Progress in the treatment of advanced gastric cancer

Zheyu Song1, Yuanyu Wu1, Jiebing Yang2, Dingquan Yang1 and Xuedong Fang1

Abstract
Gastric cancer is one of the most common malignant tumors in the digestive system. Surgery is currently considered to be the only radical treatment. As surgical techniques improve and progress is made in traditional radiotherapy, chemotherapy, and the implementation of neoadjuvant therapy, the 5-year survival rate of early gastric cancer can reach >95%. However, the low rate of early diagnosis means that most patients have advanced-stage disease at diagnosis and so the best surgical window is missed. Therefore, the main treatment for advanced gastric cancer is the combination of neoadjuvant chemoradiotherapy, molecular-targeted therapy, and immunotherapy. In this article, we summarize several common methods used to treat advanced gastric cancer and discuss the progress made in the treatment of gastric cancer in detail. Only clinical practice and clinical research will allow us to prolong the survival time of patients and allow the patients to truly benefit by paying attention to the individual patient characteristics, drug choice, and developing a reasonable and comprehensive treatment plan.

Keywords
Advanced gastric cancer, neoadjuvant chemotherapy, molecular-targeted therapies radiotherapy, immunotherapy

Date received: 8 March 2017; accepted: 5 May 2017

Background
Gastric cancer is one of the most common malignancies worldwide; it has the second highest incidence and mortality rate of all cancers. Most gastric cancers are gastric antrum cancer and gastric carcinoma, although the incidence of gastroesophageal junction carcinoma is increasing gradually.1–3 Analysis of the age of onset revealed that the incidence of gastric cancer is gradually increasing in young people.4 Patients with gastric cancer exhibit “three high and three low” characteristics, whereby the incidence, metastasis rate, and mortality rate are high, and the early diagnosis rate, radical resection rate, and 5-year survival rate are low.3 Although the exact cause of gastric cancer is unclear, its pathogenesis is the same as that of other malignant tumors: it is a multi-step, multi-factorial comprehensive disease. Gastric cancer cases can be divided into early- and advanced-stage gastric cancer. Early-stage gastric cancers are limited to the mucosa or submucosa, regardless of the size of the lesion and the presence of lymph node metastasis. Cancer that extends beyond the submucosa to invade the gastric muscular layer is middle gastric cancer, whereas tumors that infiltrate into or beyond the subserosa to nearby organs or metastasize are advanced gastric cancer. Advanced gastric cancers include intermediate and advanced tumors. The stage of the tumor determines the treatment effectiveness and treatment strategy. For example, early gastric cancer patients undergo radical surgery followed by chemotherapy, and the postoperative 5-year survival rate is 90%; therefore, the therapeutic effects of early gastric cancer are acceptable. However, the
detection rate is low because of the lack of specific signs of early gastric cancer, and therefore, most patients (>70%) develop advanced-stage disease. Some patients even lose the opportunity to undergo surgical resection. Metastatic potential may also exist in advanced gastric cancer, so the overall prognosis is poor. In recent years, a significant amount of research has been performed to improve the prognosis of patients with gastric cancer, and neoadjuvant chemotherapy, radiotherapy, and molecular-targeted therapies have become effective methods.

**Neoadjuvant chemotherapy**

A tumor is a systemic disease at an early stage. Therefore, the role of systemic chemotherapy has received attention. In addition to surgical resection and lymph node dissection, tumor recurrence and metastasis are more important than the presence of micrometastasis and the subsequent growth and proliferation. One of the reasons for the development of neoadjuvant chemotherapy for gastric cancer is the pursuit of individualized chemotherapy targets. Tumor resection can induce the production of tumor cell growth–stimulating factor, which makes tumor cells grow rapidly and produce anti-chemotherapy agents. In addition, if the number of tumor cells is low and the proliferation rate is high, the doubling time will be relatively short. In contrast, more advanced tumor cells with a low proliferation rate will have a prolonged doubling time and a decreased sensitivity to chemotherapeutic drugs. Therefore, a chemotherapy drug that does not target the cell cycle can reduce the tumor volume and improve the proliferation rate, thereby increasing the sensitivity to cell-cycle-specific chemotherapeutic drugs. Therefore, performing tumor resection before chemotherapy can not only kill the primary tumor but also inhibit cancer cell growth–stimulating factor.

