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TOPIC HIGHLIGHT

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# S-1 in the treatment of pancreatic cancer

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**Key words:** Pancreatic cancer; S-1; Chemotherapy; Randomized controlled trial; Chemoradiotherapy; Adjuvant therapy

**Core tip:** This review article focuses on clinical trials of S-1-based chemotherapy for advanced pancreatic cancer. Recently, S-1 has been demonstrated to be non-inferior to gemcitabine in overall survival for metastatic or locally advanced pancreatic cancer in a large-scale phase Ⅲ study (GEST study). Furthermore, S-1 has been shown to be superior to adjuvant chemotherapy with gemcitabine in overall survival in patients with resected pancreatic cancer in another phase Ⅲ study (JASPAC-01 study). In addition to gemcitabine, S-1 is now considered one of the key drugs in Japan.

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## Abstract

S-1 is an oral 5-fluorouracil (5-FU) prodrug, which is designed to improve the antitumor activity of 5-FU by inhibiting dihydropyrimidine dehydrogenase, the key enzyme of 5-FU catabolism. Recently, two important studies on the clinical use of S-1 for pancreatic cancer have been reported from Japan. In the first study (GEST study), S-1 demonstrated non-inferiority to gemcitabine (GEM) in overall survival (OS) for metastatic or locally advanced pancreatic cancer, but combination chemotherapy with GEM and S-1 did not show superiority to GEM in OS. In the second study (JASPAC-01 study), S-1 showed superiority to adjuvant chemotherapy with GEM in OS in patients with resected pancreatic cancer. In addition to GEM, S-1 is now regarded as the key drug in the management of pancreatic cancer in Japan. To date, many studies have investigated the effectiveness of S-1 in various settings, such as first-line chemotherapy for metastatic or locally advanced pancreatic cancer, second-line chemotherapy after GEM failure, and chemoradiotherapy for locally advanced disease. In this review, we focus on recent clinical trials of S-1-based chemotherapy for advanced pancreatic cancer.

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## INTRODUCTION

Pancreatic cancer is one of the most fatal malignancies worldwide. Gemcitabine (GEM) is accepted as the standard treatment in the management of pancreatic cancer based on a randomized controlled study reported by Burris *et al*[1] in 1997. In an effort to improve therapeutic efficacy, many clinical trials have been conducted. However, the prognosis of patients with pancreatic cancer still remains poor, with a reported 5-year survival rate of less than 10%[2]. Development of more effective therapies is urgently needed.

S-1 is an oral 5-fluorouracil (5-FU) prodrug that consists of tegafur (a prodrug of 5-FU), gimeracil [a potent dihydropyrimidine dehydrogenase (DPD) inhibitor], and oteracil (an inhibitor of phosphorylation of 5-FU in

**Table 1 Pivotal phase Ⅲ studies of first-line chemothrapy for advanced pancreatic cancer**

| Ref. | Treatment | *n* | ORR | PFS/TTP (mo) | MST (mo) |
|---|---|---|---|---|---|
| Burris *et al*[1] | GEM | 63 | 5.4% | 9 wk[b] | 5.65[b] |
| | 5-FU | 63 | 0% | 4 wk | 4.41 |
| Moore *et al*[13] | GEM | 284 | 8% | 3.55 | 5.91 |
| | GEM + erlotinib | 285 | 8.6% | 3.75[d] | 6.24[e] |
| Conroy *et al*[14] | GEM | 171 | 9.4% | 3.3 | 6.80 |
| | FOLFIRINOX | 171 | 31.6%[d] | 6.4[d] | 11.1[d] |
| Von Hoff *et al*[15] | GEM | 430 | 7% | 3.7 | 6.70 |
| | GEM + nab-paclitaxel | 431 | 23%[d] | 5.5[d] | 8.50[d] |

[b]$P < 0.01$ *vs* 5-FU; [d]$P < 0.01$ *vs* GEM; [e]$P < 0.05$ *vs* GEM. PFS: Progression-free survival; TTP: Time to progression; MST: Median survival time; GEM: Gemcitabine; ORR: Objective response rate; 5-FU: 5-fluorouracil; FOLFIRINOX: Oxaliplatin, irinotecan, fluorouracil and leucovorin.

