The long-term survival of a thymic carcinoma patient treated with S-1: a case report and literature review

Hisashi Tanaka¹
Takeshi Morimoto¹
Kageki Taima¹
Yoshihito Tanaka¹
Kunihiko Nakamura¹
Akihito Hayashi³
Akira Kurose²
Ken Okumura¹
Shingo Takanashi⁴

¹Department of Cardiology, Respiratory Medicine and Nephrology, Hirosaki University Graduate School of Medicine, Zaifu-cho, Hirosaki, Japan; ²Department of Anatomic Pathology, Hirosaki University Graduate School of Medicine, Zaifu-cho, Hirosaki, Japan; ³Respiratory Medicine, Hachinohe City Hospital, Tamukaibishamontai, Hachinohe, Japan; ⁴Hirosaki University, Health Administration Center, Bunkyo, Hirosaki, Japan

Background: Thymic carcinoma is a rare neoplasm of the thymus. Systemic chemotherapy is an important therapeutic modality for thymic carcinoma. However, no standard chemotherapy for this carcinoma has yet been established. The usefulness of second-line or later-line chemotherapy has remained unclear. A case of relapsed thymic carcinoma that was successfully treated by S-1 as second-line chemotherapy is reported herein.

Case presentation: A 73-year-old man diagnosed as having thymic carcinoma was treated with three cycles of first-line chemotherapy with ADOC (cisplatin, doxorubicin, vincristine, and cyclophosphamide) and additional radiotherapy (50 Gy). Since his serum cytokeratin 19 fragment level increased suddenly after 3 months of stable disease, he was considered to have progressive disease, and was given S-1 as chemotherapy. Two months later, he had partial response, and the S-1 treatment has been continued since July 2009. Progression-free survival of greater than 4 years was obtained with S-1.

Conclusion: A case of relapsed thymic carcinoma that was treated with S-1, and continues to show a long progression-free survival with good quality of life on treatment is described. S-1 might be an active agent against relapsed thymic carcinoma.

Keywords: thymic carcinoma, S-1, thymidylate synthase

Introduction
Thymic carcinoma is a rare cancer of the thymus arising from the thymic epithelium, which differs from thymoma with respect to its malignant nature. It is characterized histologically by clear-cut cytological atypia and a set of cytoarchitectural features similar to those of carcinoma arising from any other organ. It has been a distinct entity in the World Health Organization (WHO) classification since 2004.¹ The prognosis of patients with thymic carcinoma is poor: 5-year survival rates are reported to be about 30%.² Since approximately 50% of patients with thymic carcinoma have Stage IVa or IVb disease according to the Masaoka–Koga Staging system at the initial presentation, systemic chemotherapy is an important therapeutic modality for thymic carcinoma. However, even an optimal first-line chemotherapy regimen for thymic carcinoma has not been established, because of the rarity of the disease and the difficulty of conducting prospective clinical trials.

S-1 (Taiho Pharmaceutical Co, Ltd, Tokyo, Japan) is an orally active combination of tegafur (a prodrug of 5-fluorouracil [5-FU]), gimeracil (an inhibitor of dihydropyrimidine dehydrogenase, which degrades fluorouracil), and oteracil (an inhibitor of the phosphorylation of fluorouracil in the gastrointestinal tract resulting in a reduction of the gastrointestinal toxic effects of fluorouracil) in a molar ratio of 1:0.4:1. S-1 is
now used in the treatment of various solid tumors such as
gastric cancer, colon cancer, non-small-cell lung cancer, head
and neck cancer, pancreatic cancer, and esophageal cancer
in Japan. In relapsed thymic carcinoma, there are few case
reports indicating the novel efficacy of S-1 therapy. The
present case showed a novel effect of S-1 as second-line
therapy.

