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Advanced Gastric Carcinoma Chemotherapy with Cisplatin, Mitomycin C, BCNU, and 5-Fluorouracil in Combination

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Forty patients with advanced gastric carcinoma were treated with mitomycin C, BCNU, cisplatin, and 5-fluorouracil in combination. Mitomycin C 6 mg per sq m was given by i.v. on day 1, BCNU 60 mg per sq m was given by i.v.on day 2, cisplatin 60 mg per sq m was given by 3 hour i.v.infusion with mannitol diuresis on day 3, and 5-fluorouracil 300 mg per sq m was given by i.v. infusion on days 4, 5, and 6. Each course of the polychemotherapy was repeated every 35 days. Two patients failed to return for follow-up, thus 38 patients were available for response evaluation of this regimen.

Of the 38 patients, 25 (66%) achieved partial remission. The median duration of response was 20 weeks. Survival time was not measured. Significant bone marrow toxicities were not encountered. The major toxic side effects were gastrointestinal: anorexia, nausea and/or vomitings. Clinically significant ototoxicity or nephrotoxicity was not experienced. One patient developed a mild peripheral neuropathy. This four-drug polychemotherapy regimen appears to have substantial activity agaist advanced gastric carcinoma.

Key Words: *Gastric cancer chemoherapy, Cisplatin-based polychemotherapy*

INTRODUCTION

Gastric cancer is the leading cause of cancer death in korea. Although some patients with gastric cancer are amenable to a surgical cure, the majority of these patients have advanced diseases when a diagnosis is confirmed. In patients with loco-regional diseases, the 5-year survival rates are low because of a high recurrence rate even after curative resection of the gastric cancer.

A number of single agents have been utilized in the chemotherapy of advanced gastric cancer, 5-fluorouracil, mitomycin C, doxorubicin, and nitrosoureas are among the most active drugs. In recent years, a variety of combination chemotherapy regimens have been developed in the hope that these polychemotherapy methods could enhance antitumor effects in gastric carcinoma.

Among the carcinoma of gasrointestinal origin, gastric adenocarcinoma has seemed to be the most responsive to chemotherapy. However even with the most effective combination chemotherapy regimens, complete remissions are rare, duration of responses are usually short, and long-term survivors are rare[1].

Therefore it seems clear that new methodologic and therapeutic appoaches are needed in the chemotherapy of gastric carcinoma[2]. Cisplatin is a new cytotoxic drug, and it has recently shown substantial activity in the treatment of advanced gastric cancer[3].

Recently we have treated advanced gastric carcinoma patients with cisplatin in combination with BCNU and 5-fluorouracil. Although the response rate was 65%, the impact on meaningful survival extension was limited because the duration of responses with the regimen was rather short[4].

Mitomycin C has long been known to be one of

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the most active drugs in the treatment of advanced gastric cancer. In hope of improving the quality and duration of response, we have elected to incorporate mitomycin C as part of the combined regimen of cisplatin, BCNU, and 5-FU. The purpose of this study is to investigate the therapeutic effect of the above mentioned 4-drug combination chemotherapy regimen in the treatment of advanced gastric cancer.

PATIENTS AND METHODS

From November 1983 to May 1985, 40 patients with advanced gastric carcinoma seen in the Department of Medicine, Paik Hospital were entered in this study. The research protocol required that all patients have histological proof of adenocarcinoma of gastric origin, either primary, recurrent or metastatic, that none of them had previously received chemotherapy or radiotherapy, and that all patients have a measurable malignant lesion or evaluable diseases to serve as an objective indicator of response to therapy. Patient with linitis plastica, total disability (Eastern Cooperative Oncology Group performance scale 4), renal insufficiency or evidence of bone marrow dysfunction were excluded from the trial.

Twenty patients had measurable lesions, and another 20 patients had evaluable lesions by means of x-ray examination, endoscopy, or radionuclide scan, The patients ranged in age from 29 to 75 with a average age of 57 and composed of 34 male and 6 female. According to ECOG performance scale 2 patients scored O, 12 patients scored 1, 15 patients scored 2 and 11 patients scored 3.

