

INTRAPERITONEAL CHEMOTHERAPY FOR ADVANCED GASTRIC CANCER

Carmen Radulescu, Daniel Tufeanu, Corina Mintioan, Dusan Crstici, Nicola Traila

REZUMAT

Objective: In practica oncologică actuală, pacienții cu cancer gastric local avansat și carcinomatoză peritoneală pot beneficia de tratamente loco-regionale precum chimioterapia intraperitoneală. Diversificarea tratamentului la pacienții cu cancer gastric avansat a fost realizată prin administrarea în mod repetat a citostaticelor direct intraperitoneale, prin intermediul unui sistem implantabil port-a-cath. **Pacienți și metodă:** Din ianuarie 1996 până în decembrie 2007, 31 de pacienți, 22 bărbați și 9 femei prezentând carcinomatoză peritoneală cu punct de plecare cancerul gastric au fost supuși chimioterapiei intraperitoneale. Ea a reprezentat un tratament adițional chimioterapiei sistemice. Cisplatinul și 5-fluorouracilul au fost administrate intraperitoneal, singure sau în asociere.

Rezultate: Chimioterapia intraperitoneală folosită ca tratament paliativ în carcinomatoza peritoneală cu punct de plecare cancerul gastric, a fost în general bine tolerată de pacienți și în 11 cazuri a adus ameliorări semnificative în ceea ce privește calitatea vieții. **Concluzii:** Chimioterapia intraperitoneală poate fi considerată ca făcând parte din arsenalul chimioterapiei adjuvante și neoadjuvante. Reprezintă un tratament țintit pe diseminările peritoneale microscopice și macroscopice limitate. Sistemul port-a-cath este o modalitate eficientă de administrare în ședințe repetate a tratamentului.

Cuvinte cheie: chimioterapie intraperitoneală, cancer gastric, carcinomatoză peritoneală, sistem port-a-cath

ABSTRACT

Objectives: In the current oncological practice, patients presenting advanced local gastric cancer and peritoneal carcinomatosis can benefit from local-regional treatments as well as from intraperitoneal chemotherapy. Treatment diversification for patients with advanced gastric cancer is being covered by administration through repeated pattern of cytostatics, directly intraperitoneal by implanting a port-a-cath system. **Patients and methods:** From January 1996 until December 2007, 31 patients of which 31 males and 9 females presenting peritoneal carcinomatosis having as starting point a gastric cancer, were submitted to intraperitoneal chemotherapy. This procedure represents an additional treatment to systemic chemotherapy. Cisplatin and 5-fluorouracil were administered intraperitoneally, alone or in association. **Results:** The intraperitoneal chemotherapy used as palliative treatment in peritoneal carcinomatosis originating in gastric cancer, was generally well tolerated by patients and in 11 cases it managed to bring meaningful improvements related to life quality. **Conclusions:** Intraperitoneal chemotherapy may be considered as part of the adjuvant and neo-adjuvant chemotherapy arsenal. It represents a treatment targeted towards limited microscopical and macroscopical peritoneal disseminations. Port-a-cath systems are an efficient method of administration through follow-up treatment.

Key Words: intraperitoneal chemotherapy; gastric cancer; peritoneal carcinomatosis, port-a-cath system

INTRODUCTION

Gastric cancer is one of the most aggressive digestive cancers. More than two thirds of gastric cancer patients are diagnosed in advanced stages of the disease (II, III, IV).

After curative surgical interventions, the peritoneum frequently is the main place of rebound or it already is involved in a rather large percentage in the evolution of gastric cancer at the moment of diagnosis. Even then, when gastric resection is performable, and we have clinical and histopathological leads that allowed the performance of a curative resection, the peritoneal recurrence appears in a percentage of approximately 50%.¹

In the current oncological practice, the malignity of the peritoneal surface, clinical entity appears in gastric cancer evolution as recurrence of the treated neoplastic disease or it coexists with the disease at diagnosis momentum, may still actually benefit of local/regional therapy as an intraperitoneal

Clinical Emergency Municipal Hospital, Timisoara

Correspondence to:
Carmen Radulescu, Clinical Emergency Municipal Hospital, 5 G. Dima Str.,
Timisoara, Tel. +40-256-221553
Email: mihaela77r@yahoo.com

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chemotherapy associated with systemic chemotherapy.

During invasive surgical interventions for gastric cancers, peritoneal micro metastases are present in approximately 60% of patients. These micro metastasis may exist as carcinomatose cells already present in the peritoneal cavity or as free floating residual metastases. Extended lymph node dissection and manipulation of tissue can be responsible spreading viable tumor cells within the peritoneal cavity.

