Advanced gastric cancer: new perspectives of treatment

Matteo Nardi,[1] Luca Ansaloni,[2] Giulia Montori,[2] Marco Ceresoli,[2] Giacomo Crescentini,[1] Gian Marco Palini,[1] Filippo Paratore,[1] Mattia Trevisan,[1] Nicola Zanini,[1] Lucia Morganti,[1] Federico Coccolini[2]

[1]Department of General Surgery, Infermi Hospital, Rimini; [2]Departments of General, Emergency and Trauma Surgery, Papa Giovanni XXIII Hospital, Bergamo, Italy

Abstract

The prognosis in patients with advanced gastric cancer with carcinosis remains poor with a median survival of less than one year. High rates of peritoneal recurrence of patients undergoing resection with potentially curative intent are strictly related with lymphatic spread and penetration of the serosa. To increase survival rates, during the last thirty years different strategies about screening and treatment have been tested and proposed. Early detection of occult peritoneal micrometastasis is a base step to reduce local and serosa recurrences and to offer a tailored surgical and neoadjuvant therapeutic treatment. The complete cytoreductive surgery, however, remains the cornerstone of treatment. It could be associated with different combinations of chemotherapy regimens. Adjuvant, neoadjuvant and intraperitoneal chemotherapy have been demonstrated effective in improving the survival. In the last years, a few new molecules have been introduced which enhance the effect of chemotherapy by biologically targeting its objective. Lastly the prevention of macroscopic peritoneal carcinosis in all those patients at high risk due to serosal infiltration by treating them with intraperitoneal chemotherapy has been demonstrated to be one of the future winning approaches. In patients with peritoneal carcionosis, multimodal comprehensive treatment should be mandatory, with a pivotal role of intraperitoneal chemotherapy associate to CC0 cytoreduction. Neoadjuvant chemotherapy followed by cytoreductive surgery and intraperitoneal chemotherapy gave promising results. The new molecules as monoclonal antibodies seem to improve outcomes.

Correspondence: Federico Coccolini, Departments of General, Emergency and Trauma Surgery, Papa Giovanni XXIII Hospital, Bergamo, Italy.
Tel.: +39.0352.66464 - Fax: +39.0352.66898.
E-mail: federico.coccolini@gmail.com

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Introduction

Gastric cancer (GC) disseminate through the hematic torrent or through the peritoneal cavity fluids: this last condition is called peritoneal carcinomatosis (PC). PC is considered an end stage disease (IV) and it occurs synchronous with the primary tumor in about 14-43% and as isolated site of metastasis in 9% of patients with GC.

It has been demonstrated in recent studies, as peritoneal dissemination is more frequent than metastases through hematic torrent.

Only the 40% of patients died for GC have hepatic metastasis, while the 53-60% showed disease progression and died with PC.[1]

The two most important factors affecting prognosis in GC are the penetration of the serosa and the lymphatic spread.[2-4] When the gastric serosa is infiltrated by tumor cells, PC could be considered practically unavoidable.[5] As a consequence, up to half of the patients with advanced GC (AGC) will develop PC in spite even radical surgery.[6-9] PC is already present in 5-20% of patients explored for potentially curative resection.[5,10]

The presence of free peritoneal tumor cells (FPTCs) could be detected using several methods with different degrees of sensitivity but appears to increase the risk of peritoneal recurrence and poor overall survival.[11-15]

Recent data demonstrated the possibility to increase the overall and disease free survival by preventing the advent of macroscopic carcinosis in all those patients at high risk of cell spread (*i.e.,* all the AGC patients). The main issue is the detection of spread cells. In fact, depending by the utilized method, FPTCs in the washing could be identified in up to 24 or 40%, in patients with stage IB or II-III GC respectively.[16] These data explain the reason why GC is considered a neoplasm with easy intra-peritoneal spread, and why the recurrence patterns after complete resection can vary in different countries and in different periods. In fact it can vary from 10.2 to 33.9% as peritoneal recurrence alone, and from 29.5 to 43.9% as peritoneal recurrence combined with other site metastasis (Baiocchi *et al*., personal communication, 2013).[17-20] The well-known mechanism of neoplastic cells peritoneal spread in GC explicates probably also the reason why, even after potentially curative resection of early GC, peritoneal recurrence can be observed in a 1-2% of patients.[21,22]

