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Recent Results of Therapy for Scirrhous Gastric Cancer

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Abstract
The prognosis of patients with scirrhous gastric cancer (SGC) is extremely poor. However, recent advances in therapeutic strategies against SGC, using effective anticancer drugs, have prolonged the survival of patients with SGC. This paper reviews the recent therapeutic outcomes of this type of gastric cancer and introduces a new treatment protocol for SGC.

Key words Intraperitoneal chemotherapy · Laparoscopy · Scirrhous gastric cancer

Pathological and Biological Characteristics of Scirrhous Gastric Cancer

Scirrhous gastric cancer (SGC) is unique among gastric carcinomas. In this type of cancer, poorly differentiated carcinoma cells or signet-ring cells show diffuse infiltrative growth. When the entire stomach wall is involved with carcinoma cells, the condition is called linitis plastica. In contrast to most gastric cancers, SGC cells do not form glands and are located predominantly in the submucosa. These cells diffusely infiltrate the gastric wall and provoke reactive fibrosis, thus resulting in fibrous-like thickening of the gastric wall.[1] The characteristics of gastric cancer cell lines derived from patients with SGC have been analyzed. These cells showed microsatellite instability[2] and abnormal protein overexpression, which are thought to correlate with matrix proteinase, cell adhesion, angiogenesis, and proliferation.[3] Recently, Tanaka et al.[4] showed that ephrin-B1 is overexpressed in SGC and that reduction of ephrin-B1 expression by short interfering RNA suppresses the migration and invasion of SGC cells in vitro and in vivo. However, the biological interaction between cancer cells and fibroblasts has not been characterized. Powell[5] studied myofibroblasts in the gastric wall. Myofibroblasts may originate from progenitor stem cells and may be stimulated, differentiated, and activated by platelet-derived growth factor (PDGF), stem cell factor (SCF), or transforming growth factor beta (TGF-β) expressed by gastric cancer cells. These activated and proliferating myofibroblasts may secrete growth factors, such as epithelial growth factor (EGF), hepatocyte growth factor (HGF), and keratinocyte growth factor (KGF). Scirrhous gastric cancer cells may be affected by these growth factors secreted by myofibroblasts. In addition, Kano et al.[6] reported that TGF-β signaling inhibition, by the application of a short-acting, small-molecule TGF-β type I receptor inhibitor, suppressed the growth of diffuse-type of gastric cancer. These facts indicate that interactions between cancer cells and fibroblasts may play an important role in SGC progression, while also playing a key role in the treatment of SGC.

Diagnosis of Scirrhous Gastric Cancer

Although the accuracy in the diagnosis of other gastric carcinomas has undoubtedly improved with the advent of endoscopy,[7] the sensitivity of detection of SGC by endoscopy is only 33%–73%.[8,9] Therefore, Park et al.[10] reported that detection of SGC using an upper gastrointestinal series or endoscopic examinations at an early stage is quite difficult. Moreover, SGC tends to spread over the peritoneum with rapid growth and early metastasis. Therefore, the prognosis is poor in patients with this disease and the 5-year survival rate is low.[11]

Prognosis of Patients with SGC

Chen et al.[11] reported the 5-year survival rate of 103 patients with SGC (11.3%) to be significantly lower

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than that of 604 patients with other types of gastric cancer (44.7%). The Japanese Gastric Cancer Association Registration Committee reported the treatment results and causes of death of patients with primary gastric cancer treated in 1991 at the leading hospital in Japan.[12] In 8851 patients with primary gastric cancer, SGC was detected in 556 patients and the 5-year survival rate of these SGC patients was 16.2% (type 0: $n = 4055$, 90%; type 1: $n = 203$, 56.4%; type 2: $n = 1004$, 52.5%; type 3: $n = 1752$, 42.8%; and type 5: $n = 359$, 69.6%). Therefore, the prognosis of patients with SGC was much poorer than that of patients with other types of gastric cancer.[13] A high incidence of serosal invasion and peritoneal metastasis have been reported in patients with SGC and many reports have indicated a palliative resection of the stomach to result in poor outcomes for affected patients.[14,15] Moreover, despite a curative gastrectomy, the 5-year survival rate following a gastric resection for patients with SGC was poor. Nakamura et al.[16] reported that the 5-year overall survival rate for patients with stage II and III SGC after curative surgery was 24.3%. Therefore, Aranha and Georgen[17] suggested that surgery is not curative for the treatment of SGC.

Therapeutic Procedures Used to Treat SGC

To prolong the survival periods of patients with SGC, some surgeons have performed more radical operations, such as an en bloc total gastrectomy including the pancreatic body and tail, the spleen, the gallbladder, the transverse colon, and the left adrenal gland.[18] They reported that this method improved the survival of patients with scirrhous cancer in stage III, but was not effective for those in stage IV. Moreover, they indicated that such radical surgeries resulted in an increased the risk of operative mortality such as the formation of a pancreatic fistula (30%; control 19%). They therefore concluded that to improve the survival of patients in SGC, a new concept of treatment and supportive therapy should be used. Other treatments, such as chemotherapy,[19] radiotherapy,[20] hormonal therapy,[21] or immunotherapy[22] have been attempted.

