

Second-line Chemotherapy of Platinum Compound plus CPT-11 Following ADOC Chemotherapy in Advanced Thymic Carcinoma: Analysis of Seven Cases

SHINTARO KANDA, TOMONOBU KOIZUMI, YOSHIMICHI KOMATSU, SUMIKO YOSHIKAWA,
MITSUYO OKADA, ORIE HATAYAMA, MASANORI YASUO, KENJI TSUSHIMA,
KAZUHISA URUSHIHATA, KEISHI KUBO, MARI SASABAYASHI and AKEMI TAKAMIZAWA

First Department of Internal Medicine, Shinshu University School of Medicine, 3-1-1, Asahi Matsumoto, Japan

Abstract. *Background:* Optimal chemotherapeutic regimen in thymic carcinoma remains uncertain and the efficacy of second line chemotherapy has not been established either. *Patients and Methods:* We retrospectively evaluated the efficacy of an irinotecan plus cisplatin or carboplatin (IP) regimen as a salvage treatment for patients with unresectable thymic carcinoma that progressed after cisplatin, doxorubicin, vincristine and cyclophosphamide (ADOC) chemotherapy. Seven patients with histologically confirmed thymic carcinoma that was resistant to or who had relapsed after initial chemotherapy with ADOC were treated with IP. The treatment consisted of irinotecan (CPT-11, 60 mg/m², days 1, 8 and 15) and cisplatin (80 mg/m², day 1) or carboplatin (AUC 4) intravenously every 4 weeks, for at least 2 cycles. *Result:* Two patients achieved partial responses. Although another two patients showed a significant reduction of the primary thoracic lesion, the appearance of a new lesion was found in one and a metastatic lesion was unchanged in the other. Neutropenia over grade 3 was observed in all patients but none of the patients developed serious infections. There were no severe non-hematological toxicities, including diarrhea. *Conclusion:* We conclude that salvage chemotherapy may be useful in certain patients with thymic carcinoma and irinotecan may be a novel and alternative agent for relapsed thymic carcinoma.

Thymic carcinoma differs from thymoma not only morphologically but also biologically (1, 2). Thymic carcinoma is a thymic epithelial neoplasia with cytological malignant features and the clinical course tends to be much more aggressive than that of thymoma (3-5). Thymic carcinoma also

tends to metastasize widely, showing a highly lethal course (3-8). Thus, the role of systemic chemotherapy may be important in the treatment strategy for thymic carcinoma. Several reports demonstrated that combination chemotherapy, particularly a regimen containing cisplatin, was effective against thymic carcinoma (6-11). Among these reports, Yoh *et al.* (7) evaluated the efficacy of CODE (cisplatin, vincristine, doxorubicin and etoposide) therapy for thymic carcinoma and reported a response rate of 42%. Kitami *et al.* (8) and our group (9) reported 57% (4 out of 7 cases) and 75% (6 out of 8 cases) response rates respectively with cisplatin, doxorubicin, vincristine and cyclophosphamide (ADOC) chemotherapy. Thus, thymic carcinoma is a chemosensitive tumor. However, there is no information about second-line chemotherapy in advanced thymic carcinoma. We described seven cases of unresectable thymic carcinoma treated with irinotecan plus platinum compound (cisplatin or carboplatin) (IP) as second line chemotherapy after relapse following ADOC chemotherapy. We analyzed the efficacy of chemotherapy and discuss the role of second line chemotherapy in thymic carcinoma.

Patients and Methods

Seven cases of histologically confirmed thymic carcinoma that recurred after ADOC chemotherapy were analysed. Histological diagnosis was based on fine needle biopsy under computed tomographic (CT) guidance or on surgical specimens. Clinical staging included medical history and physical examination, complete biochemical profile, chest radiographs, chest CT scans and bronchoscopy. In addition, to examine distant metastasis, abdominal and brain CT, and bone scan were performed. According to the classification by Masaoka *et al.* (12), the patients had unresectable, locally advanced lesions: one patient was in stage IVa and the others were in stage IVb. Performance status was assessed using Eastern Cooperative Oncology Group (ECOG) scales (13).