Wilke et al. first reported the application of neoadjuvant chemotherapy for the treatment of gastric cancer. They reported the laparoscopic exploration of 34 cases of unresectable advanced gastric cancer, given etoposide, adriamycin, and cisplatin chemotherapy. Of these, 33 cases required a reoperation following cycles of postoperative chemotherapy; the remission rate was 70%. In 1994, Mai et al. reported 24 cases of advanced gastric cancer patients who were given a chemotherapy regimen with 5-fluorouracil (5-FU) + epirubicin + mitomycin (FAM) or mt/5-FU. Malignant ascites disappeared in 82% of the patients, 68% of the patients underwent radical resection, and the postoperative median survival time was 14 months. In 1997, Crookes et al. reported 56 cases of advanced gastric cancer who received preoperative chemotherapy with 5-FU + calcium folinate + cisplatin (FLP). In all, 40 patients received radical resection. There were five cases of complete remission, 12 cases were reduced to stage I, and 13 cases dropped to stage II. However, some other reports have suggested that neoadjuvant chemotherapy can improve the R0 resection rate and reduce tumor staging, but it had no obvious advantage on the long-term survival rate.

When considering neoadjuvant chemotherapy for gastric cancer, it is important not to pursue blindly the effectiveness of chemotherapy and delay the timing of surgery. Treatment and detection indicators should be reviewed regularly, and resection is the correct choice if the tumor size is reduced significantly. The use of chemotherapy drugs for gastric cancer is a dynamic process, and there is currently no uniform standard. Although patients with advanced gastric cancer with distant metastasis and peritoneal metastasis after neoadjuvant chemotherapy can experience a decreased tumor volume, the extensive metastasis and diffusion are not reversed and the tumor does not necessarily need surgery. Some patients with early-stage disease may have missed the chance to undergo surgery because of new adjuvant chemotherapy. Therefore, physicians should identify the indications according to the specific circumstances of each patient’s integrated condition to consider whether neoadjuvant chemotherapy is appropriate; delayed or excessive treatments must be avoided.

Gastric cancer is relatively sensitive to chemotherapy drugs, and neoadjuvant chemotherapy and surgery are equally important for treatment. Neoadjuvant chemotherapy is a new method for the treatment of advanced gastric cancer. There is no standard regarding how to select the agents used for adjuvant chemotherapy; the decision is based mainly on the results of computed tomography (CT), barium meal, the accurate application of a gastroscope, and even laparoscopic staging. The focal application of neoadjuvant chemotherapy can significantly reduce tumor staging, increase the surgical success rate, and prolong patient survival time. In cases of laparotomy for unresectable gastric cancer, neoadjuvant chemotherapy can make reoperation for complete tumor resection possible.

**Radiotherapy**

In recent years, radiation therapy in gastric cancer has received increased attention. Radiotherapy is being developed as a palliative treatment and adjuvant to neoadjuvant therapy for gastric cancer. Because of the anatomical and pathological morphology of gastric-specific applications, conventional radiotherapy using two-dimensional radiotherapy (2DRT) is restricted. In addition, the tolerance of the normal gastric mucosa and adjacent liver, small intestines, and other organs such as the kidneys is low. Gastric cancer is an adenocarcinoma, and a radiotherapy dose of 45–50.4 Gy can lead to serious adverse reactions. This has led to a strong requirement for the development of radiotherapy technology, particularly as related to precision, delineating the radiotherapy target area, and the formulation and
implementation of a radiotherapy plan. With radiotherapy for gastric cancer, uncertain factors such as changes in the body position during radiotherapy, the influence of diaphragmatic respiratory movements, and the change in gastric volume and gastrointestinal motility should be considered.

The palliative treatment of gastric cancer began in the 1960s, and the indications for palliative radiotherapy included a residual or unresectable tumor, local recurrence, and distant metastasis. Radiotherapy is well tolerated, and it successfully reduces the symptoms of patients with advanced gastric cancer (bleeding, obstruction, pain). Moertel et al. compared radiotherapy and 5-FU combined with radiotherapy for locally unresectable gastric cancer. The results showed that the median survival period was 5 years and that the combined treatment group had a significantly improved survival rate compared with the radiotherapy group. With the development of these new radiotherapy technologies, increasing attention has been paid to the role of radiotherapy in the treatment of gastric cancer.

