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Lung Cancer

Clinical Outcomes of Second-Line Chemotherapy in Patients with Previously Treated Advanced Thymic Carcinoma: A Retrospective Analysis of 191 Patients from the NEJ023 Study

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Thymic carcinoma • Second-line chemotherapy • S-1 • Platinum-based doublet chemotherapy

Abstract

Background. Owing to the rarity of this tumor, there is limited information about second-line chemotherapy for patients with previously treated advanced thymic carcinoma.

Material and Methods. We performed a multi-institutional, retrospective study named NEJ023 for patients with advanced thymic carcinoma. Patients without indications for curative treatment were treated with chemotherapy from 1995 to 2014 at 40 institutions in the North East Japan Study Group. Demographic and clinicopathologic characteristics, data on treatment methods, and outcomes of second-line chemotherapy were obtained from medical records.

Results. In total, 191 patients were enrolled in this study. Second-line chemotherapy included platinum-based doublets in 57.6% of patients, other multidrug chemotherapy (e.g., cisplatin, doxorubicin, vincristine, and cyclophosphamide) in 13.6%, and monotherapy in 28.8%. The median follow-up time was 50.5 months, and the median overall survival (OS) from the start of second-line chemotherapy was 22.4 (95% confidence interval, 17.5-26.7) months. The average response rate (RR) was 20.0% overall; it was 21.6% for patients treated with platinum-based doublet chemotherapy, 13.6% for those treated with other multidrug chemotherapy, and 19.6% for those treated with single agent chemotherapy. There was no significant difference in OS between platinum-based doublet chemotherapy, other multidrug chemotherapy, and monotherapy (the median OS was 22.4, 25.7, and 21.4 months, respectively).

Conclusion. The median OS was 22.4 months in patients with advanced thymic carcinoma treated with second-line chemotherapy. There were no significant differences in RR and OS between monotherapy and multidrug chemotherapy in this study. ***The Oncologist*** 2020;25:e684–e690

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Implications for Practice: Owing to the rarity of this tumor, there is limited information about second-line chemotherapy for patients with previously treated advanced thymic carcinoma. This is the largest data for those patients treated with second-line chemotherapy. This study suggests there is no significant difference in efficacy between monotherapy and multidrug chemotherapy for previously treated advanced thymic carcinoma. This result can support the adequacy to select monotherapy as treatment of those patients.

Introduction

Thymic carcinoma is a rare epithelial neoplasm with malignant cytologic features. It accounts for approximately 5%-36% of thymic epithelial tumors [1–3]. Thymic carcinoma is highly progressive and tends to metastasize and invade surrounding tissues more frequently than does thymoma [4]. The prognosis of patients with thymic carcinoma is poor, with a 5-year survival rate of only 30%–50% [5, 6].

Approximately half of patients with thymic carcinoma have advanced-stage disease at initial diagnosis [5–7]. Patients with advanced thymic carcinoma are usually treated with palliative chemotherapy or supportive care; however, there is little evidence in support of chemotherapy because of the rarity of this tumor. Furthermore, there are very few reports about second-line chemotherapy for patients with previously treated advanced thymic carcinoma, and these are all from retrospective studies with small sample sizes (Table 1) [8–21]. Owing to the limited number of studies performed, it is difficult to select a chemotherapy regimen for these patients in clinical practice.

This study aimed to evaluate the efficacy of second-line chemotherapy for patients with previously treated advanced thymic carcinoma and to identify promising chemotherapeutic regimens for clinical practice and further clinical investigation. This study was registered with the University Hospital Medical Information Network Clinical Trials Registry (identifier: UMIN000015649).

Materials and Methods

Study Cohort

Details of the study design and results regarding the efficacy of first-line chemotherapy in patients with advanced thymic carcinoma have been published previously [22]. In this observational multicenter study, we retrospectively reviewed the medical records of patients diagnosed and treated in Japan between April 1995 and March 2014. All institutions belonging to the North East Japan Study Group were invited to participate. Inclusion criteria for this study were (a) a histologic diagnosis of thymic carcinoma in each institution; (b) presence of advanced-stage disease without indications for curative-intent surgery or radiotherapy at diagnosis, or recurrent thymic carcinoma without indications for curative-intent treatment; and (c) treatment with palliative-intent chemotherapy.