Many studies showed that polymerase chain reaction using *CEA*, *CEA/CK20* target genes provides a greater sensitivity than peritoneal citology in detecting free cancer cells and it will assist in reducing understimated advanced GC cases allowing a better patients selection and resulting appropriate treatment combinations.[23-26] A recent meta-

analysis by Kai-Deng and colleagues,[27] demonstrated the prognostic value of molecular analysis of peritoneal fluid in GC patients also in cases with negative exfoliative cytology in terms of overall survival, disease free survival and peritoneal recurrence free-survival in GC patients receiving curative treatment. Literature data clearly demonstrated the necessity to prosecute on the way to prevent the PC in AGC by increasing the power of patient selection instruments and by anticipating PC with all the necessary and effective methods, especially by administering intraperitoneal chemotherapy in all those patients at high risk for PC.

Treatment and prevention of peritoneal carcinosis

The prognosis in patients with PC from GC is poor. The 5-year survival is less than 3% and the overall mean and median survival are of 6.5 (range, 0.1-48.0) and 3.1 months, respectively.[28,29] PC from GC has for sure a better prognosis than PC from pancreatic cancer (overall mean and median survival times of 2.9 and 2.1 months respectively), but worse than PC from colorectal carcinoma (overall mean and median survival times of 6.9 and 5.2 months, respectively).[29] The 5-year survival of patient with AGC and FPTCs has been reported to be almost the same as that of those with disseminating metastasis to the adjacent peritoneum of the stomach (15.3 and 14.8% respectively). As a counterpart there were no 5-year survivors among patients with metastases to the distant peritoneum.[30] Liu and colleagues reported a 5-year survival rate of 24% in patients with microscopic PC from GC.[31]

Surgery remains the cornerstone of the treatment. In a recent meta-analysis the completeness of cytoreduction has been evaluated as an increasing factor of the life expectancy in patients with PC in gastric cancer.[32] Nine trials were included (748 patients: 417 with CC0-CC1 and 324 with CC2-CC3 cytoreduction). The survival of 1, 2, 3 and 5 years is favorable to CC0-CC1 [relative risk (RR): 2.41, 8.18, 8.66, and 7.96 respectively]. CC0 *vs* CC1 survival benefit at 1 and 3 years: RR 2.28 and 6.36 respectively, favoring CC0. 1, 2, 3 and 5-year survival changes significantly above and below a peritoneal cancer index (PCI) of 12. The overall survival of 1, 2, 3 and 5-year is increased by CC0-CC1 cytoreduction in patients with PC from gastric origin. Moreover CC0 increases the 1 and 3 years survival when compared to CC1 cytoreduction.

Systemic chemotherapy improves median survival in advanced and/or metastatic GC to not more than 12 months.[33-36] The same gain in term of survival has not been described in patients with macroscopic PC.[37-40] Principally it is due to the inadequate diffusion of systemically administered drugs into the abdominal cavity which could be considered a pharmacological sanctuary.[41] Yonemura and colleagues, however, obtained good results in term of survival patients with FPTCs after radical resection using adjuvant systemic chemotherapy. In their study, they demonstrated as patients treated with adjuvant chemotherapy survived significantly longer than those of control group. One-year survival rates of adjuvant chemotherapy and control group were 88 and 44%, respectively, 2-years survival rates 53 and 9%, respectively. The mean overall survival for the two groups was 21.1 and 9.1 months respectively ($P<0.05$).[42] Many authors assumed that the ineffectiveness of systemic chemotherapy for PC is due to the presence of a blood-peritoneal barrier, poor blood supply and oxygenation of cancer cells in the peritoneum, and low apoptotic potential of such hypoxic tumor cells.[34,43-45]

