

Editorial

Detection and Treatment of the Micrometastases of Gastric Cancer

Harold O. Douglass, Jr., MD

The role of intraperitoneal chemotherapy in the treatment of gastrointestinal cancers remains a subject for debate. If there is a therapeutic role, it is in the management of true micrometastases or free-floating tumor cells. Peritoneal micrometastases and free-floating cells are poorly responsive to systemic chemotherapy.¹ How to identify the ideal candidates for intraperitoneal treatment has remained a continuing problem. Dr. Mori and his co-workers at Osaka University may have identified those ideal candidates.²

Based on a preclinical study in which the authors established a positive correlation between quantitative molecular values of carcinoembryonic antigen (CEA) mRNA and metastatic foci in mice previously injected intraperitoneally with the gastric cancer cell line MKN-45, the investigators mounted a pilot study in 19 patients with T3 and T4 gastric cancers. At preoperative laparoscopy, tumors were staged and peritoneal washings obtained from the pelvis and left subphrenic region for cytology and molecular diagnosis of CEA after amplification by reverse transcriptase polymerase chain reaction (RT-PCR). Prior preclinical studies show peritoneal molecular markers of CEA to be absent in tumor-free animals.

Patients were treated with 20 mg of mitomycin C as a single intraperitoneal infusion combined with a 5-day intraperitoneal course of 20 mg of cisplatin per day. Chemotherapy was administered in 1 L of saline, emptying the abdominal fluid 2 hours later through a drain left for this purpose at the time of laparoscopy. Patients with positive cytology or peritoneal metastases also re-

ceived systemic chemotherapy with docetaxel and cisplatin. Four weeks later, patients were restaged and peritoneal washings repeated. Resections were performed where appropriate.

Quantitative molecular analyses of CEA in the initial and postchemotherapy lavages were compared. In six patients with initial positive tests for CEA, posttherapy results were negative. Five patients had negative studies both before and after intraperitoneal chemotherapy, while in eight patients pre- and postchemotherapy levels were positive. Five of the eight patients had positive pretreatment peritoneal cytologies, whereas cytologic analyses in the remaining 14 patients in the study were negative.

Although the follow-up period is brief (13–39 months), the results of this study in terms of sites of recurrence and survival are of considerable interest. Of the 11 patients with negative intraperitoneal amplified CEA levels at the end of therapy, only two developed peritoneal metastases (with one death). Both were in the group of patients with negative pretreatment findings. Of the six patients with positive pretreatment amplified peritoneal CEA levels but negative cytologies in the peritoneal fluid, whose CEA levels converted to negative after intraperitoneal chemotherapy, none developed peritoneal metastases, although one of these six patients developed lymphatic metastases. All survived to the end of the report.

Among the eight patients whose results were positive after chemotherapy, all but one had cancer recurrence or died of disease, four having expired with peritoneal metastases within 12 months after the peritoneal studies had been performed. The single survivor, free of disease at 22 months, was the patient with the lowest positive quantitative peritoneal amplified CEA levels. This patient also had a positive cytology.

Among patients with T3 and T4 gastric cancers, peritoneal and lymphatic metastases are the most common

Received October 31, 2003; accepted November 12, 2003.
From the State University of New York at Buffalo, Williamsville, New York.
Address correspondence to: Harold O. Douglass, Jr., MD, State University of New York at Buffalo, 72 Andover Lane, Williamsville, NY 14221; E-mail: halandsandra@msn.com.

Published by Lippincott Williams & Wilkins © 2003 The Society of Surgical Oncology, Inc.

sites of cancer dissemination, with peritoneal metastases generally becoming apparent within 3 to 6 months and with death within 1 year.³ Such was the case among patients with peritoneal metastases in this 19 patient pilot study. Thus, the follow-up period, while brief, is appropriate for the purposes of evaluating the development of peritoneal metastatic disease.

Not every patient with T3 or T4 gastric cancer will die of disease.⁴ The patients in whom the cancer does not recur may be represented by some of those whose pre-chemotherapy quantitative results were negative. Unfortunately, data to evaluate the natural history of this group of patients is not available at the present time.

This is a pilot study whose results suggest significant potential benefit for a small group of gastric cancer patients. The findings are even more notable considering that the combinations of agents available for the chemotherapy of gastric cancer are considerably less than optimal. There is also a question as to whether more than a single course of intraperitoneal chemotherapy, with or without systemic chemotherapy, should be considered. Nevertheless, the results of this trial indicate the desirability of a large phase II trial.

Just who should be considered candidates for a phase II trial? Dr. Mori suggests that such a trial should be limited to amplified peritoneal CEA positive, cytology negative T3, and T4 gastric cancer patients. I would suggest that a stratified trial, perhaps with two courses of preoperative therapy, include cytologically positive re-

sectable T3 and T4 gastric cancers with no evidence of peritoneal metastases on initial laparoscopy, those with amplified intraperitoneal fluid CEA positive but cytology negative findings, and patients with peritoneal negative CEA cancers. If the results of a phase II confirm those of the pilot study, a phase III should be mounted with intraperitoneal chemotherapy (plus systemic therapy as utilized in the pilot program), randomized against neoadjuvant chemotherapy alone.

While such trials would not resolve the question of the natural history of amplified peritoneal fluid CEA negative cancers, the fact that two of five such patients progressed in this pilot trial would make them candidates for therapy. As with any piece of excellent research, this pilot trial asks more questions than it answers.

REFERENCES

1. Nomura E, Niki M, Fujii K, et al. Efficacy of intraperitoneal and intravenous chemotherapy and left upper abdominal viscerectomy for advanced gastric cancer. *Gastric Cancer* 2001;4:75–82.
2. Mori T, Fujiwara Y, Sugita Y, et al. Application of molecular diagnosis for detection of peritoneal micrometastasis and evaluation of preoperative chemotherapy in advanced gastric carcinoma. *Ann Surg Oncol* 2003;11:14–20.
3. Douglass HO Jr., Nava HR, Smith JL, Penetrante RB. Intraperitoneal surgical adjuvant chemotherapy following resection for gastric cancer. *Reg Cancer Treat* 1995;8:13–9.
4. Bando E, Kawamura T, Kinoshita K, et al. Magnitude of serosal changes predicts peritoneal recurrence of gastric cancer. *J Am Coll Surg* 2003;197:212–22.