produce durable response[J]. J Gastrointest Cancer, 2019, 50(4): 943-946.

[25] Högner A, Al-Batran SE, Siveke JT, et al. Pazopanib with 5-FU and oxaliplatin as first line therapy in advanced gastric cancer: a randomized phase-Ⅱ study-The PaFLO trial. A study of the Arbeitsgemeinschaft Internistische Onkologie AIO-STO-0510[J]. Int J Cancer, 2022, 150(6): 1007-1017.

[26] Dottermusch M, Krüger S, Behrens HM, et al. Expression of the

potential therapeutic target claudin-18.2 is frequently decreased in gastric cancer: results from a large Caucasian cohort study[J]. Virchows Arch, 2019, 475(5): 563-571.

[27] Shitara K, Lordick F, Bang YJ, et al. Zolbetuximab plus mFOLFOX6 in patients with CLDN18.2-positive, HER2-negative, untreated, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma (SPOTLIGHT): a multicentre, randomised, double-blind, phase 3 trial[J]. Lancet, 2023, 401(10389): 1655-1668.

[28] Jang J, Kim HK, Bang H, et al. Antitumor effect of AZD4547 in a fibroblast growth factor receptor 2-amplified gastric cancer patient-derived cell model[J]. Transl Oncol, 2017, 10(4): 469-475.

[29] Van Cutsem E, Bang YJ, Mansoor W, et al. A randomized, open-label study of the efficacy and safety of AZD4547 monotherapy versus paclitaxel for the treatment of advanced gastric adenocarcinoma with FGFR2 polysomy or gene amplification[J]. Ann Oncol, 2017, 28(6): 1316-1324.

[30] Hollebecque A, Doi T, Saavedra O, et al. A phase Ⅱ study of futibatinib (TAS-120) in patients (pts) with advanced (adv) solid tumors harboring fibroblast growth factor receptor (*FGFR*) genomic aberrations[J]. J Clin Oncol, 2020, 38(4_suppl): TPS470.

[31] Catenacci DVT, Rasco D, Lee J, et al. Phase I escalation and expansion study of bemarituzumab (FPA144) in patients with advanced solid tumors and FGFR2b-selected gastroesophageal adenocarcinoma[J]. J Clin Oncol, 2020, 38(21): 2418-2426.

[32] Catenacci DV, Tesfaye A, Tejani M, et al. Bemarituzumab with modified FOLFOX6 for advanced FGFR2-positive gastroesophageal cancer: fight Phase Ⅲ study design[J]. Future Oncol, 2019, 15(18): 2073-2082.

[33] Wainberg ZA, Enzinger PC, Kang YK, et al. Randomized double-blind placebo-controlled phase 2 study of bemarituzumab combined with modified FOLFOX6 (mFOLFOX6) in first-line (1L) treatment of advanced gastric/gastroesophageal junction adenocarcinoma (FIGHT)[J]. J Clin Oncol, 2021, 39(3_suppl): 160.

[34] Network CGAR. Comprehensive molecular characterization of gastric adenocarcinoma[J]. Nature, 2014, 513(7517): 202-209.

[35] Chen Q, Shen L, Chen C, et al. Cetuximab combined with cisplatin improves the prognosis of gastric cancer patients and its effect on P38 MAPK expression[J]. J BUON, 2019, 24(6):2490-2498.

[36] Gronnier C, Mariette C, Lepage C, et al. Perioperative cetuximab with cisplatin and 5-fluorouracil in esogastric adenocarcinoma: a phase Ⅱ study[J]. Cancers, 2023, 15(7): 2188.

[37] Aldana GQ, Salgado M, Candamio S, et al. First-line panitumumab plus docetaxel and cisplatin in advanced gastric and gastro-oesophageal junction adenocarcinoma: results of a phase Ⅱ trial[J]. Clin Transl Oncol, 2020, 22(4): 495-502.

[38] Maron SB, Alpert L, Kwak HA, et al. Targeted therapies for targeted populations: anti-EGFR treatment for *EGFR*-amplified gastroesophageal adenocarcinoma[J]. Cancer Discov, 2018, 8(6): 696-713.

[39] El Darsa H, El Sayed R, Abdel-Rahman O. *MET* inhibitors for the treatment of gastric cancer: what's their potential? [J]. J Exp Pharmacol, 2020, 12: 349-361.

[40] Lee J, Kim ST, Kim K, et al. Tumor genomic profiling guides patients with metastatic gastric cancer to targeted treatment: the VIKTORY umbrella trial[J]. Cancer Discov, 2019, 9(10): 1388-1405.

[41] Chung HC, Bang YJ, S Fuchs C, et al. First-line pembrolizumab/placebo plus trastuzumab and chemotherapy in HER2-positive advanced gastric cancer: keynote-811[J]. Future Oncol, 2021, 17(5): 491-501.

[42] Gatalica Z, Xiu J, Swensen J, et al. Molecular characterization of cancers with NTRK gene fusions[J]. Mod Pathol, 2019, 32(1): 147-153.

[43] U. S. Food and Drug Administration. FDA approves larotrectinib for solid tumors with NTRK gene fusions[R/OL](2018-12-14)[2023-10-05]. https://www.fda.gov/drugs/fda-approves-larotrectinib-solid-tumors-ntrk-gene-fusions.

[44] Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials[J]. Lancet Oncol, 2020, 21(2): 271-282.

[45] Doi T, Muro K, Boku N, et al. Multicenter phase Ⅱ study of everolimus in patients with previously treated metastatic gastric cancer[J]. J Clin Oncol, 2010, 28(11): 1904-1910.

[46] Ohtsu A, Ajani JA, Bai YX, et al. Everolimus for previously treated advanced gastric cancer: results of the randomized, double-blind, phase Ⅲ GRANITE-1 study[J]. J Clin Oncol, 2013, 31(31): 3935-3943.

[47] Liu WH, Chang JX, Liu MW, et al. Quantitative proteomics profiling reveals activation of mTOR pathway in trastuzumab resistance[J]. Oncotarget, 2017, 8(28): 45793-45806.

[48] Kim ST, Kim SY, Klempner SJ, et al. Rapamycin-insensitive companion of mTOR (RICTOR) amplification defines a subset of advanced gastric cancer and is sensitive to AZD2014-mediated mTORC1/2 inhibition[J]. Ann Oncol, 2017, 28(3): 547-554.

[49] O'Connor MJ. Targeting the DNA damage response in cancer[J]. Mol Cell, 2015, 60(4): 547-560.

[50] Bang YJ, Xu RH, Chin K, et al. Olaparib in combination with paclitaxel in patients with advanced gastric cancer who have progressed following first-line therapy (GOLD): a double-blind, randomised, placebo-controlled, phase 3 trial[J]. Lancet Oncol, 2017, 18(12): 1637-1651.

[51] Xu JM, Kang FQ, Wang W, et al. Comparison between heat-clearing medicine and antirheumatic medicine in treatment of gastric cancer based on network pharmacology, molecular docking, and tumor immune infiltration analysis[J]. Evid Based Complementary Altern Med, 2022, 2022: 7490279.

[52] Hojo Y, Kishi S, Mori S, et al. Sunitinib and pterostilbene combination treatment exerts antitumor effects in gastric cancer via suppression of PDZD8[J]. Int J Mol Sci, 2022, 23(7): 4002.

[53] Najafi M, Mortezaee K, Rahimifard M, et al. The role of curcumin/curcuminoids during gastric cancer chemotherapy: a systematic review of non-clinical study[J]. Life Sci, 2020, 257: 118051.

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