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The role of intraperitoneal chemotherapy in inoperable gastric cancer to change to operable tumor

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A B S T R A C T

Advanced non-operable gastric cancer is a great challenge for physicians. Intraperitoneal chemotherapy (IPC) is introduced as a treatment to reduce the size of tumor as operable. The aim of current study is to evaluate the effect of intraperitoneal chemotherapy in series of patients with non-operable gastric cancer. In this case series, 8 patients with advanced non-operable gastric cancer underwent intraperitoneal chemotherapy in three sessions with 10 days interval. In each session, Dexamethasone and Kytril were infused before chemotherapy and then cisplatin-5FU were given with doses of 100 mg/m2/day and 200 mg/m2/day with an infusion pump in to the peritoneal space via intraperitoneal catheter. After 10 days from the last session, the patient underwent relaparatomy to evaluate the possibility to resect the tumor. From eight patients, one left the study because of intolerance to first session of chemotherapy. Among seven patients, improvement in feeding and quality of life after first and second session of chemotherapy was seen in four cases. The third session was tolerated only in one patient. Two patients were alive after chemotherapy sessions with survival of 5 and 8 months till this report presentation, respectively. In both cases the tumor size was reduced. The five deceased patients had survival of 1 to 5 months. The results of this case series is not indicative of the efficacy of intraperitoneal chemotherapy in improvement of patient's status and reducing tumor size to be operable in patients with non-operable gastric cancer.

Introduction

Stomach cancer is considered as an important cause of death from cancers throughout the world, although it has occurred less frequently during the past decade (1). Even though stomach cancer mortality has decreased incredibly in

western countries since 1930 (2), this disease remains the world's second commonest malignancy (3-6). In Iran, stomach cancer ranks first among the commonest cancers for men, and ranks third among the commonest cancers for women, after breast and colon cancers (7-10). In general, stomach cancer prognosis is malignant, and 5-year survival rate varies between 8 and 26 percent (11-17).

Low survival rate in these patients is generally due to local and regional tumor recurrence as well as its belated diagnosis. In this regard, several factors such as pathological, clinical, and treatment variables have been examined in numerous retrospective studies to determine the factors contributing to prognosis of patients, and valuable results have been obtained (18-25). Due to similarities between symptoms of this disease and those of other stomach diseases, in most cases, stomach cancer is diagnosed in advanced stages of the disease, in such a way that 80% of cases are unfortunately so in our country. Clearly, at that time, most treatment methods fail to affect considerably patients' survival (26). Intraperitoneal chemotherapy (IPC) is an effective treatment for patients with advanced stomach cancer, but studies in this respect are vague and irregular. Intraperitoneal chemotherapy has been performed with different successes in different diseases including ovarian cancer, malignant peritoneal mesothelioma, and pseudomyxoma peritonei, and its survival value in these diseases has been proven. However, regarding stomach cancer, this has been performed only on operable patients (those without local metastasis, adherence, or peritoneal seeding), and has not been performed in cases of patients with advanced tumors (27-30). Only in one study, has intraperitoneal chemotherapy been reported as effective on treatment of patients with advanced stomach cancer (31).

In the present study, we investigate intraperitoneal chemotherapy treatment results in eight patients with advanced stomach cancer.

Materials and methods

In a case-series study performed on 8 patients with stomach cancer at the university surgery department, we examined intraperitoneal chemotherapy treatment results in eight patients with advanced stomach cancer.

In the present study, 8 patients with stomach cancer were selected, in which cases we realized during surgery that the tumor was inoperable (stage-IV). Their inoperability criteria included local invasion to retroperitoneal organs including great veins like aorta, celiac body, and solid organs like pancreas and its veins, and peritoneal or omental seeding or metastatic tumors with a stomach source including the Krukenberg tumor.

The study exclusion criteria included patients in whom ascites or local or spread metastasis was observed during examinations before surgery like CT-Scan, who were excluded due to observation of humanitarian and ethical issues, old patients over 65, who cannot tolerate chemotherapy, cachectic patients with albumin below 3 and edema, and patients who did not seem to be cooperative enough.

In the case of patients under study, when we realized the tumor could be rejected during operation, we placed a peritoneal dialysis catheter around the adhesion region. The distal of the catheter was out outside of the skin and then an epidural catheter was placed inside the tumor adhesion region with its distal out of the skin. The catheter was then fixed and the abdomen was shut.

10 days following the operation and prior to chemotherapy, Dexamethasone and Kytril were injected through the peritoneal dialysis catheter. Next, 100 mg/m^2/day and 200 mg/m^2/day of 5FU-Cisplantina were injected to the patient through the peritoneal dialysis catheter in three consecutive days. The injection was carried out using an infusion pump that led the medicine to the peritoneum. The patient was released afterwards. 10 days after this treatment, the operation was repeated and 10 days following the second time it was repeated again. In sum, it was conducted three times for the patients that could stand the third time.

10 days after the last treatment, the patient went through laparotomy for the second time to examine the possibility of removing the tumor and operating it. After thorough examinations, the survival rate of patients and the feasibility of performing surgery on stomach tumor were studied.

