A Rare Case of Reversible Cardiac Dysfunction Associated with Tegafur/Gimeracil/Oteracil (S-1) Therapy

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Summary
For the past 20 years, S-1 has been used in the treatment of many types of cancer. However, the clinical importance of myocardial dysfunction attributed to S-1 remains to be unclear. Thus, in this study, we report on a patient with myocardial dysfunction associated with S-1.

S-1 postoperative chemotherapy for gastric cancer was included as a treatment for a 65-year-old man. On day 8, S-1 treatment was discontinued after the patient developed an oral ulcer. He was then admitted to the hospital because of diarrhea caused by S-1. At approximately the same time, he developed dyspnea, and his chest X-rays revealed perihilar vascular engorgement and cardiac enlargement. Although his brain natriuretic peptide was 595.8 pg/mL, troponin I and creatine phosphokinase were unremarkable. Electrocardiograms showed no change in atrial fibrillations or new ST-T wave change. As per his transthoracic echocardiogram, noted were expansion of the left ventricle, global hypokinesis, and reduced left ventricular ejection fraction (approximately 40%). The patient was then diagnosed with S-1-related myocardial dysfunction. Furosemide, human atrial natriuretic peptide, dobutamine, enalapril, spironolactone, and bisoprolol were administered. Thirteen days after being diagnosed with heart failure, his symptoms disappeared, his echocardiogram showed that the left ventricular ejection fraction had increased to 65%, and the cardiothoracic ratio improved to 47% according to his chest X-rays.

S-1-related myocardial dysfunction may be reversible, as it can improve after approximately 2 weeks.

Key words: Drug-induced cardiomyopathy, Myocardial dysfunction, Heart failure, Onco-cardiology, Cardiotoxicity

Chemotherapy-related cardiac toxicity, although rare, is identified as a serious adverse event in patients with cancer. Cardiac dysfunction caused by anticancer drugs is known as a cancer therapy-related cardiac dysfunction (CTRCD). Anthracycline and trastuzumab typically cause CTRCD,1,2 which can occur when different anticancer drugs are administered.3

A combination of tegafur, gimeracil, and oteracil, known as S-1, has been used as an oral anticancer therapy approved for treating gastric cancer since January 1999 in Japan. Approximately 1 million gastric cancer cases were diagnosed, with over 700,000 persons dying from the disease in 2012 in the world.4 In 1999, S-1 use has been approved globally, and it has been used in the treatment of head and neck, colorectal, non-small cell lung, breast, pancreatic, and biliary tract cancers.

Tegafur is a fluorouracil (5-FU) prodrug. 5-FU is associated with serious cardiotoxicity, including cardiovascular dysfunction, particularly angina with coronary artery spasm and ischemic heart disease secondary to coronary artery thrombosis. Additionally, direct myocardial damage following 5-FU administration has been reported.5 However, the clinical course of myocardial dysfunction attributed to S-1 is yet to be determined. Here, we report a rare case of reversible cardiac dysfunction associated with S-1 postoperative chemotherapy in a patient with gastric cancer.

Case Report
A 65-year-old Japanese man with no smoking history was diagnosed with dysphagia. His medical history included hypertension, atrial fibrillation, and hyperuricemia, and he had been administered nifedipine, bisoprolol, and warfarin. He was later diagnosed with operable gastrointestinal cancer. During preoperative cardiac examination, his electrocardiogram showed atrial fibrillation and a normal heart rate. Transthoracic echocardiography revealed a normal left ventricular ejection fraction (LVEF) and normal left ventricular wall motion. Chest X-rays revealed no abnormal findings (Figure 1A). Surgery was then performed to remove the tumor. However, following
surgery, he was diagnosed with gastric cancer (adenocarcinoma, T3N2M0, stage IIIA), and postoperative chemotherapy was indicated approximately 1.5 months after surgery.

