The role of intraperitoneal chemotherapy in the treatment of patients with advanced gastric cancer

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AIM: *To review the published literature analyzing the role of intraperitoneal chemotherapy in gastric cancer.*
MATERIAL OF STUDY: *Peritoneal dissemination is a well recognized and important component of disease progression in gastric cancer. Considering that involvement of the peritoneal surface can be anticipated in a large number of patients who present with an advanced gastric cancer, research efforts have been focusing not only on treatment of established peritoneal disease but also on prevention of peritoneal dissemination during surgery for primary gastric cancer.*
RESULTS: *The pharmacologic rationale for intraperitoneal chemotherapy has been well studied. The role and results of HIPEC combined with cytoreductive surgery for patients with established carcinomatosis from gastric cancer has been reported by several groups and appears to be a promising modality for a selected group of patients with limited disease.*
DISCUSSION: A *possible approach to patients with carcinomatosis from gastric cancer includes the use of neoadjuvant bidirectional chemotherapy (intraperitoneal and intravenous or NIPS) with subsequent cytoreduction and HIPEC for patients with a positive response to NIPS. Even more importantly, in several randomized studies and one meta-analysis, the use of intraperitoneal chemotherapy was beneficial in patients undergoing surgery for a primary, advanced gastric cancer.*
CONCLUSION: *It appears that a significant amount of data has accumulated regarding the* KEY
optimal use of cytoreductive surgery and intraperitoneal chemotherapy in gastric cancer. An algorithm for the management of gastric cancer patients incorporating these treatment modalities can be implemented.

KEY WORDS: Carcinomatosis, Gastric cancer, Intraperitoneal chemotherapy.

Introduction

Gastric cancer is the second leading cause of cancer-related deaths worldwide and continues to be a major therapeutic challenge with modest improvements in treatment results seen in the last 20 years. This is especially true in Western countries where the disease is usually discovered at an advanced stage. Approximately 25% of gastric cancers in the US are diagnosed while still localized to the stomach, 30% have regional spread at diagnosis and an additional 30% have metastatic disease. The peritoneal surface is commonly involved in advanced gastric cancer both macroscopically and microscopically at the time of diagnosis, sometimes in the absence of regional node involvement. Even more commonly, a potentially curative treatment involving surgery for the primary tumor with or without adjuvant therapy fails with a peritoneal recurrence [1,2].

The presence of peritoneal implants or a positive peritoneal cytology are considered poor prognostic signs and often seen as indicators of incurable disease[3]. The recently updated AJCC cancer staging classifies positive peritoneal cytology as M1 disease and treatment guidelines

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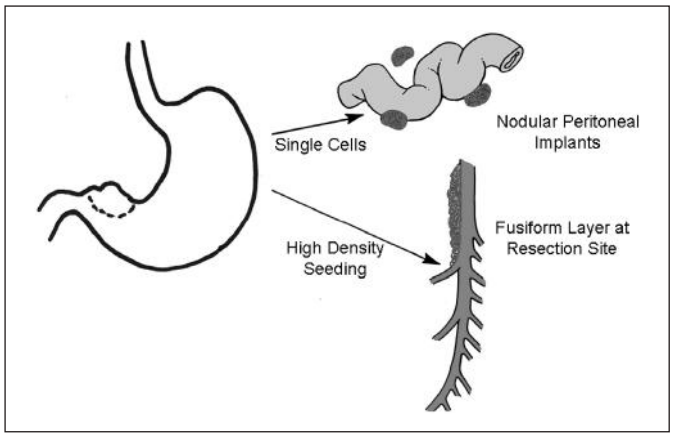

Fig. 1: Intraoperative dissemination of gastric cancer.

both from Europe (ESMO) and the US (NCCN) call for palliative treatment only with either systemic chemotherapy or supportive care. However, investigators in both eastern and western countries have continued to study potential treatment options for gastric cancer patients with limited carcinomatosis encouraged by the results of cytoreductive surgery (CRS) and heated intraoperative intraperitoneal chemotherapy (HIPEC) for carcinomatosis of appendiceal[4] and colorectal origin [5] and showed that a small but meaningful number of patients can achieve long term survival [6].