Nam et al. retrospectively analyzed 291 gastrectomy patients after D2. Of these, 83 cases of irradiation included gastric remnant and 208 did not include gastric remnant. There were no significant differences in the 5-year overall survival (OS) and disease-free survival rates between groups, so the authors suggested that radiation should be excluded from the field of the gastric stump in patients with subtotal gastrectomy D2 after surgery. A meta-analysis of 13 studies including 2811 patients published by Ohri et al. revealed that radiotherapy with or without chemotherapy improved OS in patients with gastric cancer (hazard ratio (HR) = 0.78; 95% confidence interval (CI) = 0.70–0.86; \( p < 0.001 \)), which was consistent with previous meta-analyses.

**Molecular-targeted therapies**

In the past few decades, significant advances in cancer biology have led to the identification of key factors that contribute to tumorigenesis via novel pathways. Many molecular-targeted agents have exhibited significant antitumor activity in a variety of tumor types such as hematologic malignancies, colorectal cancer, breast cancer, renal cell carcinoma, and gastrointestinal stromal tumors. A variety of molecular pathways including cell growth, the cell cycle, apoptosis, angiogenesis, and invasion provide molecular targets for cancer treatment. These therapeutic strategies include epidermal growth factor receptor (EGFR) inhibitors, angiogenesis inhibitors, cell-cycle inhibitors, and matrix metalloproteinase (MMP) inhibitors (Figure 1).

**Adverse reactions of radiotherapy**

Although the continuous development of radiotherapy technology has reduced the volume and dose administered to the irradiated stomach, radiation-induced gastric injury is still inevitable. A gastroscopy is required in patients with poor appetite, indigestion, burning sensation, nausea and vomiting, upper abdominal pain, bleeding, and perforation. Radiotherapy may also damage the small intestine. Because the tolerance of small intestinal epithelial cells to radiation is low, acute intestinal mucosal congestion, edema, and even stripping can result in dehydration, electrolyte disorders, infection, bleeding, and even death. Radiation damage can affect patient’s quality of life, although most patients return to baseline scores after 6–12 months. Nevertheless, some patients still experience a reduced quality of life, and so, medical personnel should consider treatment interruption or dose reduction during acute reactions to improve the patient’s quality of life.

Perioperative radiotherapy effectively reduces the local recurrence rate in patients with gastric cancer and improves survival. For patients who cannot be guaranteed a negative margin and D2 radical resection, preoperative chemoradiotherapy can improve the rate of complete tumor removal or increase the chances of an operation. However, the lack of heart-related randomized controlled trials means that the preoperative value of radiotherapy still needs to be explored. Postoperative radiotherapy is necessary in D1 patients, as well as D2 patients and particularly those with stage III disease. In addition, palliative radiotherapy in the clear stage IV period of gastric cancer can further improve the curative effects and reduce treatment-related adverse reactions. In addition, although the screening of new individualized radiosensitivity markers will benefit patients with gastric cancer, future research should focus on the selection of suitable populations and combined treatments.

**EGFR-targeted therapy**

EGFR is a multifunctional receptor transmembrane glycoprotein and a member of the tyrosine kinase family of growth factor receptors. Epidermal growth factor (EGF) is the specific ligand of the EGFR, and it activates the receptor by binding and phosphorylating the tyrosine kinase receptor. Receptor activation stimulates a number of intracellular signal transduction pathways and thereby promotes tumor cell division, migration, and angiogenesis. Therefore, EGFR signal transduction can be targeted and blocked to inhibit tumor proliferation, invasion, and distant metastasis during the molecular-targeted treatment of gastric cancer. The main anti-EGFR therapeutic agents include anti-EGFR monoclonal antibodies and EGFR tyrosine kinase inhibitors (EGFR-TKI). Studies have shown that combination treatment with cetuximab and irinotecan, leucovorin, and 5-FU in advanced gastric cancer patients achieved an objective remission rate of 44%.
and a median time to disease progression (TTP) of 8 months. EGFR expression levels were not related to the curative effect. However, studies have shown that anti-EGFR monoclonal antibodies do not benefit patients.

