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COMBINATION OF 5-FU AND EPIRUBICIN IN THE TREATMENT OF ADVANCED GASTRIC CANCER

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SUMMARY

This study was undertaken to assess the effectiveness of 5-FU plus epirubicin in the treatment of the advanced gastric cancer. For this purpose, 22 patients with no previous treatment were studied. All of the patients were unoperable or metastatic. Follow up checking continued for 24 months. Our selected therapeutic regimen consisted of a combination of 500 mg/m^2 5-FU dialy for five days, and 75 mg/m^2 epirubicin for one day. The response rate in this study was 47.4% and the mean survival rate was 9.7 months. By far, the most common complication was gastrointestinal disturbances and no carditoxicity was seen. Having presented the results of this study and comparing it with the other therapeutic regimens like FAM combination, this selected two drug combination seems to be a useful therapeutic protocol.

KEY WORDS: *5-FU, Adriamycin, Mitomycin-C (FAM); Central nervous system; Gastrointestinal tract (GI).*

INTRODUCTION

The world incidence of cancer has steadily declined in the last fifty years. The main reason for this decline is unknown, but the introduction of refrigerators which allows people to eat more fresh food than preserved ones, and the increased consumption of fresh or frozen fruits and vegetables during winter may be responsible in this regard (1). Gastric cancer is one of the leading neoplastic diseases which causes death (2). Gastric cancer could be related to the nutritional factors like

nitrites and other carcinogens that are present in food. Inspite of the advances in the diagnosis of the gastric cancer in the early stages, many of these patients consult physicians in the advanced stages (1,2). Antropyloric region is the most common anatomical location of the cancer (3). Currently, it is suggested that some nutritional elements like vitamin C have a protective effect on gastric mucosa because this vitamin inhibits the transformation of nitrites to nitrosamine (1). The major treatment of gastric cancer is surgical resection only (4). However, most patients have more advanced disease (either surgically unresectable or locally advanced). When a cancer is unresectable, partially resectable, or recurred locally in the gastric bed, prolonged disease free survival rate can be achieved in some instances by combining radiation to gastric bed with subsequent chemotherapy (4,5).

A new technique of "sandwiching" radiation between courses of chemotherapy is promising in the control of the locally recurrent stomach cancer (4). Data gathered from the studies which have assessed the effectiveness of chemotherapy in advanced gastric cancer have also been encouraging (4). The weight of evidence indicates that combination chemotherapy can produce a response (defined as a reduction of at least 50% in measruable tumor mass associated with palliation of symptoms) in 35 to 45% of patients with disseminated stomach cancer (2,4). In most studies the combination of 5-FU and adriamycin with or without mitomycin-C has been the most effective regimen (2,3).

However, prolonged use of adriamycin is limited by its hematological, gastrointestinal, and cardiac side effects. These complications have been tackled from various angles including more reliable monitoring of patients, different treatment schedules and development of new analogues. Among them, farmorubicin (epirubicen), a stereoisomer of adriamycin, has shown to be significantly less toxic than the patent compound in the experimental models while retaining comparable anti-tumor activity (6). These observations have subsequent'y been confirmed by a number of clinical studies which have demonstrated that farmorubicin, along with a good activity produce mild leukopenia, nausea, and vomiting while no symptoms of hepatic and renal toxicity and no severe life threatening cardiac toxicity below cumulative doses of about 1000 mg/m^2 (7).

In the light of this information, it seems useful to test the activity and safety of farmorubicin in combination with 5-fluorouracil in patients with advanced gastric cancer.

MATERIALS AND METHODS

Twenty two patients with gastric cancer have been treated with a combination chemotherapy regimen, consisting of farmorubicin and 5-fluorouracil, continued for a period of two years.

Baseline eligibility criteria included histologically proven unresectable or partially resectable gastric cancer, Karnovsk performance status not below 50, life expectancy higher than two months, a WBC count of 3500/mm^3, platelet count of 100,000/mm^3 and normal liver and kidney function tests.

Myocardiopathy, presence of CNS metastasis and documentation of prior or concomitant malignancy were the considered criteria for exclusion.

