

## Delayed onset, Long-term Efficacy of S-1 Monotherapy for an Elderly Patient with Squamous Cell Lung Cancer

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### Abstract

The efficacy of S-1 monotherapy as a 2<sup>nd</sup>-line regimen for elderly patients with non-small cell lung cancer (NSCLC) has not been reported, nor has delayed onset regression after temporary progression of tumor during an identified therapeutic regimen. Here we report a 78-year-old man was diagnosed with T3N3M1b (BRa), stage IV squamous cell lung cancer. His primary lesion progressed after whole brain irradiation and 4 cycles of 1<sup>st</sup>-line chemotherapy with docetaxel. S-1 monotherapy was prescribed as the 2<sup>nd</sup>-line treatment. Each cycle of chemotherapy comprised 14 days of S-1 (40 mg, twice daily) followed by 14 drug-free days. After 6 months of S-1 monotherapy, primary and metastatic lesions had started regressing significantly. He continued S-1 monotherapy for 19 months (20 cycles) with a comfortable daily life until reaching progressive disease. S-1 monotherapy as a 2<sup>nd</sup>-line could be a therapeutic option for elderly patients with NSCLC. Moreover, long-term use of S-1 might be worth trying if adverse events and tumor growth are tolerable and other anti-cancer drugs are not applicable, because S-1 has a potential for delayed onset efficacy.

### Key words

Lung cancer; Squamous cell; S-1; Delayed onset; Long-term; Elderly

### Introduction

For elderly patients (aged 75 years or older) with non-small cell lung cancer (NSCLC), comorbidities and age-related physiological decline often limit therapeutic strategy. The current standard 1<sup>st</sup>-line regimens for elderly patients with NSCLC include single-agent chemotherapy with vinorelbine, gemcitabine, or docetaxel [1,2]. However, the 2<sup>nd</sup>-line regimen for elderly patients has not been established.

S-1 is an orally administered fluoropyrimidine agent composed of tegafur, 5-chloro-2,4-dihydropyridine, and oteracil potassium, with reported efficacy against a variety of cancers, including gastric cancer and NSCLC. In two phase II studies, S-1 was administered as 1<sup>st</sup>-line therapy for elderly patients with NSCLC [3,4], in which the average response rates (RR) and progression-free survival (PFS) were 8.7-27.6% and 3.9-4.0 months, respectively.

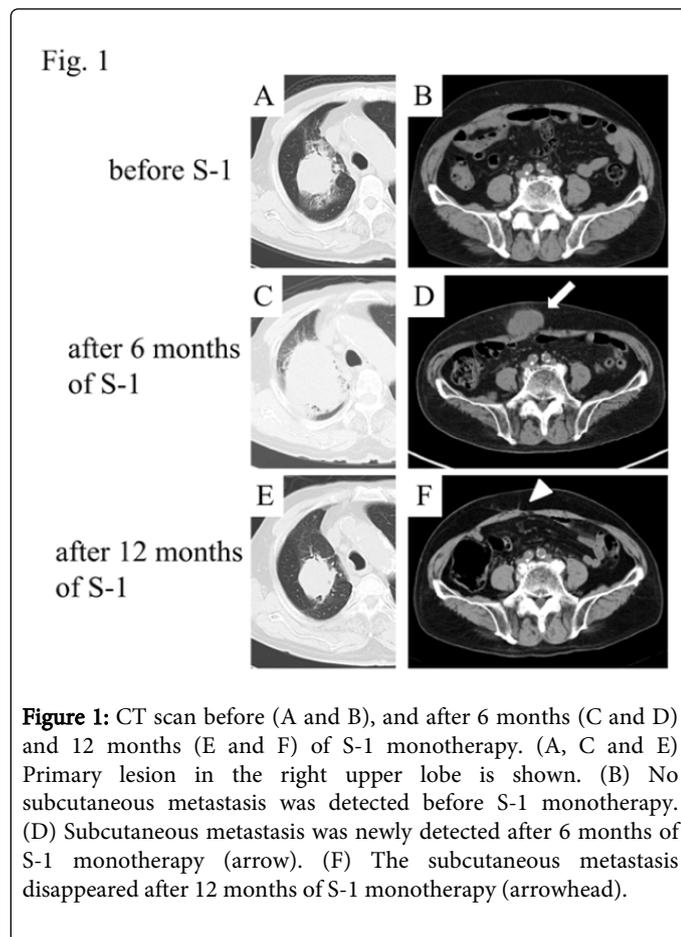
Here, we describe a case of an elderly patient with advanced squamous cell lung cancer whose tumor was successfully controlled following S-1 monotherapy as 2<sup>nd</sup>-line therapy for 19 months. Interestingly, the tumor had progressed first and then started regressing 6 months after beginning of S-1 monotherapy.