A meta-analysis from Yan and colleagues, pooling together the results from a few randomized clinical trials demonstrated the association between the improving in overall survival and the application of hyperthermic intraperitoneal chemotherapy (HIPEC) with or without EPIC after resection of advanced gastric primary cancer. In this study is reported a significant improvement in survival associated with HIPEC alone [hazard ratio (HR)=0.60; 95% confidence interval (CI) 0.43-0.83; P=0.002] or this regimen combined with EPIC (HR=0.45; 95% CI 0.29-0.68; P=0.0002). As a counterpart this study demonstrated also the increase of morbidity associated with the intraperitoneal administration of chemotherapy. In fact, intraperitoneal chemotherapy was found to be significantly associated with higher risks of intra-abdominal abscess (RR=2.37) and neutropenia (RR=4.33).[46]

Two more recent meta-analysis published by the same Chinese group of authors confirmed all these results.[47,48]

The last published meta-analysis definitively showed the effect of intraperitoneal chemotherapy (IPC) in preventing and treating PC. The effect is demonstrated at 1, 2 and 3 years. Surgery +IPC improves: 1, 2 and 3-year mortality [odds ratio (OR)=0.31, 0.27, 0.29 respectively], 2 and 3-year mortality in patients with loco-regional nodal metastasis (OR=0.28, 0.16 respectively), 1 and 2-year mortality rate in patients with serosal infiltration (OR=0.33, 0.27 respectively). Morbidity rate was increased by surgery +IPC (OR=1.82). The overall recurrence and the peritoneal recurrence rates were improved by surgery +IPC (OR=0.46 and 0.47 respectively). There was no statistically significant difference in lymph-nodal recurrence rate. Lastly the rate of hematogenous metastasis was improved by surgery +IPC (OR=0.63).[49]

Macroscopic PC could be reduced by the use of neoadjuvant chemotherapy (NACT).[23,45] A paper published by Yano and colleagues reported a complete remission of peritoneal metastasis in 4 over 26 patients (15.4%) with PC from GC after NACT.[50] Inokuchi and colleagues showed partial response in 9 of 13 patients (69%) following NACT for PC from GC.[51] NACT has a positive impact on PC but it seems to not have effect on FPTC. The reason of this could be found in the presence of the peritoneal-plasma barrier. Published data demonstrated as changes in positivity or negativity results of the research of FPTC can be detected after NACT. These changes are irrespective of the systemic response to the treatment. In this German study, 10 among 42 (24%) of the patients changed to FPTC positivity during NACT, whereas 7 among 19 (37%) with FPTC positive cytology at staging laparoscopy turned negative.[52] All the aforementioned data commonly lead to the conclusion that, considering the failure of surgery at the peritoneum, there was no role for surgery once the diagnosis of PC from GC has been made.[53]

Since the eighties Japanese surgeons have introduced the combination of cytoreductive surgery (CRS), regional hyperthermia, and intraperitoneal chemotherapy to increase effectiveness of intrabdominal treatments.[54] The introduction of HIPEC after CRS is accomplished to eliminate FPTCs and to inhibit or delay PC in GC as for other kind of PC.[53,55] CRS must be as complete as possible in order to obtain the best results. The extent of CRS in case of PC could be evaluated by the Sugarbaker's completeness of cytoreduction (CC) score.[56] Advances in the management for peritoneal carcinomatosis from gastric cancer (PCGC) encouraged the use of any diagnostic means, including staging laparoscopy, in order to plan carefully HIPEC after CRS and other multimodal treatments.[57]

On one hand some randomized clinical trials (RCTs) showed in the last 30 years a significant reduction in the rate of subsequent PC and an increase in survival of patients with AGC when radical surgery was combined with HIPEC,[6,46,58-62] and Yonemura and colleagues demonstrated that in patients with PFTCs HIPEC could improve significantly the median survival time from 15 to 48 months and the 5-years survival rate from 12 to 42%.[63] Nevertheless on the other hand, the treatment of PC from GC with CRS and HIPEC seemed to be among all the PC the one with less encouraging results in terms of survival, morbidity and mortality.[64,65] A French study group in a retrospective, multicenter cohort study published in 2010[66] evaluated toxicity and principal prognostic factors after CRS and HIPEC [and/or early postoperative intraperitoneal chemotherapy (EPIC)] for PC from non-gynecologic neoplasms. The study involved 1290 patients from 25 French institutions who underwent 1344 CRS between February 1989 and December

