Locally Advanced Unresectable Gastric Cancer Successfully Resected after Neoadjuvant Chemotherapy with FADE Regimen

Hyun Cheol Chung¹, Jae Kyung Roh¹, Yong Joon Park¹, Sang In Lee¹, Jin Sik Min², Jong Tae Lee³, Ki Byum Lee⁴ and Byung Soo Kim⁵

The prognosis of unresectable advanced gastric cancer is extremely poor. We tried a neoadjuvant chemotherapy in locally advanced unresectable stomach cancer diagnosed by initial explo-laparotomy. After chemotherapy with the FADE regimen (5-fluorouracil + adriamycin + cisplatin + etoposide), the patient was diagnosed clinically as a complete response state on re-staging with radiological gastrointestinal study, fiber-gastroscopy and computerized tomography. During the second-look operation, the advanced cancer was completely resected and the pathological diagnosis was early gastric cancer (EGC) type IIc, stage II (T1N2Mo).

Key Words: Neoadjuvant chemotherapy, FADE regimen

Gastric carcinoma remains an important international health problem as a major contributor to cancer-related death, especially in Korea, Japan, Chile, Costa Rica, Hungary, and Portugal. Over 85% of the newly diagnosed patients will succumb to their disease within five years. Moreover, the prognosis of unresectable advanced gastric cancer is invariably very poor. Until now, relatively few anticancer agents have undergone an adequate clinical trial and shown potential activity in advanced unresectable stomach cancer (Comis and Carter 1974; Moertel and Lavin 1979). But the overall response rate was around 20%. In recently published studies, some cases of complete remission were reported with cisplatin as a single agent (Lacave et al. 1983; Perry et al. 1986; Saji et al. 1987) or in combination with adriamycin and etoposide (Preusser et al. 1987), which were confirmed during the second-look operation. During a clinical trial of neoadjuvant chemotherapy with the arm of FADE, we encountered a locally advanced gastric cancer which was successfully resected following the neoadjuvant chemotherapy.

CASE REPORT

Case

A 57-year-old male patient was admitted to our hospital because of epigastric pain for one year, which was aggravated for the last 4-5 weeks. On examination, the patient appeared chronically ill. Abdominal and rectal examinations were negative. X-ray examination of the upper gastrointestinal tract revealed a large irregular, lobulated mass at the lesser curvature side of the lower gastric body and proximal antrum (Fig. 1). Fiber-gastroscopy also confirmed a Borrmann I + II type tumor at the lesser curvature side of the proximal antrum, angle and lower body (Fig. 2), and a diagnosis of poorly differentiated adenocarcinoma was made from the biopsy specimen. Computed tomography of the abdomen showed a solid mass in the antrum which infiltrated perigastric fat, and another mass which extended to the hepatic port. Para-aortic and retropancreatic lymph node enlargements were also noted (Fig. 3).

Operation

The main lesion was located at the lesser curvature side of the posterior wall of the antrum, measuring 8cm in diameter. The mass was firmly adhered to the
head of the pancreas, so it was unresectable. A 3cm-sized daughter mass, which seemed to be a conglomerated lymph node, was noted at the porta hepatis and occupied the hepatoduodenal space and compressed the biliary tract. There were multiple enlarged lymph nodes in the perigastric, peripan-
Neoadjuvant Chemotherapy in Locally Advanced Stomach Cancer

Fig. 1. Radiological findings of the gastrointestinal tract

A) Pre-chemotherapy state: A large, irregular, lobulated mass is noted at the lesser curvature side of the lower gastric body and proximal antrum (arrow).

B) Post-chemotherapy state: The previous mass is decreased markedly, but the mucosal destruction and fold retraction still remain in the same area.

Fig. 2. gastrofiberscopic findings

A) Pre-chemotherapy state: A Borman I+II type tumor mass is noted at the lesser curvature side

B) Post-chemotherapy state: Only scarring change on the gastric angle is noted. Convergent folds of mucosa are slightly clubbed (arrow).

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Neoadjuvant Chemotherapy

Eight days after operation, neoadjuvant chemotherapy was started with the FADE regimen (5-fluorouracil 1000mg/m² day 1-3, adriamycin 30mg/m² day 1-8, cisplatin 40mg/m² day 1-8, etoposide 120mg/m² day 1-3) every 3 weeks. After three courses of chemotherapy, no tumor mass was observed by fibergastroscopy (Fig. 2), and the biopsy specimen taken from the scarred area showed no malignant cells. Follow-up radiological study of the upper gastrointestinal tract and abdominal CT scan revealed a much regressed tumor mass and disappearance of pancreas infiltration and para-aortic lymph node enlargement, but lymph node enlargement in the hepatoduodenal space was still observed (Fig. 3).