In thirty two patients the diseases were too advanced to allow surgical resection, and eight patients had a recurrence of disease following primary surgical treatment.

Chemotherapy was administered on an inpatient basis. All patients were given combination chemotherapy consisting of mitomycin C, BCNU, cisplatin, and 5-fluorouracil (MBCF). Mitomycin C 6 mg per sq m was given by i.v. on day 1, BCNU 60 mg per sq m was given by i.v. on day 2, cisplatin 60 mg per sq m was gine by 3 hour i.v. infusion with mannitol diuresis on day 3, and 5-FU 300 mg per sq m was administered by i.v. infusion on days 4, 5, and 6. Each course was repeated every 35 days untill there was evidences of progression of the disease.

Objective response to therapy was determined by standard criteria. For measurable lesions a complete response was determined by total regression of all clinically recognized tumor. A partial remission was declared if there was a 50% or greater reduction in the product of the longest perpendicular diameters of the most clearly measurable malignant lesions. Stable diseases or progression of the malignant lesions were considered as non-responder. The duration of response was measured from the initial day of chemotherapy to the last day of observation, at which time the patients were classified as either responder or non-responder. Survival time was not measured.

For evaluable lesions with abnormalities disclosed by upper G-I x-ray study, gastroscopy, or isotopic liver scan which did not have clearly measurable bordres, a complete response was defined as the disappearance of all of the demonstrable lesions, and a partial response was defined by objective significant improvement of the malignant lesions.

RESULTS

Of 40 patients treated with MBCF combination chemotherapy, two patients failed to return for follow-up examinations, therefore 38 patients were available for response evaluation. Among the 38 patients, 25 patients (66%) achieved partial remission, but none were in complete remission. On the average responding patients received 4 cycles of the regimen. The median duration of response was 20 weeks. Some patients refused to continue the MBCF regimen even though they were still in remission with the regimen and were lost to follow-up, therefore the median duration of remission could not be determined. The main reasons for refusal were gastrointestinal toxicities and financial difficulties.

Analysis of the results accoding to prognosic variables showed that patients with a good performance status (ECOG O-1) responded better than those with a poor performance (ECOG 2-3).Five patients who had abdominal carcinomatosis with a huge mass showed minimal or no resonse at all to the regimen. The histological type of tumor or the degree of differentiation had no significant influence on the response.

The major, most troublesome toxicity was gastrointestinal in nature, almost all of the patients experienced some degree of nausea, anorexia,

and/or vomiting. In 30% of the patients anorexia lasted for more than one week after cessation of the chemotherapy. Serious bone marow suppression such as leukopenia below 1000 per cubic millimeter or thromboctopenia below 30,000 per cubic millimeter were not encountered. One patient developed mild peripheral neuropathy. Clinically significant ototoxicity or renal insufficiency were not experienced.

DISCUSSION

There has been some progress in the chemotherapy of gastric cnacer in the past decade. Among the gastrointestinal adenocarcinoma gastric carcinoma seems to be the tumor most responsive to cytotoxic chemotherapy[5]. 5-fluorouracil, mitomycin C, doxorubicin, and nitrosoureas (BCNU, methyl-CCNU) are known to be active drugs in the treatment of gastric cancer[5]. When used as single agent chemotherapy, reponse rate to these drugs are low, duration of response are short, and complete responses are very rare.

During the past decade various combination chemotherapy regimens have been developed in the hope that simultaneous or sequential administration of more than two active cytotoxic durgs might increase their antitumor effect in the treatment of gastric cancer[5]. The initial approaches to combination chemotherapy involved the use of 5-fluorouracil and BCNU[6]. Kovach et al. treated 34 patients with advanced gastric cancer with 5-FU and BCNU in combination, obtaining a 41% response[6]. Prior to this, Japanese investigators used mitomycin C, 5-FU, and cytosine arabinoside in combination for the treatment of gastric cancer, and their response rate was reported to be 55%[7].

