Progress in chemotherapy for advanced gastric cancer

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[Abstract] With the rapid development in cytotoxic agents and molecular targeting drugs, some progress in palliative chemotherapy for advanced gastric cancer has been achieved and the median survival of advanced gastric cancer patients is prolonged to about one year. In this review, we summarized the application of new agents, such as docetaxel, paclitaxel, oxaliplatin, irinotecan, capecitabine, S1 and targeting drugs in the treatment of patients with advanced gastric cancer. We focused on the results of phase III clinical trials and concluded that till now no standard regimens for the treatment of advanced gastric cancer are available. New combination regimens such as docetaxel-cisplatin-fluorouracil (DCF), epirubicin-oxaliplatin-capecitabine (EOX), fluorouracil-leucovorine-oxaliplatin (FLO), irinotecan, leucovorin and 5-FU (ILF), cisplatin plus xeloda, S1 plus cisplatin are considered as new options for the first-line chemotherapy of advanced gastric cancer. Due to uncertain efficacy and safety concerns, the role of molecular targeting agents in the treatment of advanced gastric cancer needs further investigation. It is suggested that neoadjuvant chemotherapy is a suitable choice for locally advanced gastric cancer.

Key words: advanced gastric cancer, chemotherapy

Gastric cancer is one of the most common tumors in human being. Although the incidence and mortality of gastric cancer have decreased significantly over the past 70 years,¹ it remains the fourth most common tumor and the second common cause for tumor–related death around the world.² There are 603,003 new cases of male patients and 330,290 new cases of female patients in the world each year. The five–year relative survival rate in most regions is about 20%, though it is up to 60% in Japan due to the practice of extensive early screening and treatment.³ Surgery is still the major therapy to treat gastric cancer, while chemotherapy and radiation therapy are also important treatments for gastric cancer. In addition, new treatments including biological therapy and gene therapy and so on are under development currently. This review analyzed and discussed progress in treatments for advanced gastric cancer.

Advanced gastric cancer refers to gastric cancers that cannot be resected or that recur postoperatively, including locally advanced unresectable gastric cancer (accounting for 30% of all gastric cancers) and metastasized gastric cancer at the time of diagnosis (accounting for 30% of all gastric cancers), as well as recurred gastric cancer after resection (gastric cancer has a 60% of recurrent rate). As a result, nearly 80% of patients will eventually progress into advanced gastric cancer. Several previous clinical trials⁴–⁷ showed that without chemotherapy, the
median survival time of advanced gastric cancer was only 3–4 months. Currently, chemotherapy can increase the median survival time to up to one year, which can also improve the life quality of the patients. However, the overall prognosis of advanced gastric cancer is still poor.

Chemotherapy for advanced gastric cancer began in the 1960s and 70s, and effective monotherapy drugs include: fluorouracil, cisplatin, anthracycline drugs (doxorubicin and epirubicin), mitomycin–c and etoposide etc. However, these monotherapy drugs have low efficiency and poor efficacy. To enhance the efficacy for the treatment of advanced gastric cancer, clinicians usually combine two or three drugs in chemotherapy. In this review, we introduced the history and current status of drug combination regimens using older generation of drugs before 2000 and newer generation of drugs after 2000 (including targeting drugs) in the treatment of advanced gastric cancer (mainly phase III clinical trials). In addition, we summarized special chemotherapy strategies for locally advanced unresectable gastric cancer.

Combination regimens using older generation of drugs before 2000

Non–platinum regimens. Fluorouracil is a classic drug for gastrointestinal cancer and has been used to treat gastric cancer since the 1960s. Between 1970s and 1980s, fluorouracil–based combination regimens were developed, among which the extensively studied ones include fluorouracil, adriamycin plus mitomycin C (FAM), etoposide, leucovorin plus fluorouracil (ELF) and fluorouracil, adriamycin plus methotrexate (FAMTX). However, the efficacies of all three regimens are relatively low. Especially for FAM and ELF, the efficacies are less than 10%, with a median survival time of about 7 months. The efficacy of FAMTX is 12%–41%, with a median survival time of about 10 months. In 1991, JCO published the result of an EORTC phase III clinical trial, showing that FAMTX regimen had higher efficacy (41% vs. 9%, \( P < 0.0001 \)) and survival time (42w vs. 29w, \( P=0.004 \)) than FAM. Therefore, FAMTX was recommended by many researchers as the standard regimen at that time.

