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Original Article

Efficacy and Safety of Uracil-Tegafur in Patients with Recurrent or Metastatic Thymic Carcinoma

Shih-Yu Huang, Cheng-Hua Huang, Harvey Yu-Li Su, Yen-Hao Chen, Tai-Jan Chiu, Yen-Yang Chen*

Division of Hematology Oncology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University, College of Medicine, Taiwan

Abstract

Background: Thymic carcinoma (TC) is a rare but aggressive thymic epithelial neoplasm, with lymphoepithelioma-like histological features resembling nasopharyngeal carcinoma. Epstein–Barr virus is a known etiology of various tumors, including nasopharyngeal carcinoma, in Asian patients. These patients have a significant response to cisplatin plus 5-fluorouracil (5-FU) combination chemotherapy. Interestingly, this regimen seems to be effective for TC s resembling nasopharyngeal carcinoma. Currently, the standard second-line therapy for advanced TC is uncertain. The use of uracil-tegafur (UFT), a combination of uracil and 5-FU prodrug, has not been reported in literature. We analyzed the effectiveness and toxicity of UFT as an optional regimen for recurrent or metastatic TC. **Materials and Methods:** This retrospective study enrolled patients verified to have recurrent or metastatic TC and who were treated with UFT between 2017 and 2019 in our hospital. All patients were treated with UFT until disease progression, the patients could no longer tolerate the treatment, or patient refusal. We assessed the safety and efficacy of UFT for TC. **Results:** Four patients were female and seven were male. The age ranged from 41 to 77 years. The histological features of TC were squamous cell carcinoma and poorly differentiated carcinomas. Grade 3 toxicity occurred in one patient. No treatment-related deaths were observed. Among the 11 patients, 6, 2, and 3 had a partial response, stable disease, and progressive disease, respectively. The objective response rate was 54.5%. The median progression-free survival and overall survival of patients who received UFT chemotherapy were 8.16 months (95% confidence interval [CI]: 0.76–15.56 months) and 19.43 months (95% CI: 17.07–21.78 months), respectively. **Conclusion:** Single-agent UFT seems to have potential effectiveness and good tolerability in patients with recurrent or advanced TC.

Keywords: Adverse effect, chemotherapy, thymic carcinoma, uracil-tegafur

Introduction

Thymic epithelial neoplasms are uncommon thoracic cancers, with a worldwide incidence of 0.13–0.32/100,000 people annually. Primary thymic carcinoma (TC) was first reported in 1982, when it was considered to be thymoma.[1] Thymoma and thymic carcinoid tumors are indolent and are limited to the chest cavity. In contrast, TC tends to behave more aggressively,

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Address for correspondence: Dr. Yen-Yang Chen, Division of Hematology-Oncology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, No. 123, Dapi Rd., Niaosong Dist., Kaohsiung City 833, Taiwan.
E-mail: chen.y9964@gmail.com

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with frequent adjacent organ involvement and disseminated metastases, which results in significantly worse prognoses.[2] The World Health Organization (WHO) histopathological classification in 2004 classified TC as a distinct entity from thymoma. Histologically, TCs, defined as thymic epithelial counterparts of thymomas, have malignant cytologic features without a normal lymphocytic component (immature T cells).[3] They are predominantly squamous cell carcinomas and undifferentiated carcinomas. TCs occur frequently between the ages of 30 and 60 years, but they can occur at any age and more frequently in men than in women (ratio 1.5:1).[4,5] Myasthenia gravis is uncommonly observed in TCs.

Although physicians follow the WHO classification in determining the approach for TC patients, there is still no standard treatment. Taking part in clinical trials is encouraged. According to the current clinical practice, for Stage I–III and selected oligo-metastatic Stage IV disease, multidisciplinary management including surgical resection ± concurrent chemoradiotherapy (CCRT) is recommended.[6] Carboplatin/paclitaxel (CbP) and cisplatin, doxorubicin, vincristine, and cyclophosphamide (ADOC) regimens are recommended as first-line therapy for TCs based on the NCCN guidelines.[7] However, data on cases who fail platinum-based or anthracycline-based chemotherapy are currently lacking.

Considering the potential association between Epstein–Barr virus (EBV) infection and TCs, although controversial, one small study in Taiwan showed a significant response rate and survival in unresectable TC patients who underwent CCRT with 5-fluorouracil (5-FU) and cisplatin combined regimen.[8] The efficacy of 5-FU and its prodrug-containing S-1 in recurrent TC has been reported in several case reports and some small case series.[9-12] Uracil-tegafur (UFT) also contains the prodrug of 5-FU, developed to improve the antitumor activity. In this study, we evaluated the safety and efficacy of UFT in patients with recurrent or metastatic TC.

