S-1 PROLONGS THE SURVIVAL OF PATIENTS WITH ADVANCED GASTRIC CANCER AND POSITIVE CYTOLOGY

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Synopsis

Background:
S-1 is a new anti-cancer drug. It was reported that the response rate of patients with gastric cancer treated with this drug is 49%. We reported that the serum and intra-abdominal concentrations of 5-FU after the administration of S-1 are almost the same. This retrospective study was undertaken to examine the clinical efficacy of S-1 in patients with advanced gastric cancer and positive cytology.

Method:
Between 1995 and 1999, 26 patients with gastric cancer and positive cytology diagnosed during the operation were surgically treated. Fifteen underwent total, distal or proximal gastrectomy with D2 lymphadenectomy and 11 underwent simple laparotomy or bypass surgery because of peritoneal dissemination. These patients were divided into the S-1 group and the 5-FU group. Survival rate and median survival time (MST) were evaluated and compared between the two groups.
Results:

The MST of the S-1 group was 579 days and that of the 5-FU group was 211 days. Among the 15 resected cases, the MST of those administered S-1 was 768 days and that of patients administered 5-FU was 215 days. The survival rate of the S-1 group was significantly higher than that of the 5-FU group (p=0.0023).

Conclusion:

We conclude that S-1 is an effective adjuvant anti-cancer drug for patients with advanced gastric cancer and positive cytology.

Introduction

Intra-operative cytology is an important predictor of peritoneal recurrence (Kitamura, Arai, Iwasaki et al., 1999) and is defined as a poor prognostic factor according to the general rules for the gastric cancer study in Japan (13th edition, Japanese Research Society for Gastric Cancer) because there is no effective chemotherapy for peritoneal dissemination (Arai, Iwasaki, Takahashi et al., 2001).

S-I is a novel oral anti-cancer drug and it was reported to be effective in 49% of the patients with gastric cancer (Sakata, Ohtsu, Horikoshi et al., 1998). There are many reports about the efficacy of S-1 against liver metastases, lymph node metastases and peritoneal dissemination (Kawai, Ohtsu Boku et al., 2003, Osugi, Takada, Takemura et al., 2002). Iizuka reported that the serum and intra-abdominal concentrations of 5-FU after the administration of S-1 were almost equal (Iizuka, Takahashi, Kakhara et al., 2002). Moreover, the level of 5-FU in ascites after administration of S-1 was found to be higher than that after the administration of other 5-FU-containing anti-cancer drugs (Seki, Takahashi, Kimura 1987). Thus, S-1 would be effective in patients with gastric cancer and positive cytology ascites. In this retrospective study we examined the clinical efficacy of S-1 in the patients with advanced gastric cancer and positive cytology.

Patients and Method

Between 1995 and 1999, 26 patients with gastric cancer and positive cytology diagnosed during the operation were surgically treated in our hospital. Twelve were administered S-1 as adjuvant chemotherapy and 14 were administered 5-FU. There was no significant difference between two groups. Seven patients of the S-1 group and 8 of
the 5-FU group underwent total, distal or proximal gastrectomy with D2 lymphadenectomy. Five patients of the S-1 group and 6 of the 5-FU group underwent simple laparotomy or bypass operation because of peritoneal dissemination. In the S-1 group, there were 7 men and 5 women with an average age of 59±10.7 years (range, 44 to 75). In the 5-FU group, there were 8 men and 6 women with an average age of 72±8.4 years (50 to 84). In the S-1 group there were none of differentiated adenocarcinoma and 12 of undifferentiated adenocarcinoma. In the 5-FU group there were 3 cases of differentiated adenocarcinoma and 11 of undifferentiated adenocarcinoma Table I.