Postoperative chemotherapy was then initiated with S-1 (120 mg/day). Eight days later (on day 8), the patient discontinued S-1 because of the appearance of an oral ulcer. Eleven days after starting S-1 treatment, he had grade 2 diarrhea (Common Terminology Criteria for Adverse Events version 5.0). By day 29, his diarrhea exacerbated to grade 3, for which he was hospitalized. Simultaneously, the patient developed dyspnea at rest; he was later diagnosed with a heart failure complication.

Vital signs on day 28 were as follows: blood pressure, 128/97 mmHg; pulse rate, 72/minute; and oxygen saturation, 98% (room air). However, at the time of heart failure (day 29), these values were as follows: blood pressure, 155/118 mmHg; pulse rate, 130/minute; oxygen saturation, 93% (room air), 97% (oxygen: 2 L/minute); and body temperature, 36.3°C. His cardiac performance according to the New York Heart Association classification score was IV. Lung/chest auscultation revealed increased respiratory sounds, indicating restricted breathing/breathing discomfort, and his physical examination revealed edema of the lower limbs. Laboratory analysis showed that the brain natriuretic peptide level was 595.8 pg/mL (normal range: 0-19.5 pg/mL), and his troponin I and creatine phosphokinase levels were within normal limits. However, the troponin level was higher than that in his stable state. Chest radiography revealed an increased cardiothoracic ratio (62%), pericardial effusion, and perihilar vascular engorgement (Figure 1B). His electrocardiogram showed atrial fibrillation, but the waveform, including the ST-T wave, remained unchanged from previous findings (Figure 2). The transthoracic echocardiogram revealed expansion of the left ventricle (diastolic diameter: 50 mm), global hypokinesis, reduced LVEF (approximately 40%), normal ventricular wall thickness, and a negligible degree of pericardial effusion (Figure 3A). Furosemide (20 mg/day), human atrial natriuretic peptides (0.0125 μg/kg/minute), and dobutamine (2 μg/kg/minute) were then administered, after which enalapril and spironolactone treatments were initiated. Bisoprolol was however discontinued because of acute heart failure but was later resumed. Thirteen days after diagnosing heart failure, his symptoms disappeared, his New York Heart Association score improved to I; the echocardiogram revealed a decrease in left ventricle size (diameter: 42.4 mm) and increase in LVEF to 66.9%, and no regional wall motion abnormality was observed (Figure 3B). Chest X-ray showed an improvement in the cardiothoracic ratio to 47% (Figure 1C).

Adenosine thallium-201 myocardial scintigraphy showed no ischemic coronary artery disease. During this
time, he did not experience chest tightness; there was no change in the ST-T wave in electrocardiogram compared with that observed for atrial fibrillation; cardiac enzymes levels, including troponin I, were also found to be not elevated, and no regional wall motion abnormalities were detected. Therefore, ischemic heart disease was excluded. Global hypokinesis is an indication of cardiomyopathy. Although atrial fibrillation was detected, his heartbeat was controlled. The patient had atrial fibrillation for at least 20 years but never had heart failure. This present case may have been due to dehydration brought about by oral ulcers and diarrhea because of the adverse events attributed to S-1. Therefore, it could not be denied that tachycardic atrial fibrillation due to hypovolemia might have been responsible for cardiac dysfunction. However, tachycardia had not been detected so far on physical examination and electrocardiogram before the onset of heart failure. In addition, the possibility of an afterload mismatch due to high blood pressure could not be ruled out. However, diastolic ventricular failure was unlikely from the data of echocardiography. From these results, we can conclude that this present case might have developed cardiac dys-

Figure 2. Electrocardiogram A: Baseline. B: At the time of heart failure. C: After recovery of heart failure.
function and heart failure with the administration of S-1. And S-1 discontinuation led to improved cardiac dysfunction, and no recurrence of myocardial dysfunction was observed. Therefore, we finally diagnosed his condition as S-1-related CTRCD. His clinical course is summarized in Figure 4. At the 3-month follow-up at our cardiovascular clinic, the patient’s stomach cancer had re-emerged, and his general medical condition exacerbated rapidly. Therefore, the patient was transferred to the palliative care unit. This present case was approved by the Institutional Review Board of the Cancer Institute Hospital, Japanese Foundation for Cancer Research.

