

New perspectives in the treatment of advanced or metastatic gastric cancer

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Abstract

Metastatic gastric cancer remains an incurable disease, with a relative 5-year survival rate of 7%-27%. Chemotherapy, which improves overall survival (OS) and quality of life, is the main treatment option. Meta-analysis has demonstrated that the best survival results obtained in earlier randomized studies were achieved with three-drug regimens containing a fluoropyrimidine, an anthracycline, and cisplatin (ECF). Although there has been little progress in improving median OS times beyond the 9-mo plateau achievable with the standard regimens, the availability of newer agents has provided some measure of optimism. A number of new combinations incorporating docetaxel, oxaliplatin, capecitabine, and S-1 have been explored in randomized trials. Some combinations, such as epirubicin-oxaliplatin-capecitabine, have been shown to be as effective as (or perhaps more effective than) ECF, and promising early data have been derived for S-1 in combination with cisplatin. One factor that might contribute to extending median OS is the advancement whenever possible to second-line cytotoxic treatments. However, the biggest hope for significant survival advances in the near future would be the combination of new targeted biological agents with existing chemotherapy first-line regimens.

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INTRODUCTION

Gastric cancer is the fourth most common cancer worldwide, with about 700 000 confirmed deaths annually. Despite an overall global decrease in incidence, gastric cancer is more prevalent in east Asia, eastern Europe, and central and south America than in other countries^[1,2].

Chemotherapy is the main treatment option for patients with advanced disease. Median overall survival (OS) of 8-12 mo has been reported in patients undergoing chemotherapy compared with 3-5 mo for those treated with best supportive care^[3]. Several drugs have shown good single-agent activity. The response rates range from 10% to 25% and the median duration of response is relatively short. Fluorouracil (5-FU), cisplatin, docetaxel, and, less commonly, paclitaxel, epirubicin, and irinotecan are major components of conventional regimens. Oxaliplatin, capecitabine, S-1, and UFT are also being used in combination chemotherapy. To date, although a large number of trials have been performed, there is no standard treatment for advanced disease.

Intravenous 5-FU remains the most widely used agent and has been the cornerstone of old combination regimens such as FAM (5-FU, doxorubicin, and mitomycin C), FAMTX (5-FU, doxorubicin, and methotrexate), ELF (etoposide, leucovorin, and 5-FU), and ECF (epirubicin, cisplatin, and continuous infusion 5-FU). Although these regimens yield overall response rates (ORRs) of up to 51%, the median survival time in patients with advanced disease has remained irredeemably below 10 mo^[4]. Evidently, there is a clear need for more active new agents and regimens.

Combination chemotherapy has been shown to be associated with a statistically significant ($P = 0.001$) survival benefit compared with monotherapy in a meta-analysis of several clinical trials^[5]. This corresponded to a small but clinically relevant 1-mo mean average survival benefit. This meta-analysis also evaluated the role of anthracyclines as part of combination chemotherapy. The authors found that including anthracyclines in a 5-FU-cisplatin combination had a modest advantage

over cisplatin-5-FU alone (HR 0.77). Finally, the meta-analysis also showed that three-drug combinations have a significant survival benefit compared with two-drug combinations.

In this context, Van Cutsem *et al*^[6] have performed a large-scale random assignment trial comparing the docetaxel, cisplatin, 5-FU (DCF) combination to a control arm of cisplatin plus 5-FU alone (the TAX325 trial). The primary end point of the study was time to progression (TTP) and it was powered to detect an increase in median TTP from 4 mo to 6 mo. The two arms of the study were well balanced for the usual prognostic factors, including weight loss, performance status (PS), and extent of disease. The median TTP was 3.7 mo for patients receiving cisplatin-5-FU, and 5.6 mo for those receiving DCF (HR 1.47; $P = 0.0004$). As a secondary end point, survival was also modestly increased from 8.6 mo for cisplatin-5-FU to 9.2 mo for DCF. The 2-year survival rate was, however, more than doubled for DCF (8.8% for cisplatin-5-FU and 18.4% for DCF). Another measure of efficacy favoring DCF was response rate (37% for DCF, 25% for cisplatin-5-FU). Although this study indicated an efficacy advantage for the three drug combination of DCF, toxicity was also increased and was very substantial. Eighty-one percent of all patients receiving DCF had at least one grade 3 or 4 non-hematologic toxicity, as well as substantially more hematologic toxicity. Despite this, the use of DCF was associated with a better preservation of quality of life and maintenance of clinical benefit compared with cisplatin-5-FU. On the other hand, there was no difference in the treatment-related mortality rate for the two arms. Therefore, like epirubicin, docetaxel, when added to cisplatin-5-FU, produces a modest improvement in efficacy.

