Original Article

Efficacy and safety of immune checkpoint inhibitors (ICIs) combined with antiangiogenic therapy for thymic epithelial tumors (TETs): a retrospective study

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Background: Immune checkpoint inhibitors (ICIs) combined with antiangiogenic therapy have shown promising antitumor activity against a range of advanced cancers. However, evidence is lacking as to whether this combination therapy could benefit thymic epithelial tumors (TETs). We aimed to explore the efficacy and safety of this combination therapy in advanced TETs.

Methods: Ten patients with pathologically proven advanced TETs who received ICIs combined with an antiangiogenic agent from 2020 to 2022 at Zhejiang Cancer Hospital were included in the study. The Kaplan-Meier method was used to compare the treatment efficacy and survival outcomes.

Results: Of the cohort of ten patients who received immunotherapy combined with antiangiogenic targeting drugs, two patients achieved a partial response (PR) with an objective response rate of 20% and seven patients achieved stable disease (SD) with a disease control rate (DCR) of 90%. The median progression-free survival (PFS) was 6.7 months [95% confidence interval (CI): 3.35–8.515] and the median overall survival (OS) was 45.6 months (95% CI: 3.265–88.001). Grade 3 treatment-related adverse events (TRAEs) were only detected in one patient. No grade 4 or above TRAEs were observed.

Conclusions: ICIs in combination with antiangiogenic targeted drugs may be a promising treatment for advanced TETs.

Keywords: Thymic epithelial tumors (TETs); antiangiogenic targeted drugs; immunotherapy; combination therapy; efficacy

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Introduction

Thymic epithelial tumors (TETs), which include thymomas (Tm) and thymic carcinomas (TC), are formed from thymic epithelial cells. According to the RARECARE project description, TETs are a type of rare malignancy in adults, with an annual incidence of 0.13 to 0.32 per 100,000 people (1). Patients with thymoma often present with autoimmune paraneoplastic syndromes, such as myasthenia gravis and pure red cell aplastic anemia. TC are more aggressive than Tm and are often diagnosed as stage IV (2).

For individuals with thymic malignancies, surgical resection is the best treatment option and the prognosis following surgery is generally good (3). After progression, however, the therapeutic options for advanced patients who have undergone first-line chemotherapy are limited. According to a number of clinical studies, immunotherapy targeting programmed death 1 (PD-1) or programmed death-ligand 1 (PD-L1) has exhibited moderate clinical effectiveness against TETs, but has been linked to severe immune toxicity, notably in Tm patients (4,5). Other therapeutic strategies, such as anti-angiogenesis therapy, present clinical benefits in the case of TETs (6-8). To improve treatment outcomes, immune checkpoint inhibitors (ICIs) coupled with antiangiogenic therapy have been examined in a wide range of advanced malignancies, and have presented encouraging anticancer efficacy (9-11). However, current research is lacking on the safety and efficacy of this combination of drugs against TETs.

Highlight box

Key findings

- Immune checkpoint inhibitors (ICIs) with antiangiogenic therapy show considerable potential as a treatment option for thymic epithelial tumors (TETs).

What is known and what is new?

- ICIs combined with antiangiogenic therapy have shown marked efficacy against a range of advanced cancers. However, evidence is lacking as to whether this combination therapy could benefit TETs.
- The combination therapy yielded a median progression-free survival (PFS) of 6.7 months and a median overall survival (OS) of 45.6 months.

What is the implication, and what should change now?

- ICIs combined with antiangiogenic therapy may be employed as a treatment option for TETs. Further large-scale studies would be done to confirm whether or not the combination therapy is the best approach.

Here, we retrospectively assessed the safety and efficacy of ICIs combined with antiangiogenic targeting agents as a chemotherapy-free regimen against TETs in a real-world setting. We present the following article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2192/rc).