A strong rationale for local-regional treatments exists for advanced gastric cancer in patients without clinical evidence of peritoneal dissemination (Fig. 1). In the surgery for resection of a large lymph node positive gastric cancer, complete R0 resection is often possible. However, containment of cancer cells to prevent carcinomatosis in the future may be more difficult. In patients with T3/T4 cancers, especially those with N2 disease, it is possible for patients to enter the operating room with a contained process and leave with disseminated disease. In selected patients with advanced gastric cancer, prevention of cancer dissemination that occurs from surgical trauma is mandatory for an optimal surgical intervention.

The rationale for the use of intraperitoneal chemotherapy in the treatment of cancers with a high likelihood of peritoneal involvement is based on the pharmacology of intraperitoneal drug delivery. The peritoneal levels of selected agents are significantly higher than plasma levels creating an AUC ratio that ranges from 50-1000 for the drugs most commonly used. This allows for a high local-regional exposure with decreased systemic toxicity[7]. The effectiveness of intraperitoneal chemotherapy can be augmented by the use of heat and by optimal timing. The perioperative period is ideally suited for intraperitoneal chemotherapy because the distribution of the drug in the peritoneal cavity will be optimized and the residual volume of disease will be lowest.

Intraperitoneal chemotherapy has been used most frequently for the treatment of established, macroscopic peritoneal disease [8,9]. In this setting, the importance of optimal cytoreduction with only minimal (ideally microscopic) residual disease has been clearly established[10,11]. Although the association of complete cytoreduction with improved outcome in cytoreductive surgery and HIPEC is complex and related to the biology of the disease, it is likely that the improved efficiency of HIPEC plays an important role. Therefore, there is a strong rationale to use intraperitoneal chemotherapy when the likelihood of peritoneal

TABLE I - *Survey of chemotherapy agents administered as HIPEC or EPIC for peritoneal surface treatment of gastric cancer. Drugs augmented by heat are often appropriate for heated intraperitoneal chemotherapy (HIPEC). Cell cycle-specific drugs are often appropriate for early postoperative intraperitoneal chemotherapy (EPIC).*

Intraperitoneal Drug	Molecular Weight (Daltons)	Area Under the Curve Ratio	Augmented by Heat	Cell Cycle Specific
5-Fluorouracil	130.08	260	O	+
Carboplatin	371.25	10	+	O
Cisplatin	300.1	7.8	++	O
Docetaxel	861.9	552	O	+
Doxorubicin	579.99	230	+	O
Etoposide	588.58	65	+	O
Floxuridine	246.2	75	O	+
Gemcitabine	299.5	500	+	O
Irinotecan	677.19	N/A	?	O
Melphalan	305.2	93	+++	O
Mitomycin C	334.3	23.5	+	O
Mitoxantrone	517.41	115-255	+	O
Oxaliplatin	397.3	16	+	O
Paclitaxel	853.9	1000	O	O
Pemetrexed	597.49	40.8	?	O

involvement is high but the burden of disease is minimal such as in the case of primary resection of a locally advanced gastric cancer or gastric cancer with positive peritoneal washings. A survey of chemotherapy agents used as a planned part of a gastric cancer surgery is shown in Table I.

Pharmacology of intraperitoneal chemotherapeutics used in gastric cancer

Mitomycin C

There is extensive experience with intraperitoneal use of mitomycin C both in association with heat (as part CRS and HIPEC) [9] and for normothermic intraperitoneal therapy, usually performed in the early postoperative period (EPIC) [12,13]. The pharmacology of intraperitoneal mitomycin C has been studied in patients with appendiceal, colorectal and gastric cancer and it is the most commonly used agent for HIPEC.
Mitomycin C is suitable for intraperitoneal use because of high molecular weight and a favorable AUC ratio of 23.5. It has a known synergy with heat and it is compatible with many other agents for simultaneous IP administration. The dose for intraperitoneal use ranges from 10 mg/m^2 when used in combination with other agents to 35 mg/m^2 as a single agent.