2007, where HIPEC was made in 1154 cases (86.4%). Although the principal origin of PC was colorectal cancer (n=523, 40.5%), the GC was the third more represented (n=159, 12.3%). With a median follow-up of 45.3 months the whole group of patients included in the study showed an overall 3- and 5-year survival rates of 49 and 37%, respectively, but the patients with PCGC displayed the worse outcome with an overall 3- and 5-year survival rates of 18 and 13%, respectively. The overall median survival of the whole group of patients included in the study was 34 months, but was only 9 months for patients with PCGC.

Then still in 2010 Li and colleagues from China reported the results of their study where in a group of 128 patients with PCGC, 54 of them (42.2%) underwent gastrectomy, of which 10 patients underwent resection with HIPEC, and the other 74 (57.8%) underwent non-resection surgery.[67] The median survival in the unresected group was 6.0 months compared to 11.8 months of in the resected patients and they observed a significantly improved survival in the patients that were treated with surgery and HIPEC compared to those that were treated with surgery alone. Although no patient died from resection-related causes, the incidence of overall post-operative complications was higher for the resection with HIPEC group than for the resection alone group (20 *vs* 13.2%, however, the difference was not significant, P=0.34). This report revealed once again the safety and the efficacy of CRS and HIPEC in PCGC, but despite this evidence supporting radical surgery and HIPEC over surgery alone or palliative chemotherapy, only a minority of all patients in this cohort was treated with HIPEC.

In 2011, Gill and colleagues published a systematic review of survival, mortality, and morbidity regarding the treatment of PCGC by CRS and HIPEC.[68] They selected for inclusion in this review studies published from 2000 to 2010 with non-randomized controlled trials, randomized controlled trials, prospective cohort series and retrospective case-series (>5 cases), including adult (>18 years old) patients with PCGC (without other sites of metastatic disease, *e.g.*, liver, lung) who underwent CRS (peritonectomy) combined with HIPEC (the primary gastric resection may be completed at the same surgery as the CRS or at a separate procedure, respectively synchronous or metachronous PCGC). A total of 10 primary studies meeting the inclusion criteria were identified and analyzed, including 1 non-randomized prospective controlled trial, 6 prospective case series and 3 retrospective case series with a total of 441 patients with an average age of 48.5 years (range 48-55 years) and a median follow-up of 46 months (range 19-74 months). In the included studies either open or closed HIPEC technique was utilized, the most common chemotherapeutic agents were cisplatin and mitomycin, with intra-abdominal temperatures typically between 40 and 44°C and duration between 30 and 120 min. The authors reported an overall median survival of 7.9 months (range: 6.1-9.2 months), 15 months (range: 9.5-43.4 months, for patients with CC scores of 0 or 1, *i.e.,* residual nodules after CRS with size less than 2.5 mm) with a 1-year survival of 43% (range: 22-68%) and a 5-year survival of 13%. The treatment-related overall mortality rate was 4.8% and the overall morbidity was 21.5% with abscess, fistula, and anastomotic leak being the most common complications reported. The length of hospital stay ranged between 7 and 16 days with an Intensive Care Unit stay ranging between 1 and 3 days. Although without any level I evidence, it could be concluded that in PCGC, CRS+HIPEC may improve survival with acceptable morbi-mortality.

