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Recent Developments in Oral Chemotherapy Options for Gastric Carcinoma

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Abstract

The incidence of carcinoma of the stomach is low in the United States, Canada, and Australia but is a significant health problem in Asia, South America, Eastern Europe, and countries of the previous Soviet Union. For patients with advanced disease, chemotherapy remains palliative. With the increasing emphasis on patients' quality of life, convenience, and cost containment, oral chemotherapy has come into increasing focus. We review oral chemotherapy agents for use in patients with advanced gastric carcinoma.

Etoposide, given intravenously, has modest activity in gastric carcinoma. We studied oral etoposide, which was administered to 28 patients at the starting dose of 50 mg/m^2/day for 21 days followed by a 7-day rest period. Five patients achieved a partial response and 4 patients achieved a minor response. The drug was well tolerated. Common toxicities included myelosuppression, alopecia, and nausea. Oral etoposide thus shows evidence of modest activity against gastric carcinoma.

In Japan, considerable advances have been made in the oral chemotherapy of gastric carcinoma. The second generation fluorouracil prodrug tegafur/uracil (UFT®) has been extensively evaluated in Japan, Korea, and Spain. Data predominantly from Japan indicate that tegafur/uracil has a response rate of approximately 20% in treatment naive patients with advanced gastric carcinoma. When combined with other active agents, tegafur/uracil has a response rate of more than 30% in these patients. The available data also suggest that tegafur/uracil is well tolerated and that patient acceptance is high. In conclusion, future clinical research is likely to focus on the development of convenient outpatient regimens with efficacy equal to that of intravenous regimens.

Gastric carcinoma continues to remain a major worldwide health problem. It is the eighth leading cause of cancer death in the United States and remains a major worldwide health problem, even though its incidence has steadily declined since World War II. In 1997, more than 22 800 new cases of gastric cancer were estimated to have occurred in the US and 14 000 deaths were expected as a result.[1] Since early detection is neither carried out nor possible in most of the world, these cancers are often diagnosed at advanced stages. Approximately 50% of patients present with unresectable, locally advanced, or metastatic disease. For patients with advanced disease, the median survival ranges from 6 to 9 months.[2]

Chemotherapy has a palliative effect in patients

with gastric cancer. Four randomised studies comparing intravenous chemotherapy and best supportive care have demonstrated an improvement in the quality of life and overall survival in patients receiving chemotherapy.[3-6] Nevertheless, each of these 4 studies involved a small number of patients and were subject to many limitations; thus, these conclusions should be viewed cautiously.

Only a limited number of single agents are active in this disease. The response rate to fluorouracil alone is less than 20%.[7] Other agents such as mitomycin,[7] etoposide (VP-16),[8] and cisplatin[9] are also considered active and result in a response rate of ≤20% when used as single agents. In a pivotal study performed by the North Central Cancer Therapy Group, the FAM (fluorouracil, mitomycin, and doxorubicin) regimen was compared with fluorouracil alone and fluorouracil plus doxorubicin.[10] No significant survival difference was detected between the 3 regimens.

In Europe, several studies comparing a variety of combination chemotherapy regimens have been performed.[11-13] However, these studies have not resulted in a standard regimen for gastric carcinoma. Recommended chemotherapy off-protocol includes cisplatin-based or fluorouracil-based combination chemotherapy. Clearly, more active agents are needed in the treatment of this disease. More recently, a number of oral agents have been investigated in gastric carcinoma.

Chemotherapy for gastric carcinoma remains in a state of continuous evolution. Increasing attention is being given to patients' quality of life, convenience, or symptom palliation. Oral chemotherapy, which potentially can be more convenient than intravenous chemotherapy and equally effective, has therefore come into focus. This review will focus primarily on the use of oral etoposide and tegafur/uracil (UFT®) in patients with gastric carcinoma.

1. Oral Etoposide

During the past several years, there has been increasing interest in oral etoposide. It appears to have an improved pharmacokinetic profile when administered daily for a prolonged period of time compared with periodic intravenous infusion.[14] Studies have been conducted to examine a variety of oral etoposide schedules.[15] Oral etoposide has also been shown to be active in patients with small cell lung carcinoma.[16,17] At the M.D. Anderson Cancer Center, we have investigated the value of oral etoposide in untreated patients with advanced gastric carcinoma.

In this trial etoposide was orally self-administered. The starting dose was 50 mg/m^2/day for 21 days followed by a rest period of 7 days; courses were repeated every 28 days. Patients received at least 2 courses of therapy unless there was evidence of rapidly progressive cancer. Response evaluation was carried out following 2 courses of oral etoposide.