Vascular endothelial growth factor–targeted therapy

Tumor growth has a clear vascular dependence; tumors grow new blood vessels to obtain nutrients from the host, which also enhances the ability of the tumor to metastasize to distant sites. In most solid tumors, angiogenesis, metastasis, and vascular formation are strongly related to the activity of the vascular endothelial growth factor (VEGF) pathway. Understanding this pathway is critical for the development of drugs targeting VEGF, including neutralizing antibodies targeting VEGF or its receptor (VEGFR) and targeted TKIs against VEGFR.

Bevacizumab is a recombinant humanized monoclonal antibody that acts by inhibiting VEGF. Bevacizumab combines with VEGF to block the activation of VEGFR, thus inhibiting tumor angiogenesis. Shah et al. assessed the effectiveness of bevacizumab and irinotecan combined with cisplatin for the treatment of advanced gastric cancer. Among 47 cases of untreated metastatic gastric or gastroesophageal junction cancer patients, the effective rate was 65%, and the median survival time was 12.3 months. The final histological evidence revealed a total remission rate of up to 75%.

Sunitinib is a tyrosine kinase inhibitor that targets VEGFR and inhibits the VEGFR, Raf, platelet-derived growth factor-beta receptor, fibroblast growth factor receptor, and c-KIT pathways. Sorafenib is a potent inhibitor of Raf and other receptor tyrosine kinase inhibitors in advanced gastric cancer. Sun et al. reported that sorafenib could inhibit the growth and angiogenesis of gastric carcinoma xenografts. When sorafenib was combined with cisplatin or docetaxel as a second-line treatment in 44 cases of advanced gastric cancer, the median progression-free survival (PFS) was 5.8 months and the median OS was 13.6 months.

Cell-cycle inhibitors

Abnormal cell-cycle regulation is closely related to cellular carcinogenesis. The expression and regulation of cyclin-dependent kinases (CDKs) play a key role in cell-cycle progression. Flavopiridol and its derivatives are small molecule inhibitors of CDKs. Flavopiridol is currently used in combination with standard chemotherapy to improve its efficacy. Motwani et al. demonstrated that flavopiridol could strengthen the inhibitory effects of docetaxel on tumor growth.

MMP inhibitors

MMPs play roles in many physiological and pathological processes such as inflammation, tissue fibrosis, angiogenesis, and
tumor invasion and metastasis.\textsuperscript{50} They can degrade the vascular basement membrane and extracellular matrix of endothelial cells, which leads to the shedding of endothelial cells from the vascular wall, angiogenesis, tumor growth, invasion, and metastasis.\textsuperscript{51} Therefore, inhibiting MMPs can inhibit tumor angiogenesis. Marimastat can inhibit MMP-1, -2, -7, -9, and -12 and thereby inhibit tumor growth, invasion, and metastasis. Kimata et al.\textsuperscript{52} administered marimastat to TMK-1 gastric cancer cells that had been injected intraperitoneally. Marimastat could decrease the peritoneal metastasis rate of the tumor cells and improve the survival rate and relieve peritoneal metastasis when combined with mitomycin C.

Like most solid tumors, the occurrence, development, and prognosis of gastric cancer depend on crosstalk between multiple complex targets and regulatory signaling pathways. In addition, tumor cells at different stages of differentiation exhibit obvious heterogeneity, including heterogeneity of drug target expression; therefore, the targeted treatment of a single pathway is often insufficient to prevent tumor progression. Currently, most targeted drugs affect only a single target; therefore, given that signal transduction mechanisms in cells are complex, multi-drug combinations that target multi-factorial cross-network systems will improve the efficiency and efficacy of antitumor therapy for gastric cancer.