Radiation therapy has been used in the treatment of patients with gastric cancer in two clinical settings: definitive therapy for locally advanced, unresectable tumors and adjuvant therapy following surgery for high-risk disease. Historically, radiation therapy has not played an important role in the treatment of patients with gastric cancer. A large phase III trial of postoperative therapy strongly suggested a multimodal approach combining radiation and chemotherapy to be beneficial after a gastrectomy. This trial, a large United States Intergroup Study 0116 (INT 0116), enrolled >550 patients who were randomly assigned to surgery alone or surgery followed by chemoradiation [fluorouracil (FU)/leucovorin (LV)] plus external-beam radiation delivered to the gastric bed and regional lymph nodes. This study showed that combined chemoradiation following gastric resection improves the median time to relapse (30 months vs. 19 months, $P < 0.0001$) and overall survival (35 months vs 28 months, $P = 0.01$).[23] The results of this trial established adjuvant chemoradiation as the standard of care for resected high-risk adenocarcinoma of the stomach in the United States. However, adjuvant chemoradiation remains controversial. In INT-0116, 90% of the patients had a limited or inadequate node dissection (D0 or D1) and 17% of patients in the chemoradiation arm had to discontinue treatment because of toxicities. As a result, it was suggested that the positive findings of this trial could be a result of inadequate surgery. In Japan, patients tend to undergo a more thorough D2 dissection. Therefore, the surgical benefit of chemoradiation should be considered after a D2 lymph node dissection. Moreover, a randomized trial performed at the National Cancer Institute (NCI) found a decrease in the local recurrence rate with the use of intraoperative radiation therapy (IORT) in comparison with no radiotherapy (44% vs 92%, respectively), although there was no advantage in terms of survival.[24] However, the number of patients was too small to recommend this as a general approach. In addition, it is not clear whether chemoradiation is effective for SGC. This adjuvant or neoadjuvant chemoradiation should therefore be considered and discussed in the treatment of SGC.

Chemoimmunotherapy has been intensively performed in Korea. Jeung et al.[25] reported a phase III trial of chemotherapy (5-FU and adriamycin) versus chemoimmunotherapy (5-FU, adriamycin, and polyadenylic-polyuridylic acid) in 280 patients with advanced gastric cancer who underwent a curative gastrectomy with a D (2–3) lymphadenectomy. Polyadenylic-polyuridylic acid is a synthetic double-stranded complex of polyribonucleotides and is thought to be a potent immunomodulator. In addition, chemoimmunotherapy significantly prolonged both the overall ($P = 0.013$) and recurrence-free ($P = 0.005$) survivals in comparison to chemotherapy alone. On the other hand, Cesana et al.[26] evaluated the effects of preoperative low-dose interleukin-2 treatment on 68 patients with gastric cancer. They concluded that the low doses of interleukin-2 administration induced and activated peripheral and peritumoral lymphocytes but did not affect the patients' prognosis. In Japan, a randomized phase III trial of postoperative adjuvant therapy with fluoropyrimidine S-1 (S-1) alone versus S-1 plus polysaccharide K (PSK) for stage II/IIIA gastric cancer has started.[27] The therapeutic efficacy of this immunochemotherapy for SGC will be elucidated in detail in the future.

UFT (tegafur and uracil) is an oral anticancer drug that has been developed in Japan. A total of 188 patients with serosal-negative (T2) and with lymph node metastasis (N1, N2) gastric cancer were randomly divided into two groups (UFT treatment for 16 months after surgery versus surgery alone) in the National Surgical Adjuvant Study of Gastric Cancer (NSAS-GC01). This study demonstrated that the adjuvant UFT chemotherapy significantly prolonged the overall survival of the patients.[28] In contrast to the NSAS-GC01 trial, the Japan Clinical Oncology Group (JCOG) 9206-2 trial could not show a survival benefit of adjuvant chemotherapy with cisplatin plus 5-FU followed by UFT for resected serosal-positive (T3 and T4) gastric cancer.[29] The efficacy of UFT was influenced by the status of enzymes involved in 5-FU metabolism such as thymidylate synthase (TS) and dihydropyrimidine dehydrogenase (DPD). Therefore, UFT cannot control the postoperative recurrence of 5-FU resistant tumors with high DPD activity. On the other hand, S-1 shows a potent inhibitory effect on DPD and an enhanced 5-FU concentration can be expected with S-1 administration.[30] Indeed, a large randomized trial in Japan demonstrated that oral S-1 adjuvant chemotherapy prolonged the overall survival of patients with stage II or III gastric cancer who underwent a gastrectomy with an extended (D2) lymph node dissection.[31] However, this trial did not show whether the adjuvant chemotherapy is useful for patients with SGC.