The peritoneal carcinomatosis that follows curative resection appears to have a rather high incidence of between 20% and 50%. (Gunderson and Sasin, 1982; Kaga et al, 1984; Wisbeck et al, 1986; Laundry et al, 1990). These data show that a large number of patients present isolated recurrences located in the peritoneal cavity and that an efficient treatment targeted towards peritoneal dissemination could actually have better results. The intraperitoneal layer recognition as a barrier defense against tumor progression suggested the hypothesis that it is possible to eradicate tumor nodules from the peritoneal surface (Sugarbaker 1990). The new pharmacological concept of peritoneum-plasma barrier performs as basis for use of chemotherapeutical agents intraperitoneally.

The standard treatment for gastric cancer consisting of surgery followed by adjuvant systemic chemotherapy may delay symptoms installation but is certainly not always of curative nature. Systemic chemotherapy is generally inefficient towards peritoneal dissemination due to poor peritoneal penetration of the chemotherapeutical drugs and only rarely has brought real benefits to patients presenting intestinal obstruction and ascites, complications that occur within peritoneal carcinomatosis evolution.²

Starting with 1996, the Second General Surgery & Oncology Clinic, Timisoara (Prof. T. Nicola) has introduced the intraperitoneal chemotherapy for neoplastic cases with peritoneal dissemination, also related to gastric cancers. The reason was obtaining a better control over peritoneal dissemination in gastric cancers with clear improvement of disease prognosis. As follows we are describing procedural means of achieving intraperitoneal chemotherapy and various pathological situations one may encounter during ongoing treatment.

MATERIALS AND METHODS

Between 1996-2007, intraperitoneal chemotherapy was applied to 31 patients, of which 31 were males and 9 females, with ages between 46 and 75 years

old (average age 60.5 years). Gastric cancer diagnosis was established preoperatively through gastroscopy followed by biopsy and histopathological examination. Standard lab test were performed, chest X-ray, abdominal and pelvic CT.

Laparotomy was suggested as intended curative treatment. Intraoperative exploration of 5 patients had revealed a neoplastic disease, apparently localized, the gastric cancer showing off on the serous, without visible disseminations of peritoneal carcinomatosis.

Subtotal gastrectomy was possible in 3 cases and total gastrectomy in 3 cases with lymphadenectomy D2, but the cytology from peritoneal lavage had emphasized carcinomatose cells. During explorative laparotomy 11 patients were classified as inoperable due to heavy penetration of the neoplastic process in pancreas and also due to disseminations present at peritoneal serous level, pre-operative CT clearly under evaluating disease stage.

15 patients presented peritoneal rebound after gastrectomy for gastric neoplasm, of which 9 revealed an ascitogenous form of peritoneal carcinomatosis and 6 patients had non-ascitogenous form. None of these patients had undergone systemic chemotherapy. (Table 1)

Table 1. Disease spectrum for patients undergoing intraperitoneal chemotherapy.

Diagnosis	No. of cases	Surgical procedure
Resectable localized gastric cancer, with serous presence; peritoneal carcinomatosis macroscopically negative & microscopically positive	5	Total gastrectomy - 3 cases Subtotal gastrectomy - 2 cases
Unresectable gastric cancer with peritoneal disseminations smaller than 5 mm	11	Mounting of port-a-cath system
Peritoneal relapse post gastrectomy	15	Mounting of port-a-cath system

Intraperitoneal chemotherapy was performed through a port-a-cath device. This is a system presenting a reservoir provided with a silicone globe, Brown camera, placed subcutaneously, and connected to a catheter which, through a minimal trajectory within the abdominal wall gets through to the peritoneal cavity. (Fig. 1) We used this system for the purpose of administrating chemotherapy drugs directly in the peritoneum in repeated sessions.



Figure 1. Port-a-cath system.

Patient selection criteria:

- Written agreement of the patient for implementation of treatment together with approval of Hospital Ethics Committee;
- Histopathological confirmation of the neoplastic gastric process being performed preoperatively through biopsy followed up by histopathological examination;
- Positive peritoneal liquid cytology for the neoplastic cells or obvious presence of millia disseminations at peritoneal serous level, with a diameter smaller than 5 mm;
- Lack of severe co morbidities;
- Lesion score of the tumor implant of 0-1;
- Absence of metastasis on the outside of the peritoneal cavity (bone, pulmonary, cerebral, skin);
- Adequate bone marrow reserve: leucocytes $>4000/mm^3$, platelets $>150000/ml$;
- Unmodified kidney function: blood urea < 45 mg/dl; serous creatinine <1.5 mg/dl;
- Karnofsky performance status $>50\%$;
- No previous history of chemotherapeutical treatment.