Immunotherapy

Immunotherapy is a novel anticancer treatment that uses immune tumor vaccines or antitumor antibodies to activate the body’s own immune system against the cancer.\textsuperscript{53} The immune system can be used to identify and clear malignant tumors via immune surveillance to inhibit tumor development.\textsuperscript{54}

Inhibiting T-cell activity via the inhibitory signaling pathways involved with immunological detection points is an important mechanism by which tumor cells evade host-mediated immune recognition and killing. Therefore, immunoregulatory antibodies that target immune cell surface antigens block immunosuppressive signals and enhance immune cell activity representing a new direction in tumor therapy. The PD-1/PD-L1 and PD-L2 immune detection pathway is of great concern. PD-1 can be combined with PD-L1 and PD-L2 to inhibit the tumor microenvironment, tumor-specific T cell function, and immune surveillance function and promote tumor cell growth.\textsuperscript{55,56} De Guillebon et al.\textsuperscript{57} evaluated the efficacy and safety of the PD-1 monoclonal antibody pembrolizumab for the treatment of advanced gastric cancer. The results showed that the response rate was 33\%, the median response duration was 24 weeks, the 6-month PFS rate was 24\%, and the 6-month OS rate was 69\%.

Dendritic cells (DCs) are the most powerful antigen-presenting cells in the immune system and play a key role in initiating and regulating the immune response. Compared with normal gastric mucosa, the number of DCs in gastric cancer tissue is relatively low; the defective DC function inhibits the innate immunity and acquired immune response of Helicobacter pylori.\textsuperscript{58} Kanazawa et al.\textsuperscript{59} injected DC cells into two patients with advanced gastric cancer by endoscopic ultrasonography, and tumor markers and ascites were reduced in one of them.

Although immunotherapy is somewhat effective, there is a need for large-scale multicenter clinical trials to evaluate its efficacy. Newly discovered mechanisms of immune tolerance, antitumor immune mechanisms, and novel technologies and methods will allow us to overcome the barriers to immunotherapy in gastric carcinoma to make it a reliable and effective treatment.

Discussion

The preferred treatment for advanced gastric cancer is surgical operation.\textsuperscript{60,61} About some patients, with no chance to have surgical treatment, the ultimate goal of comprehensive treatment is to prolong survival and improve the quality of life.\textsuperscript{62,63} Although there are currently only a limited number of reports of neoadjuvant chemotherapy, targeted therapy, immunotherapy, and radiation therapy, the benefits of neoadjuvant chemotherapy in patients with gastric cancer cannot be ignored. The emergence of novel chemotherapy, targeted drugs, and progress in tumor molecular biology research will provide new opportunities for the comprehensive treatment of gastric cancer. At the same time, immune cell adoptive therapy, tumor vaccines, monoclonal antibodies, and combined immunoassay point inhibitors may have very broad treatment-related prospects. Therefore, new research and developments will make it possible to improve the treatment of advanced gastric cancer. Achieving a more reasonable, comprehensive, personalized diagnosis and treatment plan is critical for bringing the greatest clinical benefit to patients.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Frei E, 3rd. Clinical cancer research: an embattled species. Cancer 1982; 50: 1979–1992.
2. Lee HS, Kim WH, Kwak Y, et al. Molecular testing for gastrointestinal cancer. J Pathol Transl Med 2017; 51: 103–121.
3. Li B, Liu HY, Guo SH, et al. Detection of microsatellite instability in gastric cancer and dysplasia tissues. Int J Clin Exp Med 2015; 8: 21442–21447.
4. Sun Z, Wang Q, Yu X, et al. Risk factors associated with splenic hilar lymph node metastasis in patients with advanced gastric cancer in northwest China. *Int J Clin Exp Med* 2015; 8: 21358–21364.

5. Wu H, Wang W, Tong S, et al. Nucleostemin regulates proliferation and migration of gastric cancer and correlates with its malignancy. *Int J Clin Exp Med* 2015; 8: 17634–17643.

6. Yoshikawa T, Sato T, Yamada T, et al. Neoadjuvant chemotherapy for gastric cancer. *Gan To Kagaku Ryoho* 2016; 43: 1157–1160.

7. Chang AY, Foo KF, Koo WH, et al. Phase II study of neoadjuvant chemotherapy for locally advanced gastric cancer. *BMJ Open Gastroenterol* 2016; 3: e000095.

8. Lv X, Zhang L, Huang R, et al. A clinical exploration of neoadjuvant chemotherapy with tegafur, gimeracil, and oteracil potassium capsules combined with oxaliplatin for advanced gastric cancer. *Int J Clin Exp Med* 2015; 8: 19030–19036.

