Observational Study

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# A pilot study of oral S-1 for treating heavily pretreated patients with advanced or recurrent cervical cancer among Chinese population

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**Abstract**

This pilot study retrospectively aimed to assess the feasibility effectiveness and safety of oral S-1 in heavily pretreated patients with advanced or recurrent cervical cancer (ARCC) among Chinese population.

Thirty patients with ARCC who had undergone one or more lines of chemotherapy received oral S-1 (40–60 mg/m$^2$) twice daily for 6 weeks. Outcome measurements included tumor response, time to progression (TTP), overall survival (OS) time, and occurrence of adverse events (AEs).

The overall response rate was 43.3%. After a median follow-up of 6 months, the median TTP was 4.4 months and the median OS time was 10.2 months. The most frequent grade 3 or 4 AEs were neutropenia (13.3%) and nausea (16.7%).

The results of this study show that oral S-1 is effective and well-tolerated in patients with ARCC who were heavily pretreated among Chinese population.

**Abbreviations:** AEs = adverse events, ARCC = advanced or recurrent cervical cancer, CI = confidence interval, ECOG = Eastern Cooperative Oncology Group performance, ORR = overall response rate, OS = overall survival, PR = partial response, SD = stable disease, TTP = time to progression.

**Keywords:** cervical cancer, clinical trial, S-1

## 1. Introduction

Cervical cancer is the one of the most common gynecologic cancers among women worldwide. Its annual incidence is 5.3 million, with 2.5 million deaths.[1,2] Despite the administration of a variety of chemotherapeutic agents, the prognosis of patients with advanced or recurrent cervical cancer (ARCC) remains unsatisfactory. Thus, new agents for treating ARCC are still needed.

S-1 is an oral anticancer drug composed of tegafur, gimeracil, and oteracil in a molar ratio of 1:0.4:1.[3] Among the agents used to treat ARCC (paclitaxel,[4,5] topotecan,[6,7] irinotecan,[8,9] vinorelbine,[10] capecitabine,[11,12] ifosfamide,[13,14] and S-1),[15,16] S-1 is amongst the most active, with an overall response rate (ORR) of 36.6% and a median survival time following S-1 treatment of 15.4 months.[17] Although encouraging, these findings were obtained in a study that only included patients with no or one prior chemotherapy treatment; consequently, 48.3% of the patients in the study received S-1 in the initial stages of ARCC. Hence, the effectiveness of S-1 for treating heavily pretreated patients with ARCC is still far from clear. The present phase II study aimed to assess the feasibility effectiveness and safety of S-1 in such patients in China.

## 2. Methods

This study was approved by the Medical Ethical Committee of The Affiliated Hongqi Hospital, Mudanjiang Medical University. It was conducted between January 2015 and December 2016 at The Affiliated Hongqi Hospital, Mudanjiang Medical University. Patients with a pathological diagnosis of stage IVB or recurrent cervical carcinoma were included in this retrospective study. The patients were 20 to 65 years old and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. All patients had received more than one chemotherapy treatment before this study. Additionally, they met the following criteria: absolute neutrophil count ≥1500/IL; platelets count ≥100,000 IL; hemoglobin levels ≥10 g/dL; creatinine clearance rate ≥50 mL/min; normal test results for liver function; and signing of the informed consent document. Patients with active infection; severe interstitial, cardiac, neurological, or mental disease; active brain metastasis or concomitant malignancies were excluded, as were patients who already received S-1 or other drugs that potentially interacted with S-1.

### 2.1. Treatment schedule

Patients orally received S-1 twice daily for 6 cycles. Each cycle consisted of a 2-week period in which drugs were administered, followed by a 1-week drug-free period. Dosage was based on

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body surface area (BSA): 40 mg for patients with a BSA $<1.25\ m^2$; 50 mg for patients with a BSA $<1.5\ m^2$ but $>1.25\ m^2$; and 60 mg daily for patients with a BSA $>1.5\ m^2$. When adverse events (AEs) of higher than grade 3 occurred, the dose was reduced or drug administration was temporarily interrupted.

### 2.2. Response and toxicity assessment

All patients were assessed by examining their medical history and by performing physical examinations, neurologic evaluations, and blood tests. Tumor responses were categorized in accordance with the Response Evaluation Criteria in Solid Tumors, version 1.1. Responses were defined as follows: complete response, complete disappearance of all lesions; partial response (PR), >30% reduction in the largest diameter of the lesions; progressive disease, >20% increase in the largest diameter of the lesions; and stable disease (SD), <30% reduction or <20% increase in the largest diameter of the lesions. AEs were assessed in accordance with the Common Terminology Criteria of Adverse Events, version 3.0. All participants received at least one treatment cycle for evaluation of effectiveness and toxicity. Patient whose dose was reduced or drug administration was temporarily interrupted when AEs are more than grade 3.