Moral Considerations

The written consent of all of the patients for participating in the study was obtained after providing full explanations to them. In addition, patients were assured that their participation was voluntary and that they could leave the study whenever they wanted to. They were assured no information of them would be disclosed. Moreover, no additional cost was imposed on the patients.

Result and Discussion

In the present study, 8 patients with inoperable stomach cancer were subjected to intraperitoneal chemotherapy.

Table I shows the basic pre-surgery findings for the patients. The mean age of patients was 63.00 ± 7.27 years. The majority of patients were male. Stomachache, weight loss and anorexia were among the most common problems complained about by the patients. In one of the patients, the person was first diagnosed with dysphagia and results of paraclinical examinations led to the diagnosis of cancer.

Table II presents the paraclinical findings about the patients under study. The endoscopy results of two patients were missing and the CT-Scan results of one patient were not available. The endoscopy and pathology results were not diagnostic in the case of one patient.

Table III shows the results after different iterations of chemotherapy and surgery. One of the patients left the study as a result of being unable to bear the pain. Following the first chemotherapy, 4 patients demonstrated an improvement in nourishment and life quality. One patient also demonstrated relative improvements in the aforementioned aspects. In the second time, 4 patients again demonstrated improvements.

Only two patients survived the treatment. No operation was performed on patient no. 3 and he/she lived for 5 months from the beginning of the program. Patient no. 6 also lived healthy for 8 months after the start of chemotherapy. The operation performed on this patient was as follows:

A tumor in stomach distal had led to GOO along with proximity conflict in the left lobe of his/her liver. There were also several lymph nodes around the aorta and the lower mediastinum with looped blockage from the ileum to the tumor tissue. The patient went through omentectomy, subtotal gastrectomy, subtotal hepatectomy, full mechanical lymph node dissection of the lower and para-aortic mediastinum around the celiac, and enterostomy.

Table.1 Demographic and clinical manifestation of patients

No.	Age	Sex	Diagnosis	Clinical manifestation
1	57	Male	Gastric Cancer	Abdominal pain of 2 months ago, nausea, vomiting, bloating and abdominal fullness, early satiety and weight loss
2	62	Male	gastric adenocarcinoma	Abdominal pain of 6 months, anorexia, weight loss and dysphagia to solids
3	73	Male	gastric adenocarcinoma	Anorexia and early satiety from 8 months ago, Hematemesis
4	56	Male	gastric adenocarcinoma intestinal type	Dysphagia to solids before 4 months
5	65	Male	gastric adenocarcinoma	abdominal pain of 8 months ago, vomiting and anorexia
6	53	Male	Gastric Cancer	digestive problems of A few months ago, heartburn, vomiting, weight loss and anorexia
7	71	Male	gastric adenocarcinoma diffuse type	Bilious vomiting, loss of appetite and weight loss
8	67	Female	Gastric Cancer	Abdominal pain and vomiting

Table.2 Paraclinical findings of patients

No.	Endoscopic finding	Pathologic finding	CT-Scan Finding
1	Infiltrative lesion in the gastric body and antrum	Poorly differentiated adenocarcinoma	Dilation and thickening of the antrum
2	Large ulcerated tumor in the upper stomach	Adenocarcinoma signet ring type	Irregular hypertrophy of the gastric wall and Several para-aortic irregularity
3	-	Adenocarcinoma	Increase in thickness with mass in the fundus(28 * 80 *mm*)
4	Mass casualties of LEJ* with severe stenosis	Intestinal type adenocarcinoma	Large soft tissue mass in the cardia(4*7 *cm*), infiltration of small curvature of the stomach and Lymphadenopathy
5	Infiltrative mass in the body of the stomach with necrosis	Invasive adenocarcinoma diffuse pattern	Normal
6	-	Intestinal type adenocarcinoma	-
7	Large ulcerated mass with Severe Gastric outlet Stenosis	Adenocarcinoma diffuse type	Thickening of the stomach(especially in the cardia, fundus, antrum and pylorus)
8	Gastric outlet Stenosis	No definite diagnosis	Tumor infiltration in the antrum and body

*_LEJ: Lower esophageal junction

Table.3 Outcome of patient's Following to several round of IPC

No.	First round	Second round	Third round	Surgical outcome after chemotherapy	Final outcome
1	Improve nutrition, Epigastric pain relief, The lack of improvement in QoL *	Improve nutrition and QoL	Not performed	Died	Died
2	Improve nutrition and QoL	Improve QoL	Not performed	Disease progression and conflicts surrounding organs	Died
3	Improve nutrition and QoL	Improve nutrition and QoL	Improve nutrition and QoL	Reduction in tumor size	Alive
4	Withdrew the treatment due to The first round of chemotherapy				
5	The lack of improvement in Signs and f	Died after the second round of chemotherapy			
6	Improve nutrition and QoL	Improve nutrition and QoL	Not performed(GIB¥ in pervious round)		Alive
7	Relative improvement	IPC hold due to Absence of Granulation tissue	IPC hold and underwent chemotherapy	Died one month after the third dose chemotherapy	
8	The lack of improvement in Signs and QoL	Relative improvement	Not performed	Died two weeks after the last chemotherapy	

*_QoL: Quality of Life ¥_GIB: Gastrointestinal Bleeding

From the beginning of chemotherapy operations, patients one, two, five, seven and eight lived for 5, 4, 1, 2 and 1 month (s), respectively.