The evidence lacking in this review became available in the same year, 2011, when Yang and colleagues published the final results of a phase III RCT, performed in China in order to evaluate the efficacy and safety of CRS plus HIPEC for the treatment of PCGC.[69] The authors included adult (age 20-75 years old) patients with either synchronous, or metachronous PCGC, without any lung and liver metastasis, or prominent retroperitoneal lymph node metastasis, who were randomized into two arms where the only variable in study after the CRS was the use of HIPEC (open technique, with 120 mg of cisplatin and 30 mg of mitomycin C each dissolved in 6 L of saline infused into the peritoneal cavity at a rate of 500 mL/min and a temperature of 43.0±0.5°C for 60-90 min). Sixty-eight PCGC patients, including 35 men and 33 women, aged 24-75 years (median 50 years) were randomized into CRS alone (n=34) and CRS and HIPEC (n=34) groups with a well balancing regarding major baseline clinico-pathological characteristics and surgical procedures. After a median follow-up of 32 months (7.5-83.5 months) the median overall survival was 6.5 months (95% CI 4.8-8.2 months) in CRS alone group and 11.0 months (95% CI 10.0-11.9 months) in the CRS+HIPEC group (P=0.046). This outcome was even more significant in patients with synchronous PCGC (n=51), where the median overall survival was 12.0 months (95% CI 8.1-15.9 months) in CRS+HIPEC group (n=24) and 6.5 months (95% CI 5.0-8.0 months) in the CRS group (n=27) (P=0.029). The 1-, 2-, and 3-year survival rates were 29.4, 5.9 and 0% for CRS group, and 41.2, 14.7 and 5.9% for CRS+HIPEC group. The CC influenced the survival, but HIPEC obtained a significant advantage either in CC 0-1, either in CC 2-3 patients. In the CRS+HIPEC patients, the median overall survival was 12.0 months (95% CI 8.1-16.0 months) and 8.2 months (95% CI 0.5-16.5 months) in CC 0-1 (n=20) and in CC 2-3 subgroup (n=14) respectively, (P=0.000). In CRS patients, the median overall survival was 11.0 months (95% CI 8.8-13.2 months) and 4.0 months (95% CI 1.3-6.8 months) in CC 0-1 (n = 20) and in CC 2-3 subgroup (n=14) respectively, (P=0.000). Serious adverse events (SAE), including wound infection and sepsis, respiratory failure, gastrointestinal bleeding, severe bone marrow suppression, and intestinal obstruction, arose in 9 patients, 4 in the CRS group (11.7%) and 5 in the CRS+HIPEC group (14.7%) (P=0.839). Multivariate analysis recognized CRS+HIPEC, synchronous PC, CC 0-1, systemic chemotherapy and no SAE as major independent predictors for better survival. HIPEC was about 2.6 times likely to increase survival (HR=2.617; 95% CI 1.436-4.769). From the methodological point of view, it has to be pointed out that this is the first RCT in patients with established PC where the only variable in study was HIPEC (unlike the Dutch study regarding the PC from colorectal cancer), showing an advantage in term of survival. It has to be concluded that HIPEC after CRS improves survival with acceptable morbidity in patients with PCGC especially when synchronous.

A recent meta-analysis showed as two- and five-years overall survival in patients with free cancer cells without carcinosis is incremented by intraperitoneal chemotherapy. Moreover peritoneal lavage (PL) further increases these survival rates and it also further decreases the peritoneal recurrence rate. Results from the aforementioned study showed that two- and five-years survival is increased by IPC (RR=1.62, RR=3.10). Survival of 2 and 5 years is further increased by IPC+PL (RR=2.33, RR=6.19). Peritoneal recurrence is reduced by IPC (OR=0.45) and by IPC+PL (OR=0.13).[70]

The Peritoneal Surface Oncology Group International proposed a novel comprehensive treatment with curative intent for PC from GC combining CRS and perioperative chemotherapy. In this strategy, PCI is determined by laparoscopy, and a peritoneal port is placed. Neoadjuvant bidirectional intraperitoneal/systemic chemotherapy (NIPS) is performed for 3 cycles, and then laparotomy is performed. Cytoreductive surgery with peritonectomy procedures and HIPEC are performed. Multivariate analyses showed that completeness of cytoreduction, pathologic response to NIPS and PCI level and cytologic status after NIPS, as independent prognostic factors. PCI less than cut-off level after NIPS, negative cytology after NIPS, and positive response to NIPS were identified as the indications for comprehensive treatment. Patients who hold these criteria should be considered as the candidates for CRS and HIPEC.[71,72]