### 2.3. Statistical analysis

The Kaplan–Meier method was used to analyze the outcome data. S-1 effectiveness was evaluated by determining the ORR, overall survival (OS) time, and time to progression (TTP). S-1 toxicity was assessed by recording the AEs.

## 3. Results

The characteristics of the patients are listed in Table 1. All patients were Chinese and of Han ethnicity. Twenty-five patients had an ECOG status of 0, and 5 patients had an ECOG status of 1. Eight patients had advanced disease, and 22 patients had recurrent disease. All patients had received at least one prior chemotherapy treatment (range, 1–4).

**Table 1**

**Characteristics of patients at baseline.**

| Characteristics | Variable | Values (n = 30) |
|---|---|---|
| Age, y | Median (SD) | 52.4 (10.1) |
| | Range | 35–64 |
| Race | Asian (Chinese) | 30 (100.0%) |
| Ethnicity | Han | 30 (100.0%) |
| Performance status (ECOG) | 0 | 25 (83.3%) |
| | 1 | 5 (16.7%) |
| Histology | Squamous cell | 20 (66.7%) |
| | Adenocarcinoma | 5 (16.7) |
| | Adenosquamous carcinoma | 4 (13.3%) |
| | Small cell carcinoma | 1 (3.3%) |
| Location of carcinoma | Pelvic | 3 (10.0%) |
| | Distant | 16 (53.3%) |
| | Both | 11 (36.7%) |
| Advanced disease | | 8 (26.7%) |
| Recurrent disease | | 22 (73.3%) |
| Prior chemotherapy | Mean, range | 2 (1–4) |
| | Number of regimen | |
| | 1 | 6 (20.0%) |
| | 2 | 8 (26.7%) |
| | 3 | 14 (46.7%) |
| | 4 | 2 (6.6%) |

ECOG = Eastern Cooperative Oncology Group, SD = standard deviation.

**Table 2**

**Response rates (n = 30).**

| Response | Number of patients (n) | % |
|---|---|---|
| CR | 0 | 0 |
| PR | 3 | 10.0 |
| SD | 10 | 33.3 |
| PD | 13 | 43.3 |
| Discontinuance | 4 | 13.3 |
| Response rate | 13 | 43.3 |

CR = complete response, PD = progressive disease, PR = partial response, SD = stable disease.

The response rates for all patients are listed in Table 2. Three patients (10.0%) achieved a PR, and 10 (33.3%) had SD. The ORR was 43.3%. After a median follow-up period of 6 months, the median TTP was 4.4 months [95% confidence interval (CI), 3.1–5.5] (Fig. 1), and the median OS time was 10.2 months (95% CI, 8.8–11.7) (Fig. 2).

Hematologic and nonhematologic AEs are listed in Table 3. The most frequent grade 3 or 4 hematologic AEs were neutropenia (13.3%) and leucopenia (10.0%). The most frequent grade 3 or 4 nonhematologic AEs were nausea (16.7%) and anorexia (10.0%).