Usually, neoadjuvant chemotherapy is frequently used in the treatment of SGC. Various therapeutic methods using a mixture of uracil and tegafur (UFT)/cisplatin (CDDP) chemotherapy[32], S-1 chemotherapy[33] and sequential high-dose methotrexate and fluorouracil combined with doxorubicin[34] have been reported. These treatments have been performed by oral or by intravenous administration. These neoadjuvant chemotherapies improved the curative resection rate, but did not improve the survival rate of patients with SGC.[32–34]

The common features of SGC include remarkable fibrosis, rapid invasive progression, and a high frequency of metastasis to the peritoneum. Using a nude mouse model, Hippo et al.[35] globally analyzed differential gene expression in SGC cells and thereby indicated that SGC cells showed a particularly high potential for metastasis to the peritoneal cavity. Therefore, the development of new therapeutic approaches to prevent peritoneal metastasis is an important issue.

Intraperitoneal Chemotherapy (IPC) for SGC

Intraperitoneal chemotherapy (IPC) has been applied for patients with SGC to prevent peritoneal metastatic recurrence. Hagiwara et al.[36] and Yu et al.[37] reported prognostic effectiveness of intraperitoneal administration of mitomycin-C at the time of surgery in patients with advanced gastric cancer. In addition, intraperitoneal chemotherapy using cisplatin yields a survival benefit for patients with advanced gastric cancer who have free cancerous cells in their peritoneal cavities.[38,39] However, there have also been many negative reports of randomized controlled trials. Rosen et al.[40] reported that adjuvant IPC using mitomycin-C results in an increased rate of postoperative complications and no prognostic benefits for patients with locally advanced gastric cancer. In addition, Sautner et al.[41] concluded that IPC with cisplatin monotherapy did not improve the survival probability after surgery for stage III and IV gastric cancer. A high complication rate, mainly due to intra-abdominal abscesses, was observed in the cases treated with mitomycin-C IPC. However, this high complication rate was not reported with cisplatin IPC.[39,42] Therefore, the efficacy of adjuvant IPC in patients with SGC has not been confirmed.

Shiraishi et al.[43] reported that laparoscopy was useful for evaluating peritoneal metastatic status. To avoid an unnecessary laparotomy, laparoscopy was used for the diagnosis of macroscopic peritoneal metastases or to perform peritoneal washing cytology for patients with SGC. A gastrectomy should be avoided in patients with peritoneal metastasis. Neoadjuvant IPC was administered with cisplatin during laparoscopy in these patients, regardless of the peritoneal status beginning in 2002.[44] The number of cancerous cells in peritoneal washing samples obtained just prior to and after IPC were counted in 13 patients using carcinoembryonic antigen (CEA) messenger RNA (mRNA) based real-time reverse transcription–polymerase chain reaction (RT-PCR), as described previously.[45] More than 90% of the cancerous cells were removed from the peritoneal cavity following cisplatin IPC in eight patients. Moreover, CEA-positive cells could not be detected in peritoneal wash samples from four patients after IPC. These 8 patients were grouped into the "IPC effective group." In the remaining five cases, the percent reduction in the numbers of cancerous cells after chemotherapy was less than 90%; these patients were placed in the "IPC ineffective group." The 50% survival period of the IPC effective group (9 months) was not different from that of the IPC ineffective group (10 months, $P = 0.968$) using a log-rank test based on the Kaplan–Meier method. This suggests that the chemosensitivity of cancer cells may not be a good indicator of patients' prognosis.

Recently, Morgan et al.[46] administered different doses of docetaxel intraperitoneally to 21 patients with peritoneal carcinomatosis. They concluded that intraperitoneal administration of docetaxel could be safely delivered at a dose of 100 mg/m^2 at every 3 weeks. In

addition, significant peritoneal pharmacological advantages in this route of administration were reported.[47,48] These results indicate that IPC using docetaxel may be a powerful therapeutic procedure to prevent peritoneal metastasis for patients with SGC.

Conclusion

The laparoscopic diagnosis of peritoneal metastasis is useful to avoid an unnecessary laparotomy for patients with SGC. Recent papers suggest that neoadjuvant chemotherapy might be effective for SGC in comparison to adjuvant chemotherapy. Preoperative IPC combined with systemic chemotherapy using S-1 and docetaxel may have strong survival benefit for patients with SGC. However, many questions, such as whether neoadjuvant chemotherapy is better than adjuvant chemotherapy and whether IPC is better than systemic chemotherapy, still remain to be answered. To establish a suitable treatment for patients with SGC, a large-scale randomized control study should therefore be carried out.

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