Combination regimens using newer generation of chemotherapeutic drugs after 2000. Although combination regimens using the above older generation of drugs were effective in 20%–40% of patients with advanced gastric cancer, the effective period was short and the complete remission (CR) was less than 5%, with the median time to disease progression of 4–5 months and median survival time of no more than 7–10 months. In recent years, a number of new drugs such as taxane drugs (docetaxel, paclitaxel), irinotecan, oxaliplatin, oral fluorouracil drugs (capecitabine, S1 and UFT) and targeting drugs have been developed and new combination regimens are under investigation. As a result, improved efficacy might be achieved in the future.

**Docetaxel.** Currently, the most important study to explore the effect of docetaxel regimen as first–line option in the treatment of advanced gastric cancer is the V–325 trial (also known as the TAx325 trial). Study design of V–325 consists of two parts, a phase II randomized study and a phase III trial. In the phase II study, docetaxel, cisplatin (DC) and docetaxel + cisplatin +5–fluorouracil (DCF) were compared, aiming to select the more effective regimen to enter phase III trial. A total of 155 patients were included in the study and results showed that the efficacy, time to disease progression (TTP) and overall survival (OS) of these two groups were 26% vs. 43%, 5.0 vs. 5.9 months and 10.5 vs. 9.6 months, respectively. Therefore, DCF was chosen to enter the phase III trial. In the phase III clinical trial\(^2\) (i.e., the TAX325 trial), a total of 457 patients were randomly divided into two groups using either DCF or CF as their first–line treatment. Results showed that TTP and OS of DCF group were better than those of CF Group (5.6 months vs. 3.7 months, \( P=0.0004 \); 9.2 months vs. 8.6 months, \( P=0.02 \); 18% 2–year survival rate in DCF group vs. 9% in CF Group). In addition, the OR of DCF was higher than that of CF group (37% vs. 25%, \( P=0.01 \)), and the life quality of the patients in DCF group was also better than these in the CF group. However, as for the toxic effects, incidence rate of grade 3–4 agranulocytosis was as high as 82.3% and incidence of fever caused by agranulocytic infection was as high as 30% in DCF group, which were significantly higher than that of CF group. Based on these results above, DCF could be used as a new standard regimen, but adverse reactions should be carefully monitored.

**Irinotecan.** The most important clinical trial to assess Irinotecan combination regimen as a first–line regimen to treat advanced gastric cancer drug is the V–306 trial. Similar to V–325, V–306 trial was divided
into two parts, phase II and phase III trials. The phase II trial compared IC regimen (irinotecan and cisplatin) and ILF regimen (irinotecan, fluorouracil and leucovorin). A total of 146 patients were included in the study and OR. TTP and OS of the two regimens were 26% vs. 34%, 4.5 vs. 6.5 months and 6.9 vs. 10.7 months, respectively, both with tolerable toxicity. Therefore, ILF regimen was chosen to enter the phase III trial. The phase III trial compared ILF and CF regimens. Totally 337 enrolled patients were randomly divided into two groups. Results showed that ILF tended to increase the TTP (5m median TTP in ILF Group vs. 4.2 months in CF group, P=0.08) and OR more in the ILF group than in the CF group (32% vs. 26%) but not to a statistically different level, while these two groups had similar median survival times (9m in ILF group vs. 8.7m in CF group, P = 0.53). The overall severe toxicity was lower in ILF group. For example, less bone marrow suppression and kidney damage were seen in ILF group, but diarrhea happened more often in ILF group than in CF group. Therefore, it is believed that regimen containing CPT-11 could be used as an alternative to CF. Bouche O et al. reported a phase II clinical trial to compare FOLFIRI (irinotecan, leucovorin and fluorouracil) with LF (Leucovorin and fluorouracil) or CLF (cisplatin, leucovorin and fluorouracil). Results showed that OR rate, TTP and OS of FOLFIRI were better than that of LF or CLF. Therefore, the authors suggested that FOLFIRI should be entered into phase III clinical trial.