Materials and Methods

Patients and treatment

This retrospective study was approved by Chang Gung Medical Foundation Institutional Review Board that waived the requirement to obtain informed consent (IRB No. 202000096B0). A total of 11 patients were diagnosed with recurrent or advanced TC and treated with UFT between 2017 and 2019 in our hospital. Four patients were female and seven were male. The age range was between 41 and 77 years. The histologic features of TC were squamous cell carcinomas and poorly differentiated carcinomas. All patients were treated with UFT as either first-line or later-line regimens. Two patients received UFT as first-line treatment because of their age, poor performance status, and refusal to receive intravenous chemotherapy. Nine of the 11 patients had been previously treated with cisplatin-based chemotherapy. Our planned dose of UFT was 200 mg b.i.d., 3 weeks on, and 1 week off. The dose was de-escalated to 100 mg b.i.d. or 100 mg t.i.d. if the patient experienced Grade 3 toxicity or was intolerant to the planned dose.

Response evaluation and endpoints

All the enrolled patients visited clinics regularly during the treatment period until disease progression, treatment intolerance, or death. Follow-up visits included a physical examination, laboratory tests, and imaging studies. Computed tomography of the chest was the preferred imaging tool to assess tumor response, using the Response Evaluation Criteria in Solid Tumors version 1.1. Progression-free survival (PF) was defined as the interval between the initial day of UFT treatment and the day of disease progression or any event-related death. Overall survival was defined as the time interval from the day of receiving UFT to the date of death or last contact with the patient. Observed toxicities during UFT were evaluated before each treatment cycle and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Statistical analysis

All statistical analyses were performed using SPSS 10.0 software (SPSS Inc., Chicago, IL, USA). We constructed overall and PF curves using the Kaplan–Meier method.

Results

Patient characteristics

The median age of the 11 patients was 66 years (range: 41–77 years). The histologic subtype included squamous cell carcinomas ($n = 9$) and poorly differentiated carcinomas ($n = 2$). All patients had previously received chemotherapy (one or more regimens), except for patients 1 and 2. Patient 2 received postoperative regional radiotherapy before recurrence of the disease. Eight patients were treated with a cisplatin-based regimen either alone or as part of CCRT. Five patients had previously been treated with a 5-FU combination regimen. The basic characteristics of the 11 patients are shown in Table 1.

Toxicity and dose delivery

All patients had good tolerability to oral UFT 200 mg b.i.d., except for one patient, who had the dose reduced to 100 mg b.i.d. due to performance status and old age. There were no treatment-related hospitalizations or deaths [Table 2]. The Grade 3 toxicity of palmar-plantar erythrodysesthesia syndrome was limited and resolved after treatment interruption. One patient (patient 8) discontinued treatment because of Grade 3 adverse events. His disease status slowly progressed with pleural effusion after treatment discontinuation.

Efficacy

The median PF and overall survival were 8.16 months (95% confidence interval [CI]: 0.76–15.56 months) and 19.43 months (95% CI: 17.07–21.78 months), respectively [Figure 1]. Six patients had a partial response ($n = 6$, 54.5%), stable disease (SD) was noted in two patients ($n = 2$, 18.1%), and three patients had progressive disease ($n = 3$, 27.2%) [Table 3]. Patient 5 had a significant response to lung

Table 1: Clinical characteristics, histopathology, and treatment modalities of the 11 patients

Patient number	Age	Gender	Histologic subtype	Previous chemotherapy	Previous RT or CCRT
1	67	Female	Squamous cell carcinoma	0	-
2	77	Male	Poorly differentiated carcinoma	0	+
3	62	Female	Squamous cell carcinoma	2 (TP, GP)	-
4	41	Female	Squamous cell carcinoma	2 (FP, GP)	+ with FP
5	69	Male	Poorly differentiated carcinoma	5 (FP, GP, ADOC, Ifos, Paclitaxel)	+ with FP
6	73	Male	Squamous cell carcinoma	1 (FP)	+ with FP
7	65	Male	Squamous cell carcinoma	1 (FP)	+ with FP
8	66	Male	Squamous cell carcinoma	2 (GT, G alone)	+ with G
9	53	Female	Squamous cell carcinoma	1 (GT)	+ with GT
10	64	Male	Squamous cell carcinoma	2 (EP, PAC)	+ with EP and PAC
11	70	Male	Squamous cell carcinoma	4 (FP, GT, V, CbP)	+ with V

FP: 5-FU/cisplatin, CbP: Carboplatin/cisplatin, GP: Gemcitabine/cisplatin, TP: Paclitaxel/cisplatin, GT: Gemcitabine/paclitaxel, EP: Etoposide/cisplatin, PAC: Paclitaxel/adriamycin/cisplatin, ADOC: Adriamycin/dacarbazine/vinblastine/cisplatin, Ifos: Ifosfamide, V: Vinorelbine