9. Chen Y, Guo ZQ, Shi CM, et al. Efficacy of adjuvant chemotherapy combined with immunotherapy with cytokine-induced killer cells for gastric cancer after d2 gastrectomy. *Int J Clin Exp Med* 2015; 8: 7728–7736.

10. Neves Filho EH, de Sant’Ana RO, Nunes LV, et al. Histopathological regression of gastric adenocarcinoma after neoadjuvant therapy: a critical review. *APMIS* 2017; 125: 79–84.

11. Funaki H, Fujii Y, Miura S, et al. Treatment outcomes of advanced gastric cancer after neoadjuvant chemotherapy with S-1 and cisplatin. *Gan To Kagaku Ryoho* 2016; 43: 1421–1423.

12. Wilke H, Preusser P, Fink U, et al. Preoperative chemotherapy in locally advanced and nonresectable gastric cancer: a phase II study with etoposide, doxorubicin, and cisplatin. *J Clin Oncol* 1989; 7: 1318–1326.

13. Mai M, Takahashi Y, Fujimoto T, et al. Neoadjuvant chemotherapy for far-advanced gastric carcinoma. *Gan To Kagaku Ryoho* 1994; 21: 431–439.

14. Crookes P, Leichman CG, Leichman L, et al. Systemic chemotherapy for gastric carcinoma followed by postoperative intraperitoneal therapy: a final report. *Cancer* 1997; 79: 1767–1775.

15. Gianni L, Panzini I, Tassini D, et al. Meta-analyses of randomized trials of adjuvant chemotherapy in gastric cancer. *Ann Oncol* 2001; 12: 1178–1180.

16. Schuhmacher CP, Fink U, Becker K, et al. Neoadjuvant therapy for patients with locally advanced gastric carcinoma with etoposide, doxorubicin, and cisplatinum. Closing results after 5 years of follow-up. *Cancer* 2001; 91: 918–927.

17. Mirza A, Pritchard S and Welch I. The postoperative component of MAGIC chemotherapy is associated with improved prognosis following surgical resection in gastric and gastrointestinal adenocarcinomas. *Int J Surg Oncol* 2013; 2013: 781742.

18. Kim JS, Kang SH, Moon HS, et al. Clinical outcome of doublet and triplet neoadjuvant chemotherapy for locally advanced gastric cancer. *Korean J Gastroenterol* 2016; 68: 245–252.

19. Verma V, Lin SH, Simone CB, 2nd, et al. Clinical outcomes and toxicities of proton radiotherapy for gastrointestinal neoplasms: a systematic review. *J Gastrointest Oncl* 2016; 7: 644–664.

20. Martin-Romano P, Sola JI, Diaz-Gonzalez JA, et al. Role of histological regression grade after two neoadjuvant approaches with or without radiotherapy in locally advanced gastric cancer. *Br J Cancer* 2016; 115: 655–663.

21. Moertel CG, Childs DS, Jr, Reitemeier RJ, et al. Combined 5-fluorouracil and supervalpoltage radiation therapy of locally unresectable gastrointestinal cancer. *Lancet* 1969; 2: 865–867.

22. Nam H, Lim DH, Kim S, et al. A new suggestion for the radiation target volume after a subtotal gastrectomy in patients with stomach cancer. *Int J Radiat Oncol Biol Phys* 2008; 71: 448–455.

23. Ohri N, Garg MK, Aparo S, et al. Who benefits from adjuvant radiation therapy for gastric cancer? A meta-analysis. *Int J Radiat Oncol Biol Phys* 2013; 86: 330–335.

24. Bae SH, Kim DW, Kim MS, et al. Radiotherapy for gastric mucosa-associated lymphoid tissue lymphoma: dosimetric comparison and risk assessment of solid secondary cancer. *Radiat Oncol J* 2017; 35: 78–89.

25. Ohkubo Y, Saito Y, Ushijima H, et al. Radiotherapy for localized gastric mucosa-associated lymphoid tissue lymphoma: long-term outcomes over 10 years. *J Radiat Res*. Epub ahead of print 10 January 2017. DOI: 10.1093/jrr/rrw044.