**Case presentation**

A 73-year-old Japanese man was referred to our hospital
in October 2008 because of an abnormal shadow in the
mediastinum on chest X-ray. His medical history was unremarkable, and he had taken no medications. He had smoked
50 pack-years. Physical examination revealed no significant
abnormalities except for his clubbed fingers. Laboratory
findings were within normal ranges, except the serum
cytokeratin 19 fragment (CYFRA) level of 16.6 ng/mL
(normal range, 0–3.5 ng/mL). A subsequent computed
tomography (CT) scan revealed a mass lesion in the anterior
mediastinum involving the superior vena cava, with multiple
pleural dissemination. Whole body 18F-fluorodeoxy glucose
positron emission tomography (FDG-PET) showed strong
activity in the anterior mediastinal lesions (7.1 maximum
standardized uptake values) and the multiple pleural ones.
A CT-guided needle biopsy of the main lesion in the anterior
mediastinum was performed. The pathological diagnosis was
squamous cell thymic carcinoma. Immunohistochemically,
the tumor cells showed positive staining for CD117 (c-kit)
and CD5, and negative staining for terminal deoxynucleo-
tidyl transferase (TdT) in the lymphocytes in the tumor.
The Ki-67 (MIB-1) index was more than 30%. The results
findings were as follows: 2 weeks of administration and 1 week of withdrawal
of S-1. The S-1 therapy was effective, since the main tumor
and the pleural dissemination showed remarkable reduction
in their sizes, and the serum CYFRA level became 14.0 ng/mL.
In July 2009, the serum CYFRA level increased suddenly (34.7 ng/mL). There-fore, second-line chemotherapy with S-1 (50 mg/m²) twice a
day was given. The administration of S-1 was conducted as
follows: 2 weeks of administration and 1 week of withdrawal
of S-1. The S-1 therapy was effective, since the main tumor
and the pleural dissemination showed remarkable reduction
in their sizes, and the serum CYFRA level became 14.0 ng/mL.

Figure 1 Histology of the primary tumor. The tumor cells have clear-cut cytological
atypia of polygonal nuclei with eosinophilic cytoplasm, and are arranged in broad
zones separated by fibrohyaline stroma. (A) (HE staining). Immunohistochemical
examination reveals that tumor cells are strongly positive for TS in the cytoplasm (B),
weakly positive for DPD (C), and negative for OPRT (D).

**Discussion**

The optimal chemotherapy for advanced thymic carcinoma
is still controversial. In the National Comprehensive Cancer
Network (NCCN) guidelines for thymoma and thymic
carcinoma, carboplatin and paclitaxel are recommended. The
ADOC regimen (cisplatin, doxorubicin, vincristine, and
cyclophosphamide) is also effective, but it is more toxic
than carboplatin and paclitaxel. There have been reports
showing that anthracycline-based chemotherapy or non-
anthracycline-based chemotherapy produces an objective
response rate of 24%–55% and progression-free survival
S-1 as an active anticancer agent for relapsed thymic carcinoma

(PFS) of 5.0–7.9 months. Grade 3/4 hematological toxicities occurred in more than 76% of cases treated with anthracycline-based chemotherapy.

In the present case, S-1 showed a remarkable effect against the relapsed thymic carcinoma. To the best of our knowledge, there have been no cases with long progression-free survival for more than 4 years with relapsed thymic carcinoma treated by S-1. No serious toxicities have been observed in the present case. There have been a few case reports that evaluated the efficacy of S-1 for advanced thymic carcinoma. Ten patients, including the present case have been reported (Table 1); three of them, who had no response to prior platinum chemotherapy, achieved partial response (PR) with S-1. Okuma et al reported that the response to first-line chemotherapy may be a potential surrogate for survival in advanced thymic carcinoma. However, in the present case, the patient had long PFS, and therefore S-1 might be active for relapsed thymic carcinoma or non-responders to prior platinum chemotherapy.

