Review Article

DOI: http://dx.doi.org/10.18203/2349-3933.ijam20172622

Management of peritoneal metastasis of gastric cancer

Ammar Mohammed Qaid¹, GuiJuan He², Chen Qiang^{2*}

¹Department of Medical Oncology, Fujian Medical University Union Hospital, Fuzhou, Fujian, China ²Department of Plastic Surgery, School of Medicine, Zhejiang University Affiliated Sir Run Run Shaw Hospital (SRRSH), China

Received: 25 May 2017 Revised: 27 May 2017 Accepted: 09 June 2017

*Correspondence: Dr. Chen Qiang,

E-mail: cqiang8@189.cn

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ABSTRACT

Peritoneal metastases (PM) from disseminations of gastric cancer, presented as a recurrence, its considered fatal with no definitive cure. newer agents like S1 and docetaxel have shown some advantage but nevertheless the median overall survival with the current first line chemotherapy is only 8 to 14 months which shows no great improvement when adding targeted therapy. A multidisciplinary approach combining cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) has been developed. European and Far East studies reported long-term survival benefits in case of complete cytoreduction with 5-year survival rates up to 25%. In order to prevent peritoneal recurrence and to improve overall survival, adjuvant HIPEC is the most evidence-based indication for advanced-stage gastric cancer patients without PM. The rationale for immunotherapy is solid, with ongoing studies combining CRS and intraperitoneal immunotherapeutic agent. The detection of peritoneal cancer cells is the most reasonable way for identifying the metastasis risk after operation. Peritoneal washing appears to be a sensitive method. Thus, the prevention of peritoneal recurrence mandates the use of multiple modalities and locoregional treatments strategy.

Keywords: Gastric cancer, Hyperthermic intraperitoneal chemotherapy, Immunotherapy, Peritoneal metastases

INTRODUCTION

The regional spread of gastric cancer often results in peritoneal metastases (PM). When patients are explored for curative intent resection, 10-20% of them are discovered to have peritoneal metastases. PM is present at first diagnosis of the cancer in 15-50% of cases and peritoneal recurrence occurs in 35-60% of such patients after radical resection. PM is the only site of metastasis in 40-60% of patients. Therefore, peritoneal metastases alone accounts for 20-40% of patient's mortalities.

Inadequacy and inefficiency of the conventional surgery, promoted the current treatments of the systemic

chemotherapy and palliative therapy, with again dismal hope for cure. Therefore, more aggressive surgery with multimodal loco-regional treatments are the key and have shown to prolong survival and reduced peritoneal recurrences.⁴

MECHANISM OF PERITONEAL METASTASES

The molecular mechanisms of PM are not completely understood. Chemokines are believed to be involved. They control the migration and activation of leukocytes through interactions of seven trans-membrane G protein-coupled receptors and other types of cell. Chemokines may also promote growth and survival of metastases of several cancers. There is evidence that the correlation

between CXCL12 and the receptor CXCR4 may play role in its development.⁵

the expression of CXCR4 in primary gastric tumors correlates significantly with the occurrence of PM. Moreover, cells expressing CXCR4 are discriminately attracted to its ligand CXCL12 in the peritoneum. The CXCL12/ CXCR4 axis is affected by interaction with the vascular endothelial growth factor (VEGF).⁶ VEGF level is elevated in malignant ascites and is one of the basic component of PM.⁵ Such results suggest its usefulness as a predictor for PM occurrence.

Peritoneal dissemination occurs through exfoliation from the tumor and direct invasion of the mesothelium. Surgery itself may be the culprit and it may result in intra-operative seeding of cancer cells by different ways such as injured lymphatics, intraperitoneal hemorrhage, trauma at resection margins. free cancer cells which are spontaneously exfoliated or scalpel disseminated, attach to the damaged surface; they are impeded by fibrin and activated by growth factors, leading to visceral and parietal peritoneum implants. The nodule of Metastases becomes hypoxic, and relatively impenetrable to systemic chemotherapy.⁷