Cisplatin

Cisplatin is widely used as an intraperitoneal agent due to its significant activity in ovarian and gastric cancer and mesothelioma. Although the area under the curve after intraperitoneal administration is only 8, the cytotoxicity of cisplatin is augmented by heat which makes it a suitable agent for HIPEC. Intraperitoneal cisplatin can be used without the addition of heat, as is now standard in adjuvant bi-directional chemotherapy for ovarian cancer. The usual dose for intraperitoneal cisplatin in gastric cancer is 50-90 mg/m^2 but the use of much higher doses (up to 250 mg/m^2) local-regionally (intraperitoneal or intrapleural) has been reported with the addition of systemic thiosulfate[7].

5-Fluorouracil

This well studied drug remains as a component of almost all gastrointestinal chemotherapy regimens and it is equally well studied as an intraperitoneal agent. It has a very favorable AUC ratio of 250. It is used for normothermic early postoperative intraperitoneal chemotherapy (EPIC) or as an i.v. agent administered simultaneously with heated intraoperative intraperitoneal chemotherapy as part of a bi-directional approach.

Cytoreductive surgery and heated intraperitoneal chemotherapy (HIPEC) in gastric cancer with established carcinomatosis

The number of published studies focusing on the effects of cytoreductive surgery and HIPEC in patients with established peritoneal carcinomatosis has been substantially inferior then the interest in peritoneal spread from appendiceal or colon cancer. This is certainly influenced but the common perception that few effective treatment options exist for patients with advanced gastric cancer. However, it seems that some modest improvement in the outlook for patients with gastric cancer has been made in more recent years with more effective use of neoadjuvant chemotherapy that should stimulate renewed research interest in the optimal utilization of cytoreductive surgery and HIPEC for select patients with gastric cancer and carcinomatosis [14].
As with other areas of gastric cancer research, the majority of studies on cytoreductive surgery and intraperitoneal chemotherapy come from Japan and Korea but significant experience with this treatment modality has been accumulating in France as well.
Yonemura et al. published the first large series in 1996 treating 83 patients with histologically proven peritoneal spread of gastric cancer with a regimen that included cytoreductive surgery and heated intraperitoneal combination chemotherapy [15]. The intraperitoneal chemotherapy included mitomycin C at 30 mg, cisplatin at 300 mg and etoposide at 150 mg in 8 L of saline solution heated to 42-43°C. Sixty-eight of these patients had primary gastric cancer with synchronous peritoneal seeding while 15 were treated for gastric cancer recurrence on the peritoneal surfaces. Forty patients had limited peritoneal spread (P1 and P2 according to the Japanese staging) while 43 had diffuse carcinomatosis. Twenty-eight of the 40 patients with P1 or P2 disease were able to undergo complete resection of all disease while the remaining 55 patients had incomplete resections including 7 patients whose primary tumor could not be resected but all 83 patients received the planned HIPEC treatment. Interestingly, 28 of the 55 patients with gross residual disease at the end of the procedure underwent planned second look operations to evaluate the effects of HIPEC. The median follow up was 46 months. The overall 1-year survival rate was 43% and 5-year survival was 11% (5 patients survived longer than 5 years). There was an improved outcome for patients who had complete resection of their disease with a median survival of 14.9 months versus 7.3 months for patients with incomplete cytoreduction. Overall the toxicity of the regimen was acceptable with 1 postoperative death, 3 bowel perforations (3.6%) and 2 cases of bone marrow toxicity (1.2%). This study was the first to report that long term survival was possible in this disease and pointed to the importance of complete surgical resection which was later confirmed in many reports and applies to virtually all

peritoneal surface malignancies. It also indicated that complete responses of the residual tumor nodules to HIPEC were possible in patients with small volume residual nodules.

