Review article
UDC: 616.33-006:615-085:616-037

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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.

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The manuscript was received: 15. 08. 2003.

Accepted for publication: 15.09.2003.

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/methothrexate-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 (5-FU). 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, Cascinu et al., observed a response rate of 62% (8). 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 to 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 ftorafur, 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 studied against gastric carcinoma and resulted in about 20% response rate. This agent also deserves additional investigation.

New targets (19,20)

The patterns of metastases depend on gender and histological type. However, the molecular determinants of various patterns of metastases are not known, gastric carcinoma has a variety of molecular abnormalities (p53, Her-2-neu, Lewis^Y antigen, EGFr, E-cadherin, MSI, spl, gastrin receptors, and many more). 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.

Gastrin. Gastrin hormone receptors are frequently present on cancer cells originating from a variety of tumors including gastric carcinoma. Gastrin is represented in many forms. The polypeptide hormone, G17 gastrin is a potential growth factor for tumors arising within the gastrointestinal (GI) mucosa. Sixty-nine percent of gastric cancer cells had an enhanced proliferation when exposed to G17 gastrin. Additionally, gastrin gene is activated in GI cancer cells but not in normal GI cells. Gastrin has an autocrine/paracrine growth pathway. G17DT conjugate was developed in an attempt to generate antibodies against the amino-terminal end of G17 gastrin. The peptide is cross-linked via its C-terminal cysteine residue to a carrier protein, Diphtheria toxoid (DT), using the bifunctional cross-linker eMCS to form the G17DT conjugate. Immunization with G17DT elicits antibodies that react specifically with G17 gastrin and Gly-G17 gastrin. Antibodies elicited by G17 inhibit the growth of human gastric and colorectal cancer cells, in both *in vitro* and *in vivo* animal models. In a multicenter phase II study for untreated patients with advanced gastric carcinoma with high performance status and measurable cancer were eligible. Patients received systemic chemotherapy with 5-fluorouracil (1,000 mg/m^2/d as continuous infusion on days 1-5) and cisplatin (100 mg/m^2 on day 1). This chemotherapy regimen was repeated every 28 days. G17DT at a total dose of 500 μg was given intra-muscularly on days 7, 35, and 63. Immunogenic response to G17DT were assessed and boosters were if necessary. Seventy patients have been registered. Preliminary data on 30 patients suggest that immunization is common and response rate in approximately 50%. Two phase III studies are planned.

Lewis^Y antigen. The Lewis^Y glycoprotein is an attractive target for immunoconjugate therapy since it is expressed as a glycoprotein on the surface of most (>75%) carcinomas of breast, gastrointestinal tract, lung (non-small cell), cervix, ovary, pancreas, and some melanomas. High levels (>200,000 molecules per carcinoma cell) of expression of Lewis^Y-related tumor-associated antigens have been documented in common tumor types. The BMS-182248-01 antibody is a chimeric variant of anti-Lewis^Y monoclonal antibody, which incorporates human IgG1 and is linked to doxorubicin. In preclinical *in vitro* and *in vivo* models, the conjugate internalizes rapidly and releases doxorubicin through acid hydrolysis in the endosomes and lysosomes of cells expressing the antigen. Preclinical *in vitro* and *in vivo* cytotoxic activity of the conjugate has been effective against L2987 lung carcinoma, RCA colon carcinoma, and MCF-7 breast carcinoma. The IC50 of doxorubicin in vitro studies was clearly related to the presence of Lewis^Y antigen on the surface of the cells, with the IC50 being much lower in cell lines positive for Lewis^Y than those without Lewis^Y antigen. A phase II study of BMS-182248-01 was conducted in patients with advanced, untreated gastric carcinoma that expressed Lewis^Y antigen. This multicenter study was terminated when 15 patients were accrued and no objective response was observed.

EGFR. This is a transmembrane glycoprotein with an intracellular domain possessing intrinsic tyrosine kinase activity. It has a subfamily of 4 closely related receptors. (Erb-B 1 to 4). The receptors dimerize with ligand activation. The activation can result in homodimerization or heterodimerization of one of the Erb-B family. This eventually activates intracellular signaling cascade involving activation of Ras and protein kinase. Along the way, cyclin D-1 is activated. Clycline D1 protein required for cells progress from G1 to S phase. EGFr contributes to tumorigenesis rather than cell proliferation. EGFr mediated signals appear crucial in agiogenesis, metastases, and inhibition of apoptosis. EGFr is over expressed in gastric carcinoma. This over expression is associated with advanced disease and poor prognosis. The research in this area is new and needs to be further explored. Drugs like C-225, OSI, and Iressa will be of interest. Unpublished results from a small trial of Iressa has resulted in no objective responses, however, the optimum use of these agents may be in conjunction with chemotherapy or in the adjuvant setting.

MMPIs. This class of agents has been studied only in a limited fashion and has not been pursued in well-designed studies but need to be investigated further.

Bryostatin and flavopyridol. Bryostatin is a protein kinase C inhibitor, cytokine, and immunomodulator. It results in synergistic cytotoxicity with certain chemotherapy agents. In an ongoing trial, bryostatin is being combined with paclitaxel. Early results are promising with a high response rate. The dose limiting toxicity of bryostatin is cumulative myalgia (reversible upon discontinuation of the drug). Flavopyridol is cyclin-dependent kinase inhibitor. This small molecule is capable of reversing chemotherapy resistance by inducing apoptosis. When combined with docetaxel, it results in regression of gastric cancer xenograft. It is also a radiation cytotoxicity enhancer. It is synergistic with CPT-11 and taxanes. Further studies of this compound are of great interest.

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

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