Phase II Study Of S-1 Plus Cisplatin With Concurrent Radiotherapy For Locally Advanced Thymic Carcinoma: Results Of The LOGIK1605/JART-1501 Study

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Abstract

Background: Combination chemotherapy including platinum agents is used to treat advanced thymic carcinoma; however, the therapeutic effects of such treatment are insufficient. A phase II study was conducted to investigate the efficacy and safety of concurrent chemoradiotherapy for locally advanced thymic carcinoma.

Methods: Patients fulfilling the following eligibility criteria were enrolled: unresectable locally advanced thymic carcinoma, no prior treatment, a good performance status (PS; PS=0-1), being aged 20-75, and adequate organ function. The patients received 80 mg/m^2/day S-1 orally on days 1-14 and 60 mg/m^2/day cisplatin intravenously on day 1. Two cycles of chemotherapy were repeated every 4 weeks. Thoracic radiotherapy (2 Gy, once daily, commencing on day 1; total dose: 60 Gy) was also administered. The primary endpoint of this study was to estimate the objective response rate with a target sample size of 30.

Results: Three patients were enrolled. Toxicity and survival were assessable in all patients, but the treatment response was only assessable in one patient. The study was terminated because of poor case recruitment. The patients' characteristics were as follows: male/female = 2/1; PS 0/1 = 2/1; median age (range) = 59 (55-72); and stage III/IV = 2/1. The patient in which the treatment response was assessed exhibited SD (response rate: 0%). In both non-evaluable cases, the second course of chemotherapy was judged to be post-protocol treatment because it was delayed by ≥14 days, but a complete response (CR) and partial response were achieved after the end of the study, respectively. Grade 4 leukopenia/neutropenia and grade 3 febrile neutropenia occurred in one patient each (33%). There were no treatment-related deaths. The median time to tumor progression was 17.6 months, and the 1-, 2-, 3-, and 4-year survival rates were 67%, 33%, 33%, and 33%, respectively. The median overall survival time was not reached, and the 1-, 2-, 3-, and 4-year survival rates were 100%, 67%, 67%, and 67%, respectively.

Conclusions: Although it was difficult to recruit patients, there was a long-term survivor, who survived for >4 years and seemed to have achieved a CR, indicating that such chemoradiotherapy may be effective against locally advanced thymic carcinoma.

Introduction

Thymic epithelial tumors are derived from the thymus and include thymomas and thymic carcinomas. They are rare, but they are still the most common neoplasms of the anterior mediastinum (1). They tend to be aggressive and infiltrate neighboring organs, which makes total resection very difficult. Thymic carcinoma has a poor prognosis compared with thymoma (2). The incidence of thymic carcinoma is 1.5 per 1 million person-years (3). Surgery is the mainstay of treatment in resectable cases, and multimodal approaches play an important role in advanced cases (4).

Regarding chemotherapy, regimens that are similar to the cisplatin-based regimens used for thymoma are the main treatments for clinical stage IV or recurrent thymic carcinoma. A few studies that specifically

examined the effects of chemotherapy on thymic carcinoma have also been reported, and the response rate was about 22–38%, which indicated that it had some effect (5–7). Therefore, it is recommended that chemotherapy is used in patients that are in a good general condition.
Cisplatin/doxorubicin/cyclophosphamide, etoposide/cisplatin, and paclitaxel/carboplatin regimens are commonly used to treat thymic carcinoma (8, 9). S-1 (TS-1®; Taiho Pharmaceutical Co. Ltd., Tokyo, Japan) is an oral third-generation fluoropyrimidine antitumor agent, which comprises tegafur, gimeracil, and oteracil potassium in a molar ratio of 1:0.4:1. S-1 was reported to have antitumor activity against various solid cancers, including non-small cell lung, gastric, and colon cancer (10–12). Recent years, several studies have demonstrated the effectiveness of S-1 treatment for thymic carcinoma (13–15). It is a commonly used treatment of S-1 plus cisplatin with concurrent radiotherapy for non-small cell lung cancer. The safety and marked effectiveness have been reported against thymic carcinoma (16–18).