ORAL FLUOROPYRIMIDINES

Treatment with oral fluoropyrimidines seems to offer new hope for patients with gastric cancer, which is surprising when only a few years ago, such patients were not thought to be ideal candidates for an oral treatment. In fact, difficulties with the location of primary tumors, surgery (gastrectomy), or presence of metastatic sites affecting intestinal transit (ie. metastases in the peritoneum), made the hypothetical use of an oral treatment a remote possibility. Nonetheless, findings from recent trials that assessed the role of oral fluoropyrimidines seem to place this assumption into a new promising perspective.

Accordingly, capecitabine has been shown to be effective in the treatment of advanced esophagogastric cancer in a phase III study comparing capecitabine with fluorouracil and oxaliplatin with cisplatin (the REAL trial)^[7]. Patients were randomly assigned to one of four regimens: ECF, epirubicin plus oxaliplatin and 5-FU (EOF), epirubicin plus cisplatin and capecitabine (ECX), or epirubicin plus oxaliplatin and capecitabine (EOX). Comparing ECF to EOF, ECX, and EOX, there were no significant differences in ORRs (41%, 42%, 46%, and 48%, respectively) and grade 3/4 non-hematologic

toxicity (36%, 42%, 33%, and 45%, respectively). Non-inferiority in OS was established in both oxaliplatin/cisplatin and capecitabine/5-FU comparisons in this largest randomized controlled trial. Notably, EOX resulted in a significantly improved survival time compared with the control arm ECF. A median survival time of 11.2 mo in the EOX arm was amongst the longest achieved in this setting of patients. Therefore, EOX should now be regarded as one of the standard first-line treatment options for advanced disease. Another trial that compared treatment with 5-FU plus cisplatin with capecitabine plus cisplatin confirmed that efficacy of capecitabine is equivalent to that of 5-FU^[8]. Furthermore, although both of these trials were designed to assess whether capecitabine was no worse than 5-FU, the findings generally suggested better outcome in patients who received oral capecitabine.

S-1 is a new oral anticancer drug comprised of tegafur, 5-chloro-2,4-dihydroxypyrimidine, and oteracil potassium. This drug was designed to enhance the efficacy of tegafur, a prodrug of 5-FU. Koizumi *et al*^[9] report findings of the S-1 plus cisplatin *vs* S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial). Median progression-free survival (6.0 mo *vs* 4.0 mo; $P < 0.0001$) and OS (13.0 mo *vs* 11.0 mo; $P = 0.04$) were significantly longer in the combination group. Response was also significantly improved in patients having target tumors and assigned to S-1 plus cisplatin (54% *vs* 31%). On the basis of these findings, the standard of treatment in Japan has changed, and treatment with combined S-1 plus cisplatin has become the standard of care. The findings from this trial are clearly relevant: for the first time, in a randomized study, the apparently insurmountable wall of 12 mo survival in advanced gastric cancer was crumbled. However, some considerations must be taken into account before combination S-1 plus cisplatin is implemented as standard treatment in western countries. The SPIRITS trial gives no information about the advantage of S-1 over 5-FU when each was combined with cisplatin. The First-Line Advanced Gastric Cancer Study (FLAGS), which compared S-1 with 5-FU, both combined with cisplatin, has responded to this question^[10]. This multicenter phase III trial has randomized 1053 patients primarily in the USA, Europe, and South America. Median OS was 8.6 mo in the cisplatin/S-1 arm and 7.9 mo in the cisplatin/5-FU arm ($P = 0.1983$). Statistically significant safety advantages for the S-1-based combination were observed regarding the rates of severe neutropenia (18.6% *vs* 40.0%), stomatitis (1.3% *vs* 13.8%), hypokalemia (3.6% *vs* 10.8%), and renal adverse events (all grades: 18.8% *vs* 33.5%). However, this study has not confirmed the efficacy results of the SPIRITS trial in western populations. Thus, the future role of S-1 in gastric cancer could be the inclusion of this oral drug into a three-drug regimen making DCF or ECF better tolerated. What more can we do to increase median OS?

SECOND-LINE CYTOTOXIC TREATMENT

First-line chemotherapy for the treatment of advanced gastric cancer can provide high response rates which are

of a similar magnitude to those achievable with the newer first-line combinations in colorectal cancer. However, a corresponding improvement in the median OS time has not yet been delivered by the currently available gastric cancer regimens. This lack of progress in relation to markedly improving OS times may be a result, in part, of the more limited efficacy of the currently available second- and third-line treatments for advanced disease, although it should be noted that only one third to one half of the gastric cancer patients in clinical studies may actually receive second-line treatments^[11]. Data published to date relating to this are restricted to phase II studies of small patient populations, and these investigations are therefore not able to provide definitive results. However, second-line treatments are clearly effective to some degree, with ORRs in the region of 11%-32%, median TTP of 2.5-4.5 mo, and median OS times of 5.4-9.3 mo^[12-15].