Oxaliplatin. Currently, the most interesting study on oxaliplatin combination regimen as the first–line treatment of advanced gastric cancer is the phase III REAL–2 trial reported in ASCO–06. This study used ECF as the control, and the experimental group used oxaliplatin to replace cisplatin and capecitabine to replace 5-fluorouracil. The endpoint assay of this study was the overall survival time non-inferiority, including four groups: ECF, EOX (epirubicin, oxaliplatin and fluorouracil), ECX (epirubicin, cisplatin and capecitabine) and EOX (epirubicin, oxaliplatin and capecitabine). A total of 1,002 patients were recruited into the study, 77% of metastasized and 34% of primary cancers at gastroesophageal junction, with a median age of 63 years. The main goal of this trial is to compare the survival time between these groups. Results showed that regimens containing oxaliplatin or capecitabine both had the potential to extend the overall survival time of the patients, as compared with regimens containing cisplatin or 5–fluorouracil (EOF + EOX vs. ECF + ECX: HR 0.91, CI 95% 0.79–1.04, P=0.15; ECX + EOX vs. ECF + EOX: HR 0.88, CI 95% 0.77–1.00, P=0.05). Compared with ECF, EOX increased the overall survival time significantly (median OS 11.2m vs. 9.9m; HR: 0.8; 95% CI: 0.66–0.97, P=0.02). As for the efficacy, no significant difference was detected among these four groups (ECF 41%, EOX 42%, ECX 46% and EOX 50%). Grade 3–4 neutropenia (ECF: 30%, EOX 28% vs. ECF41%, ECX 51%) and thromboembolism (ECF: 8%, EOX 8% vs. ECF 18%, ECX 15%) were less frequent in oxaliplatin–containing group, while grade 3–4 diarrhea (ECF: 11%, EOX 12% vs. ECF 3%, ECX 5%) and grade 3–4 peripheral neurotoxicity (ECF: 8%, EOX 4% vs. ECF 0.4%, ECX 2%) were more rare in platinum–group. So the authors believed that oxaliplatin could replace cisplatin and capecitabine could substitute fluorouracil. They suggested using EOX as a new standard regimen. Another phase III trial was reported in ASCO –06. A total of 220 patients with advanced gastric cancer (95% of metastatic, 21% of primary cancer at gastroesophageal junction) were randomly divided into FLC group (fluorouracil, leucovorin and cisplatin) or FLO group (fluorouracil, leucovorin and oxaliplatin). Results showed that TTP tended to increase in FLO group (median TTP 5.7 months vs. 3.8 months, log–rank P=0.08; HR 0.8, 95% CI 0.58–1.09), and FLO regimen was more efficient than FLC regimen (34% vs. 25%). The differences were statistically significant. In addition, since the overall toxicity of FLO regimen seemed to be lower, the authors suggested using FLO as an alternative to FLC.

Paclitaxel. At present, there is no report of phase III trials using paclitaxel combination regimen as the first–line treatment for advanced gastric cancer. Some phase II trials on paclitaxel combination regimen as the first–line chemotherapy regimen have been published (Table 1).