Discussion

Our patient developed S-1-related cardiac dysfunc-
tion. Discontinuation of S-1 treatment and myocardial dysfunction treatment improved his medical symptoms. As per our findings, it was determined that S-1-related myocardial dysfunction is reversible and can improve within a few weeks.

S-1 belongs to the fluoropyrimidine anticancer drug class, which includes 5-FU and capecitabine. Common cardiotoxicity due to fluoropyrimidines includes myocardial ischemia, which is caused by vasospasm and endothelial injury. Moreover, heart failure has been reported in 2% of patients who use 5-FU. Capecitabine, which is a prodrug of 5-FU, shows the same cardiotoxicity as 5-FU. S-1 contains tegafur, which is identified as another prodrug of 5-FU. However, cardiac dysfunction owing to S-1 has not been reported.

The exact mechanism underlying S-1-induced LVEF decrease in our patient could not be determined but may be related to the following: S-1 contains gimeracil, which inhibits the rate-determining enzyme in the degradation pathway of 5-FU to suppress 5-FU degradation. Cata- bolic products of 5-FU, including α-fluoro-β-alanine (FBAL), inhibit energy production in the mitochondrial citrate cycle in cardiomyocytes. Inhibition of FBAL production by gimeracil may also decrease S-1 cardiotoxicity. S-1 also contains oteracil potassium, which suppresses gastrointestinal toxicity. Moreover, S-1 causes fewer episodes of diarrhea than 5-FU. According to the package insert, the median time required for resolving S-1-induced diarrhea is 9 days. In our patient, diarrhea persisted until after S-1 was discontinued, and grade 3 diarrhea was further observed for 17 days after discontinuation. Therefore, if adverse events, including diarrhea, are present for a long time, cardiac damage may persist regardless of gimeracil administration. The antagonistic action of gimeracil on dihydropyrimidine dehydrogenase may suppress the degradation of 5-FU into FBAL, possibly resulting in reduced cardiovascular toxicity. Long-term accumulation of cardiac damage may exceed the threshold at which cardiac function can be maintained.

Cytochrome p450 2A6 (CYP2A6), which is a polymorphic enzyme responsible for metabolizing drugs or toxins, may be involved in the occurrence of adverse events associated with S-1. Genetic polymorphisms in CYP2A6 cause genotype-dependent differences in metabolic activity, affecting the drug concentration in blood. This affects treatment outcomes and adverse side effects associated with S-1. For example, CYP2A6 41319640 C > G is reportedly associated with severe neutropenia during S-1 treatment. Although we did not examine the specific effects of CYP2A6, our patient may have been a carrier of an unknown type of CYP2A6, thus making him prone to severe adverse events, including diarrhea and myocardial dysfunction.

Our patient had a medical history of hypertension, atrial fibrillation, and hyperuricemia. His blood pressure was steady, and atrial fibrillation was stable for 20 years. However, baseline cardiovascular risk factors indicate a risk of cardiotoxicity from cancer treatment. The baseline risk factors for cardiotoxicity are divided into four types: current myocardial disease; demographic and other cardiovascular risk factors; previous cardiotoxic cancer treatment; and lifestyle risk factors. Our patient had a current myocardial disease, including atrial fibrillation, and cardiovascular risk factors causing hypertension. Patients who are treated with 5-FU and have a history of heart disease are at a fourfold higher risk of cardiotoxicity than patients without heart disease. These baseline risk factors may have been among the causes of S-1-related myocardial dysfunction in our patient. Therefore, during S-1 treatment, identifying risk factors for myocardial damage and appropriate interventions and treatment for these factors is thus important. As a limitation of this case, tachy-cardiac atrial fibrillation might be considered to be involved in the cause of heart failure in this present case.