Data Analysis

Data were initially obtained from 324 consecutive patients at 40 institutions. Thirty-seven patients who did not meet eligibility requirements and one patient for whom data were missing were excluded from this analysis. Two hundred eighty-six patients received first-line chemotherapy. Among them, 95 did not receive second-line chemotherapy. In total, 191 patients who received second-line chemotherapy and were enrolled for this analysis (supplemental online Fig. 1). The institutional review boards of all participating institutions approved the protocol of this retrospective study.

The following details were extracted from the medical records: date of diagnosis, age, sex, Eastern Cooperative Oncology Group (ECOG) performance status (PS), smoking history, Masaoka-Koga stage [23], World Health Organization (WHO) TNM stage (supplemental online Table 3) [24, 25], histology, date of death or last follow-up, regimen of second-line chemotherapy, duration of chemotherapy, and efficacy of chemotherapy. Furthermore, we collected the date of initiation and progressive disease of a part of chemotherapeutic regimens (carboplatin plus paclitaxel; cisplatin plus etoposide; carboplatin plus etoposide; cisplatin plus irinotecan; cisplatin plus docetaxel; cisplatin, doxorubicin, vincristine, and cyclophosphamide [ADOC]; cisplatin, doxorubicin, and cyclophosphamide [PAC]; S-1 monotherapy; doxetaxel monotherapy; and amrubicin monotherapy). Histologic subtypes were determined based on the 2004 WHO classification in each institution [24]. Response rate (RR) and progression-free survival (PFS) of chemotherapy was evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [26]. If the patients with no measurable lesions were determined as noncomplete response and/or non-progressive disease, they were categorized to stable disease in this study.

Statistical Analysis

All categorical variables were analyzed by Fisher's exact test, as applicable. All continuous variables were analyzed using the Student *t* test. The Kaplan-Meier method was used to estimate overall survival (OS) and PFS curves. The log-rank test was used to evaluate the differences among subgroups. A p value of $<.05$ was considered statistically significant. All analyses were performed using JMP 10 for Windows statistical software (SAS Institute Japan Inc., Tokyo, Japan).

OS was defined as the period between the start of second-line chemotherapy and the date of death from any cause. PFS was defined as the period between the start of second-line chemotherapy and the development of progressive disease or death from any cause.

Results

Patient Characteristics

The clinical characteristics of the 191 patients with advanced thymic carcinoma who received second-line chemotherapy

Table 1. Previous reports for salvage chemotherapy in patients with thymic carcinoma

Author	Year	Study design	Sample size	Regimen	RR, %	mPFS, mo	mOS, mo
Gbolahan	2018	Prospective	11	PEM	9.0	2.9	9.8
Okuma	2016	Retrospective	14	S-1	42.9	8.1	30.0
Bluthgen	2016	Retrospective	15	ETP	13.0	4.0	13.0
Okuma	2015	Retrospective	11	GEM	36.4	4.3	28.5
Liang	2015	Retrospective	10	PEM	10.0	6.5	12.7
Watanabe	2015	Retrospective	13	DTX	31.0	5.5	24.0
Palmieri	2014	Prospective	8	CG	37.5	6.0	N/A
Hirai	2013	Retrospective	9	AMR	44.4	4.9	6.4
Giaccone	2009	Prospective	7	Ima	0.0	2.0	4.0
Thomas	2015	Prospective	23	Sun	26.0	7.2	N/A
Zucali	2017	Prospective	19	Eve	15.8	5.6	14.7
Giaccone	2016	Prospective	30	Pembro	24.0	36 wk	N/A
Cho	2017	Prospective	26	Pembro	23.1	6.1	N/A
Katsuya	2019	Prospective	15	Nivo	0.0	3.8	14.1

Abbreviations: AMR, amrubicine; CG, capecitabine + gemcitabine; DTX, docetaxel; ETP, etoposide; Eve; evelorimus; GEM, gemcitabine; Ima; imatinib; mOS; median overall survival; mPFS; median progression free survival; N/A, not analyzed; Nivo; nivolumab; PEM, pemetrexed; Pembro; pembrolizumab; RR; response rate; S-1, tegafur + gimeracil + oteracil; Sun; sunitinib.