Tumor cells can also disperse through spots in the peritoneal surface, thus communicating between the peritoneal and lymphatics cavities. spots are mainly composed of macrophages and B1 cells; The peritoneal free cancer cells are entangled during their passage and the immune cells onslaught.⁸ The preferential sites of distribution of PM are mainly in the omentum and in the sub- diaphragmatic areas, which in fact are the spots locations.⁹

THE TREATMENT OF PERITONEAL METASTASES

The PM arising from gastric cancer has ever been considered incurable. The prognosis of PM is very poor, and even worse than that of other metastatic sites, ¹⁰ with a median survival of only 3-7 months and 5-year survival rate of nearly 0%. ^{1,2} Palliation, whenever possible is the conventional approach.

Systemic chemotherapy

Adjuvant or neoadjuvant Systemic chemotherapy and adjuvant chemo-radiation do not have lowered the rate of peritoneal recurrence significantly. 11,12

Gastric cancer patients with PM have a significant decreased rate of tumor response to chemotherapy with variable response rates (14-25%).¹³ The poor response is due to the presence of the "blood peritoneal barrier" which as the name indicates, has an isolating effect of the peritoneal cavity from the intravenous chemotherapy.¹⁴ the median survival is only 18 months¹⁵ even with the

newer agents like S1 and docetaxel which presumably have better results against peritoneal metastases.

Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

The concept is that PM is to be considered as local disease, which can be suitably treated by cytoreductive surgery (CRS) and with loco-regional treatments such as the hyperthermic intraperitoneal chemotherapy (HIPEC). During CRS procedures, the goal is always attempting to achieve a complete cytoreduction by removal of all visible cancer along the affected peritoneum through "peritoneal stripping". ¹⁶ The aim of CRS is complete macroscopic debulking which is a prerequisite for HIPEC. The efficacy of intra- peritoneal chemotherapy gets its highest effects in the absence and/or the presence of minimal residuals that are less than 2.5. ¹⁷

The cancer cells are heat sensitive distinguishably from the normal cells. Hyperthermia has a dual action that is direct cytotoxic and indirect effects by synergistically improving the action of anti-neoplastic drugs. 42-43°C hyperthermia when applied alone may have an important therapeutic effect on tumor tissue; moreover, hyperthermia synergically enhances the chemo sensitivity to various antitumor agents. During HIPEC, the chemotherapeutic agents are added into the circuit as soon as the abdominal temperature reaches 41.5-42.5°C. Postoperative mortality rate after combined CRS and HIPEC is 2-4%, Morbidity is relatively high (25-41%) and seems to be attributed to the extension of CRS.¹⁸ Combined CRS and HIPEC is being increasingly used as a curative treatment of selected patients with PM from colorectal or ovarian cancer, pseudomyxoma peritonei, and peritoneal mesothelioma. 19 The CRS + HIPEC in PM arising from gastric cancer is a still under investigation. Several European and far east studies show the possibility of long- term survival in case of complete cytoreduction with 5-year survival rates up to nearly 25%. Glehen et al, in 2010 had published the results of a retrospective French study of 1,290 patients with PM treated with HIPEC; of them,159 had PM of gastric origin.²⁰ The 1-, 3-, and 5-year survival rates were 61%, 30%, and 23%, respectively in patients with a complete cytoreduction which is the principal independent prognostic factor at multivariate analysis.²¹ In a systematic review of 10 published studies involving 441 patients who underwent CRS and HIPEC in peritoneal metastases from gastric cancer, Gill et al, reported median overall survival of 7.9 months after HIPEC, which doubled to 15 months in case of complete cytoreduction however the 5-year survival of all the patients was 13%.²² Yang et al showed the importance of combining CRS with HIPEC in a phase III randomized clinical trial.²³ The CRS-HIPEC combination versus. CRS alone increased median significantly: 11 versus. 6.5 months. The prospective randomized clinical trial GYMSSA compared patients treated with CRS- HIPEC and systemic chemotherapy versus. systemic chemotherapy treatment alone,

demonstrating survival advantage. With the limitation of a small number of patients, it showed a longer median overall survival (11.3 versus 4.3 months) for CRS-HIPEC treatment trial arm with No patient lived more than 12 months in the systemic chemotherapy alone arm.²⁴