Since the 5-Fluorouracil plus methyl-CCNU, 5-fluorouracil plus doxorubicin plus mitomycin C, 5-fluorouracil plus doxorubicin plus BCNU, and 5-fluorouracil plus doxorubicin plus methyl-CCNU combination chemotherapy regimens have been tested as chemotherapy for gastric cancer[5]. Among these regimens the most popular polychemotherapy regimen has been the "FAM" combination consisiting of 5-FU, adriamycin (doxorubicin), and mitomycin C, which was developed by Macdonald et al. of Georgetown University. A short-term survival advantage has been seen with a variety of these regimens in some study, with occasional long-term survivors in patients with advanced gastric cancer[1]. Further more the question has been raised by some investigators in regard to the true clinical efficacy of the various regimens. Recently Killen et al. have analyzed all available data from 18 clinical trials of combination chemotherapy for the treatment of advanced gastric cancer conducted over the last 15 years[2]. According to the analysis, in 80% of the regimens studied, the response rate was less than 35%, with a median survival of less than 6.8 months. Even with identical regimens, the difference in response rate ranged from 1 to 25 percentage points, while the difference in median survival was 0 to 29 percentage points. They concluded that new therapeutic approaches and more effective regimens are needed in gastric cancer chemotherpy.

Cisplatin, a new cytotoxic drug is known to have antitumor activities in a variety of nepolastic diseases. In gastric cancer a 22% responose rate was reported when it was used alone in 36 patients with advanced cancer who had been previously treated with multiple chemotherapy[8]. Since the finding of LaCave et al., there have been several clinical trials of cisplatin-based combination chemotherapy in gastric cnacer[9].

Cisplatin in comaination with adriamycin and 5-fluorouracil (FAP) has been reported to have yielded a response rate of 20 to 50% in the treatment of advanced gastric cancer[10,11].

Levi et al. treated 35 patients with advanced gastric cancer with BCNU, adriamycin, and 5-fluorouracil in combination, and achieved a response rate of 52% with a median duration of 48 weeks[12]. From October 1981 to September 1983, we have treated 152 patients with advanced gastric cancer with a cisplatin-based combination chemotherapy. The regimen consisted of BCNU, cisplatin, and 5-fluorouracil in combination. Among the 113 patients available for response evaluation, 74 patients (65%) demonstrated objective responses including one complete response. However the duration of response was short, and in some patients it did not last until the next cycle of chemotherapy could be started (6 weeks)[4].

In an attempt to enhance antitumor activity of the regimen consisting of BCNU, cisplatin, and 5-FU, we have elected to incorporate mitomycin C into the above regimen. Instead of a 6 week cycle, the MBCF regimen was administered at 5 week interval. Of the 40 patients treated with the MBCF regimen, two patients were not followed-up. Of the 38 patients evaluated for a response, 25 patients (66%) achieved a partial response. The median

duration of response was 20 weeks. Due to various reasons some of the patients refused to continue the MBCF regimen even though they were still in remission with the regimen. This may in part account for the relatively short response time. The responders receive an average of 4 cycles of chemotherapy.

Survival time was not measured because some of the patients sought other types of treatment once they were told that they were no longer responding to the MBCF regimen or they ceased to come to our hospital for further follow-up until the time of death. Considering the doses and schedules of the drug adminstration in the MBCF regimen bone marrow toxicity was acceptable, and no serious myelosuppression was noted. No one experienced clinically significant ototoxicity, nor was nephrotoxicity encounterd. One patient developed mild peripheral neuropathy. However symptoms of gastrointestinal toxicity was troublesome although a moderate dose of dexamethasone was administered as an antiemetic at the time of cisplatin administration. Almost all of the patients experienced some degree of anorexia, nausea and/or vomiting. Vomiting was not a problem for patients who had been gastrectomized.

We believe that this four-drug combination "MBCF" regimen has substantial activity against advanced gastric cancer.

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