are shown in Table 2. The study population consisted of 137 men and 54 women, with a median age of 60 years (range, 13–83) at the start of second-line chemotherapy. One hundred seventy-three (90.6%) patients had an ECOG PS 0 or 1. One hundred twenty-five (65.4%) patients were former or current smokers. The most frequent histologic subtype was squamous cell carcinoma (70.7%), followed by undifferentiated carcinoma (14.1%) and poorly differentiated neuroendocrine carcinoma (9.4%). Masaoka-Koga stages III, IVa, and IVb were noted in 6 (3.1%), 54 (28.3%), and 95 (48.7%) patients, and WHO TNM stages III and IV were noted in 5 (2.6%) and 150 (78.5%) patients, respectively. Thirty-six (18.8%) patients had postoperative recurrence.

Chemotherapy Regimens

The second-line chemotherapy regimens are shown in Table 3. One hundred ten (57.6%) patients received treatment with platinum-based doublets. The most popular platinum-based doublet regimen was carboplatin plus paclitaxel (60 patients), followed by cisplatin plus etoposide (7 patients) and cisplatin pus irinotecan (6 patients). Other multidrug chemotherapies were administered to 26 (13.6%) patients. Of these patients, most received ADOC (17 patients). Fifty-five (28.8%) patients received single agent chemotherapy as the second-line treatment. The most popular regimen in single agent chemotherapy was S-1 (tegafur, gimeracil, and oteracil; 18 patients), followed by docetaxel (13 patients) and amrubicin (9 patients). One hundred four patients (54.5%) were treated with third-line or higher chemotherapy. The details after third-line chemotherapy are shown in supplemental online Figure 2. The more chemotherapy the patients received, the better the survival outcome.

Efficacy of Second-Line Chemotherapy Regimens

The median follow-up period was 50.5 months (95% confidence interval [CI], 36.5-76.0 months; Kaplan-Meier estimate). The efficacy of each regimen is shown in Table 3. The RR and median PFS were 21.2% and 6.9 months for patients treated with carboplatin plus paclitaxel, 38.9% and 8.3 months for those treated with S-1 monotherapy, and 21.4% and 6.7 months for those treated with ADOC, respectively. S-1 monotherapy conferred relatively good RR and PFS; however, there were no significant differences between the RR and PFS for carboplatin plus paclitaxel (RR, $p = .149$ and PFS, $p = .060$) and ADOC (RR, $p = .285$ and PFS, $p = .231$).

The comparison of OS among platinum-based doublet chemotherapy, other multidrug chemotherapy, and monotherapy as second-line regimens is shown in Table 4 and Figure 1. After stratification based on the type of regimen, the patient characteristics were well-balanced with the exception of type of the first-line chemotherapy regimen; these are summarized in supplemental online Table 1. The median OS for platinum-based doublet chemotherapy, other multidrug chemotherapy, and monotherapy was 22.4, 25.7, and 21.4 months, respectively. There was no significant difference in OS between platinum-based doublet and other multidrug chemotherapy or monotherapy (platinum-based doublet versus other multidrug chemotherapy: hazard ratio [HR], 1.116; 95% CI, 0.667–1.789, $p = .665$; platinum-based doublet versus monotherapy: HR, 1.193; 95% CI, 0.794-1.766, $p = .389$). The results of univariate and multivariate analyses for OS are shown in supplemental online Table 4. The type of first-line chemotherapy regimen was not related to OS from start of second-line chemotherapy. In univariate analysis, sex, ECOG PS, and Masaoka-Koga stage were significantly predictive for OS. In the multivariate analysis of these factors, the prognostic factors associated with good survival were ECOG PS (0-1 vs. 2-3: HR, 0.359; 95% CI, 0.225–0.599, $p < .001$) and Masaoka-Koga stage (IVa vs. IVb: HR, 0.605; 95% CI, 0.386-0.932, $p = .022$).