Methods

Patients

Thymic tumor patients who received ICIs combined with an antiangiogenic regimen in Zhejiang Cancer Hospital from April 2020 to May 2022 were included in our retrospective study. The main eligibility criteria for patients were: (I) aged 18 years or older, (II) histologically confirmed Tm or TC of clinical stage IV, and (III) an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1. The main exclusion criterion was prior immune or antiangiogenic treatment. Clinical information for each of the patients, such as sex, age, smoking history, the ECOG PS, tumor histology, Masaoka stage, surgery history, prior lines of treatment, and sites of metastases, was retrieved from electronic medical records. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Ethics Committee at Zhejiang Cancer Hospital (No. IRB-2022-63) and individual consent for this retrospective analysis was waived.

Efficacy and safety

Data were collected from enrolled patients during disease progression. All patients were administered drug doses according to the National Comprehensive Cancer Network (NCCN) guidelines or clinical trials. Patients received treatment every two or three weeks with apatinib (250 mg) or anlotinib (12 mg) in combination with sintilimab (200 mg), nivolumab (3 mg/kg), or other PD-1 inhibitors until disease progression or unacceptable toxicity levels were observed. In a variety of contexts, including normal clinical care, extended access, and compassionate use programs, all enrolled patients received ICIs in conjunction with antiangiogenic targeted drugs.

Response Evaluation Criteria in Solid Tumors (RECIST,1.1) was used to assess the tumor response. The objective response rate (ORR) is the rate of the complete response (CR) plus the partial response (PR). The disease

Table 1 Baseline characteristics of patients with thymic epithelial tumors

Characteristic	Values
Gender, n [%]	
Male	2 [20]
Female	8 [80]
Age (years)	
Median (range)	49 (34–72)
≥60, n [%]	2 [20]
<60, n [%]	8 [80]
Smoking history, n [%]	
Current/former	2 [20]
Never	8 [80]
ECOG PS, n [%]	
0	4 [40]
1	6 [60]
Histology, n [%]	
Thymic carcinoma	8 [80]
Thymoma	2 [20]
Masaoka's stage, n [%]	
IVa	2 [20]
IVb	8 [80]
History of surgery, n [%]	
Yes	3 [30]
No	7 [70]
Number of prior therapy lines, n [%]	
First-line	1 [10]
≥second-line	9 [90]

ECOG PS, Eastern Cooperative Oncology Group performance status.

control rate (DCR) is the rate of ORR plus the stable response (SD). The period from the first administration of combination therapy to progressive disease (PD), death, or the initiation of other therapeutics was defined as progression-free survival (PFS). Overall survival (OS) was defined as the period from the initial diagnosis of advanced disease to death or the last follow-up. In the safety analysis, adverse events (AEs) were assessed using the U.S. National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

Statistical analysis

Clinical data were analyzed using descriptive statistical methods. The median PFS and OS were determined by the Kaplan-Meier method and compared using the log-rank test, for both the total and subgroup values. We used SPSS version 25.0 and GraphPad prism version 9.0 to assess all of the statistical data. A P value of 0.05 was considered to indicate statistical significance.

Results

Patient characteristics

We collected data for ten advanced Tm and TC patients who were undergoing, or had received, combination therapy with PD-1/PD-L1 inhibitors and an antiangiogenic regimen at Zhejiang Cancer Hospital. The majority of these patients were female (80%), with an ECOG PS of 1 (60%). The median age of the patients was 49 (range, 34–72). Two Tm and eight TC patients were included in the group, and the TC patients included five cases of squamous cell carcinoma, two cases of poorly differentiated carcinoma and one case of sarcomatoid carcinoma. The Masaoka stage was IVb (80% of patients) or stage IVa (20% of patients). Of the patients, 70% had not undergone surgery before receiving the combination therapy. Only one patient who received the combination regimen as the first-line setting, while the others received it as a multi-line setting. *Tables 1,2* show the patient characteristics at baseline.