26 of 28 patients were evaluable in this study. The median age was 60 years (range, 28 to 80 years). The median performance status as measured by the Zubrod scale was 1 (range, 0 to 2). The median number of courses was 2 (range, 1 to 6), with a total of 69 courses delivered. The median dose of oral etoposide was 50 mg/m^2/day. Five of 26 evaluable patients (19%; 95% confidence interval, 3 to 35%) had a partial response. The median duration of partial response was 14 weeks. Four patients had a minor response, one patient had no change in the cancer, and 16 patients had progressive disease. The median duration of overall survival for all patients was 28 weeks (range, 4 to 120 weeks).

Oral etoposide was well tolerated. There were no treatment-related deaths. Common toxicities included myelosuppression, nausea, and hair loss.

As a result of increasing interest in the oral chemotherapy of gastrointestinal malignancies, it may be possible to combine oral etoposide with other oral agents for disease palliation in patients with advanced gastric carcinoma.

2. Tegafur/Uracil

Tegafur/uracil is a combination of uracil and tegafur in a 4 : 1 molar ratio. Biochemically, the combination of tegafur/uracil and calcium folinate (calcium leucovorin) offers more than intravenous

fluorouracil and folinic acid (leucovorin), because tegafur/uracil incorporates uracil. Uracil prevents the degradation of fluorouracil in the plasma and tumour tissue. Tegafur/uracil has been widely available in Japan, Korea, Singapore, and Spain. It is now also approved in many South American countries for use in gastrointestinal malignancies. Tegafur/uracil has been extensively investigated in Japan, Korea, and Spain. Tegafur, an old Russian oral fluorouracil prodrug, is considered to be the first generation of fluorouracil prodrugs. Tegafur/uracil incorporates the modulation of tegafur by uracil, thus representing a new generation of fluorouracil prodrugs called dihydropyrimidine dehydrogenase (DPD) inhibitory fluoropyrimidines (DIF).

Tegafur/uracil has been found to produce cytotoxic effects in a variety of subcutaneously implanted tumours, including Walker 256, Yoshida sarcoma, AH 130, sarcoma-180, Ehrlich tumour, Lewis lung carcinoma, and B-16 melanoma.[18,19]

Data comparing tegafur/uracil with intravenous administration of fluorouracil suggest that tegafur/uracil provides higher maximum concentration and area under the plasma concentration-time curve values than those obtained with continuous-infusion fluorouracil.[20,21]

The majority of tegafur/uracil research to date has been carried out in Japan. Some of the results from these trials, however, are difficult to interpret. In addition, the criteria for response and doses of tegafur/uracil used have varied widely in the same studies. Data are available predominantly for tegafur/uracil alone, and only limited data are available for tegafur/uracil in combination with calcium folinate.

In phase II trials, tegafur/uracil was administered at doses ranging from 300 to 600 mg/day for more than 28 consecutive days.[22-33] Ota et al. summarised the pooled data of approximately 10 phase II studies in various types of tumours, including gastric cancer.[22] Among the 286 patients with gastric carcinoma, 188 patients were evaluable for response. The overall response rate was 28% (3 complete and 49 partial responses). The median survival time for all patients was 185 days. Common toxicities were gastrointestinal, such as anorexia (24%), nausea and vomiting (12.5%), and diarrhoea (11%). Haematological toxicity was rare.[22]

In a European phase II study conducted with tegafur/uracil alone, 16 patients with gastric carcinoma were evaluated.[34] One patient achieved a partial response. Tolerance to therapy was excellent.

In 2 studies conducted in Japan, tegafur/uracil was compared with tegafur in patients with gastric carcinoma. In a retrospective review, Ota et al. compared tegafur/uracil (300 to 600 mg/day) and tegafur (800 to 1200 mg/day).[22] It was concluded that tegafur/uracil produced a higher response rate than tegafur (30 *vs* 23%, respectively). In a randomised controlled study, mitomycin plus tegafur/uracil (375 mg/m^2/day) was compared with mitomycin plus tegafur (400 mg/m^2/day).[35] Mitomycin was administered intravenously at 5 mg/m^2/week in both arms. The response rate in the tegafur/uracil arm was higher (25%; 20 of 79 patients) than in the tegafur arm (8%; 7 of 90 patients). The toxicity was similar in both arms.

Tegafur/uracil has also been combined with cisplatin. In a phase II study, tegafur/uracil was given at 400 mg/m^2/day for 28 days and cisplatin was administered intravenously at 30 mg/m^2/day for 3 days.[36] Courses were repeated every 4 weeks. Among 14 evaluable patients, there were 6 partial responses. The median duration of survival was 11.4 months. The authors claimed that this oral/intravenous regimen was preferred by the patients.