**Table 2 Phase Ⅱ studies of Gemcitabine and S-1 therapy for advanced pancreatic cancer**

| Ref. | *n* | Disease extent | ORR | PFS/TTP (mo) | MST (mo) |
|---|---|---|---|---|---|
| Nakamura *et al*[19] | 33 | Metastatic | 48% | 5.4 | 12.5 |
| Ueno *et al*[20] | 54 | Metastatic | 44.4% | 5.9 | 10.1 |
| Oh *et al*[21] | 38 | Metastatic or LA | 32% | 5.4 | 8.4 |
| Lee *et al*[22] | 32 | Metastatic or LA | 44% | 4.92 | 7.89 |
| Kim *et al*[23] | 22 | Metastatic or LA | 27.3% | 4.6 | 8.5 |

PFS: Progression-free survival; TTP: Time to progression; MST: Median survival time; LA: Locally advanced; ORR: Objective response rate.

the gastrointestinal tract) in a 1:0.4:1 molar concentration ratio[3]. After oral ingestion, tegafur is transformed into 5-FU in the liver. Gimeracil inhibits the degradation of 5-FU by inhibiting DPD, the key enzyme of 5-FU catabolism. In a preclinical study, the DPD inhibitory effect of gimeracil has been shown to be approximately 180-fold more potent than that of uracil, a DPD inhibitor combined in UFT[4]. Therefore, sufficient concentrations of 5-FU in serum and tumor tissues can be maintained. Oteracil inhibits phosphorylation of 5-FU in the gastrointestinal tract, and it is expected to reduce 5-FU-induced gastrointestinal toxicity, which may be observed in parallel with potentiated antitumor activity[5]. Clinically, S-1 is accepted as a convenient alternative to 5-FU continuous infusion in Japan because phase Ⅲ studies have shown that S-1-based regimens are non-inferior to 5-FU infusion regimens[6-8]. When compared to 5-FU continuous infusion, oral administration of S-1 can avoid the risk of complications associated with central venous catheter placement. Furthermore, for advanced gastric cancer, an S-1-based regimen (S-1 plus cisplatin) is now accepted as the standard first-line chemotherapy in Japan based on the result of a randomized controlled trial[9].

S-1 has been approved for the treatment of pancreatic cancer since 2006 in Japan, and various clinical trials have been conducted. Recently, two important studies on the clinical use of S-1 for pancreatic cancer have been reported. The first study evaluated the effectiveness of S-1 in first-line chemotherapy for metastatic or locally advanced pancreatic cancer[10]. The second study investigated the use of S-1 in adjuvant chemotherapy for resected pancreatic cancer[11,12]. In this review, we focus on recent clinical trials of S-1-based chemotherapy for advanced pancreatic cancer.

## FIRST-LINE CHEMOTHERAPY WITH S-1 FOR METASTATIC OR LOCALLY ADVANCED PANCREATIC CANCER

GEM has been the mainstay in the treatment of metastatic or locally advanced pancreatic cancer. However, the reported median survival of first-line GEM therapy is only approximately 6 to 7 mo[1,13-15]. GEM plus erlotinib is the first combination chemotherapy that has demonstrated significantly improved OS compared to GEM alone in this patient population[13]. Additionally, the FOLFIRINOX regimen (oxaliplatin, irinotecan, fluorouracil, and leucovorin) and GEM plus nanoparticle albumin-bound paclitaxel (nab-paclitaxel) regimen have now emerged as aggressive treatment options in patients with metastatic pancreatic cancer (Table 1)[14,15].

The first phase Ⅱ study of S-1 for pancreatic cancer was reported by Ueno *et al*[16] in 2005. In this study, 19 patients with metastatic pancreatic cancer received S-1 twice daily at a dose of 80, 100, or 120 mg/d according to body surface areas for 28 consecutive days followed by a 14-d rest. Four patients (21.1%) achieved partial response, and the median survival was 5.6 mo. Subsequently, Okusaka *et al*[17] reported a phase Ⅱ study for metastatic pancreatic cancer, in which a single agent of S-1 showed promising efficacy with a response rate of 37.5% and median survival of 9.2 mo. The major adverse events were gastrointestinal toxicity, such as anorexia, nausea, or diarrhea.

