REVIEW

Regional but fatal: Intraperitoneal metastasis in gastric cancer

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Abstract

Peritoneal carcinomatosis appears to be the most common pattern of metastasis or recurrence and is associated with poor prognosis in gastric cancer patients. Many efforts have been made to improve the survival in patients with peritoneal metastasis. Hyperthermic intraperitoneal chemotherapy remains a widely accepted strategy in the treatment of peritoneal dissemination. Several phase Ⅱ-Ⅲ studies confirmed that the combined cytoreducitve surgery and hyperthermic intraperitoneal chemotherapy resulted in longer survival in patients with peritoneal carcinomatosis. In addition, proper selection and effective regional treatment in patients with high risk of peritoneal recurrence after resection will further improve prognosis in local advanced gastric cancer patients.

Key words: Gastric cancer; Intraperitoneal metastasis; Regional metastasis; Cytoreductive surgery; Hyperthermic intraperitoneal chemotherapy

Core tip: The recurrence rate of gastric cancer after surgery within 2 years remains at 79%. Gastric cancer patients with peritoneal metastases have a median survival of only 3.1 mo. Understanding the influence of peritoneal metastasis on survival in gastric cancer patients, the potential molecular mechanism of peritoneal metastasis, and individualized treatment of patients with high risk of peritoneal metastasis is essential for selecting effective treatment strategies in advanced gastric cancer. In this review, we summarized

translational and clinical researches on peritoneal carcinomatosis, providing comprehensive information to better understand the fatal role of peritoneal metastasis in gastric cancer.

INTRODUCTION

Gastric adenocarcinoma is the fourth most common cancer and the second leading cause of cancer-related death worldwide[1]. Apart from countries with national screening programs such as Japan and South Korea, most gastric cancer patients present with advanced disease because early-stage tumors are usually asymptomatic and often develop metastatic recurrences even after curative resection. Despite improvements in the surgical treatment of gastric adenocarcinoma, a high recurrence rate persists, with a 5-year overall survival rate for all diagnosed patients of only 24.5% in Europe[2] and 40%-60% in Asia[3,4]. The most frequent cause of treatment failure following surgery for gastric cancer is peritoneal dissemination, mainly caused by the seeding of free cancer cells from the primary gastric cancer, which is the most common type of spread. Gastric cancer patients with evidence of macroscopic peritoneal carcinomatosis have very poor prognoses, with a median overall survival of 3-6 mo[5,6].

In this review, we aim to summarize the influence of peritoneal metastasis on survival in gastric cancer patients, the potential molecular mechanism of peritoneal metastasis, and individualized treatment of patients who have high risk of peritoneal metastasis.

PERITONEAL METASTASIS IS THE MOST IMPORTANT FACTOR FOR PROGNOSIS IN GASTRIC CANCER

The Recurrence rate of gastric cancer remains high, particularly in patients with advanced stage disease. Among patients receiving R0 resection, 79% have documented recurrences within 2 years, and the median time to death from the time of recurrence is 6 mo[7]. Many patients, especially those with stage III disease, develop locoreginal recurrence, peritoneal recurrence, or distant metastasis[8]. Many investigators have analyzed recurrence patterns of gastric cancer after curative surgery, but the data have shown variable incidences of these patterns. Schwarz *et al*[9] found that the most common pattern was distant metastasis while Eom *et al*[10] found that hematogenous

metastasis was most common among patients with early recurrence and locoregional and peritoneal recurrence among patients with late recurrence using a cutoff time of one year after curative resection for patient subgroups. This disagreement was attributed to differences in patient cohorts undergoing evaluation, the cutoff at which recurrence was determined, and the methods for determining recurrence patterns. In addition, autopsy studies revealed only end-stage disease, but not early recurrence patterns, and re-operation series probably reflect early locoregional and peritoneal recurrence. Laparoscopy and peritoneal cytology have been shown to detect occult metastatic disease not seen on conventional imaging[11].