Based on these results, we carried out a phase II study of S-1 plus cisplatin with concurrent thoracic radiotherapy for locally advanced thymic carcinoma (19). The primary endpoint of the study was overall response rate and the secondary were overall survival, progression-free survival, and safety.

Patients And Methods

The study protocol was reviewed and approved by the protocol committee of the Lung Oncology Group in Kyusyu (LOGiK) and The Clinical Research Review Board in Nagasaki University (CRB7180001) (registration number: jRCTs071180046, 14/03/2019). Written informed consent was obtained from all study participants. The study was performed by an independent collaborative (unsponsored) group. It has also been registered with the University Hospital Medical Information Network (UMIN) in Japan (registration number: UMIN000024643).

Study design and patients

The LOGIK1605/JART-1501 study was initially designed as a phase II, single-arm trial of S-1 plus cisplatin with concurrent radiotherapy as a first-line treatment for patients with locally advanced thymic carcinoma, involving two research groups, LOGiK and the Japanese Association for Research on the Thymus (JART).

The eligibility criteria for this study were as follows: a histologically and/or cytologically confirmed diagnosis of thymic carcinoma; not having previously undergone chemotherapy, radiotherapy, or surgery for thymic carcinoma; not being indicated for radical surgical resection; having locally advanced Masaoka stage III or IV disease with or without lymph node metastasis, without distant metastasis and/or dissemination; not experiencing postoperative recurrence; being eligible for radical irradiation according to the treatment plan developed by a radiotherapist; not having any other active malignancies; being aged ≥ 20 and ≤ 75 years old; having an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of ≤ 1; having adequate bone marrow function (a leukocyte count of ≥ 3,000/μl or a neutrophil count of ≥ 1,500/μl, a hemoglobin level of ≥ 9.0 g/dl, and a platelet count of ≥ 10.0 x 10^4/μl);

having alanine aminotransferase and aspartate transaminase levels of < 100 IU/l; having a serum bilirubin level of ≤ 1.5 mg/dl; having a creatinine clearance rate of ≥ 60 mL/min; exhibiting arterial O_2 pressure of ≥ 60 Torr or SpO_2 of ≥ 90%; providing written informed consent; and having a life expectancy of > 3 months. The exclusion criteria were as follows: having severe complications, such as uncontrolled angina; having suffered a myocardial infarction within the past 3 months; suffering severe heart failure or an infection; having uncontrolled diabetes or hypertension; having interstitial pneumonia, as determined by a chest X-ray; or having medical problems that were severe enough to prevent compliance with the protocol.

Assessment

Before treatment, each patient' s complete medical history was taken, and all patients underwent a physical examination, assessments of complications, blood cell counts, blood biochemistry tests, a chest X-ray, chest and abdominal computed tomography (CT), a radionuclide bone scan or positron emission tomography (PET)-CT, brain magnetic resonance imaging, and electrocardiography. Treatment responses were determined according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. All adverse events were recorded and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Treatment

The patients received chemotherapy with S-1 (80 mg/m^2) in two daily doses after meals on days 1–14 and 29–42, and cisplatin (60 mg/m^2) as an intravenous infusion on days 1 and 29. The dose of S-1 was determined according to the patient's body surface area (BSA) as follows: BSA: <1.25 m^2, 80 mg per day; BSA: 1.25 m^2 to < 1.50 m^2, 100 mg per day; and BSA: ≥1.5 m^2, 120 mg per day. As for the radiotherapy regimen, 2.0 Gy was administered once daily, 5 times a week, from day 1 until a total dose of 60 Gy had been administered. Intensity-modulated radiotherapy was not permitted. The method used to assess the area of the primary tumor on CT was described in a previous study (19).

Pathological specimens and images

The initial pathological diagnosis was obtained at each facility and was confirmed by a central review committee after the treatment had been completed. Similarly, the initial imaging-based staging and response assessments were performed at each facility and were confirmed by a central review committee.