Adjuvant HIPEC

The use of adjuvant HIPEC in case of advanced gastric cancer without metastases is to prevent patients who are at high risk from developing peritoneal recurrence

PM develops in 60% of patients after curative resection with tumors invading the serosa.²⁵ In Fujimoto's patients, HIPEC significantly reduced the incidence of peritoneal recurrence (P < 0.001) and improved the survival rate (P = 0.03).²⁶ Yonemura randomized the patients in three surgery alone, surgery plus HIPEC, and intraperitoneal chemotherapy without hyperthermia. The 5-year survival was higher in the HIPEC group 61% compared to 43% and 42% in the other two groups.²⁷ Two meta-analysis of RCTs (including 1648 and 1062 patients) on HIPEC as adjuvant therapy have been published.²⁸ The patients, presenting with gastric cancer (macroscopic serosal invasion) but without distant metastases or PM, were randomly assigned to receive surgery combined with intraperitoneal chemotherapy or surgery without intraperitoneal chemotherapy. In both analyses a highly significant improvement in survival and in peritoneal recurrence rate was demonstrated for the HIPEC group compared to the control group. Recently, a meta-analysis on effects of intraperitoneal chemotherapy in advanced gastric cancer was reported by Coccolini et al.²⁹ They extracted the data from 20 prospective studies involving 2,145 patients. Overall survival was increased when intraperitoneal chemotherapy was added to surgery; intraperitoneal chemotherapy was found to reduce the incidence of peritoneal recurrence and distant metastases. HIPEC as adjuvant treatment is reported with Level of Evidence I, grade A in the German S3-guidelines "Diagnosis and treatment of esophagogastric cancer".30 Indication of HIPEC in adjuvant setting is more evidence-based in advanced-stage gastric cancer patients. No peritonectomy procedures are needed; post-operative morbidity and mortality are the same as surgery alone. Anyway optimized "integrated" identification of high risk patients of peritoneal recurrence is necessary.³¹

Intraperitoneal immunotherapy

The disappointing survival results for the treatment of PM from gastric cancer even with HIPEC with rates of 5-year survival not more than 25% in selected cases, paved the way for more innovative therapies such as intraperitoneal immunotherapy.

Catumaxomab is a chimeric antibody, consisting of an anti-EpCAM Fab region and an anti CD3 Fab. It is characterized by its capability to bind to three different types of cells: tumor cells expressing the epithelial cell

adhesion molecule (EpCAM), T lymphocytes (CD3) and accessory cells (Fc γ receptor). In nearly 90% of gastric cancer they do express EpCAM antigen; in contrast to the peritoneal mesenchymal cells which do not.

In a randomized study of patients with symptomatic malignant ascites secondary to EpCAM positive carcinomas, a clinical effect was observed after intraperitoneal infusion of catumaxomab,66 out of 258 were from gastric cancer. Heiss and coll randomly assigned the patients to paracentesis plus intraperitoneal catumaxomab or to paracentesis alone, Puncture-free survival was significantly longer in the group treated with catumaxomab (46 versus. 11 days, P < 0.0001) but median overall survival was almost similar between the two groups: 72 days in the catumaxomab group versus. 68 days in the control group. He is a secondary to EpCAM positive carcinomatics after the secondary to EpCAM positive carcinomatics after the secondary to EpCAM positive carcinomatics after the secondary to EpCAM positive carcinomatics with support to EpCAM positive carcinomatics after the secondary the secondary the secondary the secondary the secondary the secondary that the secondary the secondary that the secondary the secondary that the secondary

Elias et al from Gustave Roussy Institute (Villejuif, France), recently proposed a randomized phase II study, combining complete cytoreductive surgery(CRS) with intraperitoneal immunotherapy.³³ The main inclusion criteria of the study are PM of minimum and/or moderate extension and macroscopic resection of all the lesions: they just follow the experience-based indications for HIPEC in PM from gastric cancer.²⁰ As applied for HIPEC, the complete resection of all macroscopic disease before starting the intra-peritoneal administration of catumaxomab is mandatory. The immunotherapy could efficiently treat microscopic residual disease.