Combination chemotherapy of GEM and S-1 (GS) has also been investigated on the basis of the preclinical findings that GEM and 5-FU have a synergistic cytotoxic effect against pancreatic cancer cells[18]. Phase Ⅱ studies of GS therapy have also shown favorable efficacy with a response rate of 27.3%-48% and median survival of 7.89-12.5 mo (Table 2)[19-23].

Based on these results, a large-scale phase Ⅲ study (GEST study) was conducted in patients with metastatic or locally advanced pancreatic cancer in Japan and Taiwan[10]. Between 2007 and 2009, 834 patients were randomly assigned to GEM alone, GS, or S-1 alone. The primary endpoints were superiority of GS therapy to GEM alone in OS and non-inferiority of S-1 to GEM in OS. In the GEST study, the median survival was 8.8 mo for GEM, 9.7 mo for S-1, and 10.1 mo for GS. The non-inferiority of S-1 to GEM was confirmed (HR = 0.96; 97.5%CI: 0.78-0.18; $P < 0.001$). Meanwhile, GS therapy did not demonstrate the superiority to GEM in OS (HR = 0.88; 97.5%CI: 0.71-1.08; $P = 0.15$). Based on the re-

**Table 3 Randomized studies of gemcitabine and S-1 therapy *vs* gemcitabine for metastatic or locally advanced pancreatic cancer**

| Study | Treatment | *n* | ORR | PFS (mo) | MST (mo) |
|---|---|---|---|---|---|
| GEST[10] | GS | 275 | 29%[b] | 5.7[b] | 10.1 |
| (PⅢ) | S-1 | 280 | 21%[a] | 3.8[c] | 9.7[d] |
| | GEM | 277 | 13% | 4.1 | 8.8 |
| GEMSAP[24] | GS | 53 | 18.9% | 5.4[a] | 13.5 |
| (rPⅡ) | GEM | 53 | 9.4% | 3.6 | 8.8 |
| JACCRO PC-01[25] | GS | 53 | 28.3%[b] | 6.15[b] | 13.7[a] |
| (rPⅡ) | GEM | 59 | 6.8% | 3.78 | 8.0 |
| Sudo *et al*[26] | GS | 51 | 21.6%[a] | 5.3[a] | 8.6 |
| | GEM | 50 | 6.0% | 3.8 | 8.6 |

[a]$P < 0.05$ *vs* GEM; [b]$P < 0.01$ *vs* GEM; [c]$P < 0.05$ non-inferiority to GEM; [d]$P < 0.01$ non-inferiority to GEM. PFS: Progression-free survival; MST: Median survival time; GEM: Gemcitabine; GS: Gemcitabine and S-1; ORR: Objective response rate.

sults of the GEST study, S-1 is accepted as an option in the treatment of metastatic or locally advanced pancreatic cancer in Japan.

However, there are no definitive criteria for the use of S-1 instead of GEM in first-line chemotherapy for metastatic or locally advanced pancreatic cancer. In this regard, there are several important observations in the GEST study results. The first is the difference in toxicity profile between GEM and S-1. Gastrointestinal toxicity, such as diarrhea, was more frequent in the S-1 arm, while hematologic toxicity was more frequent in the GEM arm. The second is the difference in objective tumor response rate. S-1 showed favorable objective response rate (ORR) compared to GEM alone in the GEST study (21% *vs* 13.3%, $P = 0.02$)[10].