Due to the anatomic demonstrations of the stomach, advanced stomach cancer (gastric cancer) is capable of local recurrence and metastasis. In addition, when the tumor penetrates into the serous and leads to the implantation of tumor in the peritoneum, the possibility of recurrence and metastasis increases drastically. As a result, the possibility of 5 years of survival declines considerably. Hence, acceptable results are not only obtained through surgery alone (32-39).

Intraperitoneal chemotherapy is known as one of the supplementary treatments for this disease. This treatment has numerous pharmacokinetics advantages and is capable of removing free cancer cells and the remaining micro metastatic or microscopic centers in the peritoneal cavity (47-50).

Intraperitoneal chemotherapy also reduces the possibility of recurrence and thus it combines the effects of in-port chemotherapy on liver with the direct effects of chemotherapy on peritoneum and the resection area. Intraperitoneal chemotherapy is reported as very valuable strategy for the treatment of stomach cancer (30, 47-48).

According to previous findings, it was assumed that intraperitoneal chemotherapy can lead to acceptable results in patients with inoperable advanced gastric cancer. Hence, this research was aimed to attain this goal. 8 patients were selected for primary assessments and were subjected to intraperitoneal chemotherapy. Of the 8 patients under study, one patient was excluded from the study due to his/her inability to bear the treatment. Of the remaining 7 patients, 4 patients demonstrated improved nourishment and life quality following the first and second rounds of chemotherapy. Only one patient could bear the third stage of chemotherapy and the rest of the patients did not experience this stage as a result of their inability to bear the disease or outbreak of complications such as gastrointestinal bleeding.

Zhao et al. performed two rounds of hyperthermic intraperitoneal chemotherapy

as well as two rounds of radiotherapy on patients with inoperable gastric cancer. Symptoms such as pain and the high level of ascites were shown to be reduced. Results of this study also reflected the improvement of quality of life of the patients (31). Costa et al. also carried out a study on 10 patients with advanced inoperable gastric cancer. They subjected the patients to hyperthermic intraperitoneal chemotherapy and surgery. The treatments led to the full improvement of the quality of life and clinical condition of the patients. Unlike the present research, in this study only 5 patients managed to go through the all three rounds of treatment (46).

In the present study, only two patients survived the chemotherapy sessions. According to the follow-ups, the first case lived for 5 months and the second lived for 8 months. In both cases the size of the tumor was reduced but the resection operation was only performed on the second patient. The 5 deceased patients also lived for 1 to 5 months.

In the research by Zhao et al., the lifetime of the patients in the intraperitoneal chemotherapy and radiotherapy groups increased considerably (31). In the study by Costa et al. the rate of post-surgical complications was reported to be 50% and no mortality was observed (46).
According to the results of clinical studies regarding the effectiveness of intraperitoneal chemotherapy for gastric cancer patients, intraperitoneal chemotherapy can be classified into five major categories: intraoperative hyperthermic intraperitoneal chemotherapy; intraoperative hyperthermic intraperitoneal chemotherapy with post-operative intraperitoneal chemotherapy; intraoperative normothermic intraperitoneal chemotherapy; post-operative normothermic intraperitoneal chemotherapy; and postoperative hyperthermic intraperitoneal chemotherapy (43-45). All of these classifications only apply to operable cancers and there are no studies of inoperable cases available. The existing studies of inoperable cancer have also addressed the hyperthermic methods (31, 46).

Perhaps the initial failure of the research results can be ascribed to the samples. No precise screening method is available for early diagnosis of stomach cancer and these patients usually visit clinics at the last stages of their sickness. Many of the symptoms of this disease are also seen in other diseases. Many of the patients suffering from this disease do not take it seriously and only visit a physician as their general health declines. Hence, all of the patients under study were in the last stages of their disease and the medical team was therefore unable to treat them.

In the second round, the treatment protocol, the determined chemotherapy dosage, and the type of chemotherapy drug contributed to the acceptance of treatment. These factors also increased the cytoreduction capability and reduced its complications. The hyperthermic or normothermic nature of chemotherapy can also influence the results.
If patients during the early or last stages of their disease are examined with a better chemotherapy method, better results are obtained.

Conclusion

Results of this multi-case study do not confirm the effectiveness of intraperitoneal chemotherapy for the enhancement of the condition of patients and the reduction in the size of tumor size in patients with inoperable gastric cancer.

Suggestions

Due to the relative effectiveness of two-stage chemotherapy for peritoneum, it is recommended to conduct other studies to examine the role of two-stage treatment in the improvement of the survival of patients.
It is also recommended to perform other studies using different protocols to obtain better results. However, as mentioned, the results of this study do not confirm the effectiveness of intraperitoneal chemotherapy for this group of patients.

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