Sequence of First- and Second-Line Chemotherapies

Treatment sequences of 191 patients are shown in Figure 2. In total, 114 patients were treated with platinum-based doublets

Table 2. Patient characteristics

Characteristics	*n* (%)
Age, median (range), yr	60 (13–83)
Sex, male/female	137/54 (71.7/28.3)
ECOG PS	
0	73 (38.2)
1	100 (52.4)
2	13 (6.8)
3	1 (0.5)
Unknown	4 (2.1)
Smoking status	
Never	64 (33.5)
Former or current	125 (65.4)
Unknown	2 (1.0)
Histology	
Squamous cell carcinoma	135 (70.7)
Undifferentiated carcinoma	27 (14.1)
Lymphoepithelioma-like carcinoma	1 (0.5)
Adenocarcinoma	2 (1.0)
Sarcomatoid carcinoma	1 (0.5)
Basaloid carcinoma	1 (0.5)
Papillary adenocarcinoma	1 (0.5)
Poorly differentiated neuroendocrine carcinoma	18 (9.4)
Well differentiated neuroendocrine carcinoma	5 (2.6)
Staging	
Masaoka-Koga staging	
Stage III	6 (3.1)
Stage IVa	54 (28.3)
Stage IVb	95 (49.7)
Postoperative recurrence	36 (18.8)
WHO TNM staging	
Stage III	5 (2.6)
Stage IV	150 (78.5)
Postoperative recurrence	36 (18.8)

Abbreviations: ECOG; Eastern Cooperative Oncology Group, PS; performance status, WHO; World Health Organization.

as the first-line chemotherapy, 72 with other multidrug chemotherapy, and 5 with monotherapy. Among the 114 patients who received platinum-based doublets as first-line chemotherapy, about half were treated with platinum-based doublets again, and 40 were treated with single agent chemotherapy in the second-line setting. Among the 72 patients who received other multidrug chemotherapy as the first-line therapy, about 70% were treated with platinum-based doublets as the second-line chemotherapy. The details of relationship between first and second-line chemotherapy efficacy are shown in supplemental online Table 2.

Discussion

To our knowledge, this study is the largest retrospective analysis of second-line chemotherapy for patients with advanced thymic carcinoma. The results show that there was no significant difference in OS among chemotherapeutic regimens, including platinum-based doublet and monotherapy.

Previous results from studies on second-line chemotherapy in patients with thymic carcinoma are summarized in Table 1. No comparative trial had been conducted, and the number of patients enrolled in these studies was very small. In the National Comprehensive Cancer Network guideline, several chemotherapy regimens (pemetrexed, paclitaxel, gemcitabine, etoposide, 5-FU with leucovorin, and ifosfamide) are described as candidates for second-line chemotherapy in patients with advanced thymic carcinoma. However, these regimens are not strongly recommended in this guideline, owing to limited evidence [27].

Unexpectedly, carboplatin plus paclitaxel was the most common regimen in the second-line setting in this study. Even if patients received platinum-based doublet or other multidrug chemotherapy as the first-line treatment, platinum-based doublets were often selected again as second-line chemotherapy (Fig. 2). The cause of this selection is unclear, but the lack of evidence for monotherapy for patients with thymic carcinoma may be a contributing factor. In this study, there were no significant differences in efficacy between monotherapies and platinum-based doublets used to treat previously treated advanced thymic carcinoma. However, the toxicities of platinum-based doublets, especially bone marrow suppression and gastrointestinal toxicities, are reportedly more severe than those of monotherapies [8–12, 28–30]. These data support the use of monotherapy as second-line chemotherapy for patients with previously treated advanced thymic carcinoma.

In single agent chemotherapy, the most frequently investigated chemotherapeutic regimen is S-1. S-1 is an oral fluoropyrimidine agent containing the 5-fluorouracil prodrug tegafur and two enzyme inhibitors, namely, 5-chloro-2, 4-dihydroxypyridine and potassium oxonate, which can reduce the adverse effects of tegafur. This regimen conferred a relatively good RR and PFS in our study. Similarly, several previous reports support the efficacy of S-1 [9, 31]. Currently, a prospective phase II trial to evaluate the efficacy of S-1 for patients with previously treated advanced thymic carcinoma is ongoing (UMIN000010736). It has been demonstrated that the anticancer activity of S-1 is related to the intratumoral expression of dihydropyrimidine dehydrogenase and thymidylate synthase in advanced gastric cancer [32]. The combination of a relatively low expression of thymidylate synthase and high expression of orotate phosphoribosyltransferase suggests a better antitumor effect of 5-FU drugs in thymic carcinoma than in lung carcinoma [33]. Immunohistological examination of these enzymes in thymic cancer may be helpful in elucidating the pharmacological mechanisms of S-1 action. Furthermore, docetaxel and amrubicin were selected as monotherapy regimens in this study but showed poor efficacy. However, previous reports showed promising effects of these regimens for previously treated thymic carcinoma [11, 12]. Larger studies to evaluate efficacy of single agent chemotherapy for these patients are warranted.

