Advances in systemic treatment of metastatic gastric cancer

KEYWORDS: Stomach Neoplasms; Carcinoma; Antineoplastic Agents; Antineoplastic Combined Chemotherapy Protocols; Neoplasm Metastasis

ABSTRACT

Gastric carcinoma is a frequent malignancy throughout the world and endemic in many of its regions. Advanced gastric carcinoma is often diagnosed. Patients with advanced gastric cancer have a median survival of 6–8 months, and chemotherapy is palliative. Even in patients with resectable disease 5-year survival is generally poor. Chemotherapy is usually accepted as standard treatment for advanced disease. None of existing chemotherapy regimens has been established as standard, and chemotherapy within the controlled clinical trials is still the best option for advanced gastric cancer patients. In some trials a response rate of more than 50% has been achieved for multidrug regimens. It seems that the important story in gastric cancer is not told by focusing on the response rates in serial phase II or even phase III trials. In this disease, the success with respect to high response rates has been virtually canceled out by the fact that tumor shrinkage seems to be evanescent. There has not yet been a regimen reported that leads to a 50% survival probability at one year. A 2-year survival rate of 14% is considered noteworthy as a "long-term survival". Toxicity, including nausea, vomiting, asthenia, anorexia, neutropenia, and treatment related morbidity, in patients with gastric cancer remain substantial issues, especially with multidrug therapy. Among the newer agents, oral fluoropyrimidines, taxanes, irinotecan and oxaliplatin appear to be relevant candidates for improved palliation and extension of survival. Further clinical studies are certainly needed to define the optimal role for these drugs. Gastric carcinoma has a variety of molecular abnormalities. Many of these molecules can be targeted theoretically, however, practical applications are yet to be fully developed. Limited number of studies has been done using specific targets against gastric carcinoma.

INTRODUCTION

Gastric carcinoma is a frequent malignancy throughout the world and endemic in many of its regions. Advanced gastric carcinoma is often diagnosed. Patients with advanced gastric cancer have a median survival of 6–8 months, and chemotherapy is palliative. Even in patients with resectable disease 5-year survival is generally poor. Chemotherapy is usually accepted as standard treatment for advanced disease.

HISTORICAL DATA

Chemotherapy often results in symptomatic improvement with improved quality of life, but the median survival of patients with advanced disease continues to be dismal (1). Importantly, several small, randomized trials suggest that chemotherapy can have a significant effect on survival when compared with the best supportive care (2). Second-generation combination chemotherapy regimens (epirubicin/cisplatin/5-fluorouracil-ECF; etoposide/doxorubicin/cisplatin-EAP; etoposide/leucovorin/5-fluorouracil-ELF; 5-fluorouracil/leucovorin/etoposide/cisplatin-FLEP; 5-fluorouracil/doxorubicin/methotrexate-FAMTX; 5-fluorouracil/epirubicin/5-fluorouracil/epirubicin/methotrexate-FEMTX; cisplatin/epirubicin/leucovorin/5-fluorouracil-PELF) appear to have a higher complete response rate and a longer survival than regimens such as 5-fluorouracil/doxorubicin/mitomycin (FAM) that were widely used until the late 1980s. Initial phase II studies of those regimens reported response rates of approximately 50% with high complete response rates. However, additional phase II and III trials demonstrated lower response rates (3). No one chemotherapy regimen has been established as standard and chemotherapy within the controlled clinical trials is still the best option for AGC patients. Doxorubicin, etoposide and cisplatin (EAP) comprise one of the second-generation regimens. The uniqueness of this regimen is that it is the only combination regimen in AGC that does not use 5-fluorouracil (4). A summary of phase II studies using EAP regimen in a series with at least 25 patients shows response rate of 18–72%, median survival of 7.5–11 months, an average of 9% complete responders and an average of 3% of toxic deaths (2). The only randomized study that compared EAP with one of the second-generation regimen (FAMTX) found that FAMTX was not significantly more effective than EAP (4). This study was closed prematurely because of the unacceptable toxicity of EAP. The excessive hematological toxicity, which was described in other studies with limited number of patients (2), led doctors to avoid the combination in the clinical practice. In our previous phase III study, we have not confirmed unacceptable toxicity of EAP and high rates of toxicity-related deaths described in trials with limited numbers of patients (5). Nowadays, EAP is still being used as an active regimen for AGC both as front line chemotherapy in routine practice and as standard arm in clinical trials (6). In some trials a response rate of more than 50% has been achieved for multidrug regimens (7). In a phase II study using weekly PELF, Cascini et al., observed a response rate of 62% (6). In two recent studies using combination of docetaxel and cisplatin in AGC, the authors reported response rates of 56% (9) and 37% (10). But, it seems that the important story in gastric cancer is not told by focusing on the response rates in serial phase II or even phases III trials. In this disease, the success with respect to high response rates has been virtually canceled out by the fact that tumor shrinkage seems to be evanescent. There has not yet been a regimen reported that leads to a 50% survival probability at one year. A 2-year survival rate of 14% is considered noteworthy as a “long-term survival” (11). Toxicity, including nausea, vomiting, asthenia, anorexia, neutropenia, and treatment related morbidity, in patients with gastric cancer remains a substantial issue, especially with multidrug therapy. In some trials, 38% of patients had WHO grade III toxicity or greater, despite the use of glutathione and filgrastim to mediate the side effects of therapy (8).
CURRENT TREATMENT OPTION