Capecitabine. Given the convenience to use capecitabine, many studies tested the possibility for it to replace intravenous 5–FU. Two important phase III clinical trials were recently published and results showed the non–inferiority of capecitabine compared with continuous intravenous infusion of 5–FU. One study is the above–mentioned REAL–2 trial, showing that the efficacy of capecitabine combination (ECX + EOX) was not significantly different from that of the
5-fluorouracil combination (ECF + EOF), and the overall survival time of the former was non-inferior to the latter regimen (10.9m vs. 9.6m, HR=0.86, 95% CI: 0.8–0.99). Another phase III clinical study20 (ML17032 trial) compared cisplatin + capecitabine regimen with cisplatin + fluorouracil continuous infusion regimen, which was also a non-inferiority trial of the first regimen to the second regimen. The results found that the first regimen had a tendency to improve PFS (HR: 0.8; 95% CI: 0.63–1.03; P=0.08) and OS (HR: 0.85; 95% CI: 0.64–1.13), and it had higher efficacy but similar toxicity than the latter (41% vs. 29%, P=0.03). These above results suggest that the efficacy of capecitabine is non-inferior to continuous intravenous 5-FU in the treatment of gastric cancer. Plus its good tolerability, oral administrability and shortened hospitalization time, it can replace fluorouracil as chemotherapy for advanced gastric cancer.

**5-FU**

**S-1** is an oral 5-FU precursor developed in Japan. Recent studies showed that S-1 is a promising new generation of oral fluorouracil drug. In 2007, Boku et al. reported the JCOG9912 trial27. A total of 704 patients were randomly divided into three groups including 5-FU monotherapy group, S-1 monotherapy group and CP group (irinotecan + cisplatin). Results showed that the efficacies of S-1 monotherapy group and CP group were significantly higher than that of 5-FU monotherapy group (9% in 5-FU group vs. 28% in S-1 group vs. 38% in CP group), and the median PFS was 2.9m in 5-FU group, 4.2m in CP group and 4.8m in S-1 group.

Grade 4 neutropenia was less frequent in 5-FU/CP/S-1 group, and the median survival time (MST) was 10.8 months/11.4 months/12.3 months, respectively, suggesting that S-1 is superior to 5-FU. In 2007, Narahara et al. also reported the SPIRITS trial.30 A total of 305 enrolled patients were randomly divided into S-1 monotherapy group and S-1 + DDP group, and results showed that the MST in S-1 group was 11m while that of S1 + DDP group was 13m, suggesting the superiority of S1 + DDP regimen to S1 monotherapy (log-rank P=0.0366, hazard ratio: 0.774, 95% CI: 0.608 – 0.985). Efficacies of the two groups were 31.1% (S-1 monotherapy group) and 54.0% (S1 + DDP group), respectively. Comparing toxicity of the two groups, the most common grade 3/4 toxicities were: leukopenia 2.0% vs. 11.5%, neutropenia 10.7% vs. 39.9%, anemia 4.0% vs. 25.7%, nausea 1.3% vs. 11.5% and anorexia 6.0% vs. 30.4%. No treatment-related death was found in both groups. So the conclusion of this trial was that the overall survival of S-1 and DDP combination to treat advanced gastric cancer was superior to that of S-1 monotherapy, and this regimen was both effective and well tolerated. At present, S-1 + DDP regimen has become a standard regimen to treat advanced gastric cancer in Japan.

A large-scale multi-center (including 23 countries) phase III clinical trial (the FLAGS trial) to compare S-1 + DDP and CF regimens has completed the process of subject recruiting. Although no result has been published yet, the phase III trial to assess the safety and efficacy of this regimen had been reported at ASCO in 2006. This phase II trial preliminarily showed that S-1 + DDP regimen had higher efficacy and lower toxicity, so we are looking forward for the final results of the phase III trial.

**Targeting drug**. Targeting drug is one of the hot studies in recent years. Given limited effectiveness of chemotherapeutic drugs for gastric cancer, many researchers seek combination regimens containing targeting drugs and hope for a better efficacy. Currently, many targeting drugs have been applied in studies of gastric cancer, including small molecule