In 1997, Fujimoto et al. published a series of 48 patients with primary gastric cancer and synchronous peritoneal seeding treated with aggressive cytoreductive surgery and HIPEC and a matched group of 18 control patients treated with cytoreductive surgery alone[16]. For the HIPEC group, the abdomen was perfused with 3 to 4 L of peritoneal dialysis solution containing 10 Ìg/mL of mitomycin C heated to 44.5-45°C for 120 minutes. The control group received normothermic intraperitoneal and/or intravenous mitomycin C for a total dose of 35 to 50 mg and weekly intraperitoneal OK-432 (immunostimulant). Both groups received similar adjuvant chemotherapy. In the HIPEC group, 21/48 patients had P1 disease, 8 had P2 and 19 had P3 disease compared with the surgery alone group were 8 patients had P1 disease and 10 had P2. There was no difference between the two groups in the T and N stages of the primary tumor, the histological types or the type of surgery performed. The rate of complete versus incomplete cytoreduction was not reported. The 1-year, 3-year, 5-year and 8-year survival of the HIPEC group was 54%, 41.5%, 31% and 25.4%. There was a significant difference in overall survival between the HIPEC and the surgery alone groups. When further analyzed by extent of peritoneal disease, the difference in outcome was present both for P1 and P2 patients: none of the surgery alone patients survived longer than 2 years while the 8-year survival for P1 HIPEC patients was 55.6% and for the P2 HIPEC patients was 20%. When the different subgroups of HIPEC patients were analyzed, there was no difference in survival between the P1 and P2 groups but the P3 group had inferior survival. Another interesting observation was that only 27.1% of patients in the HIPEC group who ultimately died had peritoneal recurrence.

In the US, Hall et al. published their experienced with 34 patients with synchronous carcinomatosis who underwent gastric resection combined with cytoreductive surgery and HIPEC in 2004 [17]. The drug used was mitomycin C at a fixed dose of 30 mg in 3 L of perfusate. Twelve of the 34 patients were able to have a R0 or R1 resection (defined as complete removal of all gross tumor with either positive cytology or a positive microscopic margin). As in other studies, the completeness of cytoreduction was a key predictor of outcome. Patients who had a R0 or R1 resection had a median survival of 11.2 months compared with only 3.3 months for the R2 group. The R0/R1 group had a 2-year survival of 45% but only the R0 group had some long term survivors with a 5-year survival of 21%.

The largest European experience was published in 2004 by Glehen et al. who treated 49 consecutive patients with cytoreductive surgery and HIPEC [18]. They used 4-6 L of perfusate containing 10 mg/mL of mitomycin C to perfuse the abdomen using a closed technique. Of the 39 patients, 10 had an unresectable primary tumor and were among the 24 patients who had an incomplete cytoreduction. The remaining 25 patients had either an R0 or a R1 resection. Similar to the experience from Japan and the US, completeness of cytoreduction was found to be the most important predictor of outcome. This study also confirmed the initial experience from Japan that long term survival can be achieved in a small subset of patients. In this series, the overall 5-year survival was 16% but it was 29% for patients who were able to have complete cytoreduction (CCR-0 or CCR-1).

Another important finding reported was the correlation of completeness of cytoreduction with the extent of carcinomatosis. All of the patients with limited carcinomatosis (Stage P1 or P2) were able to have a complete cytoreduction while only 25% of the ones with more advanced carcinomatosis did. However, the authors suggest that more advanced carcinomatosis in gastric cancer should not be considered an absolute contraindication to cytoreductive surgery and HIPEC but careful consideration should be given to patient selection.