Statistical analysis

The primary endpoint of this study was the response rate, which was assessed by an independent review committee. The secondary endpoints included overall survival, progression-free survival, and safety. The estimated required number of patients for an accurate binomial test was determined to be > 27 based on the following assumptions: threshold response rate P0 = 0.45, expected response rate P1 = 0.70, one-sided α = 0.05, and ß=0.20. As some patients may be ineligible, the target sample size was set at 30. The enrollment period was set at 3 years, and the follow-up period was scheduled to last for 1.5 years.

Results

Three patients from 2 institutions were enrolled in this trial between December 2016 and November 2019. Due to the difficulty of recruitment, case registration was terminated without extending the recruitment period. One patient received the planned treatment and underwent evaluations of the treatment response, toxicity, and survival. The remaining two patients also received the planned treatment; however, the start of the second cycle of chemotherapy was delayed by > 14 days in these cases, which met the protocol treatment discontinuation criteria, and hence, the second cycles were judged to be post-protocol treatment regimens by an independent committee. Thus, these two patients underwent the evaluations of toxicity and survival, but not the treatment response evaluation.

Treatment administration

A total of 4 cycles of S-1 plus cisplatin were administered as protocol treatment to the three patients: 1 cycle was administered to 2 patients (cases 1 and 3) and 2 cycles were administered to one patient (case 2). In case 1, a second cycle of S-1 plus cisplatin was administered as post-protocol treatment 27 days later due to myelotoxicity, and a total of 4 cycles of S-1 plus cisplatin were eventually administered. In case 3, the patient developed severe nausea and weight loss and was considered to be cisplatin-intolerant. Therefore, S-1 plus cisplatin was terminated after one cycle, and S-1 alone was administered in the second cycle as a post-protocol treatment. The S-1 treatment was delayed 53 days because of leukopenia, neutropenia, febrile neutropenia, and weight loss. Sixty Gy of thoracic radiotherapy was administered to 2 patients (cases 1 and 2), and 40 Gy of thoracic radiotherapy was administered to one patient (case 3) due to a reduction in their PS.

Efficacy

The patients' characteristics, the administered treatments, and the efficacy of the administered treatments are shown in Table 1. The treatment response was assessed in one patient (case 2), who exhibited stable disease (SD), resulting in an overall response rate of 0%. The treatment response was not evaluable in 2 patients (cases 1 and 3) because of the administration of early post-protocol treatment; i.e., S-1 plus cisplatin (case 1) and S-1 (case 3), respectively. The median potential follow-up time was 41.1 months. Two patients survived, and the other patient died during the follow-up period. The median progression-free time of the 3 patients was 17.6 months, and the 1-, 2-, 3-, and 4-year progression-free survival rates were 67%, 33%, 33%, and 33%, respectively. The median overall survival time was not reached, and the 1-, 2-, 3-, and 4-year overall survival rates were 100%, 67%, 67%, and 67%, respectively. CT images of cases 1 and 3 are shown in Figs. 1 and 2, respectively. In case 1, after 1 cycle of the protocol treatment with full radiotherapy and 3 cycles of post-protocol treatment the tumor continued to shrink, and after 56.9 months it was still asymptomatic and had not progressed. In case 2, the tumor shrank, but only by 27%; therefore, it was classified as SD. No exacerbation was observed until 17.6 months later, when a new lesion appeared. Post-protocol treatment with carboplatin and paclitaxel was administered, and so far the patient has survived for 41.1 months. In case 3, the tumor shrank, as shown in Fig. 2;

however, a tumor developed in the neck outside of the irradiation field after 9.1 months. The patient' s condition gradually deteriorated, and he died 13.9 months later.