GS therapy significantly improved progression-free survival (PFS) (HR = 0.66; 97.5%CI: 0.54-0.81, $P < 0.001$; median, 5.7 mo *vs* 4.1 mo) and ORR (29.3% *vs* 13.3%; $P < 0.001$) compared to GEM alone in the GEST study[10]. Other small-randomized studies reported from Japan also support the superiority of GS therapy to GEM alone with respect to PFS (Table 3)[24-26]. In contrast, the superiority of GS therapy in OS was not demonstrated in the GEST study. The authors of the GEST study explained the cause for the discrepancy as a consequence of second-line chemotherapy with S-1 in the GEM group. Indeed, approximately 50% of patients in the GEM group received second-line chemotherapy with S-1-based regimens[10]. Considering the results of the GEST study, which is the only phase Ⅲ study with the primary endpoint of OS, GS therapy (as well as other GEM and fluoropyrimidine combinations) is not accepted as the standard chemotherapy for metastatic or locally advanced pancreatic cancer in Japan[27-29]. In contrast, some investigators consider that GS therapy may be beneficial in a selected patient population based on the following two studies. A meta-analysis of GS therapy *vs* GEM alone, including the GEST study and two randomized phase Ⅱ studies (GEMSAP and JACCRO), has suggested that GS therapy is associated with better OS (HR = 0.79)[30]. In addition, a pooled analysis of the above three studies has shown that GS therapy significantly improves OS, especially in locally advanced pancreatic cancer (HR = 0.708; 95%CI: 0.527-0.951)[31].

**Table 4 Phase Ⅱ studies of S-1 for gemcitabine refractory pancreatic cancer**

| Ref. | *n* | ORR | PFS (mo) | MST (mo) |
|---|---|---|---|---|
| Morizane *et al*[34] | 40 | 15.0% | 2.0 | 4.5 |
| Sudo *et al*[35] | 21 | 9.5% | 4.1 | 6.3 |

PFS: Progression-free survival; MST: Median survival time; ORR: Objective response rate.

## SECOND-LINE THERAPY AFTER GEMCITABINE FAILURE

It is important to establish effective second-line therapies for tumors refractory to GEM. The results of a randomized controlled study reported by Pelzer *et al*[32] have provided the first evidence for the benefit of second-line chemotherapy compared to best supportive care (BSC) alone in patients with GEM refractory pancreatic cancer. Although the study was terminated because of insufficient accrual, oxaliplatin, folinic acid, and 5-FU (OFF) significantly improved second-line survival compared to BSC alone (median, 4.82 mo *vs* 2.3 mo; $P = 0.008$)[32]. Moreover, the results of the CONKO-003 study have demonstrated a significant improvement in OS with the addition of oxaliplatin to 5-FU plus folinic acid[33]. In clinical practice, fluoropyrimidine based therapy is commonly used for patients previously treated with GEM.

Phase Ⅱ studies of S-1 in patients with GEM-resistant pancreatic cancer have demonstrated moderate activity (ORR = 9.5%-15%; Disease control rate, 52%-58%; median survival, 4.5-6.3 mo) with acceptable toxicity (Table 4)[34,35]. Although there has been no confirmed evidence based on phase Ⅲ studies, S-1 would be a feasible treatment option in this patient population.

S-1-based combination regimens have also been investigated (Table 5). Mizuno *et al*[36] reported a randomized phase Ⅱ trial of S-1 *vs* S-1 plus irinotecan (IRIS) in which 127 patients were randomly assigned to IRIS or S-1 alone. The primary endpoint was PFS. IRIS did not improve PFS (HR = 0.767; 95%CI: 0.527-1.114; $P = 0.1750$) or OS (HR = 0.749; 95%CI: 0.512-1.093; $P = 0.1338$) compared to S-1 alone. Okusaka *et al*[37] reported a randomized phase Ⅱ study of S-1 plus oxaliplatin (SOX) *vs* S-1 in patients with GEM refractory pancreatic cancer. The primary endpoint was PFS, and 264 patients were randomly assigned to SOX or S-1 alone. However, SOX did not improve PFS (HR = 0.838; 95%CI: 0.649-1.082; $P = 0.1795$) or OS (HR = 1.031; 95%CI: 0.791-1.344; $P = 0.8235$) compared to S-1 alone.