The French Surgical Society (AFC) published a special report in 2008 summarizing the experience of 15 treatment centers on the results of cytoreductive surgery and HIPEC for gastric cancer and peritoneal seeding between 1989 and 2007[19]. One hundred and 59 patients were treated during this time period: 56% had a CC-0, 25% a CC-1 and 19% a CC-2 cytoredutcion. Mitomycin C was used for HIPEC in 83% of the cases. The median survival for the entire group was 7 months, with 3-year survival at 18% and 5-year survival at 14%. An analysis of factors associated with survival was performed: on univariate analysis the use of neoadjuvant chemotherapy, male sex, extent of carcinomatosis and the time period of treatment were associated with better outcomes. However, on multivariate analysis, only the completeness of cytoreduction remained a significant prognostic factor. Interestingly, in this report only CC-0 cytoreduction was associated with long-term survival (5-year survival of 25%); there were no survivors at 2 years in the group of patient undergoing CC-1 or CC-2 cytoreduction. A separate analysis of the subgroup of patients with CC-0 cytoreduction showed that extent of disease measured by PCI was very important: no patients with a PCI greater then 19 survived beyond 1 year despite a complete cytoreduction.

Neoadjuvant intraperitoneal and systemic chemotherapy (NIPS) for patients with gastric cancer and carcinomatosis

Yonemura et al. developed a treatment strategy for patients with carcinomatosis from gastric cancer using a

neoadjuvant bi-directional approach in an attempt to increase the number of patients with complete cytoreduction and therefore improve outcomes.

The initial series was published in 2006 and described 61 patients treated with neoadjvant combination IP and IV therapy [20]. The IP protocol consisted of docetaxel at 40 mg/m^2 and carboplatin at 150 mg/m^2 given in 1 L of saline weekly. Simultaneously, patients received methotrexate and 5-FU intravenously. A minimum of 2 cycles of treatment were given but some patients received up to 6 cycles depending on the results of peritoneal washing cytology. Patients with persistently positive cytology were continued on therapy for 2 additional cycles and the test repeated for a maximum of 6 cycles. All 61 patients had P3 stage of carcinomatosis and 33 of them had clinical ascites. Twenty-eight of 61 patients had primary tumors of the stomach with synchronous carcinomatosis.

Thirty-nine patients had positive peritoneal cytology before starting treatment and following NIPS this reverted to negative in 22. After NIPS, 30 patients proceeded to surgery while 31 did not due to either progression of disease (19 patients) or patient refusal (12 patients). Half of the patients who were operated on had a complete cytoreduction (14/30). The results of the treatment were significantly better in the group of patients with synchronous carcinomatosis: 13 of 28 were able to have a complete cytoreduction. In contrast, patients with carcinomatosis as a manifestation of recurrent disease did very poorly: only 1 of 32 patients had a complete cytoreduction and 11 additional patients had surgery but received incomplete cytoreduction. The median survival for the entire group was 14.4 months, with a significant difference between patients who had surgery (18 months) versus the ones who did not (9.6 months). The patients who had a complete cytoreduction had a median survival of 20.4 months.

The principals of NIPS but with some changes in the chemotherapy regimen were again applied to a protocol published in 2009 on the results of treatment of 75 patients[21]. The treatment plan consisted of oral S-1 given twice a day for 21 days combined with intraperitoneal cisplatin and docetaxel on days 1, 8 and 15 of each cycle. S-1 is given at a dose of 40-60 mg/m^2. Docetaxel and cisplatin are given at 30 mg/m^2 in 500 mL of saline solution and administered through an implantable peritoneal port. Peritoneal washing immunohistochemistry was performed before and after NIPS on each patient. Sixty-five (82%) of the patients had positive immunohistochemistry pre-NIPS but only 27(34%) were positive following this treatment. Of the 75 patients initially enrolled, 41 went on to have a laparotomy while 38 did not because of progression of disease. The extent of carcinomatosis prior to treatment was not reported. Among the patients who had a laparotomy, the rate of complete cytoreduction was very high at 78% (32 of 41 patients). Among the subgroup of patients with a primary tumor in place who were able to have a resection with D2 lymphadenectomy, the rate of complete cytoreduction was even higher at 86%. The status of the peritoneal washings after NIPS was closely correlated with completeness of cytoreduction: 51% of patients with negative washings went on to have a complete cytoreduction versus only 14% of patients whose cytology was positive after NIPS. In contrast with post-NIPS cytology, pre-treatment cytology was not predictive of completeness of cytoreduction. Post-NIPS cytology was also predictive of survival.