Toxicities

The toxicities experienced during the protocol treatment are listed in Table 2. Toxicities were assessable in all 3 patients. Two (67%) patients experienced grade 3 or 4 hematological toxicities, and 1 (33%) developed grade 4 toxicities. The principal grade 3 or 4 hematological toxicity was leukopenia, which occurred in 2 (67%) patients, and the principal grade 4 toxicities were leukopenia and neutropenia, which occurred in 1 (33%) patient. Febrile neutropenia occurred in 1 (33%) patient. The major non-hematological toxicity was nausea, which occurred in all 3 (100%) patients. Esophagitis was observed in 2 (67%) patients, but it was not severe. In case 3, the patient developed severe nausea and could not eat at all, resulting in a PS of 4. It was considered that she had experienced grade 3 nausea, weight loss, and fatigue.

Discussion

As far as we know, the LOGIK1605/JART-1501 study was the first prospective study designed to evaluate the efficacy of third-generation cytotoxic agents plus cisplatin with concurrent radiotherapy for patients with locally advanced unresectable thymic carcinoma. Unfortunately, only three patients were enrolled, and the study was terminated because of poor case recruitment. In addition, the treatment response could only be evaluated in one case, which involved SD, and hence, the response rate was 0%. However, among the cases involving post-protocol treatment there was one long-term (> 4 years) survivor, who seemed to achieve a complete response (CR) after S-1/cisplatin plus concurrent radiotherapy, indicating that chemoradiotherapy may be effective against locally advanced thymic carcinoma.

One of the reasons why the case recruitment did not go well is that the eligibility criteria included unresectable cases in which preoperative induction chemoradiotherapy had not been performed. Cases in which surgical excision was planned after chemoradiotherapy were considered resectable, and hence, were ineligible. Even locally advanced cases involving infiltration of the great vessels or the pericardium were considered resectable by the surgical researchers and hence, were ineligible. Further progression leads to pericarditis and pleuritis, and chemotherapy alone is used instead of chemoradiotherapy in such cases. Extended surgery including the heart, great vessels, and mediastinal lymph node metastasis was also performed for non-small cell lung cancer from 1970 to the 1990s (20–22); however, its use has gradually decreased since prospective clinical trials demonstrated the long-term survival benefits of concurrent chemoradiotherapy (23, 24). Since thymic carcinoma is rare, it is difficult to conduct prospective clinical trials of treatments for the disease, especially for locally advanced cases. Nevertheless, it is necessary to continue to develop effective concurrent chemoradiotherapy regimens for thymic carcinoma. Since we had no experience in conducting prospective trials of chemoradiotherapy for thymic carcinoma, unlike for lung cancer, it was difficult to determine the protocol rules with regard to the

irradiation methods (19). Although the case recruitment was unsuccessful this time, we believe that our experience with this prospective clinical trial will aid the development of treatments for this disease.

As for the effects of chemoradiotherapy on thymic carcinoma, Chen YY et al. retrospectively examined the cases of 29 patients who received concurrent chemoradiotherapy with a cisplatin combination regimen for unresectable thymic carcinoma (25). The response rate was 50%, and half of the responders achieved a CR. In addition, the 3- and 5-year survival rates were 74.5% and 67.7%, respectively, and only mild adverse events were seen. Kashima J et al. retrospectively examined the effects of chemoradiotherapy in 14 patients with thymic carcinoma and found a response rate of 57% (CR: n = 0; PR: n = 8), progression-free survival of 15.1 months, and median overall survival of 31.4 months (26). Their 5-year survival rate of 25.7% was lower than that reported by Chen et al., and they mostly used cisplatin regimens, but they also used carboplatin regimens. Prospective studies of neoadjuvant chemoradiotherapy have also been conducted. Korst RJ et al. conducted a prospective phase II trial of neoadjuvant chemoradiotherapy in 22 patients with locally advanced thymic tumors, including 7 with thymic carcinoma, and a trend towards a greater radiographic response (as measured by tumor size) was seen (27). In addition, we also experienced a case in which long-term recurrence-free survival was achieved after chemoradiotherapy-induced tumor shrinkage followed by complete resection (28). In the current study, there was a long-term survivor who seemed to have achieved a CR, and the 4-year overall survival rate was 67%, suggesting the usefulness of chemoradiotherapy for locally advanced thymic carcinoma.