More recently, the results of a randomized phase II study of S-1 plus leucovorin (SL) *vs* S-1 alone in patients with GEM refractory advanced pancreatic cancer have been reported[38]. In this study, SL significantly improved PFS, which was the primary endpoint of this study, compared to S-1 alone (HR = 0.56; 95%CI: 0.37-0.85; $P =$

**Table 5 Randomized phase Ⅱ studies of S-1 based chemotherapy after gemcitabine failure**

| Ref. | Treatment group | *n* | ORR | PFS (mo) | MST (mo) |
|---|---|---|---|---|---|
| Mizuno *et al*[36] | S-1 + irinotecan | 60 | 18.3% | 107 d | 208 d |
| | S-1 | 67 | 6.0%[a] | 58 d | 176 d |
| Okusaka *et al*[37] | S-1 + oxaliplatin | 134 | 20.9% | 3.0 | 7.5 |
| | S-1 | 130 | 11.5%[a] | 2.8 | 7.0 |
| Okusaka *et al*[38] | S-1 + leucovorin | 69 | 27.5% | 3.8 | 6.3 |
| | S-1 | 71 | 19.7% | 2.7[b] | 6.1 |

[a]$P < 0.05$ *vs* S-1; [b]$P < 0.01$ *vs* S-1. PFS: Progression-free survival; MST: Median survival time; ORR: Objective response rate.

**Table 6 Phase Ⅱ studies of S-1 and radiotherapy for locally advanced pancreatic cancer**

| Ref. | *n* | ORR | PFS/TTP (mo) | MST (mo) |
|---|---|---|---|---|
| Sudo *et al*[47] | 34 | 41% | 8.7 | 16.8 |
| Ikeda *et al*[48] | 60 | 27% | 9.7 | 16.2 |
| Shinchi *et al*[49] | 50 | 30% | 6.7 | 14.3 |
| Kim *et al*[50] | 25 | 24% | 6.5 | 12.9 |

PFS: Progression-free survival; TTP: Time to progression; MST: Median survival time; ORR: Objective response rate.

0.003; median, 3.8 mo *vs* 2.7 mo). A phase Ⅲ study of SL *vs* S-1 alone is now ongoing (GRAPE study).

## CHEMORADIOTHERAPY FOR LOCALLY ADVANCED PANCREATIC CANCER

The prognosis of patients with locally advanced pancreatic cancer is dismal with a reported median survival of 6.4 mo if managed with only best supportive care[39]. Chemoradiotherapy (CRT) using 5-FU has been a conventional option in the management of locally advanced pancreatic cancer. The rationale of this combination approach is to control local tumor growth using 5-FU as a radiosensitizer[40]. However, the efficacy of CRT using 5-FU remains limited with a reported median survival time of approximately 10 mo[41,42]. Because distant metastases are the major cause of treatment failure, more effective systemic therapies are necessary to improve patient outcome[42]. In this regard, S-1 is an attractive alternative to 5-FU infusion because it has systemic activity for metastatic or locally advanced pancreatic cancer as shown in the GEST study. Furthermore, a recent preclinical study has demonstrated that gimeracil, a DPD inhibitor included in S-1, enhances antitumor activity of radiotherapy[43].

To date, several schedules of S-1 and concurrent radiotherapy have been investigated in phase Ⅰ/Ⅱ studies for locally advanced pancreatic cancer (Table 6). Sudo *et al*[44] and Ikeda *et al*[45] reported that the standard daily dose of S-1 for systemic chemotherapy (80 mg/m$^2$ per day) can be combined with radiotherapy (50.4 Gy in 28 fractions). Shinchi *et al*[46] reported that S-1 at a dose of 80 mg/m$^2$ per day given on days 1 to 21 can be combined with radiotherapy (50 Gy in 40 fractions for 4 wk).

**Table 7 Randomized phase Ⅲ studies of adjuvant therapy in pancreatic cancer**

| Study | Treatment | Endpoint | *n* | DFS (mo) | MST (mo) |
|---|---|---|---|---|---|
| ESPAC-1[55] | CRT (5-FU + RT) | OS | 145 | 10.7 | 15.9 |
| | No CRT | | 144 | 15.2[a] | 17.9 |
| | 5-FU + leucovorin | | 147 | 15.3[c] | 20.1[b] |
| | No chemotherapy | | 142 | 9.4 | 15.5 |
| CONKO-001[56] | GEM | DFS | 179 | 13.4[d] | 22.1 |
| | Surgery alone | | 175 | 6.9 | 20.2 |
| JSAP-02[58] | GEM | OS | 58 | 11.4[e] | 22.3 |
| | Surgery alone | | 60 | 5.0 | 18.4 |
| ESPAC-3[59] | GEM | OS | 537 | 14.3 | 23.6 |
| | 5-FU + folinic acid | | 551 | 14.1 | 23.0 |
| JASPAC-01[11,12] | GEM | OS | 191 | 11.2 | 25.9 |
| | S-1 | | 187 | 23.2[f] | NA[f] |