Table 2: The uracil-tegafur-associated hematological and nonhematological adverse events

n=11	Grade 1-2	Grade ≧3
Hematological		
Leukopenia	1	0
Anemia	0	0
Thrombocytopenia	0	0
Elevated ALT or AST	0	0
Nonhematological		
Gastrointestinal upset	0	0
Palmar-plantar erythrodysesthesia syndrome	2	1
Skin rash	1	0
Fatigue	1	0

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase

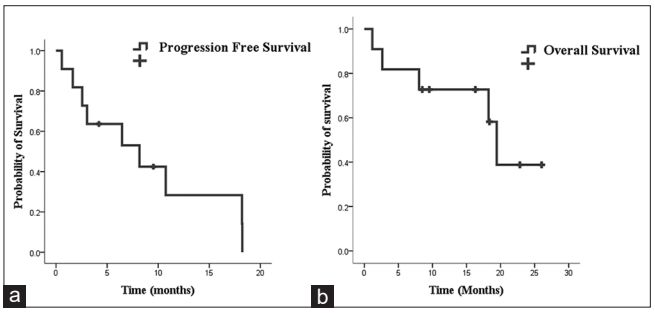

Figure 1: The survival curve of the patients with advanced thymic carcinoma treated with uracil-tegafur (n = 11). Kaplan–Meier curve shows (a) the progression-free survival (median: 8.1 months) and (b) overall survival (median: 19.4 months)

metastases after UFT treatment for 3 months as fifth-line chemotherapy. The chest X-ray is shown in Figure 2.

Discussion

TCs have heterogeneous histologic features, and their subtypes include squamous cell carcinoma, mucoepidermoid carcinoma, and rare variants such as basaloid carcinoma, clear cell carcinoma, spindle cell carcinoma, anaplastic carcinoma, adenocarcinoma, and rhabdoid carcinoma.[4] The clinical course of TCs tends to be more aggressive than that of ordinary thymoma. Nearly 80% of TC patients have been reported to have an anterior mediastinal mass invading the contiguous structure with presentations including cough, chest pain, phrenic nerve palsy, or superior vena cava syndrome. Approximately 40% of cases involve spread to the lymph nodes, pleura, pericardium, lungs, liver, and bones.[13] The survival rate for TCs varies depending on stage (stages 1–2: 91%; stages 3–4: 31%) and resectability (R0 resection).[14]

For patients with advanced thymic neoplasms, based on previously published retrospective and prospective studies, the ADOC regimen is recommended as first-line therapy because it has demonstrated better response and survival rates. One small study enrolled a total of eight Japanese patients with advanced TCs, all of whom were treated with the ADOC regimen. Six of the eight patients obtained a partial response after ADOC chemotherapy, the overall clinical response rate was 75%, and the median survival time was 19 months.[15] In a multicenter prospective study, CbP in previously untreated patients with advanced TC also resulted in a significant overall response rate of 36% (one complete response and 13 partial responses) and a median PF of 8.1 months (5.4–13.1). The 2-year survival rate was 71% (95% CI, 54%–83%).[16] However, some details should be taken into consideration. First, most previous studies grouped thymomas together with TCs, which makes interpreting the efficacy in TC-specific patients difficult. Second, the different geographical areas (Taiwan vs. Western countries) may mean there were differences in the epidemiology, prevalence, and etiology of TCs.

The EBV is a ubiquitous B-cell lymphocytic virus that can replicate in epithelial cells and is strongly associated with undifferentiated nasopharyngeal carcinomas, which tend to appear in Southern China, Malaysia, Singapore, and Taiwan. As an undifferentiated tumor, lymphoepithelioma-like carcinoma of the thymus has histopathological characteristics similar to those of undifferentiated nasopharyngeal carcinomas. In 1985, Leyvraz *et al*. first addressed the possible association between

Table 3: The response and survivals of uracil-tegafur in advanced thymic carcinoma patients

Patient number	PFS (months)	OS (months)	Response	Status	Reason for stopping treatment
1	18.2	18.36	PR	AWD	Disease progression
2	3.03	8.03	PD	DOD	Disease progression
3	18.2	26.03	SD	AWD	Disease progression
4	10.7	19.43	PR	DOD	Disease progression
5	8.16	18.23	PR	DOD	Disease progression
6	4.20	22.83	PR	AWD	Treatment continued*
7	1.63	2.63	PD	DOD	Disease progression
8	2.56	8.50	SD	AWD	Intolerance to AE
9	6.46	16.30	PR	AWD	Disease progression
10	9.53	9.53	PR	AWD	Treatment continued
11	0.56	1.16	PD	DOD	Disease progression