Between 1996 and 2006, all patients were initially treated with a combination of ADOC chemotherapy including cisplatin (50 mg/m²) and doxorubicin (40 mg/m²) on day 1, vincristine (0.6 mg/m²) on day 3, and cyclophosphamide (700 mg/m²) on day 4. This regimen was

Correspondence to: Tomonobu Koizumi, MD, First Department of Internal Medicine, Shinshu University School of Medicine, 3-1-1, Asahi Matsumoto, 390-8621, Japan. Tel: +81 263 37 2631 Fax: +81 263 36 3722, e-mail: tomonobu@hsp.md.shinshu-u.ac.jp

Key Words: Salvage chemotherapy, thymic malignancy, irinotecan, cisplatin.

Table I. Clinical characteristics in seven patients with thymic carcinoma.

Patient	Age (year)	Gender	Performance status	Histology	Stage	Distant metastasis
1	45	F	1	Small cell	4b	Lung, liver
2	59	M	0	Undifferentiated	4a	
3	56	M	0	SCC	4b	Bone
4	60	M	1	SCC	4b	Liver
5	36	M	0	SCC	4a	
6	47	F	1	SCC	4a	
7	71	F	1	SCC	4b	Liver

M: male; F: female; SCC: squamous cell carcinoma.

repeated every 3 to 4 weeks. If the patient showed progressive disease during or relapsed after ADOC chemotherapy, second-line chemotherapy was administered. cisplatin (80 mg/m², day 1) plus irinotecan (60 mg/m² days 1, 8 and 15) chemotherapy was administered as second-line chemotherapy in six patients and carboplatin (AUC; 4) was administered instead of cisplatin in one patient (patient 7, in Table I) due to insufficient renal function. Patients were required to have a white blood cell count (WBC) of more than 4,000/ μ l and platelets more than 100,000/ μ l before IP chemotherapy was initiated. Chemotherapy was administered for four weeks and repeated for two to four courses. Partial response (PR) was defined as more than 50% decrease in the size of the main measurable lesions. Stable disease (SD) was defined as less than 50% regression of measurable lesions. If measurable lesions increased or new lesions appeared after chemotherapy, these were defined as progressive disease (PD). Patients were evaluated after two courses of chemotherapy. Duration of response and survival were measured from the start of the first course of ADOC chemotherapy. Toxicities associated with chemotherapy were evaluated by Community Toxicity Criteria of the National Cancer Institute (NCI-CTC) version 2.0 (14). Survival was measured from the start of the first course of ADOC and IP chemotherapy, respectively. One patient (patient 5) received thoracic radiotherapy (60 Gy) after IP chemotherapy. None of the other patients received thoracic radiotherapy before or during either chemotherapy regimen. Written informed consent was obtained from all patients.

Results

Patient characteristics. The clinical profiles of the seven patients are shown in Table I. The median patient age was 56 years old with a range of 36 to 71 years of age. There were four males and three females. All patients showed a good performance status of 0 or 1 before IP chemotherapy. The histological subtypes of the seven patients were squamous cell carcinomas in five, small cell carcinoma in one, and undifferentiated carcinoma in one. In six patients, four courses of ADOC chemotherapy had been carried out, but in the remaining one patient, only one course of ADOC therapy had been administered because PD became apparent despite ADOC chemotherapy.

Serial responses to chemotherapy and disease-free intervals following each chemotherapy regimen are summarized in Table II. Total response to IP chemotherapy was observed in two patients and stable disease (SD) in three, resulting in a 28.6% overall response rate. Grade 3/4 neutropenia occurred in all patients and was treated by granulocyte-colony stimulating factor as needed. There were no febrile infections. The most commonly occurring grade 3/4 nonhematological toxicity was nausea/vomiting (57.1%) but there was no diarrhea over grade 3.

Three patients survived for 25-35 months after the initial chemotherapy. Four patients died between 10 months and 17 months after the initial chemotherapy. The survival curve of seven patients after initial ADOC and IP chemotherapy by the Kaplan-Meier method are shown in Figures 1 and 2, respectively. The median survival time was 17.5 months and the 1- and 2-year survivals were 85.7% and 42.8%, respectively.

The clinical course in patient 4 demonstrated a noteworthy response to IP and is shown in Figure 2. Recurrent pleural disseminations were observed after surgical resection (Figure 2A). ADOC chemotherapy was started, but PD was observed after only one course of the initial ADOC chemotherapy (Figure 2B). Four courses of IP chemotherapy were administered and the pleural tumors showed reductions (Figure 2C). However, a new hepatic metastasis appeared and the final evaluation was PD.