Regarding toxicities, severe nausea and weight loss developed in case 3, and the patient could not eat at all, resulting in a PS of 4. Occasionally, we encounter patients who are cisplatin-intolerant. Ueda et al. reported a female patient with advanced gastric cancer who suffered from life-threatening adverse events, including severe myelosuppression, during chemotherapy involving S-1 plus cisplatin. She was hospitalized because of weight loss and severe dehydration, which led to grade 4 leukopenia/neutropenia (29). The latter case is similar to our case 3. Before treatment, the patient in case 3 was fine and had a PS of 0. Two weeks after treatment, grade 2 nausea, weight loss, and fatigue were observed together with grade 0 leukopenia and neutropenia. However, the nausea, weight loss, and fatigue continued for the next 2 weeks, and the leukopenia and nausea worsened to grade 4, and febrile neutropenia also developed and worsened, resulting is a PS of 4. The lack of sufficient chemotherapy and radiotherapy in case 3 also affected the efficacy of treatment, who was the only patient to experience short overall survival.

Hypersensitivity is a serious side effect of platinum agents, such as cisplatin and carboplatin (30), but we do not think that our patients were affected by hypersensitivity. In case 1, myelotoxicity was prolonged and the start of the second course was delayed by 2 weeks, and the treatment deviated from the protocol treatment. However, the treatment was generally tolerated, and in case 2, the treatment was performed as planned. Considering that this treatment can be performed effectively in lung cancer patients (16, 17), and severe nausea and weight loss were only seen in case 3, it is probably tolerable for patients with locally advanced thymic carcinoma.

In conclusion, the LOGIK1605/JART-1501 study attempted to prospectively evaluate S-1 plus cisplatin chemotherapy with concurrent radiotherapy for locally advanced thymic carcinoma. Although case recruitment was difficult, there was a long-term survivor, and it was indicated that chemoradiotherapy may be effective against locally advanced thymic carcinoma.

Declarations

The study was conducted in compliance with the 1964 Declaration of Helsinki and Ethical Guidelines for Medical Research for Humans (2014 Ministry of Education, Culture, Sports, Science and Technology / Ministry of Health, Labor and Welfare Notification No. 3, Japan)

ETICS APPROVAI AND CONSENT TO PARTICIPATE

The study protocol was approved by The Clinical Research Review Board in Nagasaki University (CRB7180001) (registration number: jRCTs071180046). Written informed consent was obtained from all study participants.

CONSENT FOR PUBLICATION

Written informed consent for publication was obtained from all study participants.

AVAILABILITY OF DATA AND MATERIAL

The datasets generated during and analyzed during the study are available from the corresponding author on reasonable request.

COMPETING INTERESTS

Dr. Fukuda reports personal fees from AstraZeneca K.K., Bristol Myers Squibb, Chugai, Eli Lilly Japan, Kyowa Kirin, MSD K.K., Nippon Kayaku, Novartis, Pfizer Japan Inc., Taiho Pharmaceutical Co., and Takeda, grants from AstraZeneca K.K. and Eli Lilly Japan, outside the submitted work;

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AUTHORS' CONTRIBUTIONS

MF, study design, management of the trial, data collection, wrote the main manuscript; MY, data collection, reviewed the manuscript; TY, management trial for radiotherapy, reviewed the manuscript; SF, management of the trial, reviewed the manuscript; HM, data collection, reviewed the manuscript; JF, management of trial for pathological diagnosis, reviewed the manuscript; KN, management of trial for pathological diagnosis, reviewed the manuscript; HT, management of trial for pathological diagnosis, reviewed the manuscript; KA, management of trial for image diagnosis, reviewed the manuscript; NT, management of trial for image diagnosis, reviewed the manuscript; MH, management of trial for image diagnosis, reviewed the manuscript; TS, study design, data collection, reviewed the manuscript; MO, supervision, reviewed the manuscript; KS, supervision, reviewed the manuscript.

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DATA AVAILABITY

All data generated or analyzed during the study are included in this published article and its supplementary information files.

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Tables

Tables 1-2 are available in the Supplemental Files section.