### Cases report

A 78-year-old man was diagnosed with T3N3M1b (BRa), stage IV squamous cell lung cancer. The primary lesion was in his right upper lobe and multiple metastases in supraclavicular lymph nodes and brain

were evident. Whole brain irradiation (30 Gy) led to regression of brain metastasis. Because his age was over 75 and his performance status was 2, docetaxel monotherapy (60 mg/m<sup>2</sup>, day 1), but not combination chemotherapy with platinum, was started as 1<sup>st</sup>-line chemotherapy. As a result, the primary lesion and supraclavicular lymph nodes regressed. However, neutropenia (grade 3) and stomatitis (grade 3) had appeared at the 2<sup>nd</sup> cycle even at a decreased dose (48 mg/m<sup>2</sup>), which led to strong oral pain and loss of appetite, and significantly decreased his quality of life. After 2 additional cycles of docetaxel at a further decreased dose (36 mg/m<sup>2</sup>), tumors progressed. Serum concentration of squamous cell carcinoma-related antigen (SCC) was 1.0 ng/ml. S-1 monotherapy was prescribed as 2<sup>nd</sup>-line treatment, although at a lower dose than his body surface area (1.6 m<sup>2</sup>) would indicate. Each cycle of chemotherapy comprised 14 days of S-1 (40 mg, twice daily) followed by 14 drug-free days. For 6 months after commencing S-1, the primary lesion progressed and subcutaneous nodules thought to be metastases were found on his abdomen (Figure 1A-1D), and serum concentration of SCC increased to 7.1 ng/ml. He did not select another anti-cancer drug and expected continuation of S-1 monotherapy. After 6 months of S-1 monotherapy, however, these lesions had started regressing. At 12 months of S-1 monotherapy, the primary lesion regressed significantly and the subcutaneous nodules disappeared (Figure 1E and F). In addition, serum concentration of SCC decreased to 0.5 ng/ml. He and his wife clearly denied any change of life-style or any additional treatment including so-called health foods and supplements that may have immuno-modulatory activity. No adverse effects of S-1 were observed except for a decrease in hemoglobin (grade 1). The sizes of supraclavicular lymph nodes and brain metastasis were not significantly changed during S-1 treatment. He continued S-1 monotherapy for 19 months (total 20 cycles) with comfortable daily life until tumor regrowth; the primary lesion and

subcutaneous nodule progressed again, axillary lymph nodes appeared, and his general condition deteriorated.



## Discussion

Several phase II trials or retrospective analyses of S-1 monotherapy as 2<sup>nd</sup> or further lines have been reported for patients with NSCLC, who were generally younger than 75 years of age [5-11]. Reported average RR and PFS were 5.7-26.7% and 43 days to 4.2 months, respectively. In a phase II trial of 1<sup>st</sup>-line S-1 monotherapy for elderly patients, the average PFS was 4.0 months; the longest was 9.8 months [4]. In the present case, we were able to continue S-1 monotherapy for a much longer period (19 months) despite 2<sup>nd</sup>-line use, without any intolerable adverse effect. To the best of our knowledge, this is the first report of such long-term efficacy for S-1 monotherapy in NSCLC, although S-1 use in the current case might be a category of the "beyond progressive disease (PD)". Moreover, the current case also shows, for the first time, delayed onset efficacy (after 6 months) during an identical chemotherapy, which is interesting in considering the continuation of anti-cancer drugs beyond PD.

As fluorouracil is both dose-dependent and time-dependent [12,13], long-term administration of S-1 may be beneficial. In the present case, marked tumor regression was observed 6 months after initiation of S-1, which implies that long-term use of this agent can be worthwhile. This delayed onset efficacy might also be due to altered host immunity against the tumor. However, he had continued his life-style as same as before, and no additional treatment was started,

including so-called health foods and supplements that may have immunomodulatory activity. In some clinical settings such as paraneoplastic syndromes, particularly paraneoplastic neurological syndromes, spontaneous regression of small cell lung cancer without treatment has been reported [14-16], which suggests an immune response directed against both the nervous system and the cancer [17]. In the current case, however, histology was squamous cell carcinoma and no neurological symptom was observed. Recently, blockade of programmed death 1 (PD-1), an inhibitory receptor expressed by T cells, has been reported to overcome immune resistance; an anti-PD-1 antibody showed an 18% response rate in NSCLC [18]. Interestingly, some tumors progressed for several months during treatment with anti-PD-1 antibody and then regressed significantly [18]. Although the reason why S-1 monotherapy showed a delayed-onset efficacy in the present case remains unknown, S-1 might also have immunomodulatory activity against cancer cells, such as inhibiting PD-1.

When a cancer progresses, another chemotherapeutic regimen is usually selected. However, the present patient selected continuation of S-1 monotherapy after 6-month of its use despite disease progression, because he was concerned about potentially painful adverse effects of other anti-cancer drugs, such as stomatitis. Although S-1 might have a delayed-onset tumor-regressing efficacy, continuation of the same regimen at progressive disease is challenging and should be avoided if next regimen can be applied.

Regular doses of S-1 depend on body surface area; a dose of 40 mg (<1.25 m<sup>2</sup>), 50 mg (1.25-1.5 m<sup>2</sup>), or 60 mg (>1.5 m<sup>2</sup>). In the present case, body surface area was 1.6 m<sup>2</sup>, for which 60 mg would ordinarily be the regular dose. However, we selected the lowest dose-40 mg because of concerns over adverse events such as loss of appetite and neutropenia, because he was over 75 years old, and because he developed grade 3 neutropenia during his 1<sup>st</sup>-line chemotherapy with a decreased dose. As a result, no obvious adverse events were observed during S-1 monotherapy. However, we cannot conclude that lower doses of S-1 could be a standard or reasonable choice for elderly patients.

## Conclusion

Second line S-1 monotherapy can be a therapeutic option for elderly patients with NSCLC. Additionally, long-term administration of S-1 might be worth trying if adverse events and tumor growth are tolerable and other anti-cancer drugs are not selected for some reason, because S-1 has a potential for delayed onset efficacy.

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