Discussion

Chemotherapy is commonly administered to patients with unresectable and/or metastatic thymic carcinoma (3-10). We present here our experiences with second-line IP chemotherapy for patients resistant to and/or developing relapse following ADOC therapy.

Recent developments of more effective chemotherapy agents, including taxans, irinotecan, gemcitabine, and navelbine and others have resulted in better outcomes for several malignancies. IP chemotherapy is one of many standard regimens for several malignancies, including lung cancer (15, 16). Compared with other new agents, irinotecan showed an equal efficacy in patients with non-small cell lung cancer (16). In small cell lung cancer, IP also showed an equal or greater efficacy compared to etoposide plus cisplatin (17). In addition, topotecan, a topoisomerase I inhibitor similar to irinotecan, was effective in the treatment of recurrent small cell lung cancer after cyclophosphamide, doxorubicin and vincristine therapy (18). Thus, we speculated that irinotecan may be a potential agent for salvage chemotherapy after ADOC, even in advanced thymic carcinoma.

Regarding the response rate, subsequent IP chemotherapy after ADOC achieved PR in two patients in our series. Furthermore, response of the primary thoracic lesions only to

Table II. Clinical courses of each patient.

Patient	No. of ADOC courses	Response to ADOC	PFT after ADOC	No. of IP courses	Response to IP		Overall survival	Outcome
					Primary site	Other sites		
1	4	PR	5 M	2	PR	SD	4 M	17 M Dead
2	4	PR	1 M	2	PR	SD	1 M	10 M Dead
3	4	SD	5 M	4	SD	SD	6 M	15 M Dead
4	1	PD	0 M	4	PR	PD	0 M	15 M Dead
5	4	SD	3 M	4	SD	SD	11 M	35 M Alive
6	4	SD	7 M	2	SD	SD	5 M	25 M Alive
7	4	PR	3 M	4	PR	PR	3 M	28 M Alive

PFT, progression-free time; IP, irinotecan plus cisplatin or carboplatin chemotherapy.

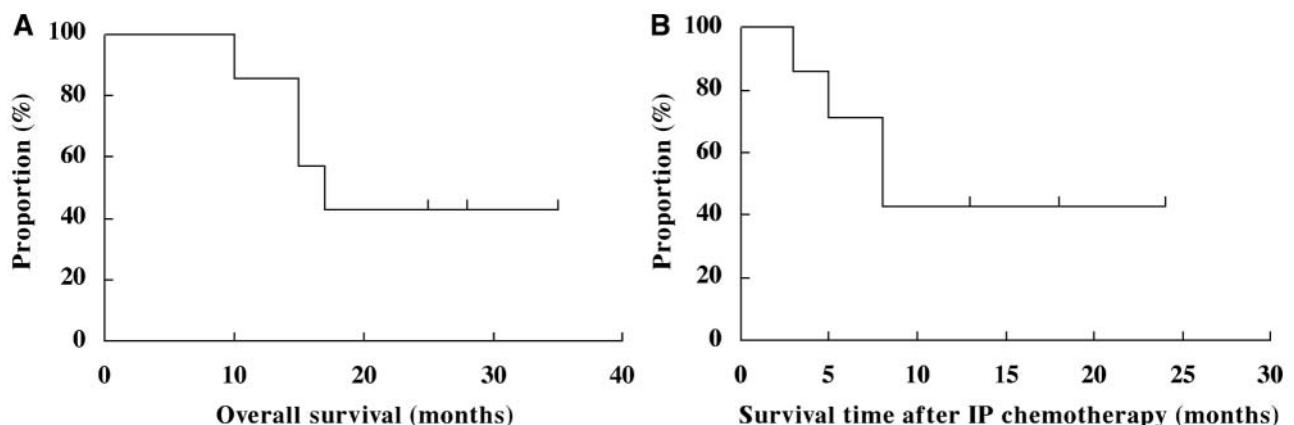


Figure 1. Survival curve of seven patients after initial ADOC (A) and after IP (B) chemotherapy by the Kaplan-Meier method.