Recently, several new treatment strategies for thymic carcinoma have been evaluated, including molecular targeted

Table 3. Regimens and efficacy of second-line chemotherapy

Regimen	Patients, *n*	RR, %	mPFS, mo	MST, mo
CBDCA+PTX	60	21.2	6.9	25.3
S-1	18	38.9	8.3	21.4
ADOC	17	21.4	6.7	17.8
DTX	13	0.0	2.3	21.7
AMR	9	14.3	2.9	40.4
GEM	8	28.6	N/A	31.8
CDDP+VP-16	7	33.3	7.8	14.4
CDDP+CPT-11	6	33.3	6.9	45.9
Other platinum doublet	37	21.2	N/A	20.8
Other multidrug chemotherapy	9	0.0	N/A	30.2
Other monotherapy	7	15.4	N/A	16.8
All regimens	191	20.0	N/A	22.4

Breakdown of other platinum doublet: carboplatin and amrubicin (*n* = 4), carboplatin and irinotecan (*n* = 4), carboplatin and docetaxel (*n* = 3), carboplatin and gemcitabine (*n* = 6), carboplatin and S-1 (*n* = 2), carboplatin and vinorelbine (*n* = 1), carboplatin and etopocide (*n* = 4), cisplatin and amrubicin (*n* = 1), cisplatin and docetaxel (*n* = 2), cisplatin and gemcitabine (*n* = 2), cisplatin and vinorelbine (*n* = 2), nedaplatin and gemcitabine (*n* = 4), nedaplatin and etopocide (*n* = 2); other multidrug chemotherapy: gemcitabine and docetaxel (*n* = 1), cisplatin, doxorubicin, and cyclophosphamide (*n* = 2), carboplatin, doxorubicin, and cyclophosphamide (*n* = 2), paclitaxel and gemcitabine (*n* = 1), S-1 and irinotecan (*n* = 1), epirubicin, dacarbazine, and S-1 (*n* = 1), folinic acid, fluorouracil, and oxaliplatin (*n* = 1); other monotherapy: carboplatin (*n* = 1), irinotecan (*n* = 1), gefitinib (*n* = 1), imatinib (*n* = 1), pemetrexed (*n* = 1), paclitaxel (*n* = 1), vinorelbine (*n* = 1).
Abbreviations: ADOC, adriamycin + cisplatin + vincristine + cyclophosphamide; AMR, amrubicin; CBDCA, carboplatin; CDDP, cisplatin; CPT-11, irinotecan; DTX, docetaxel; GEM, gemcitabine; mOS, median overall survival; mPFS, median progression free survival; N/A, not analyzed; PTX, paclitaxel; RR, response rate; S-1, tegafur + gimeracil + oteracil; VP-16, etopocide.

Table 4. Comparison of efficacies between types of chemotherapy regimen

Regimen	Patients, *n*	RR, %	MST (95%CI), mo	HR (95% CI)	*p* value
Platinum doublets	110	21.6	22.4 (16.1–28.4)	1.00	
Other multidrug chemotherapy	26	13.6	25.7 (11.5–37.0)	1.116 (0.667–1.789)	.665
Monotherapy	55	19.6	21.4 (13.5–31.8)	1.193 (0.794–1.766)	.389
All regimens	191	20.0	22.4 (17.5–26.7)		

Abbreviations: CI, confidential interval; HR, hazard ratio; MST, median survival time; RR, response rate.