Surgical Technique

Port-a-cath system mounting was performed in the same time with laparotomy. After complete exploration of the peritoneal cavity and full inventory of existent lesions we mounted the port-a-cath system. The catheter is being separated by the camera and the most adequate entrance trajectory through the peritoneal cavity is being chosen. It is preferred that the laparotomy line to be sidestepped. The catheter traverses the trajectory from the entrance point into the peritoneal cavity until the location chosen to create the pocket where the reservoir is to be mounted, in our case – Brown camera. Depending on the chosen trajectory, the location of the port pocket may be located over the right or left rib cage. Once the trajectory is being established, over the chosen side of the rib cage, on the median clavicular line a small transversal incision is being performed and through

dissection a pocket is being prepared where the Brown camera will be fixed. Afterwards a tunneling of the abdominal wall is to be performed starting from the entrance location of the catheter into the peritoneal cavity until the location of the port pocket. It has to be carefully controlled that the tunneling system will form a trajectory of a width approximately equal with catheter width. After its insertion, the catheter is to be connected to the Brown camera. To prevent camera migration or its rotation inside the pocket, this must be fixed in four cardinal points with unresorbable threads. The pocket should be created at an approximate distance of 2 cm from the incision line. The part of catheter that remains in the peritoneal cavity has to have an approximate length of 10-15 cm as to prevent migration of the catheter in the subcutaneous tissues.

After complete fixing, the system should be washed with 10-20 cc heparin saline solution. This means ensures a check-up of the permeability and air tightness of the system. Also, the wash-up will ensure maintenance of system functionality. The washing procedure is to be performed after each usage of the system for interperitoneal chemistry procedure.

If the system is positively functional then the procedure of perfect closure of the operation is performed. Drainage of the peritoneal cavity is suggested if gastric resection is also being performed but is to be abolished before starting the intraperitoneal chemotherapy to prevent later losses of ascites liquid or fluids used for intraperitoneal chemotherapy. Great consideration should be given for the catheter not to be involved in the incision closure .

Technical incidents and prevention methods

Access problems of the port system can be avoided by strong anchorage of the Brown camera on the rough plan of the rib cage. It is being mentioned in literature trials of mounting on the anterior-superior iliac spine and inguinal ligament. If Brown camera is being mounted in a location where there is no strong plan of support then repeated camera access would be unsecured or much impaired. The port system that is being used has to be big enough and the anchorage of the Brown camera on the rib cage is being done with unresorbable thread. We have not encountered any case of camera migration from the place of implant.

Avoiding losses of intraperitoneal liquid (ascites or treatment fluids) is being implemented through performing a trajectory with dimensions that correspond to catheter diameter in use. The catheter has to have a certain firmness and its diameter to be big enough..Our patients did not suffer any loss of

intraperitoneal liquid.

Tumor implants at port pocket level were mentioned in literature by Walker JL, especially when the system was mounted through laparoscopy.¹ This aspect may be avoided by starting as soon as possible chemotherapeutical sessions. We have not encountered such complications.

Chemotherapeutical flow obstruction through the port system may be determined by catheter twisting, and penetration into various intraperitoneal adherences or its warping with fibrin. Whatever the cause, once the system is warped the intraperitoneal chemotherapy is to be abandoned. Four of our patients had to have their treatment abandoned due to system warping – one patient after the third treatment session and three patients after the fifth session.

Hematoma present at port pocket location can be avoided through a light dissection of the tissues and a careful haemostasis.

Treatment Complications

Chemical or infectious peritonitis may become intraperitoneal chemotherapy inconveniences.¹⁷ If the patient that undergoes treatment, reports abdominal pains accompanied by signs of peritoneal irritation, fever and an increased number of leucocytes, then a peritonitis is to be suspected. Bacteriological examinations may be performed by port irrigation and implicitly peritoneal cavity irrigation followed up by fluid vacuuming. Intraperitoneal chemotherapy administration may result in pain due to fluid expansion. This type of pain decreases in time. Three of the patients had presented intense pain at the second intraperitoneal chemotherapy session and had abandoned the treatment altogether. We did not encounter any case of infectious peritonitis.