### TABLE I

<table>
<thead>
<tr>
<th>Clinicopathological characteristics of the S-1 and 5-FU groups</th>
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<tbody>
<tr>
<td><strong>S-1 GROUP</strong></td>
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<td>----------------</td>
</tr>
<tr>
<td><strong>Total No of patients</strong></td>
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<tr>
<td><strong>Mean age (years)</strong></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
</tr>
<tr>
<td>Male</td>
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<tr>
<td>Female</td>
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<td><strong>Histological type of tumor</strong></td>
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<td>Differentiated</td>
</tr>
<tr>
<td>Undifferentiated</td>
</tr>
<tr>
<td><strong>Surgical treatment</strong></td>
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<tr>
<td>Resected</td>
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<tr>
<td>Non resected</td>
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</table>

All the patients had an ECOG performance status 0~1. S-1 was administered orally at a dose of 80-120 mg/day. One course consisted of S-1 for 28 consecutive days followed by rest for 14 days. Oral 5-FU was administered continuously at a dose of 150 mg/day without rest. Informed consent was obtained regarding the administration of S-1. The mean survival time (MST) of each group was examined and compared. The survival rate was calculated by the Kaplan-Meier method and survival curve differences were measured with the log-rank tests. Statistical significance was assumed for P values of less than 0.05.

**Results**

The MST of the S-1 group was 579 days and that of the 5-FU group was 211 days. As for the 19 resected cases, the MST of the S-1 group was 768 days, and that of the 5-FU group was 215 days. The survival rate of the S-1 group was significantly higher
**Figure 1.** (LEFT) Kaplan-Meier survival curves for patients with positive cytology. The rate of S-1 group was significantly longer than that of the 5-FU group.

**Figure 2.** (RIGHT) Kaplan-Meier survival curves for patients with positive cytology who underwent resection. The rate of S-1 group was significantly longer than that of the 5-FU group.
than that of the 5-FU group (p=0.0023) (Figure 1). Moreover the survival rate of the resected cases was significantly higher in the S-1 group than that in the 5-FU group (p=0.0087) (Figure 2). Adverse reactions consisted of grade 1-2 nausea in each group. However any other toxicity was not observed.

Discussion

It is reported that drugs administered intravenously hardly penetrate the peritoneal cavity, because of the blood peritoneal barrier. Similarly intraperitoneal chemotherapy might induce a low response because drug delivery through the peritoneum reaches only 10-20μm from the peritoneal surface (Jacquet, Sugarbaker 1996). However it was reported by Nomura et al., that chemotherapy of both intraperitoneal and intravenous administration at the same time was effective against peritoneal dissemination of gastric cancer (Nomura. Niki, Fuji et al., 2001). So the local concentration of drug in peritoneum was supposed to be the most important.

Nowadays many basic studies have shown what were effective against peritoneal dissemination through the blood peritoneal barrier (Okamoto, Yamaguchi, Otsuji et al., 1998; Igarasgi, Kubota, Otani et al., 1999; Yoshikawa, Tanoma, Tsuburaya 2000; Yonemura, Endo, Fujita 2001). We have previously reported that intraperitoneal concentration of 5-FU was almost the same as the serum concentration of after the administration of S-1 (Iizuka, Takahashi, Kakihara 2002). Moreover, the level of 5-FU in ascites of the administration of S-1 were found to be observed higher than other 5-FU-containing anticancer drug (Seki, Takahashi, Kimura et al., 1987). Thus, S-1 might be effective against peritoneal dissemination.

The survival rate of the S-1 group was significantly higher than that of the 5-FU group and the MST of the S-1 group was the same or longer than that found in other studies (Nomura, Niki, Fujii et al., 2001; Nor, Yoo, Chung et al., 2001; Yonemura, Fujimura, Fushida et al., 1999). The same result was obtained in the resected cases, indicating that S-1 was useful drug not only as chemotherapy for peritoneal dissemination but also as post-operative adjuvant chemotherapy in patients with advanced gastric cancer and positive cytology.

Osugi et al. reported the efficiency of S-1 for gastric cancer patients with positive cytology (Osugi, Takada, Takemura 2002). They did not refer to the difference of the two
groups including the patients who did not undergo laparotomy in only S-1 group. In our report all patients underwent laparotomy and there was no significant difference between two groups.

S-1 is an anti-cancer drug for oral use, thus it contributes to the patient’s QOL. This was a retrospective study and the cases were only 26, therefore it is important to conduct a randomized control trial involving a larger number of patients to evaluate the usefulness of S-1 as adjuvant chemotherapy for patients with advanced gastric cancer and positive cytology.

References