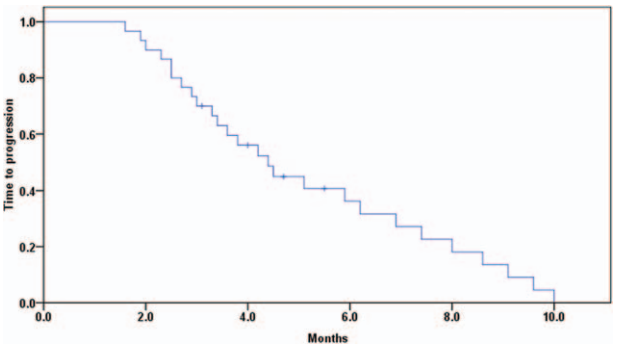


**Figure 1.** Time to progression.

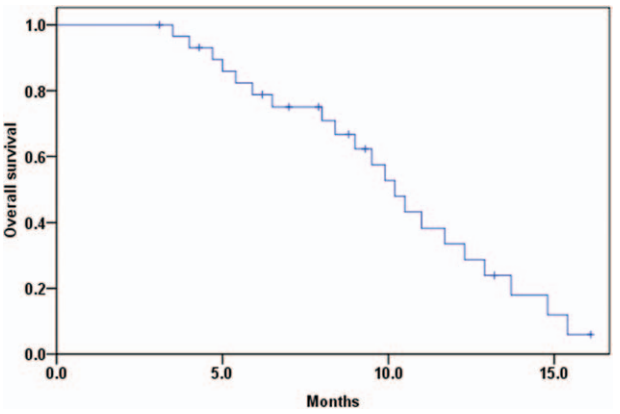


**Figure 2.** Overall survival.

**Table 3**

**Summary of adverse events (n=30).**

| Adverse events | Grade | | | | |
|---|---|---|---|---|---|
| | I | II | III | IV | III/IV (%) |
| Hematologic | | | | | |
| Leucopenia | 4 | 4 | 3 | 0 | 3 (10.0) |
| Thrombocytopenia | 5 | 1 | 0 | 0 | 0 (0) |
| Neutropenia | 7 | 5 | 4 | 0 | 4 (13.3) |
| Anemia | 6 | 2 | 2 | 0 | 2 (6.7) |
| Nonhematologic | | | | | |
| Nausea | 9 | 5 | 4 | 1 | 5 (16.7) |
| Vomiting | 3 | 3 | 1 | 0 | 1 (3.3) |
| Anorexia | 7 | 4 | 2 | 1 | 3 (10.0) |
| Fatigue | 5 | 3 | 0 | 0 | 0 (0) |
| Skin rash | 4 | 2 | 2 | 0 | 2 (6.7) |
| Diarrhea | 6 | 4 | 2 | 1 | 3 (10.0) |
| Pneumonitis | 3 | 0 | 0 | 0 | 0 (0) |
| Hyperpigmentation | 3 | 0 | 0 | 0 | 0 (0) |
| Mucositis | 3 | 1 | 1 | 0 | 1 (3.3) |

## 4. Discussion

Previous studies have shown that S-1 is effective and well-tolerated in patients with ARCC among Japanese population only.[15,17] Although one study explored the effectiveness of S-1 in Japanese patients with ARCC, it did not address that all the included patients were heavily treated previously. Its results demonstrated that S-1 was tolerable, with a promising response rate and prolonged survival time.[17] In that study the ORR was 30.6%, the response rate for patients with prior chemotherapy was 31.8%, the median TTP was 5.2 months, and the median survival time was 15.4 months; 16% of the patients had anemia, 16% had anorexia, and 22% had diarrhea, and the most frequent AEs were grade 3 or 4. The other study also conducted in Japanese patients with ARCC only. Although it utilized S-1 to treat heavily pretreated patients with ARCC, no Chinese patients were included in this study. Additionally, a total of 28 patients were included. Of those, 22 had received prior chemotherapy (not including chemoradiotherapy), and 27 had underwent prior radiotherapy. Its results showed encouraging efficacy and tolerability of S-1 in Japanese patients with ARCC.[15] For all patients, the disease control rate was 42.8%, the median TTP was 4.2 months, and the median OS time was 9.92 months; for patients with stage IVB ARCC, the overall and progression-free survival times were 26.2 and 6.7 months, respectively. However, neither study included patients who had received more than one chemotherapy treatment.[15,17]

The results of the present study are consistent with those of previous studies.[15,17] In this study, we only included 30 Chinese patients with ARCC who had received heavily pre-treated chemotherapy. Furthermore, all 30 patients only received chemotherapy previously, but not the chemoradiotherapy, or radiotherapy. All those unique issues are different from the previous studies, although those studies also addressed the effectiveness of S-1 in patients with ARCC.[15,17]

In this study, we assessed the effectiveness and safety of S-1 in Chinese patients with ARCC who had received more than one chemotherapy treatment. The response rate was 43.3%, the median TTP was 4.4 months (95% CI, 3.1–5.5), and the median OS time was 10.2 months (95% CI, 8.8–11.7) after a median follow-up period of 6 months. The most frequent grade 3 or 4 hematologic AE was neutropenia (13.3%), and the most frequent grade 3 or 4 nonhematologic AE was nausea (16.7%).

The present pilot study had several limitations. First, we recruited only a small number of patients. Second, the study was conducted at only one hospital and only with patients of Han ethnicity, which may limit its generalization to other hospitals and ethnicities. Third, this was a retrospective study and thus may include inherent selection bias. Further studies with a large sample size may strengthen our results.

## 5. Conclusion

The results of the present study show promising effectiveness and tolerability of oral S-1 in patients with ARCC who have been heavily pretreated among Chinese population. Future studies are needed to confirm our results.

## Author contributions

**Conceptualization:** Li Ma, Hui Li.
**Data curation:** Jin-miao Liu, Jing Zhang, Hui Li.
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**Investigation:** Jin-miao Liu.
**Methodology:** Jin-miao Liu.
**Project administration:** Li Ma, Hui Li.
**Resources:** Li Ma, Hui Li.
**Software:** Jin-miao Liu.
**Validation:** Jing Zhang.
**Visualization:** Jing Zhang.
**Writing – original draft:** Li Ma, Hui Li.
**Writing – review & editing:** Li Ma, Jin-miao Liu, Jing Zhang, Hui Li.

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