Infection of port, catheter or peritoneal cavity may be directly linked with an infection of the system while its mounting procedure (peritonitis due tegument microorganisms), it may appear in time through enteric lesions or suture opening (peritonitis due to enteric microorganisms). For gastrectomy patients, to prevent opening of digestive suture, we had started intraperitoneal chemotherapy only after 14 days.

Cellulites at port pocket level manifests with pain, erythema and movement from the place of port implant. It is necessary to perform an incision, drain the area and extract the system followed by antibiotics treatment. Patients' evolution should be monitored in order to capture any signs of peritonitis. This complication may be avoided by proper sterile port access.

Discomfort at port pocket level is usually negligible; none of our patients presented major discomforts.

General complications related to intraperitoneal chemotherapy treatment administration are usually of rather low importance compared with effects of systemic chemotherapy, and they manifest through loss of appetite, nausea, vomiting, diarrhea, abdominal pain, leucopenia, thrombocytopenia, anemia, fatigue. They may be of reduced intensity and controllable through symptomatic medication until severe medication is needed when treatment should be abandoned.

RESULTS

Intraperitoneal chemotherapy was performed using 5-fluorouracil and cisplatin, three consecutive days with a break of 28 days between sessions. After performance of intraperitoneal chemotherapy the patients were forwarded to the Medical Oncology service for systemic treatment. The number of treatment sessions is shown in Figure 2.

Ten of the patients had undergone post surgery treatment sessions and had been missing from our database later on. Four patients had abandoned treatment due to system warping, which brought it out of use, one after 3 sessions and three after 5 sessions. Three patients had presented intense abdominal pain and abandoned treatment after the second intraperitoneal chemotherapy session. Four patients had undergone 4 treatment sessions. Two of them developed infections at catheter insertion point which required its extraction and other two had disappeared from our database. Eight patients had undergone the entire recommended treatment (8 sessions in total) and two patients had undergone 7 sessions of intraperitoneal chemotherapy.

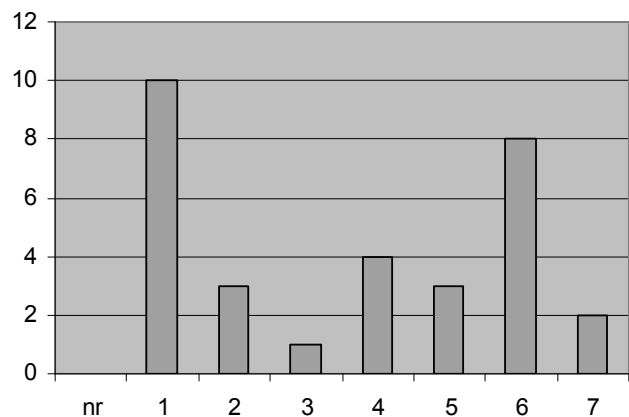


Figure 2. Number of treatment sessions vs. number of patients.

Treatment regimens were diverse depending of patient tolerance. Patients with ascites liquid had presented remission during treatment. No digestive perforations were registered. Nausea, vomiting and diarrhea were of light intensity and resolved with symptomatic treatment. Patients that had undergone total or subtotal gastrectomy were submitted to intraperitoneal chemotherapy only after 14 days post surgery to allow digestive suture consolidation. No inpatient death had been recorded.

DISCUSSION

Between various types of existent gastrointestinal cancers, the gastric cancer presenting peritoneal disseminations deserves increased concern due to its aggressive behavior that considerably shortens the average survival rate. Also, the prognosis of gastric cancer patients with macroscopically negative but with microscopically positive peritoneal dissemination is generally poor. An overall analysis regarding survival rate at 2 years after surgery was of 0% between 1975 and 1981. Between 1982 and 1988 an improvement of 38% has been recorded 2 years after surgery but of 0% 5 years after surgery.⁴ Therefore peritoneal lavage cytology undergone during surgical procedure in case of stomach cancers is of utmost importance and extremely efficient for outlining malignant cells. To make note of, is the fact that after surgical manipulations, in the peritoneal cavity may be left over viable, floating malignant cells, that later on inoculate and give birth to peritoneal relapse. Therefore, a local treatment, targeting free tumor cells may bring considerable prognosis improvement.