*Patient had interrupted treatment course due to toxicity. PR: Partial response, SD: Stable disease, PD: Progressive disease, PFS: Progression-free survival, OS: Overall survival, AWD: Alive with disease, DOD: Die of disease, AE: Adverse events

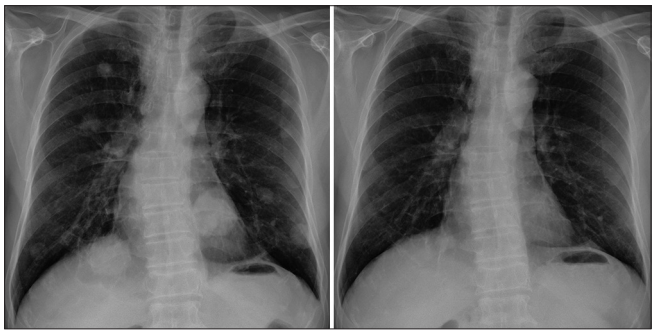

Figure 2: Chest X-ray showing significant tumor regression after three cycles of uracil-tegafur treatment. Multiple lung metastases were noted before uracil-tegafur (left) and all decreased tumor size after 3 months uracil-tegafur (right)

TC and EBV.[17] Although the association is still controversial, a single case and small series studies of the presence of EBV in lymphoepithelioma-like TC have been reported in both Western[18-22] and Asian[23-26] countries. Induction chemotherapy with cisplatin and FU (PF) has been widely used as a first-line regimen in nasopharyngeal carcinoma patients for many years. Therefore, PF has been discussed as a potentially effective regimen for TCs. Chen *et al*. reported 29 patients with unresectable TC receiving CCRT with a PF regimen, and four (25.0%) patients had complete responses and four (25.0%) had partial responses. The overall cumulative survival rates at 1, 2, 3, and 5 years were 93.8%, 81.3%, 74.5%, and 67.7%, respectively.[8] No large randomized trial has yet been conducted because of the rarity of the disease.

In addition to first-line therapy, several studies have evaluated salvage chemotherapy in recurrent or platinum-refractory TCs. Litvak *et al*. reported the results of 11 TC patients treated with pemetrexed, who had neither responses nor survival benefits, and the median time to progression was 5.1 weeks.[27] Koizumi *et al*. reported six relapsed TC patients who were treated with amrubicin, an anthracycline, in combination with platinum-based chemotherapy, of whom two had partial responses, and the median PF and overall survival were 4.5 and 9 months, respectively.[28] Komatsu *et al*. reported three patients with advanced TC who had previously received an ADOC regimen and received carboplatin plus paclitaxel combination therapy as second- or third-line chemotherapy, of whom two showed partial responses and one had SD.[29] Currently, there are no effective agents for patients who fail to receive platinum-based or anthracycline-based chemotherapy. Thus, it is necessary to explore novel drugs and treatment strategies to improve the current circumstances. Prolonged administration of metronomic chemotherapy at relatively low drug doses, at shorter intervals in consecutive doses, and without interruption in order to exert a sustained cytotoxic or apoptotic effect, has been proposed. The antitumor mechanism is thought to be the inhibition of angiogenesis, stimulating adaptive T, possibly innate NK cell-mediated immunity and direct tumor cell killing.[30]

S-1 contains tegafur as a prodrug of 5-FU and has been shown to have clinical efficacy for NSCLC patients as postoperative adjuvant therapy as well as palliative chemotherapy in unresectable disease. Therefore, some studies have reported that S-1 may have potential effectiveness in TCs. Wang *et al*. analyzed salvage monotherapy with S-1 in Stage IV TC patients. Among 44 patients, the disease control rate was 80% (30% of PR and 50% of SD), and the median PF and overall survival were 6 months and 15 months, respectively. However, nine patients had rapid progression and six patients had grade ≥3 bone marrow suppression.[12] Similarly, acting as a metronomic chemotherapy agent, UFT is an orally administered 5-FU derivative drug composed of tegafur and uracil in a 1:4 molar ratio. It has been approved for several cancers such as breast, lung, head and neck, gastric, and colon cancers as either adjuvant or palliative therapy. However, no previous study has investigated the efficacy of UFT for advanced thymic TC. Thus, we analyzed the feasibility and response of UFT as palliative chemotherapy in patients with metastatic and recurrent TC. Although our analysis was a retrospective study and the number of cases was small and limited, the response rate of all patients treated with UFT was 54% and the median PF was longer than 8 months. Regarding toxicity, only one patient had interruption of UFT due to Grade

3 adverse events. No hematological or nonhematological adverse events were observed.

Conclusion

UFT seems to have potential effectiveness and to be less toxic than anthracycline-based regimens or S-1-based chemotherapy.

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Conflicts of interest

There are no conflicts of interest.

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