The effectiveness of adjuvant intraperitoneal hyperthermic chemoperfusion after cytoreductive surgery in locally advanced gastric cancer

Erdem Erhan, Alagöl Haluk
Department of General Surgery, Ankara Oncology Training and Research Hospital, Turkey.

ABSTRACT

Background: Intraperitoneal hyperthermic chemoperfusion (IHCP), which is a locoregional treatment used in peritoneal micrometastases in intra-abdominal tumours was first applied in 1980, and since then it has been used as an adjuvant treatment in locally advanced tumours and as palliation in inoperable tumours, especially in tumours of genital and gastrointestinal system origin.

Aim: In this study the effectiveness of adjuvant IHCP in treating gastric cancer with serosal invasion after curative surgery was investigated.

Setting and design: This study was designed in the Department of General Surgery in the Ankara Oncology Hospital. IHCP was done immediately after cytoreductive surgery.

Methods: After cytoreductive surgery in 10 patients with locally advanced gastric cancer, two drains were placed into the peritoneal cavity and after the closure of the wound, IHCP was done with 10mg/L mitomycin-C at 42°C for 60-90 minutes.

Results: No systemic and local complications were seen after perfusion except atelectasis in one patient. Local recurrence and metastatic tumour at the porta hepatis was seen in one patient each, hepatic metastases in five patients, and one patient died from myocardial infarction. The survival analysis was done with Kaplan-Meier method and the 1, 2, and 5-year overall and disease-free survival rates were 80, 70, 40% and 90, 60, 30% respectively.

Conclusion: Although this study was conducted for a small number of patients it appears that IHCP can be used safely in the adjuvant locoregional treatment of gastric cancer.

KEY WORDS
Hyperthermic chemoperfusion, gastric cancer

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INTRODUCTION

Hyperthermic perfusion chemotherapy is a locoregional treatment modality that is used as adjuvant treatment in locally advanced operable tumours, and as palliation in inoperable tumours. Thus intraperitoneal hyperthermic chemoperfusion (IHCP) is also a method of locoregional treatment that is used in peritoneal seedings and peritoneal micrometastases in intra-abdominal tumours, especially in the gastrointestinal system and genital tumours. Intraperitoneal administration of chemotherapy has the benefit of higher concentrations of drugs delivered locally to the site of the tumour while diminishing the systemic toxic effects. This method is regarded as the best treatment for the prevention and/or healing of peritoneal seeding from gastrointestinal cancer, especially for gastric cancers, which have a high rate of locoregional
recurrence and peritoneal micrometastases. It's known that in these cases systemic chemotherapy is mostly ineffective.

The purpose of this study was to assess the role of IHCP as an adjuvant therapy in locally advanced gastric cancer patients after radical surgery.

MATERIALS AND METHODS

Ten patients who were diagnosed microscopically as having gastric cancer underwent macroscopic cytoreductive surgery and IHCP between December 1996 and December 2001. The study was approved by the Ethics Committee of the Ankara Oncology Training and Research Hospital (procedures followed in accordance with the standards ethical committee on human experimentation and with the Helsinki Declaration of 1975). Cytoreductive surgery consisted of the removal of all gross tumours and involved organs or peritoneum. So R₀ gastric resection was undertaken in all patients with greater and lesser omentectomy, splenectomy and localized peritonectomy (left or right upper quadrant) if there was any involvement or metastasis at peritoneal surface, then D₂ lymph node dissection was added. At the end of the operation two drains were inserted in the peritoneal cavity and after the closure of the abdomen, an extra-corporeal circuit conducted IHCP, allow perfusate circulation with at 300-500 ml/min and hyperthermia ranging 40-42°C for 60-90 minutes. The perfusate consisted of 3 L. of saline solution with cytotoxic drugs. We used 10-mg/L mitomycin-C because of its high penetration rate to micronodules and low absorption rate across the peritoneal surface. At the end of the perfusion 1 L. of perfusate was emptied and the rest of it was left in the abdomen for 12 hours.

Statistical Analysis

The Kaplan-Meier method was used for the calculation of the overall and disease-free survival rates.