Treatment response and survival analysis

Among the ten patients analyzed, none achieved a CR, two achieved a PR, seven achieved SD and one achieved PD. The ORR and DCR were 20% and 90%, respectively. At the cutoff date, seven patients showed disease progression and four had died. Treatment with ICI and antiangiogenic drug combined therapy yielded a median PFS of 6.7 months [95% confidence interval (CI): 3.35–8.515, *Figure 1A*] and a median OS of 45.6 months (95% CI: 3.265–88.001, *Figure 1B*). Patients who received first- or second-line treatment had a longer median PFS and OS compared with those receiving third-line treatment or more; however, the P values were not significant (PFS: 10.32 *vs.* 6.68 months, P=0.67; OS: 56.47 *vs.* 45.63 months, P=0.12). No significant

Table 2 Individual patient characteristics and their best tumor responses

Patient number	Gender/age (years)	Smoking	Surgery	Histology	Stage	Metastatic site	Agent of combination strategy	Lines of therapy	Best tumor response
1	Female/34	No	No	Squamous cell carcinoma	IVa	Pleura	PD-1 + apatinib/ anlotinib	2	SD
2	Female/50	No	No	Squamous cell carcinoma	IVb	Liver	PD-1 + apatinib	2	SD
3	Female/47	No	Yes	Type AB thymoma	IVa	Pleura	PD-1 + apatinib	1	PR
4	Female/35	No	No	Poorly differentiated carcinoma	IVb	Liver, bone	PD-1 + apatinib	3	SD
5	Female/60	No	No	Poorly differentiated carcinoma	IVb	Pleura, lung	PD-1 + apatinib	4	PR
6	Male/47	Yes	Yes	Sarcomatoid carcinoma	IVb	Pleura, bone	PD-1 + anlotinib	2	SD
7	Female/49	No	No	Thymoma	IVb	Bone	PD-1 + apatinib	3	SD
8	Female/53	No	No	Squamous cell carcinoma	IVb	Lung, liver	PD-1+ lenvatinib	5	SD
9	Male/72	Yes	No	Squamous cell carcinoma	IVb	Liver	PD-1 + anlotinib	4	SD
10	Female/49	No	Yes	Squamous cell carcinoma	IVb	Lung, liver, bone	PD-L1 + anlotinib	4	PD

PD-1, programmed death 1; SD, stable response; PR, partial response; PD-L1, programmed death-ligand 1; PD, progressive disease.

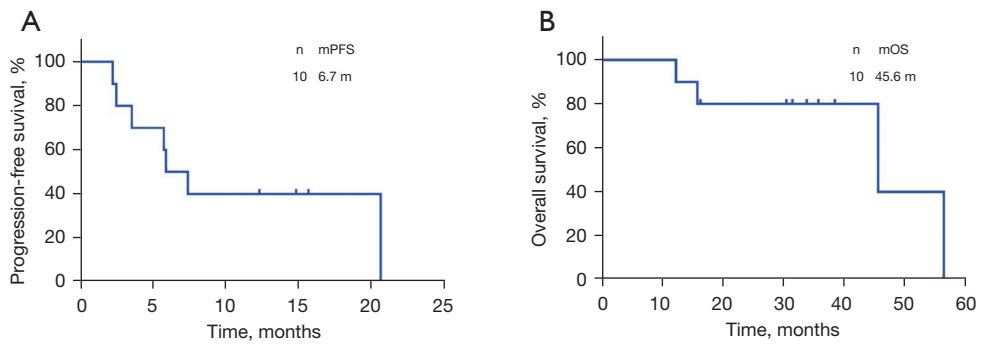

Figure 1 Kaplan-Meier curves for PFS and OS for the enrolled patients. mPFS, median progression-free survival; mOS, median overall survival.

correlation was observed between PFS and sex (P=0.45), tumor histology (P=0.97), Masaoka stage (P=0.97), or surgery history (P=0.19). *Figure 2* depicts the swimming plot for PFS.