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**Table 1** Regimens containing taxanes as the first-line treatment for advanced gastric cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (%)</th>
<th>TTP (months)</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yamaguchi (T)</td>
<td>40.0</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Grujitzer (T oral)</td>
<td>33.0</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>Gadgle (T-CBDP)</td>
<td>33.0</td>
<td>4.9</td>
<td>7.5</td>
</tr>
<tr>
<td>Korek (T-DDP)</td>
<td>44.0</td>
<td>7.0</td>
<td>11.2</td>
</tr>
<tr>
<td>Honecker</td>
<td>48.0</td>
<td>8.0</td>
<td>11.0</td>
</tr>
<tr>
<td>(T-DDP-5-FU/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kollmannsberger</td>
<td>51.0</td>
<td>9.0</td>
<td>14</td>
</tr>
<tr>
<td>(T-DDP-5-FU/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kang (T-X)</td>
<td>48.9</td>
<td>5.6</td>
<td>11.3</td>
</tr>
<tr>
<td>Park</td>
<td>41.0 vs. 30.0</td>
<td>4.8 vs. 4.5</td>
<td>11.9 vs. 9.2</td>
</tr>
</tbody>
</table>

OR: objective response; TTP: time to progression; OS: overall survival; T: paclitaxel; CBDP: carboplatin; DDP: cisplatin; 5-FU/L: 5-fluouracil / leucovorin; X: capecitabine, D: docetaxel.
Table 2  Phase II clinical studies integrating drugs directed against new therapeutic targets in first or second line treatment in advanced gastric cancer

<table>
<thead>
<tr>
<th>Regimen</th>
<th>First line/second line</th>
<th>OR (%)</th>
<th>TTP (months)</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-CDDP-Beva</td>
<td>First line</td>
<td>65.0</td>
<td>8.3</td>
<td>12.3</td>
</tr>
<tr>
<td>Doc-Beva</td>
<td>Second line; 80%</td>
<td>27.0</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>FOLFIRI-Getux</td>
<td>First line</td>
<td>44.0</td>
<td>8.0</td>
<td>16.0</td>
</tr>
<tr>
<td>FUFOX-Getux</td>
<td>First line</td>
<td>65.2</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Ir-Getux</td>
<td>Second line</td>
<td>13.0</td>
<td>2.5</td>
<td>3.5</td>
</tr>
<tr>
<td>Getinib</td>
<td>Second line</td>
<td>15.0</td>
<td>–</td>
<td>5.5</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>Second line</td>
<td>11.0</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor Gefitinib (Iressa) and Erlotinib (Tarceva) that were effective in lung cancers, anti-EGFR monoclonal antibody Cetuximab (Erbitux) and anti-vascular endothelial growth factor (VEGF) receptor monoclonal antibody Bevacizumab (Avastin) that were effective in the chemotherapy of colon cancer, and anti-HER2 monoclonal antibody Trastuzumab (Herceptin) that was effective for breast cancer. The table below (Table 2) listed a series of phase II research results in recent years. As shown in the table, some regimens have achieved high efficiency and survival rate. However, the number of cases included in these trials was relatively small, so the conclusion is not yet clear, and their efficacy, safety and ultimate benefits still need to be further studied. Currently, a phase III clinical trial on Bevacizumab combination regimen is in progress. In addition, another phase III clinical trial receiving broad attention is the TOGA trial. This study recruited advanced gastric cancer patients with over – expressed HER2 receptor. Patients in the experimental group were treated with XP regimen or FP regimen plus Herceptin, while the control group was treated with XP or FP regimens alone. The main endpoint assay of this study was the overall survival. Currently, subject recruitment has been completed. Since Herceptin showed good efficacy for breast cancer, we expect that the TOGA trial should also lead to a breakthrough in the chemotherapy of gastric cancer.