TARGETED BIOLOGICAL AGENTS

The main hope for significant advances in the near future is the combination of new targeted biological agents with existing chemotherapy first-line regimens. A number of different classes of targeted agents have shown promising activity in clinical studies of advanced gastric cancer, including epidermal growth factor receptor (EGFR) and human epidermal growth factor (HER)-2-targeted monoclonal antibodies, antiangiogenic and antiangiogenic/antitumor compounds, and the proteasome inhibitor bortezomib^[16-20].

High response and/or disease control rates have been reported for EGFR-targeted cetuximab combined with irinotecan and infusional 5-FU and leucovorin^[16-17] and VEGF-targeted bevacizumab combined with irinotecan and cisplatin^[19]. In particular, the FOLCETUX study has demonstrated that the addition of cetuximab to the FOLFIRI regimen increased survival in 38 untreated patients with confirmed advanced gastric/gastroesophageal adenocarcinoma. The treatment was delivered for a maximum of 24 wk, and then cetuximab alone was allowed in patients with a complete response (CR), partial response (PR) or stable disease (SD). Consequently, the overall response rate (ORR) was 44% with a CR in four patients and a PR in 11 patients. Sixteen patients had SD. Median expected OS was 16 mo^[16]. In another multicenter phase II study, 47 patients with metastatic or unresectable gastric cancer received bevacizumab plus irinotecan and cisplatin. With a median follow-up of 12.2 mo among 34 assessable patients, the ORR was 65%, with 20 patients achieving a PR and two patients a CR. Twelve patients had SD. Median survival was 12.3 mo^[19].

Trastuzumab exhibits activity in human gastric cancer cells that overexpress HER2/neu. A phase II trial has determined the efficacy and tolerability of trastuzumab plus cisplatin in patients with advanced gastric cancer with HER2/neu overexpression/amplification. Preliminary results showed that 6 (35%) out of 17 assessable patients achieved response, 3 (17%) stabilization. There was no grade 4 toxicity^[18].

In considering such studies, it is notable that the first-line cytotoxic regimens that have been selected for combination with biological agents tend to be those that are generally considered not to be optimal for the treatment of advanced gastric cancer. This begs the question as to whether the impressive potential of these targeted agents might be more profitably explored in the future within combinations that include standard cytotoxic backbones such as ECF, DCF, EOX, or perhaps S-1 plus cisplatin. Indeed, a number of randomized phase III studies incorporating targeted agents in first-line regimens have recently been initiated: the ToGA (Trastuzumab with Chemotherapy in HER2-Positive Advanced Gastric Cancer) study is investigating the effect on progression-free survival of trastuzumab in combination with a fluoropyrimidine plus cisplatin *versus* chemotherapy alone in patients with HER-2-positive advanced gastric cancer, AVAGAST (Avastin® in Gastric Cancer) is investigating OS time in advanced gastric cancer patients receiving either capecitabine and cisplatin plus bevacizumab or chemotherapy alone plus placebo, and the REAL-3 study is investigating the benefit of adding panitumumab to an EOX regimen in patients with locally advanced or metastatic esophagogastric adenocarcinoma.

However, new biological agents could be useful in the management of advanced disease after the failure of first-line treatment. In this context, it is possible that targeted agents may have a future role as single-agent maintenance treatments. Two recent phase II studies have pursued this concept^[21-22]. A Japanese study has evaluated the activity and safety of everolimus (RAD001), an oral inhibitor of the mammalian target of rapamycin serine-threonine kinase, in 54 pretreated patients with metastatic gastric cancer. At interim analysis, no objective responses were observed but disease control rate was 55% and median TTP was 83 d. Main adverse events were stomatitis (74%), anorexia (51%), fatigue (47%), rash (45%), peripheral edema (23%), thrombocytopenia (21%), diarrhea (19%), pneumonitis (13%), and hyperglycemia (9%). The multicenter AIO phase II trial has evaluated tolerability and efficacy of sunitinib in highly pretreated Caucasian patients with unresectable metastatic cancer of stomach, esophagogastric junction or lower esophagus. Among 14 response-evaluable patients, 5 of them showed tumor control for at least 6 wk. With regard to survival, 5 patients experienced early death caused by progressive disease, 7 patients survived > 60 d. Twelve patients were still in follow-up or withdrew informed consent within 60 d after start of therapy. Again, 3 of them survived > 60 d. No serious adverse events occurred.

In conclusion, these studies constitute a potentially important advance, indicating a role for biological agents in the treatment of advanced gastric cancer. Further trials are now needed to clarify their respective position with reference to chemotherapy.

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