Figures

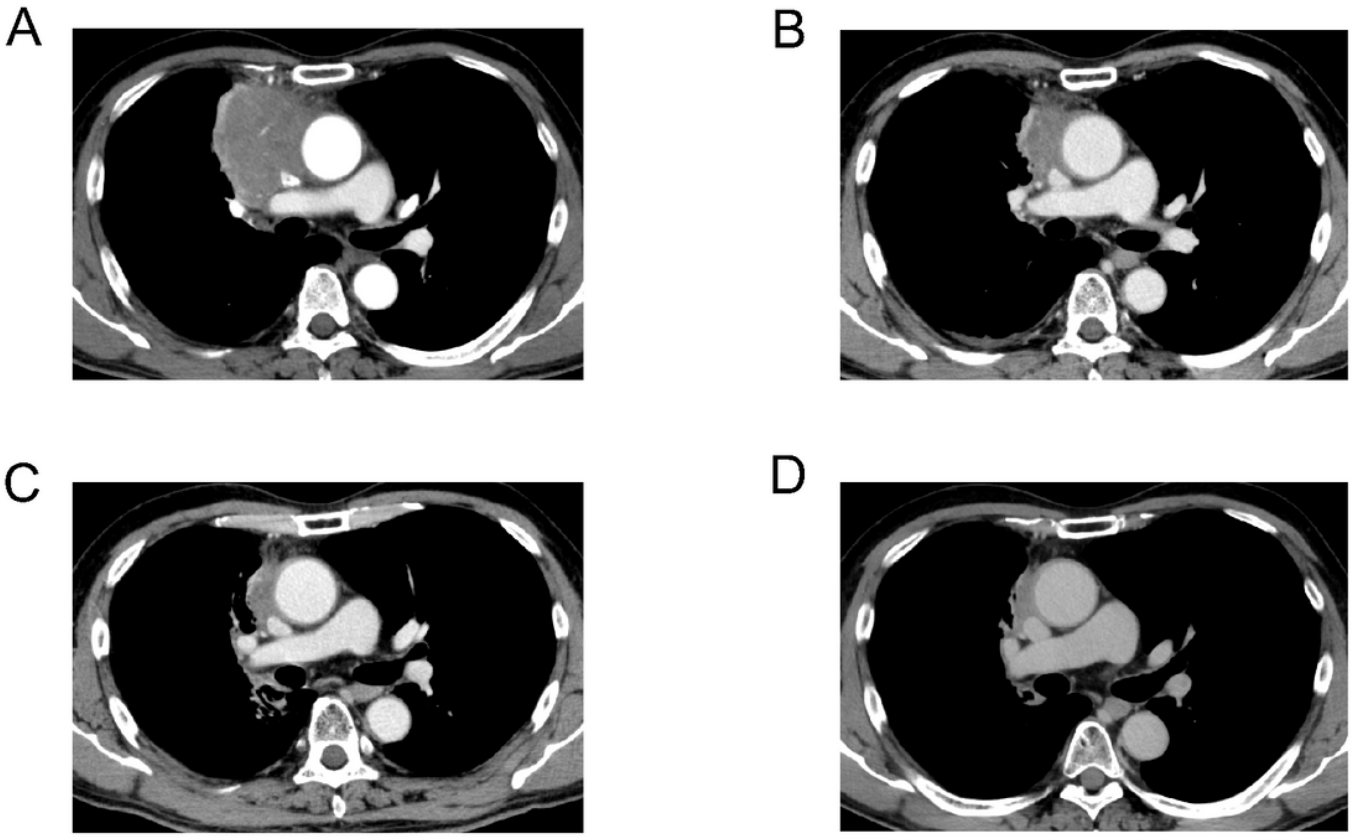

Figure 1

Course of CT images of Case 1

A) Before treatment, B) 3 months after treatment, C) 10 months after treatment, and D) 4 years and 8 months after treatment