In our patient, cardiac function improved to a normal range after 2 weeks. Therefore, myocardial injury caused by S-1 was deemed reversible. It was supposed that the direct impairing effect on the myocardium by S-1 was not strong. Heart failure resulting from a 5-FU-induced LVEF decrease improves after 2 weeks. Cardiac dysfunction is caused by ATP depletion resulting from FBAL-induced mitochondrial damage. Discontinuation of 5-FU may increase mitochondrial ATP levels and repair myocardial damage, resulting in the improvement of cardiac dysfunction. The specific cause of the reversibility of S-1-related cardiac dysfunction remains unclear. However, myocardial damage caused by S-1 may involve a mechanism similar to that caused by 5-FU. Moreover, the observed clinical outcomes of our patient were similar to the reported clinical course of 5-FU, and our patient showed improvement in cardiac dysfunction after 2 weeks.

A previous study has recommended the simultaneous use of angiotensin-converting enzyme inhibitors and beta-blockers for CTRCD. Enalapril and bisoprolol were administered to our patient with S-1-related myocardial damage. Our patient could recover from heart failure and show a recovery of LVEF value successfully after an optimal continuous cardioprotective combination therapy with bisoprolol, enalapril, and spironolactone. However, the present case developed heart failure when he had been administered bisoprolol. Regarding the efficacy of cardioprotective therapy for the primary prevention of cardiotoxicity in patients with cancer undergoing chemotherapy, a bisoprolol alone therapy might not have good efficacy for the primary prevention and treatment of cardiotoxicity from the experience of the present case. Indeed, the previous paper has reported that the efficacy of cardioprotective therapies in preventing cardiotoxicity in patients with cancer undergoing chemotherapy has not been elucidated yet. Even if it were for the efficacy, it would be weak efficacy for the primary prevention of CTRCD. The theme of the efficacy of cardioprotective therapies for the primary prevention of cardiotoxicities remains to be uncertain. We are considering that it is very important to highlight the need for investigation of the utility of cardioprotective therapy in the primary prevention of CTRCD.

S-1 is currently used in Asian and European countries. As per our findings, we have determined that S-1 relates to adverse effects such as CTRCD and myocardial dysfunction. As more patients are being covered by medical insurance, S-1 will likely be administered more frequently, potentially increasing the cases of myocardial...
dysfunction. The possibility of cardiac dysfunction should be considered during S-1 treatment, which is relevant to cardio-oncology. Because the negative effects of S-1 therapy may be reversible, oncologists, and cardiologists should cooperate to prescribe an appropriate treatment.

Disclosure
Conflicts of interest: Taro Shiga received personal fees from Daiichi-Sankyo and Bayer, while the other authors declare no conflicts of interest.