A recent published study demonstrated an increase in overall and disease free survival in patients with AGC treated with neoadjuvant chemotherapy, surgery and *prophylactic* HIPEC. The four groups of the study are patients with PC and patients with AGC without PC treated

with HIPEC and, patients with AGC with T4 disease and patients with AGC with T3 disease treated with neoadjuvant chemotherapy and surgery alone. Prophylactic intraperitoneal chemotherapy associated to neo-adjuvant chemotherapy increases the disease-free survival and overall survival (OS) in patients with AGC without carcinosis. Moreover, patients with AGC without PC treated with neoadjuvant chemotherapy, surgery and *prophylactic* HIPEC have an overall and disease free survival better than all those T3 patients treated with neoadjuvant chemotherapy and surgery alone.[73] In any case, even if these results are promising, more data from larger studies are mandatory.

In the last ten years an interesting new drug to be applied for intraperitoneal treatment of GC has been developed in Germany. Catumaxomab[73] is a rat-mouse hybrid monoclonal antibody that is made up of one *half* (one heavy chain and one light chain) of an anti-epithelial cell adhesion molecule (EpCAM) antibody and one half of an anti-CD3 antibody, binding both EpCAM and CD3. EpCAM is an epithelial differentiation antigen that is expressed on normal epithelial cells and on almost all carcinomas (especially gastrointestinal and ovarian carcinomas) and functions as cell adhesion molecule. In addition, the Fc-region can bind to an Fc receptor on accessory cells like other antibodies, which has led to calling the drug a trifunctional antibody. Actually catumaxomab is used to treat malignant ascites, because the intraperitoneal application of this anti-EpCAM antibody has shown significant benefits in puncture-free survival (survival without repeated paracentesis) for patients with malignant ascites in a phase II/III randomized trial.[74] In this study although the difference in median OS (secondary endpoint) for the whole group of patients (72 days for paracentesis plus catumaxomab compared to 68 days for paracentesis alone, P=0.08) was not significant, the same outcome (*i.e.,* the difference in OS) was statistically significant in patients with GC (median 71 *vs* 44 days; P=0.03).[74] The same result, *i.e.,* an improved progression-free survival, has been replicated in phase II studies with the use of intraperitoneal catumaxomab in gastrointestinal EpCAM+ tumors.[75] Furthermore two phase 2 studies are ongoing (follow-up phase) where resectable AGC patients are treated with adjuvant catumaxomab. The first study included 55 patients randomized to either surgery plus catumaxomab (10 g Catumaxomab infused directly after surgery intraoperative, followed by four ascending i.p. doses) or surgery alone.[76] A total of 78% of the patients received all five catumaxomab infusions and there were no clinically relevant differences in the incidence of surgical complications between the surgery alone and the surgery plus catumaxomab group. In the second study,[77] 54 patients with radically resected AGC were treated intra-operatively and i.p. in adjuvant setting with catumaxomab after they received NACT. For both studies final results are awaiting.

One last issue, which should be taken into account, concerns the evaluation of the quality of life in patients undergoing intraperitoneal chemotherapy. There is a lack of comparative data on the quality of life regarding intraperitoneal chemotherapy for gastric cancer patients. One recent phase-III trial conducted by Armstrong *et al.* assessed quality of life as an outcome measure in patients receiving adjuvant postoperative intraperitoneal chemotherapy for ovarian cancers.[78]

Conclusions

In patients with peritoneal carcionosis, multimodal comprehensive treatment should be mandatory, with a pivotal role of intraperitoneal chemotherapy associate to CC0 cytoreduction. Neoadjuvant chemotherapy followed by cytoreductive surgery and intraperitoneal chemotherapy gave promising results. The new molecules as monoclonal antibodies seem to improve outcomes.

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