DIAGNOSIS OF PM AND RISKS OF PERITONEAL RECURRENCE

The era of the methods of detecting peritoneal free cancer cells is evolving. It's well known that the positive peritoneal cytology correlates with the depth of gastric wall invasion and it has a prognostic value.³⁴ similarly, it's also well known that cumulative risk of peritoneal recurrence is based on the gastric serosa infiltration.³⁵ Cytological examination of peritoneal washing at the time of primary tumor resection is frequently positive. Free peritoneal cells are associated with an average survival of 4 months versus. 21 months for patients with negative cytology.³⁶

According to the 7th edition of the American Joint Committee on Cancer, positive cytology in the absence of visible peritoneal implants is considered as M1 disease.³⁷ Peritoneal washing for cytology is mandatory in staging/treatment protocols of advanced gastric cancer.³⁸

The identification of patients at high risk of peritoneal recurrence and the diagnosis of intra-peritoneal free cancer cells are probably intermingled aspects of the same challenge. The vast majority of patients with positive cytology on peritoneal washing develop PM even though it may also occur in patients with negative cytological results. These observations indicate that conventional cytology lacks both the sensitivity for the

detection of residual cancer cells and the prediction of peritoneal spread. several reports have emphasized the clinical significance of molecular diagnosis using reverse transcriptase-polymerase chain reaction analysis for more sensitive detection of gastric cancer cells in peritoneal washing. Fujiwara analyzed the survival of 123 patients with serosa-invading gastric cancer.³⁹ The prognosis was very poor of the 29 patients with positive cytology in the peritoneal washing, and most of them died within 1 year postoperatively. Among the 93 patients with negative cytology ,49 had a positive genetic diagnosis and a significantly poorer prognosis than those with negative genetic results. Half or more of the patients with positive PCR and negative cytology developed peritoneal recurrence after surgery, while almost all patients with dual negativity (PCR and cytology) had no peritoneal recurrence after surgery.³⁹ These results have been supported by many studies. All the authors concluded that molecular diagnosis based on peritoneal washing is useful to predict peritoneal recurrence for patients with serosal invasion; positive PCR has significant correlation with overall survival and with peritoneal recurrence rate. 40 Two third of patients with negative cytology can be positive on PCR detection; questioning the credibility of R0 surgery (i.e. no macroscopic, microscopic and cytological residual disease) for advanced gastric cancer.

Molecular biological techniques are anyway time consuming. A new rapid gene detection system, One-step nucleic acid amplification has been recently suggested. Its simplicity and rapidity potentiates its routine use in the clinical laboratory. It also provides valuable clinical information for choosing the appropriate treatment for negative cytology patients: such patients are potential candidate to intraperitoneal therapy, such as HIPEC, immunotherapy or both

CONCLUSION

The peritoneal metastatic spread of gastric cancer is a very aggressive disease with very poor prognosis. In selected patients with low peritoneal tumor load, more aggressive multiple modality strategies with CRS plus intraperitoneal treatment as HIPEC may obtain longterm survival results with up to 25% 5-year survival rates in case of complete cytoreduction. Moreover, there are strong evidences for HIPEC in adjuvant regime after radical surgery for preventing PM in high risk gastric Intraperitoneal immunotherapy. cancer patients. combined with radical surgery, may have a very interesting perspective for the future and sounds promising.

The detection of free peritoneal cancer cells is a feasible and actual method for the identification of patients at high risk of PM after surgery. The routine use of techniques of molecular detection in peritoneal washing appears to be a sensitive method. Such patients are potential candidate for multiple therapeutic modalities

and loco regional treatments to prevent peritoneal recurrence.

Funding: No funding sources Conflict of interest: None declared Ethical approval: Not required

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Cite this article as: Qaid AM, He G. Management of peritoneal metastasis of gastric cancer. Int J Adv Med 2017;4:870-5.