A recent study of 1178 patients with metastatic or recurrent gastric cancer showed that about 46% of patients had peritoneal metastases and about 30% had liver metastases[12]. Several other clinical studies have reported recurrence patterns in a population of patients with early stage to advanced disease[7,9,13-15], showing that 30%-54% of patients had peritoneal recurrence alone or in combination.

Our unpublished data showed in a total number of 349 patients with stage III and IV gastric cancer, peritoneal metastasis was detected in 62.8% of the patients. And 81.1% of the patients developed metastasis in peritoneal cavity (peritoneal and liver) at the time of recurrence or diagnosis. Furthermore, peritoneal cancer involvement is associated with poor prognosis and quality of life compared with metastasis to other organs. Our research showed that stage IV patients with peritoneal metastasis had shorter survival (7.5 mo *vs* 14 mo) and a higher risk of mortality (HR = 2.026, *P* = 0.004).

MOLECULAR MECHANISMS OF PERITONEAL METASTASIS

Cancer cells are thought to undergo the following sequential steps to form peritoneal metastases: (1) penetration of cancerous tissues into the visceral serosa; (2) exfoliation of the cancer cells from the primary tumor; (3) dissemination and survival of the cancer cells within the abdominal cavity; (4) adhesion of cancer cells to the peritoneum; (5) invasion of cancer cells through the peritoneal membrane; and (6) formation of the peritoneal metastasis[16]. However, the mechanisms governing the formation of peritoneal metastasis remain poorly understood. A global expression profile of 21168 genes was analyzed in a gastric cancer cell line established from a primary main tumor and other cell lines established from the metastasis to the peritoneal cavity. They found that 24 genes of cell adhesion, epithelial markers, drug metabolism and signal transduction were up-regulated and 17 genes of immune response, cell cycle and adhesion were down-regulated[17] (Table 1). Loss of hypoxia inducible factor-1α may accelerate

Table 1 Twenty-four up-regulated and 17 down-regulated genes in gastric cancer cells from malignant ascites compared with those from primary lesions

Gene expression level	Gene name	Gene function
Down-regulated		
	Nucleobinding 2	Signaling (apoptosis)
	Acyl-Coenzyme A dehydrogenase	Signaling
	Chaperonin containing TCP1	Signaling
	FKBP54	Signaling
	Histone deacetylase 3	Signaling
	p27kip	Signaling
	PAK-interacting exchange factor alpha	Signaling
	CD4	Immune response
	IL4 stat	Immune response
	L2 receptor gamma	Immune response
	IGFBP2	Growth and metabolism
	RAD51 homologue C	Chromosome stability
	Heterogenous nuclear ribonucleoprotein	Cell adhesion
	Integrin β4	Cell adhesion
	Tubulin beta-1 chain	Cell adhesion
	Death associated protein	Apoptosis
	H2A histone family member L	Apoptosis
Up-regulated		
	Dopa decarboxylase	Signaling or progression
	Caveolin-3	Signaling (modification)
	CD9	Signaling
	Dystroglycan1	Signaling
	Inositol triphosphate receptor	Signaling
	LMO 7	Signaling
	Sodium/hydrogen exchanger, isoform 1	Signaling
	Cystein protease (legumain)	Invasion
	Myosin 6	Intracellular organelle transport
	Destrin (actin depolymerising factor)	Interaction with extracellular matrix
	Renal tumor antigen RAGE1	Immune response
	Aldehyde dehydrogenase	Drug metabolism
	Aldo-keto reductase family 1	Drug metabolism
	Keratin 14	Cell adhesion, invasion
	Keratin 7	Cell adhesion, invasion
	Keratin 8	Cell adhesion, invasion
	CD44	Cell adhesion
	Desmoplakin (DPI, DPII)	Cell adhesion
	Galectin 3 (lectin)	Cell adhesion
	Integrin alpha3	Cell adhesion
	Occludin	Cell adhesion
	S100 A10 (ligand of Annexin II)	Cell adhesion
	Leukocyte elastase inhibitor	Apoptosis
	TGFb-induced anti-apoptotic factor	Apoptosis