26. Gao P, Tsai C, Yang Y, et al. Intraoperative radiotherapy in gastric and esophageal cancer: meta-analysis of long-term outcomes and complications. *Minerva Med* 2017; 108: 74–83.

27. Shen Z, Li C, Zhang K, et al. The up-regulation of miR-300 in gastric cancer and its effects on cells malignancy. *Int J Clin Exp Med* 2013; 6: 6773–6783.

28. Zhang ZZ, Wang CJ, Niu L, et al. Analysis of plasma micro-RNAs to identifying early diagnostic molecule for gastric cancer. *Int J Clin Exp Med* 2015; 8: 3700–3706.

29. Chen G, Tang Y, Wu JH, et al. Role of microRNAs in diagnosis and treatment of the pathogenesis of gastric cancer. *Int J Clin Exp Med* 2014; 7: 5947–5957.

30. Wu Y, Li Z, Zhang C, et al. CD44 family proteins in gastric cancer: a meta-analysis and narrative review. *Int J Clin Exp Med* 2015; 8: 3595–3606.

31. Huang J, Yang Y, Yang J, et al. Regenerating gene family member 4 promotes growth and migration of cancer through protein kinase B pathway. *Int J Clin Exp Med* 2014; 7: 3037–3044.

32. Becker JC, Muller-Tidow C, Serve H, et al. Role of receptor tyrosine kinases in gastric cancer: new targets for a selective therapy. *World J Gastroenterol* 2006; 12: 3297–3305.

33. Johnston JB, Navaratnam S, Pitz MW, et al. Targeting the EGFR pathway for cancer therapy. *Curr Med Chem* 2006; 13: 3483–3492.

34. Arteaga CL. Overview of epidermal growth factor receptor biology and its role as a therapeutic target in human neoplasia. *Semin Oncol* 2002; 29: 3–9.

35. Krozely P. Epidermal growth factor receptor tyrosine kinase inhibitors: evolving role in the treatment of solid tumors. *Clin Oncol Nurs* 2004; 8: 163–168.

36. Lordick F, Luber B, Lorenzen S, et al. Cetuximab plus oxaliplatin/leucovorin/5-fluorouracil in first-line metastatic gastric cancer: a phase II study of the Arbeitsgemeinschaft Internistische Onkologie (AlO). *Br J Cancer* 2010; 102: 500–505.

37. Waddell T, Chau I, Cunningham D, et al. Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for
patients with previously untreated advanced oesophago-gastric cancer (REAL3): a randomised, open-label phase 3 trial. *Lancet Oncol* 2013; 14: 481–489.

38. Hsu JT, Chen TD, Chung HC, et al. Vascular endothelial growth factor expression is an independent poor prognostic factor for human epidermal growth factor receptor 2 positive gastric cancer. *J Surg Res* 2017; 208: 40–50.

39. Lin Y, Zhai E, Liao B, et al. Autocrine VEGF signaling promotes cell proliferation through a PLC-dependent pathway and modulates Apatinib treatment efficacy in gastric cancer. *Oncotarget* 2017; 8: 11990–12002.

40. Lv Y, Song L, Chang L, et al. Bevacizumab followed by chemotherapy is potential therapy for gastric cancer. *J BUON* 2016; 21: 1466–1470.

41. Shah MA, Ramanathan RK, Ilson DH, et al. Multicenter phase II study of irinotecan, cisplatin, and bevacizumab in patients with metastatic gastric or gastroesophageal junction adenocarcinoma. *J Clin Oncol* 2006; 24: 5201–5206.

42. Ohtsu A, Shah MA, Van Cutsem E, et al. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a randomized, double-blind, placebo-controlled phase III study. *J Clin Oncol* 2011; 29: 3968–3976.

43. Moehler M, Mueller A, Hartmann JT, et al. An open-label, multicentre biomarker-oriented AIO phase II trial of sunitinib for patients with chemo-refractory advanced gastric cancer. *Eur J Cancer* 2011; 47: 1511–1520.

44. Sun W, 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 Clin Oncol* 2010; 28: 2947–2951.

45. Kumari S, Puneet Prasad SB, Yadav SS, et al. Cyclin D1 and cyclin E2 are differentially expressed in gastric cancer. *Med Oncol* 2016; 33: 40.

