Gastric Cancer
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Gastric cancer, the major cause of cancer death in Asia, Central America, and South America, has been the leading cause of death from a gastrointestinal malignancy at the Dade County and Sylvester/Jackson Memorial Hospital in southern Florida. The problems of gastric cancer in our Center, its effect on an otherwise vigorous middle-aged population (with a median age of 55 years), and aggressive endoscopic and surgical policy provided the impetus for our clinical and translational research efforts.

Adjuvant Chemotherapy for Gastric Cancer

Postoperative gastric cancer adjuvant strategies have not yet been decisively successful in improving overall survival. Moreover, the advanced stage of presentation for most unscreened gastric cancer patients allows postoperative adjuvant treatment to be directed to no more than 50% of patients.

A prospective, randomized, preoperative chemo-therapy trial from Korea presented to the American Society of Clinical Oncology in May 1996. Despite statistically significant downstaging and significant increase in curative resections for patients who received chemotherapy, overall survival showed only a trend to improvement for chemotherapy (P=0.114). Nevertheless, preoperative neoadjuvant strategy that is designed to treat gastric cancer patients who appear to have clinically resectable (curable) tumors remains attractive because it offers systemic chemotherapy to a greater number of patients with a poor prognosis than postoperative programs. A 50% recurrence rate in the peritoneal cavity and the peritoneal pharmacology of a specific chemotherapeutic of agents are compelling reasons for adding postoperative intraperitoneal (IP) chemotherapy of the gastric cancer. Nevertheless, a recent report of a prospective, randomized IP trial did not demonstrate improved survival for the treated group. The primary goal of the current intergroup protocol for gastric cancer is aimed at decreasing peritoneal recurrence by randomizing patient between two arms: surgery alone and 5-FU postradiation following surgery. At our institute, we have developed an intensive program for advanced resectable gastric cancer consisting of neoadjuvant and adjuvant chemotherapy with molecular markers as tools in assisting in the decision making (selection) of the chemotherapy drugs that were used.

Chemotherapy for Gastric Cancer

Although no cancer of the gastrointestinal tract is more responsive to a variety of single agents and to different chemotherapy combinations than gastric cancer, only a few trials have reported results that indicate survival, palliative, or cost benefit for patient treated with chemotherapy.

The introduction of the combination of 5-FU, doxorubicin, and mitomycin (FAM) as an effective regimen in gastric cancer is usually cited as the beginning of the modern era of the combination chemotherapy in gastrointestinal malignancies. The activity of cisplatin, the toxicity of mitomycin, and the failure of the FAM regimen in the postoperative adjuvant setting have paved the way for testing second-generation combinations in advanced gastric cancer. However, no post-FAM chemotherapy combination has emerged as a standard. For example, the European Organization for Research and Treatment of Cancer (EORTC) postoperative randomized trial tested 5-FU, doxorubicin, and methotrexate vs etoposide, leucovorin, 5-FU vs cisplatin and 5-FU. Response rates were approximately 25% for each combination, and none had a statistically significant impact on survival. In choosing agents for neoadjuvant gastric cancer, it was apparent that 5-FU and cisplatin together or in combination with other agents would emerge as consistently more active. This activity and our experience in safely administering cisplatin and 5-FU to patients undergoing an experimental preoperative treatment program for esophageal carcinoma made this combination most attractive.

Clinical Programs

From August 1993 through November 1997, 20 patients with invasive primary gastric adenocarcinomas considered to be resectable for cure entered clinical trial with preoperative intravenous chemotherapy with two cycles of eight treatments. The treatment consisted of cisplatin administered at 100 mg/m² on day 1, followed 24 hours later by the infusion of fluorodeoxyuridine at 75 mg/kg administered over 24 hours. Weekly fluorodeoxyuridine at a dose of 150 mg/kg and leucovorin 500 mg/m² were administered over 24 hours for two weeks, and then the cycle was repeated. In order to assess response, all patients underwent endoscopic ultrasound to determine the extent of the disease both prior to neoadjuvant chemotherapy and at the end of adjuvant chemotherapy. After 16 weeks of therapy, all patients underwent operation to remove the gastric carcinoma and, based on the pathological findings, they received adjuvant chemotherapy or no therapy.

Pathologically, if no disease was found at the primary site and no lymph nodes were negative (ie, complete pathological response), no further therapies were given. This was the case in four of 20 patients (20%). An additional 12 patients (60%) achieved greater than partial response pathologically, and the remaining four patients (20%) progressed. Patients who achieved greater than 50% pathological response were offered a similar chemotherapy as the neoadjuvant chemotherapy in a postoperative setting. Patients who demonstrated advancement of the disease were removed from the study.

Translational Interface

The excellent responses of some primary gastric tumors treated in the program described earlier, plus the fact that some tumors were emphatically resistant to this therapy, were striking. Furthermore, the ability to obtain samples of the gastric carcinomas before and at the time of surgery allowed us to examine these samples.

Hypotheses regarding specific molecular parameters determining a tumor’s response of 5-FU or cisplatin have been elucidated.

Thymidylate Synthase and 5-FU Resistance

Antimetabolite 5-fluorouracil and 5-fluorodeoxy-uridine blocked DNA and mRNA synthesis by inhibiting the conversion of uracil to thymidine and inhibiting the incorporation of 5-FU and mRNA. Specifically, 5-fluorodeoxyuridine, the active metabolite of 5-FU, suppresses the conversion of dUMP to dTMP by forming a stable covalent ternary complex with thymidylate synthase (TS), a folate cofactor. Although the therapeutic efficacy of the resistance of 5-FU depends in part on the degree to which FdUMP (fluorodeoxyuridine monophosphate) is effectively bound in determining complex, the status of TS can be a mechanism for 5-FU resistance. Overproduction of TS as a result of gene amplification has been shown to be associated with 5-FU resistance.

Measuring intratumoral TS, the polymerase chain reaction (PCR), are highly sensitive and efficient method of amplifying specific DNA segments present at low concentration provides an approach for estimating the relative quantities of a specific genetic expression in tumors from various small amounts of tissue. By amplifying
To test the hypothesis that PCR quantitation of the TS gene within a primary adenocarcinoma of the stomach has an inverse relation to response and survival, we prospectively analyzed primary gastric tumors prior to systemic chemotherapy with 5-FU and cisplatin as described earlier. Of the 20 patients entered on our neoadjuvant protocol, the tumor measurement demonstrated low TS gene expression in 15 patients, and the remaining five were classified as having tumors with high TS gene expression.

**Response/Survival and TS mRNA Levels**

Tumors demonstrated low TS gene expression in four patients who achieved a complete pathological response. The difference between the low and high TS gene is statistically significant.

Of the four patients who achieved the complete pathological response, tumors demonstrated a low TS gene expression with a lead follow-up of three years. All four patients are alive and have no demonstrable disease. Of the 12 patients who achieved greater than partial response pathologically, eight are alive with a median follow-up of three years. Patients with a high TS gene expression achieved no pathologic response. Median survival was six months, and four of them died.

**Future Trials at Sylvester Comprehensive Center**

We intend to continue our phase II study of neoadjuvant/adjuvant chemotherapy for gastric adenocarcinomas. Our overall intent is to increase the pathological complete response in our patient population. Paclitaxel has been incorporated in the neoadjuvant and adjuvant chemotherapies.

**References**


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