Safety and tolerability

Table 3 presents the AEs that occurred during combination therapy. Treatment-related adverse events (TRAEs) occurred in 80% (8/10) of patients in this study and most were of grade 1–2. Proteinuria (40%) and an increase in glutamyl transpeptidase (GGT) (30%) were the most frequent AEs, followed by decreased appetite, fatigue, rash, hand-foot syndrome, and hypertension, which each occurred in 20% of patients (2/10). No grade 3 or higher AEs were observed, except for one patient receiving anti-

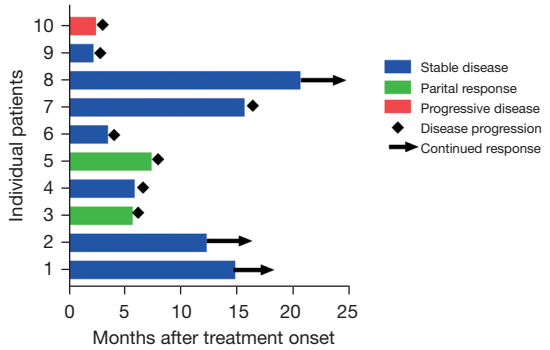

Figure 2 The swimming plot for PFS. PFS, progression-free survival.

Table 3 Treatment-related AEs in all patients who received combination therapy of PD-1 inhibitors and antiangiogenic agents

AEs	Grade 1, n [%]	Grade 2, n [%]	Grade 3, n [%]
General disorders			
Decreased appetite	1 [10]	1 [10]	
Fatigue	2 [20]		
Headache	1 [10]		
Dermatological toxicity			
Rash	1 [10]		1 [10]
Hand-foot syndrome	1 [10]	1 [10]	
Hematological toxicity			
Thrombocytopenia	1 [10]		
Leukopenia	1 [10]		
Gastrointestinal toxicity			
Diarrhea	1 [10]		
Endocrine toxicity			
Hypothyroidism		1 [10]	
Renal toxicity			
Proteinuria	2 [20]	2 [20]	
Hypertension	1 [10]	1 [10]	
Hepatotoxicity			
GGT increased	3 [30]		
AST increased	1 [10]		
ALT increased	1 [10]		

AEs, adverse events; PD-1, programmed death 1; GGT, glutamyl transpeptidase; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

PD-1 drugs paired with apatinib that developed a grade 3 rash. Apatinib medication was replaced with anlotinib in this patient.

Association between TRAEs and treatment outcomes

The association between TRAEs and the efficacy of combination therapy was further explored. The median PFS of patients who developed TRAEs was longer than those without TRAEs (7.43 *vs.* 2.5 months, P=0.03). Patients without TRAEs had lower median OS rates compared with those with TRAEs, although this difference was not significant (15.8 *vs.* 45.6 months, P=0.32).

Discussion

In our study, immunotherapy combined with antiangiogenic therapy achieved an ORR of 20% and a median PFS of 6.7 months. These outcomes confirmed that ICIs plus antiangiogenic agents are an effective option for the treatment of advanced TETs, especially for early-line therapy during the process of clinical management.

At present, second-line and posterior-line treatment of patients with TETs lack standard drugs, and some studies have explored immune and antiangiogenic therapeutic strategies. *Table 4* presents a summary of studies published in recent years on immunotherapy or antiangiogenic therapy for advanced TETs. According to previous studies, antiangiogenic monotherapy exhibited an ORR ranging from 6% to 40% and a median PFS ranging from 3.7 to 9.3 months in patients with TETs (6-8,12,13). A multi-center phase II clinical study by our group reported that apatinib yielded an ORR of 40%, a median PFS of 9.0 months, and an OS of 24 months among 25 patients with TETs (12). Our results were in accordance with prior studies on antiangiogenic therapy. With the development of immunotherapy, the efficacy of ICIs against advanced TETs has also been investigated. Pembrolizumab showed an ORR of 19.2% and PFS of 6.1 months in 26 patients with TC, compared with an ORR of 28.6% and PFS of 6.1 months in seven patients with Tm (4). Katsuya *et al.* reported that among fifteen TC patients in a PRIMER study, none achieved tumor shrinkage, with PFS and OS rates of 3.8 and 14.1 months, respectively (14). A multi-center retrospective study by our group found that combined immunotherapy was effective in advanced TC patients, especially those with high expression of PD-L1, with an ORR of 34.5% and

Table 4 Efficacy of different immunotherapies and anti-angiogenesis therapies in studies of patients with thymic epithelial tumors