Importantly, in both of these studies, the incidence of systemic toxicity was low (10% or less) and there were no mortalities. NIPS appears to be a viable option that may help with better selection of patients that should go on to aggressive cytoreduction. It seems to also be useful for patients with synchronous carcinomatosis by clearing free cancer cells in the peritoneal cavity and allowing a high rate a complete cytoreduction in this subgroup.

Adjuvant intraperitoneal chemotherapy for primary advanced gastric cancer without established carcinomatosis

The frequency of peritoneal spread in the natural history of gastric cancer has long been recognized but optimal therapeutic and especially preventive strategies are still evolving. The use of intraperitoneal chemotherapy as an adjuvant approach to minimize the risk of peritoneal recurrence in patients who have advanced gastric cancer has clear theoretical advantages: intraperitoneal delivery of drugs ensures high intraperitoneal drug levels targeting tissues at greatest risk. It is also reasonable to expect that adjuvant treatment of patients that do not have established carcinomatosis but are at high risk for intraperitoneal dissemination of cancer cells would have better results than treatment of patients with higher tumor burden. Building on these theoretical premises, many randomized and non-randomized studies have been carried out exploring the use of perioperative intraperitoneal chemotherapy as an adjuvant treatment in patients undergoing primary resection of an advanced gastric cancer.

In 2007, Yan et al. published a systematic review and meta-analysis of 13 randomized studies that compared surgery for primary gastric cancer combined with intraperitoneal chemotherapy versus surgery without IP therapy[22]. In these studies, a total of 1648 patients were enrolled: 873 randomized to receive IP therapy and 775 randomized to no intraperitoneal therapy. An analysis of quality of the studies was made using standard criteria evaluating the randomization process, adequate reporting of baseline patient characteristics, intention to treat analysis and patients lost to follow-up. Ten of the 13 studies were entered into the meta-analysis. In these 10

studies, three different types of intraperitoneal chemotherapy were used: heated intraoperative intraperitoneal chemotherapy (HIPEC) [23-26], normothermic intraoperative intraperitoneal chemotherapy (NIIC)[25, 12,13,27,28], early postoperative intraperitoneal chemotherapy (EPIC) [29,30] and delayed postoperative intraperitoneal chemotherapy (DPIC). The meta-analysis showed a significant improvement in survival associated with HIPEC (HR 0.60; 95% CI = 0.43 to 0.83; p=0.002) or HIPEC combined with EPIC (HR=0.45; 95% CI 0.29 to 0.68; p=0.0002) while there was no statistical significant improvement with NIIC, EPIC alone or DPIC. Six studies analyzed the pattern of disease recurrence: in two studies it was reported only for patients who died and both showed a reduction of incidence of peritoneal metastases in the IP chemotherapy groups. In the remaining 4 studies, there was no reduction in incidence of peritoneal recurrence with either HIPEC or NIIC. One study using EPIC showed a 49% reduction of peritonea recurrence in the treatment group.
Whenever adjuvant chemotherapy is studies, the assessment of morbidity and mortality associated with treatment must be carefully evaluated. All of the studies included in this meta-analysis reported perioperative mortality data and there was no difference between the two groups. Regarding morbidity, there was no difference between the two groups in the rate of anastomotic complications and fistula but there was an increase in the incidence of intraabdominal abscess and neutropenia associated with intraperitoneal chemotherapy.
Therefore, there is data to support the use of HIPEC or HIPEC combined with EPIC as an adjuvant to resection of primary, high risk gastric cancer. The available data does pose some limitations however in that it was predominantly obtained from Asia which could limit its applicability to western patients. Because the use of adjuvant intraperitoneal chemotherapy, specifically HIPEC, is still not widely accepted in Western centers, even the ones with extensive experience in intraperitoneal chemotherapy treatment for other indications, a multi-institutional randomized study by the EUNE is in the final planning stages.