the development of peritoneal dissemination *via* the upregulation of matrix metalloproteinases (MMP) -1 in gastric cancer cells, which was manifested in a mouse model[18]. MMP-7-positive gastric cancer patients have significantly poorer overall survival and die more frequently of peritoneal recurrence than those patients with MMP-7-negative tumors in a Japanese cohort[19]. Another comparative analysis between the parental cell line GC9811 and its highly metastatic peritoneal counterpart, cell line GC9811-P revealed and confirmed that recombinant human S100 calcium binding protein A4 (S100A4) and cadherin-associated protein beta 1 (CTNNB1) were upregulated and phosphatase and tensin homolog deleted on chromosome ten was downregulated in GC9811-P cells. Identification of these differentially expressed genes could disclose the molecular mechanisms involved and provide new targets for therapeutic intervention to avoid peritoneal dissemination of gastric adenocarcinoma[20]. A recent study revealed that intraoperative hemorrhages were strongly correlated with peritoneal recurrence, probably due to an increased ability of cancer cells and mesothelial cells to adhere to each other in the presence of factors in plasma[16]. Zinc protoporphyrin IX[21] andro-quoishomeobox protein 1 (IRX1)[22] was reported to inhibit peritoneal metastasis *via* neovascularization. Identification of these differentially expressed genes could disclose the molecular mechanisms involved and provide new targets for therapeutic intervention to avoid peritoneal dissemination of gastric adenocarcinoma. At present, chemokinereceptor 5 antagonism can reduce the potential for gastric cancer cell dissemination[23]. P38- mitogen-activated protein

kinase inhibition by targeted small molecule inhibitor was demonstrated to be beneficial in preventing the peritoneal dissemination in poorly differentiated gastric cancer[24]. Nevertheless, the molecular mechanisms of peritoneal dissemination need to be further clarified to provide more information for peritoneal dissemination therapy.

EFFECTIVE TREATMENTS FOR PATIENTS WITH PERITONEAL METASTASIS

Patients with peritoneal carcinomatosis of gastric origin have an extremely bad prognosis. Systemic chemotherapy improves median survival in metastatic gastric cancer to 7-10 mo, but in patients with peritoneal carcinomatosis from gastric cancer, the same improvement has not been reported[25]. And 20%-50% of patients treated with radical surgery will develop postoperative peritoneal recurrence[26], and intraperitoneal spread of tumor cells was observed in 54% of patients who died of recurrence after surgery for advanced gastric cancer[27].

At present, hyperthermic intraperitoneal chemotherapy (HIPEC) is the most widely accepted strategy among the treatment options for peritoneal dissemination which is the most frequent metastatic pattern in gastric cancer[28]. The theoretical advantage of the HIPEC is to add the direct cytotoxic effects of heat to a high local concentration of used cytostatic drug[29,30]. In addition to the mechanical washing effect, HIPEC also has the theoretical advantage of delivering a higher anticancer drug concentration into abdominal lavage with reduced systemic toxicity. There are many molecular explanations for the effect of HIPEC. For example, induction of apoptosis, alterations of cell membrane property, changes in intracellular proteins and in their synthesis and heat inhibition of DNA repair enhanced by inhibitors of the cellular heat-shock response[31,32].

In gastric cancer patients with peritoneal carcinomatosis, surgical treatments aiming at removing the primary lesion of peritoneal dissemination is palliative. The combination of cytoreductive surgery (CRS) and HIPEC was first described in 1980 by Spratt *et al*[33]. In the following years, Sugarbaker and his colleagues applied and introduced this innovative technique for peritoneal carcinomatosis[34]. Phase Ⅱ-Ⅲ studies revealed that patients who received CRS plus HIPEC obtained better survival results only if completeness of cytoreduction (CCR-0) resection was achieved. However, the survival benefit of HIPEC remains extremely low if cytoreductive surgery can not accomplish sufficient down-staging of the carcinomatosis burden[35-37]. The largest experience published so far was a retrospective French study involving 159 patients which confirmed this combination advantage in a selected CCR0 group of patients[35]. The dismal effect of HIPEC in patients with extensive peritoneal carcinomatosis not amenable to downstaging to CCR-0 may be explained by limited drug penetration leading to no anti-tumor effect on the deeply invasive microfoci[38]. Thus, drug delivery system with high permeability has the potential perspective role in the treatment of extensive peritoneal carcinomatosis cases[39].