[a]$P < 0.05$ *vs* CRT; [c]$P < 0.05$ *vs* No chemotherapy; [b]$P < 0.01$ *vs* No chemotherapy; [d]$P < 0.01$ *vs* Surgery alone; [e]$P < 0.05$ *vs* Surgery alone; [f]$P < 0.01$ *vs* GEM. DFS: Disease-free survival; MST: Median survival time; NA: Not available; OS: Overall survival; 5-FU: 5-fluorouracil.

Phase Ⅱ studies of S-1 and concurrent radiotherapy have demonstrated an acceptable toxicity profile and promising efficacy with a response rate of 24%-41% and median survival of 12.9-16.8 mo[47-50]. Furthermore, some patients (0%-4%) underwent curative resection after S-1 and radiotherapy in these studies.

Instead of using S-1, capecitabine-based CRT has been reported in Western countries[51,52]. Capecitabine is an oral fluoropyrimidine carbamate, which is converted to 5-FU predominantly in tumor tissues[53]. Saif *et al*[51] reported a phase Ⅱ study of capecitabine and radiotherapy in patients with locally advanced pancreatic cancer with a response rate of 20% and a 1-year survival rate of 58%. A recent randomized phase Ⅱ study of GEM-based or capecitabine-based CRT for locally advanced pancreatic cancer (SCALOP study) has suggested that capecitabine-based CRT might be preferable to GEM-based CRT[54].

## ADJUVANT CHEMOTHERAPY FOR RESECTED PANCREATIC CANCER

Adjuvant chemotherapy with GEM has been accepted as the standard treatment in patients with resected pancreatic cancer based on the results of randomized controlled studies (Table 7)[55-59]. In a phase Ⅲ study of adjuvant chemotherapy with GEM *vs* observation in patients with resected pancreatic cancer (CONKO-001), adjuvant GEM significantly improved disease-free survival (median, 13.4 mo *vs* 6.9 mo, $P < 0.001$) compared with the observation group[56]. Adjuvant chemotherapy with GEM improved disease-free survival (median, 11.4 mo *vs* 5.0 mo, $P = 0.01$) in another phase Ⅲ study conducted in Japan (JSAP-02)[58]. The European Study Group of Pancreatic Cancer (ESPAC) conducted a phase Ⅲ study of 5-FU plus folinic acid *vs* GEM following pancreatic cancer resection (ESPAC-3). This study showed no difference in OS between arms (median OS = 23.0 mo *vs*

23.6 mo, $P = 0.39$), but treatment-related serious adverse events were more frequent in patients treated with 5-FU plus folinic acid[59].

Recently, Uesaka *et al*[11] reported on a randomized phase Ⅲ study of GEM *vs* S-1 in patients with pathological stage Ⅰ, Ⅱ or Ⅲ (with celiac axis resection) macroscopically resected (R0 or R1 resection) pancreatic cancer (JASPAC-01)[12]. Between April 2007 and June 2011, 385 patients were randomly assigned to adjuvant GEM ($n$ = 193) or S-1 ($n$ = 192). The primary endpoint was non-inferiority of S-1 compared to GEM in OS. At the interim analysis, S-1 showed non-inferiority to GEM and, surprisingly, superiority to GEM in OS with a hazard ratio of 0.56 (95%CI: 0.42-0.74; $P < 0.0001$ for non-inferiority; $P < 0.0001$ for superiority). The 2-year survival rates were 53% (95%CI: 46%-60%) for GEM and 70% (95%CI: 63%-76%) for S-1. The quality of life analysis was significantly better in the S-1 arm ($P < 0.0001$). The frequency of grade 3 or 4 toxicities was similar in both arms, except for leukopenia, which was lower in the S-1 arm. The findings of the JASPAC-01 study suggest that adjuvant chemotherapy with S-1 is a more effective alternative to the standard adjuvant chemotherapy with GEM for resected pancreatic cancer.