Chemotherapy for locally advanced gastric cancer

Locally advanced gastric cancers include gastric cancers with deeper tumor penetration, larger local tumor size or unresectable tumor due to extensive adhesion with surrounding tissues, i.e., T stage and later N stage tumors. Previously, patients with these cancers received only palliative treatments once the tumor became unresectable. Since the introduction of neoadjuvant chemotherapy, prognosis of these patients has been improved. Neoadjuvant chemotherapy has several advantages. First of all, it is believed that neo – adjuvant chemotherapy is effective for patients at advanced T and N stages, since it can lower the staging of tumor and increase the resectable rate. Secondly, patients with locally advanced gastric cancer may also have distant micrometastases. If surgical strategy were used first, the metastasis often could not be timely treated for a few weeks and therefore could interfere with the post – operative treatments. Preoperative chemotherapy could help this situation. Third, neo–adjuvant chemotherapy may improve chemotherapy tolerability of the patients, since postoperative adjuvant chemotherapy may cause severe toxic reactions due to high energy consumption and complications. Sometimes even the chemotherapy cannot be completed. In addition, neoadjuvant chemotherapy can test the responsiveness of patients to the drug, and therefore is beneficial for the choice of drugs in postoperative regimen. In 2005, Cunningham et al. reported the results of MAGIC trial, which was published in the New England Journal of Medicine in 2006. This study is a stringently designed, randomized, controlled phase III clinical trial. 503 recruited patients were randomly divided into surgery alone and treatment groups. The treatment group received 3 courses of ECF regimen before and after the surgery. Results showed that the treatment group had higher rate of T1 and T2 tumors (51.7% vs. 36.8%) than the surgery alone group in postoperative pathological test. In addition, the 5–year survival rate of the treatment group was about 13% (36% vs. 23%) higher than the surgery alone group. Since some patients failed to cooperate, only 42% of patients in the treatment group completed postoperative ECF adjuvant chemotherapy. So the results of MAGIC trial primarily reflect the efficacy of preoperative chemotherapy. In addition, preoperative chemotherapy could decrease diameter of the tumor and depth of invasion, as well as improve lymph node status, and therefore achieve the effect of tumor...
downgrading. However, the complication and mortality rates of the treatment group were similar to that of the surgery alone group.

Since neoadjuvant chemotherapy (preoperative chemotherapy) allows conversion of some unresectable tumors to resectable tumors, so to achieve a potential radical cure, chemotherapy for these patients is different from that for patients with metastasized advanced gastric cancer. Chemotherapy for metastasized advanced gastric cancer is mainly palliative chemotherapy, focusing on improving life quality and prolonging survival. So the dose of chemotherapy should not be too high to avoid serious toxicity. On the contrary, the purpose of neoadjuvant chemotherapy is to improve the resection rate, and eventually aiming at a complete cure. So regimens for neoadjuvant chemotherapy usually combine two or three drugs, and adequate dose should be used. Currently, clinical trials on various regimens of neoadjuvant chemotherapy are ongoing and we expect more ideal results.

Summary and prospects for chemotherapies of advanced gastric cancer

The chemotherapeutic results for advanced gastric cancer are not satisfactory so far. Older generation of chemotherapy is only effective in 20%–40% patients with advanced gastric cancer and the effective time is short, with a median survival time of no more than 7–10 months. When combination regimens containing docetaxel, irinotecan, oxaliplatin, paclitaxel, capecitabine and S-1 and so on were used, efficacy was usually improved, with a median survival time of up to 1 year. From the existing phase III clinical trial results, we concluded that some new combination regimens such as DCF regimen containing docetaxel, EOX and FLO regimens containing oxaliplatin, EOX regimen including capecitabine, cisplatin + xeloda, ILF regimen containing irinotecan and S1 + DDP regimen could be used as the first-line treatment of advanced gastric cancer. Currently, there have been no experimental results to compare between these above regimens, so new studies are needed, particularly on treatment with combination of targeting drugs.

However, even with these above new drug combination regimens or combined targeting drugs, improvement of gastric cancer survival is still very marginal, but the economic cost is huge. Taking into account the economic situation in China, we should consider both the cost and efficacy of cancer treatment, i.e., at equivalent efficacy and toxicity, we should choose the more economical regimen, for example the CF regimen. In addition, since the prognosis of advanced gastric cancer is still poor, we encourage patients to participate in well-designed clinical trials to explore new treatment. We also hope that future trials could combine the biological prognosis of gastric cancer and prediction factors, in order to choose the optimal regimen for individual patient. As a result, implementation of individualized treatment should greatly enhance the efficacy of the treatment.

References


