Perspective

Multidisciplinary approach for the treatment of gastric cancer

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Submitted Jun 29, 2012. Accepted for publication Jul 23, 2012.
DOI: 10.3978/j.issn.2224-4778.2012.07.06
Scan to your mobile device or view this article at: http://www.amepc.org/tgc/article/view/952

In the past, gastric cancer (GC) with stage IV was considered as a terminal illness and a generalized form of cancer. Even though, patients with stage IV GC were offered a palliative chemotherapy or a best supportive care, median survival was 6 to 12 months.

In the late 1990s, TS-1, irrinotecan, taxanes and oxaliplatin (OHP) were introduced for gastric cancer treatment. The response rates after monotherapy with these drugs were around 20%. While chemotherapy in combination of two or three of these drugs have shown an excellent response rate of 42% to 74% with a prolonged survival (1,2). However, treatment failure as a result of toxicity was also reported (3,4). More recently, combination chemotherapy with an oral fluoropyrimidine (S-1 or capecitabine) and platinum (cisplatin: CDDP or OHP) has been recognized as standard chemotherapy for metastatic gastric cancer all over the world (5).

Even though high response rate to systemic chemotherapy was achieved, GC with stage IV is still dismal. Overall survival by systemic chemotherapy alone is less than 5% for 5-year, whereas, no survival benefit has been reported by cytoreductive surgery (CRS) alone.

The current state-of-the-art treatment to improve the long-term survival for GC with stage IV consists of a comprehensive management strategy using CRS and perioperative chemotherapy. The strategy is now performed in a curative intent. CRS plus perioperative chemotherapy including neoadjuvant chemotherapy, intraoperative intraperitoneal chemotherapy combined with hyperthermia, early postoperative intraperitoneal chemotherapy confers a prolonged survival period (6).

The aims of neoadjuvant chemotherapy (NAC) are stage reduction, eradication of micrometastasis outside the surgical field, and the improvement of resectability. Systemic chemotherapyis used for bulky lymph node metastasis or liver metastases. S1 plus CDDP can be given as a standard first-line chemotherapy, and the one-year survival rate of CRS after NAC with S1 plus CDDP was 75% (2).

The most frequent form of distant metastasis from GC is peritoneal carcinomatosis (PC). However, systemic chemotherapy shows little effects on the PC. Intraperitoneal (IP) chemotherapy for PC offers potential therapeutic advantages over systemic chemotherapy by generating high local concentrations of chemotherapeutic drugs in the peritoneal cavity (7,8). This concentration difference enables to eradicate small PC nodules before CRS and lowers the systemic toxicity.

Recently, bidirectional chemotherapy combined with simultaneous administrating intravenous and IP chemotherapy was developed (9). Bidirectional diffusion gradient can create a wider treatment area than single treatment. This approach was given in acronym neoadjuvant intraperitoneal and systemic chemotherapy (NIPS). NIPS is used before surgery to reduce the peritoneal surface involved by peritoneal dissemination, and to eradicate peritoneal free cancer cells. Accordingly, NIPS can increase the incidence of complete cytoreduction, resulting in the survival improvement (9). In addition, NIPS did not add to the morbidity and mortality of further surgical treatment (9).

Extensive intraoperative peritoneal lavage (EIPL) treatment is a new modality to remove peritoneal free cancer cells by the extensive washing of peritoneal cavity with saline (10). Briefly, after a potentially curative operation, the peritoneal cavity was irrigated with 1 liter of normal saline, extensively shaken and washed, then followed by the complete aspiration of the fluid. This procedure was done 10 times. According to a prospective randomized study

(RCT) in patients with intraperitoneal free cancer cells (Cy1) without overt peritoneal metastasis (P0) (P0/Cy1), the EIPL group had a significantly lower incidence of peritoneal recurrence. EIPL therapy is strongly recommended as a prophylactic strategy for patients with P0/Cy1 status (10).

An abundance of experimental and clinical evidence has indicated that malignant cells are selectively destroyed by hyperthermia in the range of 41-43 ℃. Hyperthermia impairs DNA repair, protein denaturation, and the inhibition of oxidative metabolism in the microenvironment of malignant cells and increases cell death. Hyperthermia enhances chemotherapy efficacy, and the combination of heat and anti-neoplastic drugs frequently results in increased cytotoxicity. Some chemotherapeutic agents augment cytotoxicities in combination with mild hyperthermia. Such effects have been reported for mitomycin C, cisplatinum, docetaxel, gemcitabine and irinotecan. An additional factor *in vivo* is increased drug penetration, which is observed at temperatures above 39-42 ℃ (7).

To date, intraperitoneal chemotherapy and hyperthermia have been investigated as possible treatment options for PC from ovarian (11), colorectal (12,13) and gastric cancer (14,15). In gastric cancer, two RCTs have been reported for the prevention of peritoneal recurrence after curative resection (16,17). A recent meta-analysis of RCTs for gastric cancer indicated that HIPEC with CRS is associated with an improved overall survival (18).

It is expected that the use of molecular targeting agents combined with CRS plus chemotherapy will lead to remarkable progress in the near future.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Yonemura Y, Canbay E, Ishibashi H, Fushida S. Multidisciplinary approach for the treatment of gastric cancer. Transl Gastrointest Cancer 2012;1(2):178-180. DOI: 10.3978/j.issn.2224-4778.2012.07.06