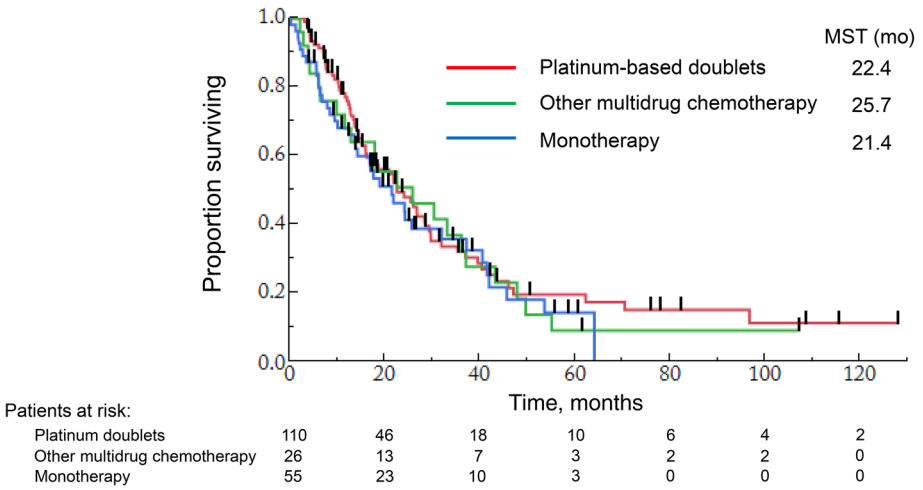

Figure 1. Overall survival in patients treated with each second-line regimens.
Abbreviation: MST, median survival time.

agents. Specifically, sunitinib and everolimus have been reported to have promising efficacies in thymic carcinoma. Sunitinib is a multikinase inhibitor that inhibits c-Kit and platelet-derived growth factor, and everolimus is a rapamycin analog that inhibits mammalian target of rapamycin. The RR and PFS for thymic carcinoma were 26% and 7.2 months with

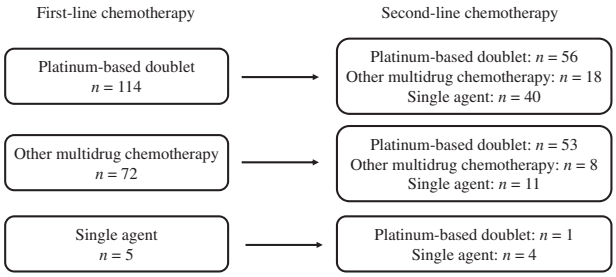

Figure 2. Sequence of first and second-line chemotherapies.

sunitinib [17] and 25% and 12.1 months with everolimus [18], respectively. Another new strategy is immunotherapy. Pembrolizumab is a humanized, monoclonal antibody designed to bind to programmed cell death 1 (PD-1) and block the interaction between PD-1 and its ligands. The RR and PFS of pembrolizumab were 19.2%–22.5% and 4.2–6.1 months, respectively, in patients with previously treated advanced thymic carcinoma [19, 20]. These results are certainly promising; However, the cost of these agents differs. Molecular targeted agents and immunotherapies are more expensive than cytotoxic chemotherapy agents. In Japan, the treatment costs for a 6-week course of sunitinib, everolimus, and pembrolizumab are 838,000 yen (approximately $7,800), 874,000 yen (approximately $8,100), and 1,458,000 yen (approximately $13,500), respectively. However, the cost for a 6-week course of S-1 monotherapy in 87,900 yen (approximately $818). In addition, no comparative studies and limited biomarker analysis has been conducted following these new treatments. Therefore, there are not enough data currently available to select an appropriate treatment for each patient. Further evaluations of new treatments are warranted, including cost-benefit analyses and measurement of disease biomarkers.

There were several limitations to our study. First, this was a retrospective study. However, thymic carcinoma is a very rare disease, making it difficult to perform a prospective study, especially in the second-line setting. To our knowledge, the sample size of our study is by far the largest among retrospective studies for second-line chemotherapy of advanced thymic carcinoma. It is hoped that based on our study, an appropriate prospective study would be conducted in the future. Second, pathological reviews of samples were only conducted in each institution. Therefore, there may be some variability in pathological diagnosis due to difficulties in the pathological diagnosis for thymic epithelial tumors. The lack of a central pathology review is a weakness of this study. Further studies should include a central pathological review to evaluate the accuracy of diagnosis across institutions.

Conclusion

The second-line chemotherapy regimens for advanced thymic carcinoma were platinum doublets in 57.6% of patients, monotherapy in 28.8%, and other multidrug chemotherapy in 13.6%. The median OS was 22.4 months in patients with advanced thymic carcinoma treated with second-line chemotherapy. There were no significant differences in RR and OS between monotherapy and multidrug chemotherapy in this study.

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Disclosures

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