RESULTS

In a total of 10 patients, 5 underwent total and 5 subtotal gastrectomies with omentectomy, splenectomy and D₂ lymph node dissection. Localized peritonectomy was also added in 3 of them who had peritoneal involvement. The patients' tumours were all T₃ or T₄ and none had organ metastases at the time of surgery. On microscopic examination 1 had musinous and 9 had adenoid cancer and 6 of them had histopathologically proven lymph node metastasis. The patients consisted of 6 women and 4 men with an average age of 59 years (range 25-74). All patients underwent IHCP with mitomycin-C after the surgery. The average hospital stay was 10 days and no systemic and local complications were seen except one atelectasis. The patients were followed-up with regular physical examinations including haematological analysis and tumour markers (CEA, CA 19-9, CA-125) every 3 months, abdominal ultrasonography and upper gastrointestinal endoscopy every 6 months, and abdominal computerized tomography every year. At the end of the first year 2 patients died, one of them from myocardial infarction and she had no evidence of tumour, and the other one from hepatic metastases. In the 24-48 months period 4 other patients also died from liver metastasis and only one of them had peritoneal recurrence. Four patients who completed 5-year survival are still alive and only
one of them has a tumour at porta hepatis. Three patients have no complaints, no evidence of tumour or elevation of tumour markers. The 1, 2 and 5-year overall and disease-free survival rates were 80, 70, 40% and 90, 60, 30% respectively (Figures 1a, 1b).

**DISCUSSION**

The intraperitoneal administration of cytotoxic agents has been used since 1980. The first aim of this method is the eradication of microscopic residual disease. It has the benefit of higher concentrations of drugs delivered locally to the tumour site while preventing the systemic toxic effects compared with intravenous administration. The efficacy of a drug is calculated by the ratio of the peritoneal cavity area under the concentration/time curve (AUCc) to the plasma area under the concentration/time curve (AUCp). This ratio is between 250-1400 for 5-Flourourasil, 12-20 for cisplatin and 75-80 for mitomycin-C. The efficacy is increased with the slow absorption rate of the cytotoxic drug. Hydrophilic drugs like 5-Flourourasil, cisplatin and mitomycin-C are absorbed very slowly from the peritoneal surface so they are the most useful drugs for IHCP. Beyond this the direct tumour absorption of drugs occurs to a level of 5 mm beneath the tumour surface, that means tumour nodules exceeding 5 mm are not suitable for IHCP. In this technique hyperthermia also enhances the efficacy with its own cytotoxic effect by maximizing the diffusion of the drugs to the tumoral nodules.

In gastric cancer IHCP can also be used as neoadjuvant aim for down-staging but the most preferential use is the adjuvant route. Takahashi and Hagiwara used activated carbon particles in the peritoneal cavity, which adsorbed a large amount of mitomycin-C in gastric cancer patients with definite serosal involvement. They found 14 and 18% of survival advantage in 2 and 3-year times respectively compared with control groups. In other studies that used cisplatin or mitomycin-C in early postoperative intraperitoneal chemotherapy, statistically significant survival advantages were found against control groups. In this technique hyperthermia also enhances the efficacy with its own cytotoxic effect by maximizing the diffusion of the drugs to the tumoral nodules.

With the help of these data the treatment algorithm has been evolved for the management of operable gastric cancer was determined in 1996 by Kelsen. Today this algorithm is still valid, but has been modified to included IHCP (Figure 2). In the use of IHCP there are also some restrictions in that IHCP only treats peritoneal disease so it is contraindicated when extraperitoneal metastases are found. Beyond this, macroscopic cytoreductive surgery must be performed before IHCP. The residual disease or the nodules in the peritoneal cavity must be smaller than 5 mm, and there must be no adhesion in the peritoneal cavity that restrict the homogeneity of distribution of the cytotoxic agents.

In this study, although the number of patients is small, the effective control of local peritoneal recurrence (10%) and improved overall and disease free survival have been encouraging.

![Figure 2: Treatment algorithm in operable gastric cancer](modified from 25). CT: Chemotherapy, IHCP: intraperitoneal hyperthermic chemoperfusion.)
REFERENCES