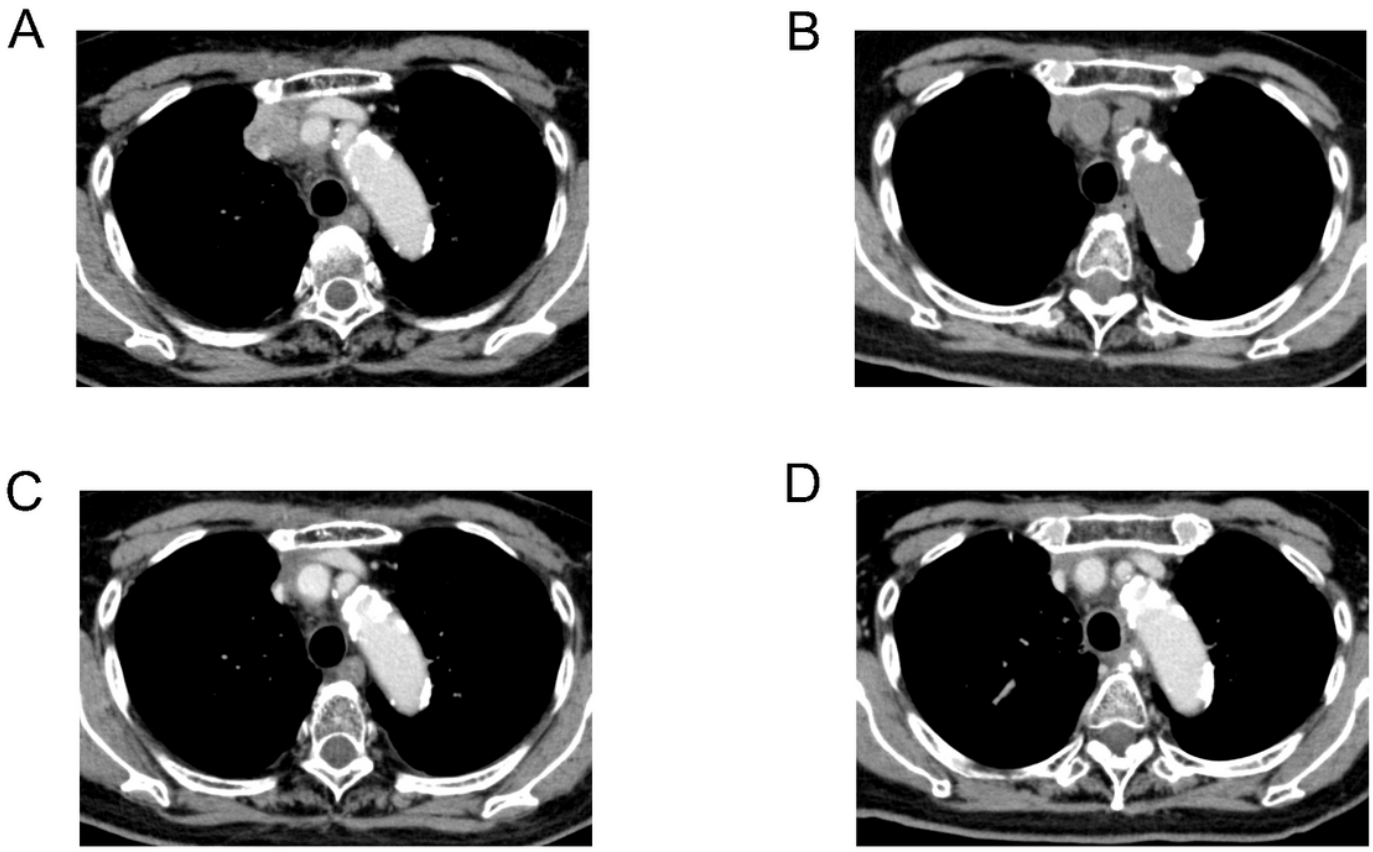

Figure 2

Course of CT images of Case 3

A) Before treatment, B) 1 month after treatment, C) 3 months after treatment, and D) 9 months after treatment

Supplementary Files

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- 4table.pdf