The rationale for adjuvant chemotherapy lies in eliminating micrometastases and subsequently improving prognosis. The JASPAC-01 study suggests that adjuvant chemotherapy with S-1 achieves better OS and is presumably more effective in eliminating micrometastases. Preclinical studies have suggested that postoperative chemotherapy with S-1 has a moderate effect on eliminating micrometastases[60,61], and the efficacy is higher in smaller micrometastases[61]. As shown in the GEST study, S-1 has significantly higher ORR compared with GEM in patients with metastatic or locally advanced pancreatic cancer. The superior antitumor activity of S-1 might have inhibited micrometastases and resulted in the improvement of OS in an adjuvant setting. Further investigations are necessary to elucidate the basic mechanisms of the efficacy of S-1 in adjuvant chemotherapy. S-1 is also accepted as the standard adjuvant chemotherapy in patients with curatively resected gastric cancer based on a randomized study in Japan[62].

## FUTURE PERSPECTIVES

S-1 is now accepted as one of the important key drugs in the management of pancreatic cancer in Japan. Oral administration of S-1 is a convenient option for first-line chemotherapy for metastatic or locally advanced pancreatic cancer because it has shown non-inferiority to GEM in OS. However, there are no definitive criteria for its use instead of GEM, and more aggressive therapies, such as FOLFIRINOX and GEM plus nab-paclitaxel, may be preferable for patients with metastatic pancreatic cancer with good performance status. In adjuvant chemotherapy for resected pancreatic cancer, S-1 is a more effective alternative to the standard chemotherapy with GEM. S-1-based second-line chemotherapy for GEM refractory pancreatic cancer and CRT using S-1 for locally advanced disease appear to be promising strategies. However, the efficacy of these therapies should be confirmed in future randomized controlled studies.

In reported studies, one of the important features of S-1-based therapy is favorable ORR. Considering this advantage, some investigators are hopeful that S-1-based therapy may be useful in neoadjuvant therapy for potentially resectable or borderline resectable pancreatic cancer. The main goal of neoadjuvant therapy is to downsize tumors and increase the likelihood of curative resection. To date, many studies have evaluated the effectiveness of neoadjuvant CRT or neoadjuvant chemotherapy[63-66]. However, the effectiveness of neoadjuvant therapy still remains controversial, and no standard regimen has been established. In Japan, clinical studies of S-1-based therapies, such as GS therapy or CRT using S-1 in neoadjuvant settings, are now ongoing (*e.g.*, JASPAC-05 and Prep-02/JSAP-05)[67].

In contrast, there are some problems to be resolved with regard to the clinical use of S-1 for pancreatic cancer. Randomized controlled studies of S-1 are conducted mainly in Japanese populations, and it remains unclear if S-1 is also effective in Western populations. Cytochrome P450 2A6 activity is different among ethnic groups[68], which is the key enzyme in converting tegafur to 5-FU[69]. Gastrointestinal toxicity, such as diarrhea, has been reported to be more severe in Caucasian patients[70]. This clinical question should be addressed in future studies. In Western countries, capecitabine, another oral fluoropyrimidine, has been in use in clinical practice, although limited evidence supports its use for pancreatic cancer.

Including S-1, we now have several options in first-line chemotherapy. However, there are no definitive criteria for treatment choice for each patient. In the next step, we should make an effort to develop a predictive biomarker for treatment efficacy. Human equilibrative nucleoside transporter protein expression has been reported to be a possible predictive marker of benefit from adjuvant GEM in patients with resected pancreatic cancer[71,72]. Thymidylate synthase or DPD gene expression levels have been reported as possible predictive markers of the efficacy of adjuvant chemotherapy with S-1 in patients with resected gastric cancer[73]. In the future, understanding of the molecular mechanism of drug sensitivity and cancer pathogenesis is essential to develop personalized cancer treatment. Given the recent advances in molecular biology, further progress in this field is highly expected.

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