A clinical study initiated by the Medical Center of Baylor University, Dallas Texas started since 1997 had underlined a survival prognosis improvement for peritoneal carcinomatosis patients.²⁸ Fujimara observed a survival improvement 3 years after surgery for gastric cancer patients T₃N₁ of 51% undergoing surgical procedure followed by intraperitoneal chemotherapy in normo-thermic regimen and only a 23% for patients that had undergone simple surgical intervention.²⁸

An important concept related to tumor behavior is presented by Weiss (1986). He concludes the following: even if a large number of malignant cells reach the liver through the blood stream, only few of them attach themselves to the endothelium in such a way as to develop a metastasis. This phenomenon, so called "metastatic inefficiency" are characteristic to hematogenous disseminations of the disease.

In comparison, the free cancerous cells from the peritoneal cavity implant themselves and grow easily. Scott and his colleagues had been evaluating the prognosis significance of the isolated tumor cells detected in the bone marrow and peritoneal lavage of 84 patients with gastric cancer and 109 patients with colon rectum cancer. The cancerous cells identified in the bone marrow had a limited prognosis significance, while the free cancerous cells from the peritoneal cavity had been closely correlated with a limited survival rate in time.

Therefore, from this conceptual perspective, the intraperitoneal chemotherapy has the meaning of altering these cells that are left viable inside peritoneal cavity after curative surgical interventions reason for which we have been performing it for the five patients with gastric resection and positive peritoneal cytology.^{17,19}

For the unresectable gastric cancer, a combined therapy, intraperitoneal as well as systemic, may conduct towards an improvement of their general condition also presenting an ongoing improvement of performance status.²⁴ We managed to obtain an improvement of the general condition for five patients out of 11 from the studied group. Therefore, intraperitoneal chemotherapy combined with systemic therapy, through biochemical modulation, may bring prognosis improvement to this type of patients.

Peritoneal recurrence may also benefit from intraperitoneal chemotherapy as palliative treatment.¹⁶ In cases presenting peritoneal recurrence of ascite type, we recorded a slowing of the rhythm of formation of ascites and even regression of it. In cases where peritoneal disseminations are severe, this treatment does not bring significant improvements to the patients due to the fact that the maximum effect of chemotherapy drugs penetration in depth is of maximum 3 mm. Japanese researchers support the idea that intraperitoneally administrated taxanes are very efficient towards the localized control of peritoneal dissemination from gastric cancer.^{19,25}

There is no standard therapy related to the type of chemotherapy drugs used and their dosage. With good results there were used: 5-FU, CDDP, mitomycin C, etoposid, floxuridine, leucovorin and others.^{15,17,23}

Inconvenients of those methods are the following: abandoning treatment was encountered in 25.8 % of the cases for technical reasons: warping of the system used (4 cases), infection located in port implant area (2 cases) and peritoneal adherences that did not permit a proper distribution of the fluid within the peritoneal cavity (2 cases), patients accusing intense pain post infusion.

Also, it must be taken in consideration the fact that this type of treatment cannot be applied in patients with extensive peritoneal dissemination, because of its inefficiency under the circumstances. Leaders in this domain apply intraperitoneal chemotherapy after a complete surgical cytoreduction (resections of invaded organs associated with intraperitoneal techniques of peritonectomy). They support the idea that the effect of the intraperitoneal chemotherapy is maximized by the surgical reduction of the disease at microscopical level.

Besides the inconveniences presented above, this method of intraperitoneal infusion with chemotherapy may associate intraperitoneal abscesses, ileus, neutropenia, dissolution of anastomoses or digestive perforations.³⁰ Most of the time these resulting inconveniences are proportional with the amplitude of a surgical intervention.

CONCLUSIONS

Intraperitoneal chemotherapy may be implemented as adjuvant treatment after gastric resection upon gastric cancer presenting peritoneal dissemination that is macroscopically negative but microscopically positive. It has the most effective potential of destructing leftover cancerous cells after neoplastic gastric surgery due to the fact that, in comparison, the systemic chemotherapy presents a reduced penetration into the peritoneal cavity with too little influence over disseminations present at this level.

As palliative treatment for advanced gastric processes, unresectable and with minimal tumor implant at peritoneal level, this treatment may be used in combination with intra-arterial and systemic chemotherapy. It also may be used as palliative treatment for prognosis improvement, to control peritoneal recurrences.

Treatment regimens should be established together with an oncology specialist.

Proper patient selection for intraperitoneal chemotherapy implementation requires a calculation of quantitative indicators of the carcinomatosis, as well as patients' performance status. For intraperitoneal disseminations if the quantitative indicators are high, then this type of treatment is inefficient and does not apply.

Implantable port-a-cath systems facilitate treatment administration through successive sessions whenever it is required. As an integrated part of gastric cancer treatment management it is very much hoped to arrive towards improved prognosis indicators for this disease.

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