References
1. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, et al. 2016 ESC position paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for practice guidelines: the task force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). Eur Heart J 2016; 37: 2768-801.
2. Floyd JD, Nguyen DT, Lobins RL, Bashir Q, Doll DC, Perry MC. Cardiotoxicity of cancer therapy. J Clin Oncol 2005; 23: 7685-96.
3. Herrmann J. Adverse cardiac effects of cancer therapies: cardiotoxicity and arrhythmia. Nat Rev Cardiol 2020; 17: 474-502.
4. den Hoed CM, Kuipers EJ. Gastric cancer: how can we reduce the incidence of this disease? Curr Gastroenterol Rep 2016; 18: 34.
5. Shiga T, Hiraide M. Cardiotoxicities of 5-fluorouracil and other fluoropyrimidines. Curr Treat Options Oncol 2020; 21: 27.
6. Saif MW, Shah MM, Shah AR. Fluoropyrimidine-associated cardiotoxicity: revisited. Expert Opin Drug Saf 2009; 8: 191-202.
7. Ng M, Cunningham D, Norman AR. The frequency and pattern of cardiotoxicity observed with capecitabine used in conjunction with oxaliplatin in patients treated for advanced colorectal cancer (CRC). Eur J Cancer 2005; 41: 1542-6.
8. Caspar F, Peter M, Marino V. Safe administration of s-1 after 5-fluorouracil-induced cardiotoxicity in a patient with colorectal cancer. BMJ Case Rep 2017; bcr2016219162.
9. Kobayakawa M, Kojima Y. Tegafur/gimeracil/oteracil (S-1) approved for the treatment of advanced gastric cancer in adults when given in combination with cisplatin: a review comparing it with other fluoropyrimidine-based therapies. Onco Targets Ther 2011; 4: 193-201.
10. Chen XD, He FQ, Chen M, Tang LC, Tang XL. Can S-1 replace fluorouracil for advanced gastric cancer? A PRISMA-compliant systematic review and meta-analysis. Medicine 2016; 95: e3916.
11. Ikeda K, Yoshiue K, Matsushima E, et al. Bioactivation of tegafur to 5-fluorouracil is catalyzed by cytochrome P-450 2A6 in human liver microsomes in vitro. Clin Cancer Res 2000; 6: 4409-15.
12. Kaida Y, Inui N, Suda T, Nakamura H, Watanabe H, Chida K. The CYP2A6*4 allele is determinant of S-1 pharmacokinetics in Japanese patients with non-small-cell lung cancer. Clin Pharmacol Ther 2008; 83: 589-94.
13. Jeong JH, Park SR, Ahn Y, et al. Associations between CYP2A6 polymorphisms and outcomes of adjuvant S-1 chemotherapy in patients with curatively resected gastric cancer. Gastric Cancer 2017; 20: 146-55.
14. Yang L, Yang Y, Qin Q, et al. Dose-finding study on adjuvant chemotherapy with S-1 plus oxaliplatin for gastric cancer. Mol Clin Oncol 2014; 2: 93-8.
15. Labianca R, Beretta G, Clerici M, Fraschini P, Luporini G. Cardiac toxicity of 5-fluorouracil: a study on 1083 patients. Tumori 1982; 68: 505-10.
16. Mishra T, Shokr M, Ahmed A, Afonso L. Acute reversible left ventricular systolic dysfunction associated with 5-fluorouracil therapy: a rare and increasingly recognised cardiotoxicity of a commonly used drug. BMJ Case Rep 2019; 12: e230499.
17. Fakhri Y, Dalsgaard M, Nielsen D, Lav Madsen P. 5-Fluorouracil-induced acute reversible heart failure not explained by coronary spasms, myocarditis or takotsubo: lessons from MRI. BMJ Case Rep 2016; 2016: bcr2015213783.
18. Neubauer S. The failing heart-an engine out of fuel. N Engl J Med 2007; 356: 1140-51.
19. Zhang SC, Yu MY, Xi L, Zhang JX. Tegafur deteriorates established cardiovascular atherosclerosis in colon cancer: a case report and review of the literature. World J Clin Cases 2019; 7: 89-94.
20. Vaduganathan M, Hirji SA, Qamar A, et al. Efficacy of neurohormonal therapies in preventing cardiotoxicity in patients with cancer undergoing chemotherapy. JACC CardioOncol 2019; 1: 54-65.
21. Muro K, Van Cutsem E, Narita Y, et al. Pan-Asian adapted ESPMO clinical practice guidelines for the management of patients with metastatic gastric cancer: a JSMO-ESMO initiative endorsed by CSCO, KSMO, MOS, SSO and TOS. Ann Oncol 2019; 30: 19-33.
22. Waddell T, Verheij M, Allum W, et al. Gastric cancer: ESMO-ESSO-ESTRO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013; 24: vi57-63.