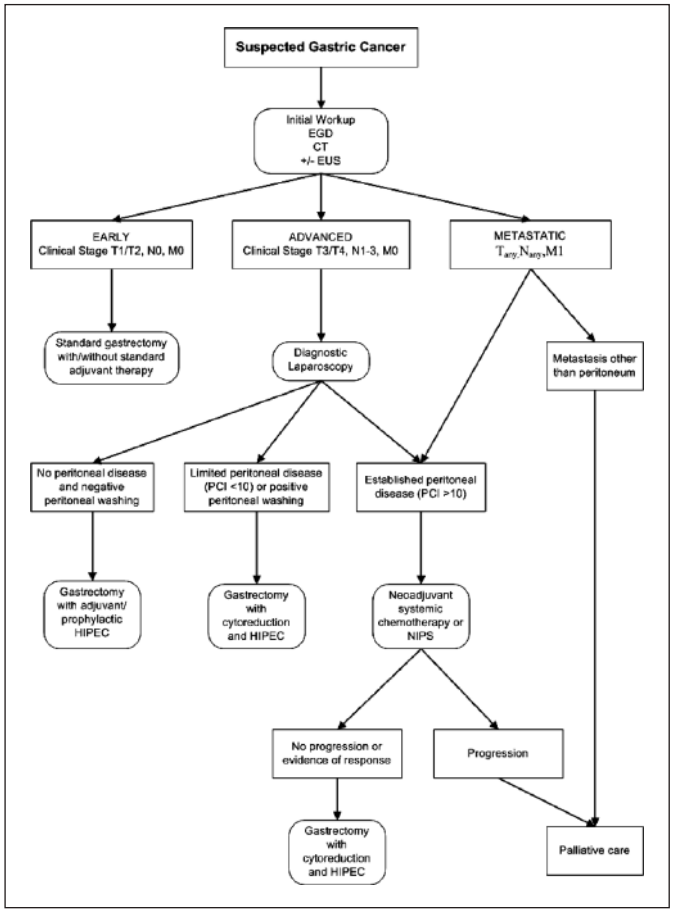

Fig. 2: Treatment algorithm for gastric cancer to prevent or treat peritoneal dissemination.

Conclusions

Local-regional dissemination is a prominent component of the natural history of gastric cancer. Intraperitoneal chemotherapy has been used to treat patients with peritoneal carcinomatosis and in an adjuvant setting for patients with advanced primary disease in the absence of carcinomatosis. In patients with carcinomatosis, neoadjuvant bidirectional (intraperitoneal and intravenous) chemotherapy is suggested to be beneficial in patient selection for surgical intervention and in long term survival (Fig. 2).

Riassunto

La diffusione peritoneale è una componente ben riconosciuta e importante di progressione di malattia nel cancro gastrico. Considerando che il coinvolgimento della superficie peritoneale può essere anticipato in un gran numero di pazienti che presentano un cancro gastrico avanzato, gli sforzi di ricerca si sono concentrati non solo sul trattamento di una malattia peritoneale, ma anche sulla prevenzione della diffusione peritoneale primaria durante un intervento chirurgico per cancro gastrico.
Il razionale farmacologico per la chemioterapia intraperitoneale è stato ben studiato. Il ruolo dei risultati dell' HIPEC combinati con la chirurgia citoriduttiva nei pazienti con carcinomatosi da cancro gastrico è stata riportata da diversi gruppi e sembra essere una metodica promettente per un gruppo selezionato di pazienti con malattia limitata.
Un possibile approccio per i pazienti con carcinomatosi da cancro gastrico prevede l'impiego di chemioterapia neoadiuvante bidirezionale (intraperitoneale e per via

endovenosa o NIPS) con citoriduzione successiva e HIPEC per i pazienti con una risposta positiva alla NIPS. Sembra che una quantità significativa di dati si sia accumulata per quanto riguarda l'uso ottimale della chirurgia citoriduttiva e la chemioterapia intraperitoneale nel cancro gastrico, per tale motivo un algoritmo gestionale per i pazienti affetti da cancro gastrico che inglobi l' inserimento di tale modalità di trattamento può essere realizzato.

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