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SHORT COMMUNICATION

Long-term follow up of patients who were positive for peritoneal lavage cytology: final report from the CCOG0301 study

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Abstract
Background In gastric cancer patients who have positive results for peritoneal lavage cytology the disease is defined as CY1, and classified as stage IV, and this population has generally suffered a dismal outcome. For this population, we had conducted a phase II trial, with the 2-year survival rate as the primary endpoint, to test the strategy of D2 dissection followed by chemotherapy with single-agent S-1 (1 M tegafur–0.4 M gimestat–1 M otastat potassium). Forty-eight patients were enrolled, of whom 47 were found to have been eligible for analysis. The 2-year survival rate of 46 % exceeded our expectations.
Methods Further follow up was conducted to confirm whether radical surgery could be recommended for the CY1 population.
Results The 5-year overall and relapse-free survival rates were 26 and 21 %, respectively.
Conclusions Gastrectomy with curative intent could be considered for patients with CY1 disease provided they are scheduled to receive effective postoperative chemotherapy.

Keywords Gastric cancer · S-1 · Cytologic examination · Peritoneal carcinomatosis

Introduction

Stage IV gastric cancer is generally considered incurable and this population is usually ineligible for radical surgery. Treatment options for this population, recommended by the Japanese Guidelines, are chemotherapy, radiotherapy, palliative surgery and palliative care medicine [1]. However, several case series suggest that the possibility of cure cannot be ignored in some carefully selected populations of stage IV patients, given the improvements in multimodal treatment [2–4]. Patients with free cancer cells in the peritoneal cavity could constitute such a population. Detection of free cancer cells by peritoneal lavage cytology predicts the risk of peritoneal carcinomatosis with high specificity [5]. When cancer cells are detected, the positive cytology status is designated as CY1 by the *Japanese classification of gastric carcinoma, 2nd English edition* [6]. Patients with CY1 status are classified as stage IV even in the absence of macroscopic evidence of peritoneal seeding. Whether this population should be treated radically or palliatively has been an issue for debate [7].

For the Chubu Clinical Oncology Group

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The outcome in CY1 patients has been reported to be poor in the East as well as in the West [8, 9], but the recent introduction of novel anticancer agents has changed the picture to some extent. We conducted a phase II trial, named CCOG0301, exploring D2 dissection followed by treatment with 1 M tegafur–0.4 M gimestat–1 M otastat potassium (S-1), in which 48 patients were registered, of whom 47 were eligible for analysis, and we achieved a two-year survival rate of 46 %, which exceeded the initial expectations [4]. The choice of a sample size of 50 patients in this study had been based on the hypothesis that the two-year survival rate would be 36 % and the lower limit of the 90 % confidence interval would exceed 23.5 %, which was the upper limit of the 90 % confidence interval for the historical controls whose two-year survival rate had been 13.3 %. While this phase II trial was ongoing, a pivotal phase III trial comparing postoperative adjuvant S-1 monotherapy with treatment by surgery alone in patients with stage II/III gastric cancer turned out to show positive results for the S-1 monotherapy arm. Moreover, the incidence of relapse, as peritoneal carcinomatosis, was found to be significantly lower in the S-1 monotherapy group [10]. This finding suggests that S-1 is effective against microscopic residual disease in the peritoneal cavity that is undetectable by peritoneal lavage cytology, and also suggests the potential of S-1 to control micrometastases in the peritoneal cavity. Encouraged by these findings, we were motivated to follow the patients for longer, to see what proportion of the patients who were entered in the CCOG0301 trial were actually cured, in order to reconsider the indication for curative surgery in patients with CY1 disease.

Patients and methods

Forty-seven patients who were registered between February 2002 and July 2006 for the CCOG0301 study underwent further follow up (for a median of 2,337 days or until death) to evaluate the long-term outcome.

