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Editorial

IS PERITONEAL CARCINOMATOSIS AN INCURABLE DISEASE OR CONTROLLABLE LOCOREGIONAL CONDITION? — CHALLENGE OF SURGEONS WITH INTRAPERITONEAL HYPERTHERMIC CHEMOTHERAPY

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Peritoneal carcinomatosis is the most common terminal feature of abdominal cancers. For gastrointestinal surgeons and medical oncologists, it is a vexing condition because, although the disease is limited to the peritoneal surface, complete surgical removal is impossible and systemic chemotherapy is powerless. Peritoneal carcinomatosis is generally considered to be an untreatable condition that makes clinicians abandon further aggressive treatments.

Gynecologists have some different views on ovarian cancer. They have tried extensive debulking surgery for the peritoneal disease followed by intraperitoneal (i.p.) cisplatin-based chemotherapy. A large, randomized controlled trial has recently shown significant survival benefit of i.p. cisplatin as compared with intravenous cisplatin in patients with stage III ovarian cancer and residual tumor masses of 2 cm or less (1). This treatment strategy for ovarian cancer is, needless to say, based on the high sensitivity of the tumor to the agents. In such situations, cytoreductive surgery may even be regarded as neoadjuvant treatment to chemotherapy. In gastrointestinal cancers, however, no chemotherapeutic regimen has shown such effectiveness.

A theoretical advantage of i.p. administration is that a high local concentration of a potentially effective drug can be achieved while its serum concentration remains low, thereby minimizing systemic adverse effects. The peritoneum/plasma ratio of drug concentration is high for many chemotherapeutic agents including mitomycin-C and cisplatin. In clinical practice, however, the response rates of gastrointestinal carcinomatosis to i.p. chemotherapy were low.

Gastrointestinal surgeons may have found a breakthrough in hyperthermia. It is known that tumor cells are sensitive to heat, probably owing to their susceptible microenvironment with low pH, low oxygen tension and loss of adaptive vasodilatation. Although the effect of hyperthermia alone is limited because the heat penetrates only 1–3 mm from the surface of the solid tumors, experimental studies showed synergistic effects of chemotherapy and hyperthermia. This synergism is explained by an increase in cell membrane permeability and active drug transport and altered cell metabolism. The idea of intraperitoneal perfusion of heated fluid containing chemotherapeutic agents emerged on the basis of these findings.

Spratt et al. (2) first reported the clinical application of intraperitoneal hyperthermic chemotherapy in 1980. This exciting experience was described in detail in *Cancer Research* as a case report: a patient with recurrent pseudomyxoma peritonei, desperately looking for a new treatment, contacted the researcher by telephone after reading the paper and insisted on being the first patient to be treated using the newly constructed perfusion system. The patient underwent debulking surgery followed by perfusion therapies (thiotepa and methotrexate, 42°C) and returned to social life safely.

Since this report, numerous basic and clinical studies have been conducted on hyperthermic chemotherapy (3,4). The perfusion system has undergone several improvements. In their first case, Spratt et al. started peritoneal perfusion after closure of the abdomen. Other surgeons later developed open abdominal methods using a 'peritoneal cavity expander' (5) or 'Coliseum technique' so that all the peritoneal surface of the bowel is sufficiently exposed to the heated perfusate. In this open system, the surgeons usually spend an hour stirring the warm abdominal 'bath' by hand. Meanwhile, pharmacokinetic studies have demonstrated a high peritoneal/plasma ratio and increased cytotoxicity associated with hyperthermia for a wide variety of agents. Not only the well-known mitomycin-C and cisplatin but also doxorubicin, irinotecan, tumor necrosis factor (TNF)-α and interleukin 1 α, etc., exhibit *in vitro* synergism with hyperthermia.

In this issue of the Journal, Dr Paul Sugarbaker, one of the pioneers and most dedicated proponents of intraperitoneal hyperthermic chemotherapy, has written a review article on his own vast experience and publications (6). It covers all the theoretical and practical aspects of the treatment established by his group, including the plasma–peritoneum barrier theory, the completeness of cytoreduction (CC) score, the 'Coliseum technique' and their standardized order forms for perioperative management. He insists, on the basis of the survival results of his patients, that surgeons should accept responsibility for knowledgeable management of peritoneal carcinomatosis.

Today, more than 30 institutions worldwide have considerable experience of hyperthermic chemoperfusion for peritoneal carcinomatosis (3). In other words, it is still a very special modality available only in specialized institutions. It can be easily imagined that the extensive cytoreductive surgery and

immediate hyperthermic perfusion with cytotoxic agents will cause various treatment-specific morbidities. Perfusion equipment will need significant initial and on-going resources for safe and effective use. Hence this is not a treatment that could be started anywhere immediately. Showing high-level evidence of benefit and establishing an appropriate training system are needed for the wide use of chemoperfusion.

The majority of the published studies on this treatment are retrospective analyses of limited numbers of patients with various primary tumor sites treated with diverse regimens over a long period. This is understandable in pioneering works, especially in the field of surgical oncology. Now is the time to design prospective studies to clarify various points. Technical problems to be addressed include the methods of perfusion (closed or open with peritoneal expander techniques), temperature range (41–44°C), length and number of times of perfusion, selection of chemotherapeutic agents and extent of cytoreductive surgery. The morbidity and mortality together with the toxicity of each regimen should be prospectively recorded. The survival of patients must be strictly analyzed according to each primary tumor histology. Collaboration of specialized centers seems essential.

Randomized controlled studies would give evidence and such a trial is ongoing in The Netherlands for peritoneal carcinomatosis from colorectal cancer (7). However, considering the specialty and availability of the technique, the chances of phase III studies appear very limited. For the meantime, accumulation of well designed, prospective phase II studies are of great importance for scientific evaluation of this promising treatment for a condition that is generally considered incurable.

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