Among the newer agent, oral fluoropyrimidines, taxanes, irinotecan and oxaliplatin appear to be relevant candidates for improved palliation and extension of survival. Further clinical studies are certainly needed to define the optimal role for these drugs.

Taxanes. One of the taxanes that has undergone more advanced evaluation in gastric carcinoma is docetaxel. Following demonstration of activity of taxanes as single agent against gastric carcinoma, docetaxel when combined with other active agents (example, 5-FU and cisplatin) has resulted in doubling of response rate in patients with advanced gastric carcinoma (8). A phase II randomized study comparing docetaxel / cisplatin / 5-FU resulted in a higher response and slightly higher toxicity for the 3-drug combination (12). Currently, a phase III trial is comparing 5-FU / cisplatin (control) to docetaxel / cisplatin / 5-FU in patients with advanced gastric carcinoma.

Camptothecins. Two types of camptothecins have been under investigation. CPT-11 has been studied more extensively and Rubitecan is also undergoing investigations (13,14,15). Both agents appear to modest single agent activity against gastric carcinoma. CPT-11 combined with either cisplatin or 5-FU results in high response rates. In a phase II randomized trial CPT-11/folinic acid / 5-FU was compared with CPT-11/cisplatin. Here also, 3-drug combination resulted in a higher response rate and a better toxicity profile. A phase III study comparing 5-FU / cisplatin (control) is comparing CPT-11 / folinic acid / 5-FU.

Platinols. Among all the platinols studies in gastric carcinoma, cisplatin appears most active, however, it is also most toxic. Carboplatin may be combined with taxanes and results in modest response rates. Nevertheless, oxaliplatin is of great interest (16,17). It has been studied against gastric carcinoma in combination with 5-FU and folinic acid and results in high response rates (40% to 50%) with a very acceptable toxicity profile. Oxaliplatin has also been combined with other agents and is currently under investigation in a phase III trial in Europe. Oxaliplatin is also a radiotherapy enhancer.

Oral fluoropyrimidines. Particularly, S-1 is of interest. S-1 is a combination of florafur, CHDP (a potent DPD inhibitor), and oxonic acid (prevents diarrhea by preventing phosphorylation of 5-FU in the gut). Single agent data from Japan has been very impressive and resulted in its approval for gastric carcinoma (18). Further studies of this compound in combination with other agents are planned. The other oral agent, capecitabine, has been sparingly investigated in the US.

New agents. Among the newer agents, oral fluoropyrimidines, taxanes, irinotecan and oxaliplatin appear to be relevant candidates for improved palliation and extension of survival. Further clinical studies are certainly needed to define the optimal role for these drugs.

Future. COX-2 inhibitors, MMP inhibitors, anti-angiogenic agents will be the subject of investigation in the future. There will also be new and less toxic drugs available.
REFERENCES


