Editorial

Intraperitoneal chemotherapy and its evolving role in management of gastric cancer with peritoneal metastases

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Abstract: Advanced gastric cancer (GC) has been recognized as lethal disease when peritoneal metastases (PM) occurred. There is no standard treatment for advanced GC with PM. Until 1980s, the therapeutic arena for these patients had remained stagnant, with no therapeutic approach having shown a survival gain in GC with PM. However, cytoreductive surgery (CRS) with peritonectomy procedures and intraperitoneal chemotherapy (IPC) promising new combined therapeutic approach to achieve disease control for GC with PM. The recent publications changed the GC with PM treatment landscape by providing an evidence that CRS and IPC led to prolongation in overall survival (OS). This review will provide an overview of the evolving role of CRS and IPC in the management of advanced GC with PM in the current era.

Keywords: Gastric cancer (GC); peritoneal carcinomatosis; intraperitoneal and systemic induction chemotherapy; cytoreductive surgery (CRS); hyperthermic intraperitoneal chemotherapy (IPC)

Submitted Jan 30, 2014. Accepted for publication Feb 12, 2014.
doi: 10.3978/j.issn.1000-9604.2014.02.06
Scan to your mobile device or view this article at: http://www.thecjcr.org/article/view/3337/4170

Introduction

Peritoneal metastases (PM) of gastric cancer (GC) have been considered a terminal stage of disease (1). The traditional goal of PM of GC has been palliation rather than curative. However, half of the advanced stage GC patients do not respond to chemotherapy with the lowest response rate in GC patients with PM (2). This occurs because PM of GC are penetrated less efficiently than disease at other sites. A poor response to systemic treatment provides the rationale for a local-regional strategy for treatment.

Over the past three decades, a new multimodal treatment called cytoreductive surgery (CRS) with intraperitoneal chemotherapy (IPC) was proposed (3,4). In this review we summarized current knowledge in management of GC with PM.

Rationale of heated IPC in GC with PM

The addition of heat to the IPC treatments was first explored in a pseudomyxoma peritonei patient by Spratt *et al*. (5). They established both heat and chemotherapy were well tolerated in this patient and had the potential to develop into an effective treatment strategy for patients with the dissemination of cancer to the peritoneal surfaces.

As shown in *Table 1*, Fujimoto and colleagues performed an early trial in 15 patients with PM developed secondary to advanced GC to test the efficacy of heated intraoperative intraperitoneal chemotherapy (HIPEC) in 1988 (6). They reported acceptable postoperative morbidity and slightly longer mean overall survival (OS) [7.2±4.6 months (mo)].

In 1991, Yonemura and colleagues focused on CRS as an essential component of treatment (4). They reported that

Table 1 Survival analysis in GC patients with PD treated with CRS and HIPEC

Authors	Patients No.	Agent used in HIPEC	Mortality/morbidity (%)	Survival
Fujimoto *et al*. (1988) (6)	15	MMC	–	7.2±4.6 mo
Yonemura *et al*. (1991) (4)	41	MMC + CDDP	0-29.3	3-year 28.5%
Fujimoto *et al*. (1997) (7)	48	MMC	–	5-year 31%, 8-year 25.4%
Glehen *et al*. (2004) (8)	49	MMC	4-27	5-year 16%, CC0/1 29.4%
Hall *et al*. (2004) (9)	34	MMC	0-35	2-year 45%, (CC0/1) 8% (CC2/3)
Yonemura *et al*. (2005) (10)	107	MMC + CDDP	2.8-21.5	5-year 6.7%
Glehen *et al*. (2010) (11)	139	MMC ± CDDP or LOHP ± irinotecan	6.5-27.8	5-year 13%, CC0/1 23%
Yang *et al*. (2011) (12)	34	MMC + CDDP	0-14.7	3-year 5.9%, CC0/1 23%
Magge *et al*. (2013) (13)	23	MMC + CDDP	4.3-52.2	1-year 50%, 3-year 18%

GC, gastric cancer; CRS, cytoreductive surgery; HIPEC, heated intraoperative intraperitoneal chemotherapy.

CRS plus continuous hyperthermic peritoneal perfusion with mitomycin C (MMC) and cisplatin (CDDP) was performed in 41 GC patients with PM after resection. The overall median survival was 14.6 months and the 3-year survival rate was 28.5%. In 1997, Fujimoto and colleagues performed HIPEC using MMC combined with surgery in 48 GC patients with PM, and reported a 5-year survival of 31%, and 8-year survival 25.4% (7).

Yonemura and colleagues published one of the largest series; when the complete cytoreduction (CC0/1) was achieved 5-year survival rate was in 13% in GC patients with PM compared to 6% in those with incomplete cytoreduction (CC2/3) (10). Completeness of cytoreductive score was described by Jacquet and Sugarbaker (14) and they divided into four in respect of size residual disease left behind following CRS. CC0: no residual disease; CC1: tumor nodules <2.5 mm; CC2: tumor nodules between 2.5 mm to 2.5 cm; and CC3: tumor nodules >2.5 cm. Glehen and colleagues reported the results of 159 patients as a retrospective French multi-institutional study (11). They reported that when complete cytoreduction was achieved 5-year survival rate was increased up to 23% compared to 13% in patients with incomplete cytoreduction.

Effects of bidiractional intraperitoneal and systemic chemotherapy prior to cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in GC patients with PM

Bidirectional intraperitoneal and systemic chemotherapy was developed by Yonemura and colleagues to reduce the tumor burden and to eradicate peritoneal free cancer cells prior to CRS and HIPEC in GC patients with PM (15). This treatment was designed to eradicate dissemination from both peritoneum and subperitoneal blood vessels. Recently, this group published the results of treatment of 194 synchronous and metachronous GC patients with PM (16). Of these 194 patients, 152 (78.3%) patients underwent CRS and HIPEC following bidirectional intraperitoneal and systemic treatment. Treatment-related mortality was 3.9%, and major complications occurred in 23.6% of these patients. The median survival rate was 15.8 months, with 1-, 2-, and 5-year survival rates of 66%, 32% and 10.7%, respectively.

Recently, a meta-analysis on effects of IPC in advanced GC was reported by Coccolini and colleagues (17). They pooled the data from 20 prospective studies involving 2,145 patients. Their conclusion was that IPC benefits GC patients with PM after curative resection. The odds ratio was 0.99 with a 95%confidence interval at 0.71-1.37.

Coccolini and colleagues concluded OS is increased when IPC was added to surgery. OS was not changed with nodal involvement, and mortality rates were not changed with serosal infiltration. IPC was found to reduce the incidence of peritoneal recurrence and distant metastases. They found that morbidity was increased with inraperitoneal chemotherapy. Lymph node involvement was not contraindication for IPC.

Conclusions

These studies suggest that IPC in preoperative and peroperative settings are of benefit in GC with PM. A bidirectional approach combined with CRS and HIPEC

was shown to improve OS in GC patients with PM. Further studies will be required for optimize the effects of IPC combined with surgery in these patients.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Canbay E, Yonemura Y, Brucher B, Baik SH, Sugarbaker PH. Intraperitoneal chemotherapy and its evolving role in management of gastric cancer with peritoneal metastases. Chin J Cancer Res 2014;26(1):1-3. doi: 10.3978/j.issn.1000-9604.2014.02.06