OPTIONAL AGENTS FOR INTRAPERITONEAL TREATMENT

Even though multimodal treatment strategies have been used to improve the prognosis of gastric cancer patients with peritoneal recurrence, the results remain unsatisfactory[40]. The oral anticancer drug S1 is a fluoropyrimidine derivative, combining tegafur with two modulators. A recent meta-analysis showed that the use of S1 monotherapy was associated with a significant survival benefit (HR = 0.48, 95%CI: 0.32-0.70, P = 0.0002)[41]. The advantage of S1 over other chemotherapeutic agents is its ability to attain higher concentrations intraperitoneally, due to the higher concentrations of 5-FU and CDHP achieved in peritoneal tumors than in plasma[42,43].

In addition to S1, paclitaxel and docetaxel, which binds to tubulin, leading to microtubule stabilization, and mitotic arrest, also have high sensitivity against diffuse-type adenocarcinoma, which is a common type of peritoneal tumor. And some of these compounds are transported into the peritoneal cavity when administered intravenously[44].

There have been numerous studies evaluating intraperitoneal drug delivery in gastric cancer. Intraperitoneal administration of anticancer drugs enables an extremely high concentration of drugs to directly contact the target cancer lesions in the peritoneal cavity. However, intraperitoneal administration of mitomycin C or cisplatin yielded no apparent therapeutic effects against peritoneal metastasis of gastric cancer due to immediate absorption through the peritoneum[45]. In contrast to these drugs, intraperitoneal administration of paclitaxel was developed to enhance antitumor activity against peritoneal metastasis by maintaining a high concentration of the drug in the peritoneal cavity over a long period, and its clinical effects have been verified by a number of convincing clinical trials in ovarian cancer with peritoneal metastasis.These superior results were due to the pharmacokinetic advantage of taxanes after regional delivery[46]. Taxanes are absorbed through the openings of lymphatic system, such as the milky spots and the stomata which are important sites for the formation of peritoneal dissemination[47], due to their large molecular weight and fat solubility[48]. A phase Ⅰ/Ⅱ study of intraperitoneal docetaxel plus S1 for the gastric cancer patients with peritoneal carcinomatosis demonstrated a superior 1-year overall survival rate of 70%, and peritoneal cytology turned negative in 81% of the patients[49]. Fujiwara *et al*[50] also reported a median survival of 24.6 mo ingastric

cancer with peritoneal carcinomatosis treated with intraperitoneal docetaxel combined with S1.

Although intraperitoneal paclitaxel showed a profound pharmacokinetic advantage 1000 times higher than systemic administration, the main problem of intraperitoneal chemotherapy is the limited depth of penetration of anticancer drugs directly into the tumor. Accordingly, optimum use of paclitaxel may consist of intraperitoneal and intravenous administration, because intraperitoneal paclitaxel reaches the systemic circulation in only a small amount[51]. Actually, Ishigami *et al*[48] established intraperitoneal paclitaxel with S1 plus intravenous paclitaxel as systemic chemotherapy. The phase Ⅱ study showed an overall response rate of 56% of patients with target lesions and decrease or disappearance of malignant ascites in 62% of the patients.

Another recent phase Ⅱ trial in serosa-positive gastric cancer patients showed a higher similar response rate of 71.4%, and the 3- and 5-year OS rates of 78.0% and 74.9%, respectively[52].

In addition, the efficacy of intraperitoneal irinotecan has been demonstrated in several animal studies. The AUC ratio of SN-38 varied between 3.7 and 14.8 depending on the concentration of administered irinotecan[53]. Moreover, pemetrexed has been proven to be an option when used intraperitoneally in a phase Ⅰ trial in ovarian cancer[54].