Tegafur/uracil and cisplatin have been administered to patients with potentially resectable gastric carcinoma. Tegafur/uracil was administered at 400 mg/day for 14 days prior to surgery, and cisplatin was administered at 40 mg/m^2 intravenously once.[37] A histopathological response occurred in 67% of patients (16 of 24 patients). In addition, a correlation was found between response and tumour thymidylate synthase inhibition rate.[38,39]

Two other studies have examined the combination of tegafur/uracil with etoposide and cisplatin or with etoposide, cisplatin, and mitomycin. Both

studies reported a response rate of approximately 40%.[40,41] In Spain, the Oncopaz Cooperative Group studied the combination of tegafur/uracil with etoposide and calcium folinate and found a response rate of 36% (16 of 46 patients); complete responses were observed in 4 of the 16 responders.[42] The median overall survival was 9 months. This combination was easily administered in the ambulatory treatment centres. A study of Kim et al.[43] combining tegufur/uracil with folinic acid also demonstrated activity against gastric carcinoma.

Adjuvant therapy for patients with resected gastric carcinoma is frequently prescribed in Japan and Korea. In Japan, tegafur/uracil is now part of the adjuvant therapy of gastric carcinoma. Previously, the combination of mitomycin plus tegafur was employed as standard postoperative adjuvant chemotherapy.[44,45] Two studies (Arima et al.[46] and Maehara et al.[47]) have demonstrated the superiority of tegafur/uracil over tegafur, resulting in the substitution of tegafur by tegafur/uracil for this indication in Japan. Nevertheless, routine use of adjuvant chemotherapy for gastric carcinoma is not recommended in the US because of the lack of studies demonstrating a benefit in patients with this disease.

3. S-1

S-1 is a combination of tegafur (fluorouracil prodrug), 5-chloro-2,4-dihydropyrimidine (an inhibitor of DPD), and potassium oxonate (to inhibit phosphorylation of fluorouracil in the gastrointestinal mucosa and thus reduce diarrhoea). Available data on S-1 are as yet preliminary. In a phase II study of 51 patients, Ohtsu et al. administered S-1 orally at 80 mg/m^2 twice daily for 28 days followed by a 7-day rest period.[48] The overall response rate was 49% (95% confidence interval, 36 to 62%). The median duration of response was 4.6 months and the median survival of all patients was approximately 8.5 months. Additional studies of this agent are warranted in the West.

4. Discussion

There is now increasing emphasis on patient convenience, quality of life, and effective palliation. The focus on these issues occurs in parallel with efforts to develop new therapies to improve cure rates and prolong survival. In many Asian countries, the use of oral chemotherapy for patients with gastric carcinoma is traditional, and drugs such as tegafur/uracil and tegafur have been employed for a number of years. Oral chemotherapeutic agents provide a number of theoretical advantages – such as ease of administration, favourable toxicity profile, and patient convenience – over their intravenous counterparts. In addition, in a number of instances the efficacy of oral agents is not necessarily compromised. The pharmacokinetic profile is often comparable to, or occasionally more advantageous than, intermittent administration of the corresponding intravenous agent. The potential disadvantages of oral administration of the drug include patient noncompliance and unpredictability of gastrointestinal absorption.

When compared with intravenous use of the agent, oral etoposide appears to offer some level of convenience and a similar level of activity. It has potential in the development of an effective palliative regimen for the treatment of gastric carcinoma. The toxicity profile is similar whether the drug is administered orally or intravenously.

Tegafur/uracil is the first second generation oral fluorouracil prodrug with an advantage over the previous generation, since it contains uracil as a modulator. Given its biochemical advantage and superiority with regard to preclinical and clinical efficacy, it may be a better agent than tegafur. In addition, the toxicity profile is similar to that of tegafur. Tegafur/uracil is easily administered orally and seems to provide results comparable either to those with low dose continuous intravenous infusion or bolus infusion of fluorouracil (with or without the addition of folinic acid). Currently, tegafur/uracil is under investigation for patients with advanced colon carcinoma, in adjuvant therapy of colorectal carcinoma, for use with concurrent radiotherapy in rectal carcinoma, and for

gastric and oesophageal carcinomas. Only randomised, controlled trials will address the issues of quality of life, patient convenience, and efficacy. A number of second generation fluorouracil prodrugs such as S-1 are becoming available for investigation in North America and Europe. Oral bioavailability is also being investigated with other classes of agents, including topoisomerase inhibitors and taxanes.

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