Second-look Operation

Four weeks after the third course of chemotherapy, a second-look operation was performed. The main lesion was an ulcerative mass which involved the body along the lesser curvature, and measured 2cm in extent. The gross finding of serosa was negative (So). Several lymph nodes were enlarged. The largest one, which was located in the right side of the celiac trunk, measured about 3cm in diameter. The second largest one, located in the left side of the celiac trunk, measured 2cm in diameter. The liver was grossly normal (Ho), and the rectal shelf was negative (Po). Curative gastric resection with lymph node dissection was performed (R3) (JRSCG '1985).

Pathologic Findings

Histologic diagnosis revealed moderately well differentiated adenocarcinoma confined to the submucosa (EGC type IIc). Foreign body reaction was observed at the submucosa. Definite carcinomatous tissue was seen only at the submucosa, and the mucosa showed only hyperplasia of epithelium with pyloric and intestinal type metaplasia. There were glands that seemed to be abnormal structurally but not cytologically in the mucosa, which suggested necrotic change from chemotherapy and renewal of metaplastic epithelium. Marked aggregation of foamy cells was observed in lymph nodes. There were 3 metastatic lymph nodes among 29; the infra-pyloric lymph node (1/8) and lymph nodes along the common hepatic artery (2/3). The final histological stage was II, i.e., cancer cells localized within submucosa (T1), lymph node metastasis (N2), and no distant metastasis (M0) (Fig. 4). During the chemotherapy, there were no significant side effects except nausea...
Fig. 4. Pathologic findings of the stomach and lymph nodes

A) Stomach: The mucosa shows hyperplasia of the epithelium with metaplasia from the chemotherapy effect, but no foci of carcinoma are found. Moderately well differentiated adenocarcinoma is confined to the submucosa.

B) Lymph node: Massive coagulation necrosis (Grade III) was found in the entire node which suggested the chemotherapeutic effect.

and vomiting of a mild degree.

**DISCUSSION**

Locally advanced unresectable gastric cancer is defined as those cases in which surgery with curative intent could not be undertaken because of overt or microscopic residual disease in regional lymph nodes or adjacent organs. The GTSG designed a controlled trial for this locally unresectable gastric cancer, using 5-fluorouracil and a methyl CCNU arm. With con-
continued follow-up, no survival advantage with chemotherapy was found (GTSG 1979). After that, MacDonald et al. (1980) reported a 42% response rate and a nine month duration of remission in a phase II trial document of the FAM regimen. But the survival rate was not improved with this trial either. In recent reports, the response rate of cisplatin single therapy appears to be higher than those of other chemotherapies (Lacave et al. 1983; Perry et al. 1986). Moreover, in combination with adriamycin and etoposide, the reported response rate increased up to 73% with a median response duration of 7 months (Preusser et al. 1987). But the poor response of late stage patients has served to dampen the enthusiasm of clinical investigators. To obtain useful data and to avoid toxicity in terminal phase patients, case selection became an essential requirement. With these concepts, there were some isolated case reports of successful curative gastric resection for the locally advanced gastric cancer after neoadjuvant chemotherapy with cisplatin alone (Saji et al. 1987) or in combination arms (Tanemura et al. 1987).

In the Japanese study of preoperative chemotherapy in resectable stomach cancer, the histological effects on metastatic lymph nodes in gastric cancer after chemotherapy were the same as those on the primary site (Kawamura et al. 1985), and caused considerable damage to “micro-solitary metastatic foci” in metastatic lymph nodes (Fujimoto et al. 1985). On the basis of the above evidence, Papaioannou et al. (1986) treated patients with initial systemic chemotherapy and followed the patients for at least one year. They reported a better mean survival without evidence of disease or a better disease-free interval in the preoperative chemotherapy group. Therefore, it is advisable for prolongation of survival to perform operative treatment for the primary or metastatic lesions in the responders to neoadjuvant chemotherapy.

Based on these results, several trials were reported to investigate the role of neoadjuvant chemotherapy with the arms of multi-drug combinations in locally advanced unresectable stomach cancer. Verschuren et al. (1988) tried four courses of methotrexate 1.5g/m² and 5-fluorouracil 1.5g/m² every four weeks. Among 17 enrolled patients, they could perform a second laparotomy in 13 patients, and 7 patients were considered resectable. They reported 40% tumor resectability in this situation without compromising the postoperative course. Wilke et al. (1988) tried an EAP regimen (etoposide + adriamycin + cisplatin) in 27 patients. They could operate in 15 patients (56%) with a relapse rate of 20% after a median follow-up of 14 months.

Actually, our case showed a complete response following three courses of FADE combination chemotherapy during the phase II study at our institution, as evaluated by radiological gastrointestinal study, abdominal computerized tomography, fibergastroscopy and second-look operation. Further effort to determine the effect of neoadjuvant chemotherapy with the arm of FADE in locally advanced unresectable stomach cancer is needed.

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