Characteristics of the patients who were enrolled in the CCOG0301 study

Eligible patients had to meet all of the following criteria: (1) a confirmed diagnosis of gastric adenocarcinoma and age less than 80 years; (2) gastrectomy with systemic D2 lymphadenectomy performed (splenectomy could be omitted at the discretion of the surgeons); (3) no distant metastasis, with the exception of minimal peritoneal deposits that were completely resected; (4) no prior treatment besides surgery; (5) positive cytologic results for cancer cells on examination of peritoneal washings (CY1); and (6) adequate organ function [4]. Of the 47 eligible patients, 7 patients had peritoneal deposits, which were co-resected at surgery. Seven patients were intraoperatively confirmed to have invasion to adjacent organs (T4), and 38 others had serosal invasion. All but five patients were confirmed to have nodal involvement on pathological examination; six patients had metastasis to the paraaortic lymph nodes [4].

Treatment protocol of the CCOG0301 study

The interval from surgery to the start of therapy was not to exceed 6 weeks. Patients received S-1 at an oral dose of 40 mg per square meter of body-surface area twice daily for 4 weeks, followed by 2 weeks without chemotherapy. Patients with a body-surface area of less than 1.25 m^2 received 80 mg daily; those with a body-surface area of 1.25 m^2 to less than 1.5 m^2 received 100 mg daily; and those with a body surface area of 1.5 m^2 or greater received 120 mg daily. This 6-week cycle was repeated in an outpatient setting under medical supervision until disease progression, unacceptable adverse events, or the patient's withdrawal of consent. Adequate dose modification and changes in the treatment schedule were conducted, as described previously [4, 10].

Disease status was assessed once every 3 months on the basis of serum tumor markers and at least once every 6 months by computed tomography (CT) scanning for the first 2 years. Follow-up visits including a CT scan were performed once every 6 months until the patients were considered disease-free at 5 years after the surgery.

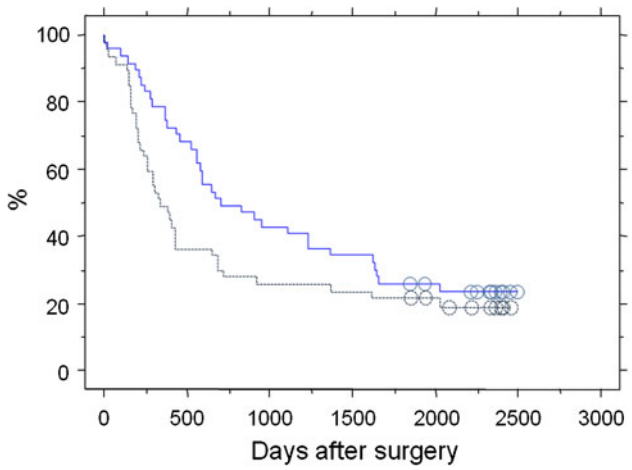

Fig. 1 Overall survival (*solid line*) and relapse-free survival (*dotted line*) of patients with gastric cancer who had free cancer cells in the peritoneal cavity and underwent surgery followed by S-1 monotherapy

Results

Overall survival and relapse-free survival from the day of surgery are shown in Fig. 1. Median overall survival time was 705 days, and relapse-free survival time was 376 days. The 2- and 5-year survival rates were 46 and 26 %, respectively, and the 5-year relapse-free survival rate was 21 %. The most frequent pattern of disease recurrence was peritoneal carcinomatosis, occurring in 29 patients (62 % of all patients enrolled). Other patterns of recurrence were hepatic in 4 patients, lymphatic in 4, locoregional in 2, pulmonary in 1, and osseous in 1. Three patients died of disease other than gastric cancer, at 5, 1371, and 2023 days after surgery. Details on treatment compliance, dose intensity, and toxicity have been reported previously [4].

Conclusions

Patients with CY1 disease with no other non-curative factors could be indicated for surgery with curative intent, provided adequate chemotherapy is given. Although post-operative treatment with S-1, now a standard of care for stage II/III gastric cancer, remains as an option, further trials are warranted to decide on the optimal chemotherapeutic regimen and whether to deliver it before or after surgery.

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