PFS of approximately 6.8–18.0 months has been reported in thymic carcinoma. In the present case, the patient showed PFS of more than 4 years. The reason for this is unclear, but there may be possibilities of anticancer activity of 5-FU and its metabolites. Kaira et al reported that expressions of TS, OPRT, and DPD tend to increase as the grade of thymic epithelial tumors increases from low to high. They also showed that the biomarkers are closely associated with cell cycle control and angiogenesis, and that positive expressions of TS and DPD are useful for predicting poor outcome. In patients with thymic carcinoma treated by S-1, one patient of three who achieved PR had a remarkable expression of TS. On the other hand, no consistent relationship was seen between

Figure 2 Chest computed tomography before the first-line treatment (A and B), after the first treatment followed by radiotherapy (C and D), and after the S-1 chemotherapy (E and F). The sizes of the anterior mediastinal tumor and the multiple pleural dissemination are remarkably reduced.

Figure 3 The serum CYFRA level during treatment is shown. It declines drastically after S-1 treatment.

Abbreviation: CYFRA, cytokeratin 19 fragment; ADOC, cisplatin, doxorubicin, vincristine, and cyclophosphamide.
Table 1 Summary of the patients’ characteristics in published case reports

<table>
<thead>
<tr>
<th>Author</th>
<th>Age</th>
<th>Sex</th>
<th>Stage</th>
<th>Histology</th>
<th>Treatment line</th>
<th>Response to prior therapy</th>
<th>Response to S-1</th>
<th>PFS (months)</th>
<th>Grade ≥3 AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koizumi et al⁴</td>
<td>48</td>
<td>F</td>
<td>IVa</td>
<td>Sq</td>
<td>Sixth</td>
<td>SD</td>
<td>PR</td>
<td>≥18</td>
<td>–</td>
</tr>
<tr>
<td>Ono et al⁴</td>
<td>67</td>
<td>M</td>
<td>IVb</td>
<td>Sq</td>
<td>Fourth</td>
<td>SD</td>
<td>PR</td>
<td>≥8</td>
<td>–</td>
</tr>
<tr>
<td>Okuma et al⁴</td>
<td>66</td>
<td>M</td>
<td>IVb</td>
<td>Sq</td>
<td>Third</td>
<td>PR</td>
<td>PR</td>
<td>6.8</td>
<td>+</td>
</tr>
<tr>
<td>Shimizu et al⁴</td>
<td>70</td>
<td>F</td>
<td>IVb</td>
<td>Sq</td>
<td>Second</td>
<td>SD</td>
<td>SD</td>
<td>9.8</td>
<td>+</td>
</tr>
<tr>
<td>Kaira et al⁷</td>
<td>79</td>
<td>F</td>
<td>U</td>
<td>Sq</td>
<td>First</td>
<td>–</td>
<td>PR</td>
<td>NE</td>
<td>–</td>
</tr>
<tr>
<td>Present case</td>
<td>73</td>
<td>M</td>
<td>IVa</td>
<td>Sq</td>
<td>Second</td>
<td>SD</td>
<td>PR</td>
<td>≥48</td>
<td>–</td>
</tr>
</tbody>
</table>

Abbreviations: NE, not evaluated; Sq, squamous cell carcinoma; Ud, undifferentiated carcinoma; PFS, progression-free survival; SD, stable disease; PD, progressive disease; PR, partial response; AE, adverse effect.

DPD or OPRT expression and tumor response to S-1. In the present case, TS was markedly expressed in the tumor cells. That might be the reason why the S-1 treatment was effective for thymic carcinoma. TS might be a good biomarker to predict response. However, TS, DPD, and OPRT have not yet been fully evaluated in thymic carcinoma. Further studies are needed to confirm the optimal chemotherapy for thymic carcinoma and to find a useful biomarker to predict the tumor response. At present, a prospective Phase II study (UMIN000010736) that evaluates the efficacy of S-1 against relapsed thymic carcinoma is ongoing in Japan.

A relapsed thymic carcinoma patient treated with S-1, who had a long PFS with good QOL was described. In conclusion, S-1 treatment might be effective for relapsed thymic carcinoma.

Disclosure
The authors report no conflicts of interest in this work.

References