Except for chemotherapeutic agents, catumaxomab, a rat-mouse hybrid monoclonal antibody, was registered for the treatment of malignant ascites of various epithelial cell adhesion molecule (EpCAM) positive malignancies, including ovarian, gastric, breast and colorectal cancer. Two studies[55,56] demonstrate that this drug seems to improve progression-free survival in patients with gastric cancer (median 71 d *vs* 44 d, *P* = 0.03) and that it seems to improve the survival of patients with gastrointestinal anti-EpCAM positive tumors in intraperitoneal use.

SELECTED POPULATION FOR INTRAPERITONEAL CHEMOTHERAPY

Positive peritoneal cytology was classified as metastatic disease (M1) in the 7th edition of the American Joint Committee on Cancer tumor node metastasis staging system for gastric cancer[57]. Intraperitoneal free cancer cells isolated during peritoneal washing in patients with gastric cancer have been demonstrated to be significantly and independently related to the prognosis, influencing both recurrence and survival. It is important to prevent peritoneal recurrence after curative surgery to improve the prognosis of gastric cancer patients. However, to apply this modality, selection of patients who are at high risk for peritoneal recurrence is crucial. And, the recent trend in treatment is the administration of adjuvant intraperitoneal chemotherapy immediately after

resection in patients who are at high risk of peritoneal recurrence[58,59].

Although the precise mechanism driving peritoneal recurrence remains unclear, the presence of malignant cells in the peritoneum at the time of surgery can lead to peritoneal recurrence[60,61]. Therefore, examination of peritoneal fluids has emerged as an option for identifying patients who are at high risk for peritoneal recurrence after curative resection.

Although conventional peritoneal cytology is the standard and reliable method for detecting free cancer cells in the peritoneal wash and for predicting peritoneal metastasis, in large-sample studies, approximately 4%-11% of patients will have cytology positive and therefore it is not practical or cost-effective to perform it in all patients[62]. Furthermore, it lacks sensitivity for the detection of residual cancer cells and prediction of peritoneal spread[63,64]. A recent prospective clinical study demonstrated that conventional cytology is not beneficial for predicting peritoneal recurrence after curative surgery for gastric cancer, because peritoneal washing cytology was not able to predict peritoneal recurrence or survival in gastric cancer patients[65].

A study including 655 patients indicated that intraoperatively assessed macroscopic serosal changes confer a poor prognosis and increased peritoneal recurrence for patients with curatively resected gastric cancer. Macroscopic serosal changes were defined as changes in color or nodular texture of the serosal surface on inspection and palpation. Macroscopic assessment of serosal changes may be a useful indicator that allows better risk stratification of patients with resected gastric cancer in terms of prognosis and peritoneal recurrence[66].

Recently, genetic detection using reverse trans-criptase polymerase chain reaction analysis has been found more sensitive than conventional cytology. The target genes of carcinoembryonic antigen (CEA), heparanase, matrix metalloproteinase-7, cytokeratin 20, telomerase, zinc-finger E-box binding homeobox 1 and melanoma-associated gene in single or in combination were used as potent molecular markers[67-69].

However, the amplified mRNA may be derived from dead cells or phagocytes that have engulfed tumor cells, and can be released from hematopoietic cells in an inflammatory context[70]. Therefore, the clinical issue of false-positive cases remains to be addressed. Using DNA methylation or flow cytometry to identify intraperitoneal tumor cells is another valuable alteration for selecting patients who might have a high risk of peritoneal metastasis[71,72].

CONCLUSION

Gastric cancer is the second leading cause of cancer death worldwide and more than half of the gastric cancer patients show disease progression and

die of peritoneal carcinomatosis. Proper selection of intraperitoneal chemotherapy in patients with peritoneal metastasis or patients with potential risk of peritoneal recurrence may be a promising approach to improve the prognosis of advanced gastric cancer patients. Administration of chemotherapeutic agents with a maintaining high concentration and a high permeability in the peritoneal cavity is an ideal choice for intraperitoneal chemotherapy. Moreover, the study of potential biomarkers from peritoneal washing could provide valuable information for a better selection of subsequent treatment combinations.

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