Study regimen	Phase/clinical trial	Nation	N	Type of cancer	ORR	PFS/OS (months)
Pembrolizumab	II/NCT02607631	Korea	7	Tm	28.6	6.1/NR
			26	TC	19.2	6.1/14.5
Pembrolizumab	II/NCT02364076	USA	40	TC	22.5	4.2/24.9
Nivolumab	II/NCCH1505	Japan	15	TC	0	3.8/14.1
Avelumab	I/NCT01772004	USA	8	TETs	57	NA/NA
Sunitinib	II/NCT01621568	USA	23	TC	26	7.2/NR
			16	Tm	6	8.5/NR
	Retrospective study	France	28	TETs	22	3.7/15.4
	Part of II/NCT01621568	USA	13	TC	8	5.0/16.0
Lenvatinib	II/UMIN000026777	Japan	42	TC	38	9.3/NR
Apatinib	II/ChiCTR-ONC-17013108	China	25	TETs	40	9.0/24.0
Avelumab + axitinib	II/2017-004048-38 CAVEATT	Italy	32	TETs	34	7.5/26.6

ORR, objective response rate; PFS, progression-free survival; OS, overall survival; Tm, thymomas; NR, not reached; TC, thymic carcinomas; TETs, thymic epithelial tumors; NA, not available.

median PFS of 8.0 months (15). The proportion of patients with stage III and IVA tumors in their study (54.5%) was larger than that in our study (20%). The combination of ICIs and antiangiogenic agents has proven potential in the treatment of several types of cancer (16). The CAVEATT study was the first study to report the use of immunotherapy in combination with antiangiogenic therapy in patients with TETs. This study reported an ORR of 34% in patients with advanced type B3 Tm and TC patients treated with axitinib plus avelumab, among which 41% (13/32) patients had received pretreatment with an anti-angiogenesis drug (17). Our study, which enrolled histologically-confirmed Tm or TC advanced patients, resulted in ORR and DCR rates of 20% and 90%, respectively, with median PFS and OS values of 6.7 and 45.6 months, respectively. In addition, patients treated earlier with ICIs combined with antiangiogenic targeting agents showed a higher median PFS. The results of our study were consistent with the results of the CAVEATT study; however, the CAVEATT study did not enroll Chinese patients, and thus efficacy data for the Chinese population are lacking. Because of the small sample size in our study, larger studies in the Chinese population are needed to determine whether these patients will benefit from combination therapies. Relevant, real-world research is ongoing. In patients previously treated with B3-Tm and TC, the phase II study PECATI (NCT04710628), which is continuing to test the clinical outcomes of lenvatinib coupled with pembrolizumab, is helping to support immunotherapy strategies for TETs (18).

The toxicity found in our study was in line with that reported in other solid tumor patients treated with ICIs plus antiangiogenic therapy (9,19). Some researchers have reported a high incidence (13% to 38%) of grade 3–4 AEs in patients with TETs (20). In our study, only one patient exhibited a grade 3 TRAE, with no grade 4 or higher TRAEs observed. A previous study on TETs patients indicated that immunotherapy increased the risk of autoimmune toxicity, with AEs such as myasthenia gravis (21). However, we did not observe autoimmune toxicity in our study. Proteinuria and hypertension were the main manifestations of toxicity related to antiangiogenic therapy in our study, both of which were grade 1 or grade 2. In summary, compared with immunotherapy or antiangiogenic monotherapy, combination therapy did not significantly increase related AEs and most AEs that did occur were reversible and manageable. Interestingly, we found that patients who developed TRAEs showed better median PFS than those who did not develop TRAEs. The association between the clinical effects and TRAEs warrants further investigation.

As a retrospective analysis, retrospective bias is unavoidable. The major limitation of our study is the small sample size. Hence, future studies with larger sample sizes are needed to explore the efficacy, toxicity, and biomarkers

of this combination therapy regimen.

Conclusions

Patients with advanced TETs may receive some clinical benefit from ICIs combined with antiangiogenic targeting agents.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2192/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2192/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2192/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Ethics Committee at Zhejiang Cancer Hospital (No. IRB-2022-63) and individual consent for this retrospective analysis was waived.

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