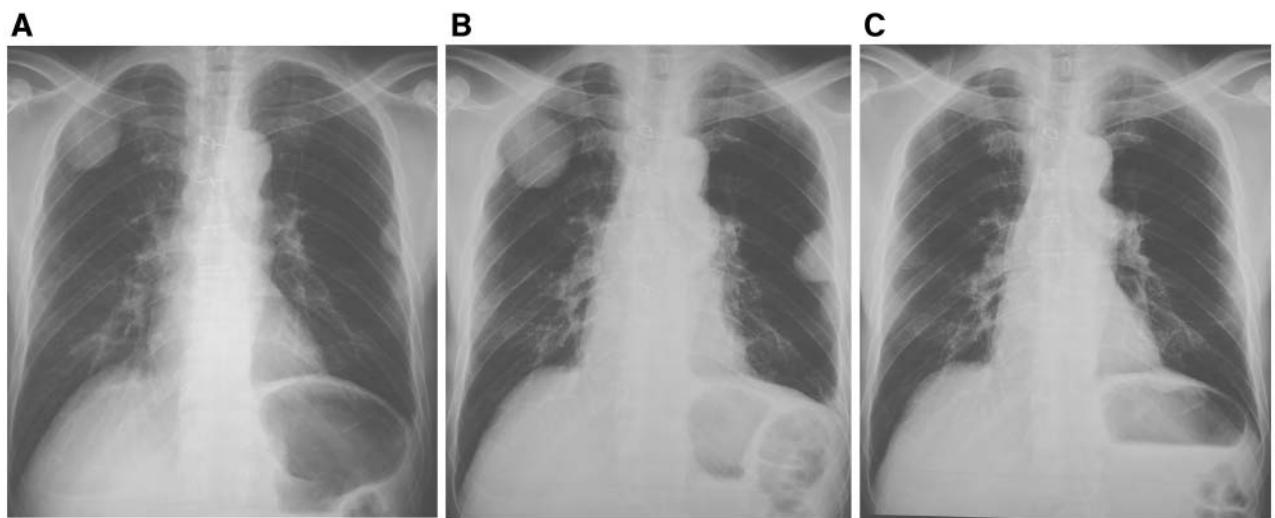


Figure 2. Radiographic findings after IP chemotherapy in patient 4. A) Recurrence after surgical resection. Bilateral extrapleural tumors were exhibited. B) After 1 course of ADOC chemotherapy. Each tumor enlarged despite chemotherapy. C) After 4 courses of IP chemotherapy. Pleural tumors diminished significantly. Four courses of IP chemotherapy induced a reduction of the pleural disseminations and symptoms such as right shoulder pain and left chest pain improved. However, new liver metastasis appeared, resulting in an evaluation of progressive disease.

IP chemotherapy was observed in three patients (patient 1, 2 and 7). Two of these were responders to ADOC chemotherapy but the disease-free intervals after ADOC chemotherapy were relatively short. The other patient who showed a good response to IP chemotherapy (patient 4) was resistant to the prior ADOC chemotherapy. Unfortunately, the evaluation of the response to IP chemotherapy was PD in that patient. However, based on the results in the present series, we think that the second-line chemotherapy with IP is moderately sensitive in patients with relapsed and/or resistant thymic carcinoma.

A limitation in the present study is that we did not evaluate whether the patients who relapsed after ADOC were actually resistant to the previously used agents. Thus, the potential lack of cross-resistance between irinotecan and the other agents previously used remains unknown. However, patients with SD in response to ADOC chemotherapy failed to respond to subsequent IP, and patients who relapsed after a relatively long interval following PR to prior ADOC did not have a favorable response to IP chemotherapy.

The overall survival period in the present study ranged from 10 months to 35 months, with a median survival period of 17 months. The estimated 1- and 2-year survival rates were 85.7% and 42.8%, respectively. These survivals might be longer than that reported by Yoh *et al.*, (7).

Although the precise role of salvage chemotherapy remains unclear in thymic carcinoma, we consider that thymic carcinoma is chemo-sensitive and that beneficial salvage chemotherapy may contribute to better outcomes in certain patients. A definitive recommendation cannot yet be made regarding the efficacy of IP as second-line chemotherapy in patients with advanced thymic carcinoma. However, our observation suggested that CPT-11 should be added as a useful agent for thymic carcinoma.

In summary, we would like to emphasize that thymic carcinoma is a chemotherapy-sensitive tumor. Although the number of patients in the present study is very small, our treatment experiences with second-line chemotherapies for thymic cancer following ADOC chemotherapy suggest that CPT-11 may be a novel and alternative agent for advanced thymic carcinoma.

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Received March 28, 2007

Revised June 5, 2007

Accepted June 12, 2007