46. Mikhail S, Albanese C and Pishvaian MJ. Cyclin-dependent kinase inhibitors and the treatment of gastrointestinal cancers. *Am J Pathol* 2015; 185: 1185–1197.

47. Jung CP, Motwani MV and Schwartz GK. Flavopiridol increases sensitization to gemcitabine in human gastrointestinal cancer cell lines and correlates with down-regulation of ribonucleotide reductase M2 subunit. *Clin Cancer Res* 2001; 7: 2527–2536.

48. Jung C, Motwani M, Kortmansky J, et al. The cyclin-dependent kinase inhibitor flavopiridol potentiates gamma-irradiation-induced apoptosis in colon and gastric cancer cells. *Clin Cancer Res* 2003; 9: 6052–6061.

49. Motwani M, Rizzo C, Sirotnak F, et al. Flavopiridol enhances the effect of docetaxel in vitro and in vivo in human gastric cancer cells. *Mol Cancer Ther* 2003; 2: 549–555.

50. Huang H, Wu K, Ma J, et al. Dopamine D2 receptor suppresses gastric cancer cell invasion and migration via inhibition of EGFR/AKT/MMP-13 pathway. *Int Immunopharmacol* 2016; 39: 113–120.

51. Peng Z and Zhang Y. Propofol inhibits proliferation and accelerates apoptosis of human gastric cancer cells by regulation of microRNA-451 and MMP-2 expression. *Genet Mol Res* 2016; 15: 1–9.

52. Kimata M, Otani Y, Kubota T, et al. Matrix metalloproteinase inhibitor, marimastat, decreases peritoneal spread of gastric carcinoma in nude mice. *Jpn J Cancer Res* 2002; 93: 834–841.

53. Li Y, Wang C, Xu M, et al. Preoperative NLR for predicting survival rate after radical resection combined with adjuvant immunotherapy with CIK and postoperative chemotherapy in gastric cancer. *J Cancer Res Clin Oncol* 2017; 143: 861–871.

54. Cai XY, Wang XF, Li J, et al. High expression of CD39 in gastric cancer reduces patient outcome following radical resection. *Oncol Lett* 2016; 12: 4080–4086.

55. Tang W, Chen Y, Chen S, et al. Programmed death-1 (PD-1) polymorphism is associated with gastric cardia adenocarcinoma. *Int J Clin Exp Med* 2015; 8: 8086–8093.

56. Li J, Chen L, Xiong Y, et al. Knockdown of PD-L1 in human gastric cancer cells inhibits tumor progression and improves the cytotoxic sensitivity to CIK therapy. *Cell Physiol Biochem* 2017; 41: 907–920.

57. De Guillebon E, Roussille P, Frouin E, et al. Anti program death-1/anti program death-ligand 1 in digestive cancers. *World J Gastrointest Oncol* 2015; 7: 95–101.

58. Chang LL, Wang SW, Wu IC, et al. Impaired dendritic cell maturation and IL-10 production following H.pylori stimulation in gastric cancer patients. *Appl Microbiol Biotechnol* 2012; 96: 211–220.

59. Kanazawa M, Yoshihara K, Abe H, et al. Case report on intra-tumor injection therapy of dendritic cells in advanced gastric cancer. *Gan To Kagaku Ryoho* 2004; 31: 1773–1776.

60. He W, Tu J, Huo Z, et al. Surgical interventions for gastric cancer: a review of systematic reviews. *Int J Clin Exp Med* 2015; 8: 13657–13669.

61. Tang HN and Hu JH. A comparison of surgical procedures and postoperative cares for minimally invasive laparoscopic gastrectomy and open gastrectomy in gastric cancer. *J Int Clin Exp Med* 2015; 8: 10321–10329.

62. Canyilmaz E, Soydemir G, Serdar L, et al. Evaluation of prognostic factors and survival results in gastric carcinoma: single center experience from Northeast Turkey. *Int J Clin Exp Med* 2014; 7: 2656–2666.

63. Lordick F and Terashima M. Gastric cancer adjuvant therapy. *Best Pract Res Clin Gastroenterol* 2016; 30: 581–591.