Treatment program consisted of 500 mg/m2 5-fluorouracil intravenously for a course of five days, and 75 mg/m^2 epirubicin intravenously on the first day.

Cycles were repeated every three weeks; dose reductions or treatment delays were applied on the basis of hematological and/or gastrointestinal toxicity evaluated according to the World Health Organization (WHO) scoring system for cancer treatment (8). In case of bone marrow depression, dosages of the drugs were reduced or treatment discontinued temporarily on the basis of the following values:

WBC < 3500 > 3000 and platelets < 100000 > 75000 = 75% of the total dose;
WBC < 2900 > 2000 and platelets < 74000 > 50000 = 50% of the total dose;
WBC < 1990 and platelets < 50000 = discontinuation of therapy until values return to baseline.

Clinical and instrumental assessments were used to determine the response to the therapy, which was evaluated according to the conventional criteria outlined by WHO guidelines (8).

Cardiac function was monitored every cycle by

the ECG. Treatment was stopped in the case of cardiac toxicity which was defined as WHO grade III and IV alterations of cadiac rhythm, and clinical and/or instrumental signs of heart failure. Patients were evaluated for tumor response, after 2-3 courses of treatment; in the case of tumor response, treatment was continued until the disease progression or reaching the total cumulative dose of epirubicin of 10000 mg/m^2. If a minimal response occurred, the drug dose would be increased by 25% in non-responder patients or in the case of progressive disease, the treatment would be stopped.

RESULTS

As it has already been mentioned, 22 patients were admitted for this study. Among them, three patients who received less than three courses of chemotherapy or stopped the treatment without any particular reason were set aside from the evaluation of the protocol.

Table 1 shows main characteristics of the patients admitted for the study.

Nine patients showed a tumor regression, giving therefore, an overall response rate of 47.3%. A relationship between the response and duration of survivance has been shown in Table 2.

Side effects were typical, depending on the chemotherapeutic regimen. The type and incidence are shown in Table 3.

DISCUSSION

Gastric cancer is the most chemosensitive malignant tumor of the GI tract. Many symptoms are interpreted as less improtant GI disturbances of the old age. Since the stomach is a hollow organ and obstructive lesions appear later, gastric cancer often progresses to the advanced stage before symptoms and signs develop (2,3). In this stage, surgical resection is not usually recommended and most of them are unoperable (3). Stomach has a very rich lymphatic system and close connection with the gastric and liver vascular systems which allows the tumors to spread to another site at early stages (2,3). Therefore, the importance of chemotherapy of gastric cancer is obvious. In this regard, the efficacy of drugs such as 5-FU, dixorubicin and mitomycin-C is known from long time ago. Many investigators, prefer the combination of 5-FU, doxorubicin, and mitomycin-C (FAM) and initial response rate of more than 42% have been reported with this regimen including some clinical remissions (9). The patients with gastric cancer are usually old and some of them have underlying heart diseases, in other words, cardiotoxicity of doxorubicin is a problem. Therefore, if we were able to document the efficacy of epirubicin that is less cardiotoxic than doxorubicin, one of the selected goal of this study would be achieved. No cardiotoxicity was seen. The response rate in this study was 47.4% and the mean survival rate was 9.7 months.

Table 1. Patients' characteristics

Characteristics	No. (%)
Sex	
Male	16 (73)
Female	6 (27)
Age (years)	
Mean (range)	56.5 (43-75)
Pathological type	
Adenocarcinoma	22 (100)
Well-differentiated	8 (37)
Poorly-differentiated	14 (63)
Types of surgery	
Unoperable (metastatic)	15 (68)
Partially operable or diagnostic	7 (32)

Table 2. Relationship between response to treatment and survivance

No. of Responses (Total 9)	Response (%)	Survival duration (months)
9/9	100	4
9/9	100	5
7/9	77	7
5/9	56	7
5/9	56	8
4/9	44	9
2/9	22	10
2/9	22	11
1/9	11	12
1/9	11	14
1/9	11	18

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