Review Article

Narrative review of indication and management of induction therapy for thymic epithelial tumors

Hitomi Ajimizu[1#^], Yuichi Sakamori[2#^]

[1]Department of Respiratory Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan; [2]Department of Respiratory Medicine, Japanese Red Cross Society Wakayama Medical Center, Wakayama, Japan

Contributions: (I) Conception and design: Both authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: Both authors; (V) Data analysis and interpretation: Both authors; (VI) Manuscript writing: Both authors; (VII) Final approval of manuscript: Both authors.

[#]These authors contributed equally to this work.

Correspondence to: Yuichi Sakamori, MD, PhD. Department of Respiratory Medicine, Japanese Red Cross Society Wakayama Medical Center, 4-20 Komatsubara-dori, Wakayama 640-8558, Japan. Email: u1sakemori@gmail.com.

Background and Objective: Thymic epithelial tumors (TETs) are rare and originate from the thymus. Thymomas and thymic carcinomas are the most common types of TETs. Of the two, thymomas tend to have a better prognosis and are typically localized, while thymic carcinomas have a worse prognosis and are more likely to spread. The Masaoka-Koga staging system is commonly used to determine the stage of TETs. Complete resection is the preferred treatment option, but treating locally advanced TETs can be challenging due to the invasion of surrounding structures. In such cases, induction therapy is administered to downstage the tumors and enable complete resection. We conducted this narrative review to evaluate the current progress in induction treatment for locally advanced TETs.

Methods: The literature search was performed using PubMed and Web of Science in June 2023. Prospective and retrospective published trials, systemic and narrative reviews, and meta-analyses were included.

Key Content and Findings: Induction chemotherapy is often used as a preoperative treatment for advanced TETs. Platinum and anthracycline-based chemotherapy regimens are commonly used for treating thymoma (response rate, 37–100%), and complete resection is highly common. Treatment with cisplatin and etoposide, carboplatin and paclitaxel, docetaxel and cisplatin have also demonstrated effectiveness, particularly in patients with thymic carcinoma or thymoma who cannot tolerate anthracycline regimens. The emergence of immunotherapy and targeted therapies may provide additional options for the treatment of TETs. Induction radiotherapy, as the sole treatment for TETs, is not widely practiced due to concerns about potential damage to surrounding tissues. However, combining modern radiation techniques with surgery has shown promising results in selected patients. Induction chemoradiotherapy, which combines chemotherapy and radiation, is an emerging approach for treating TETs. Despite the lack of randomized trials comparing chemotherapy with chemoradiotherapy, concurrent chemoradiation with radiation doses of 40–50 Gy is often considered the optimal induction therapy for thymic carcinoma patients or in more advanced special situations, such as great vessel invasion.

Conclusions: Overall, the optimal treatment for locally advanced TETs remains controversial. Induction therapy, including chemotherapy, radiotherapy, or chemoradiotherapy, is administered to downstage tumors and improve resectability. The choice of treatment depends on individual factors such as tumor stage, histology, and overall patient condition. However, further research and well-designed studies are needed to determine the most effective treatment strategies for locally advanced TETs.

^ ORCID: Hitomi Ajimizu, 0000-0001-6625-7464; Yuichi Sakamori, 0000-0001-6421-7266.

Keywords: Thymic epithelial tumors (TETs); locally advanced; induction therapy; chemotherapy; chemoradiotherapy

Received: 08 December 2023; Accepted: 01 March 2024; Published online: 31 May 2024.
doi: 10.21037/med-23-30
View this article at: https://dx.doi.org/10.21037/med-23-30

Introduction

Background

Thymic epithelial tumors (TETs) are rare tumors originating from the epithelial cells of the thymus and include thymomas, and thymic carcinomas (TCs). The annual incidence of TETs ranges from 1.3 to 3.2 persons per million per year, with similar rates in both sexes, and the average age at diagnosis is 50–60 years. Thymoma is the most common primary tumor of the anterior mediastinum, yet it is rare, with an incidence of 0.2 to 0.5 cases per million people per year. On the other hand, TC is extremely rare (1). Thymomas exhibit slow behavior and present as localized disease, but they have the potential for intrathoracic and extrathoracic metastasis. In contrast, patients with TC have a worse disease course and histology than patients with thymoma and a higher rate of nodal and systemic metastasis (2).

The World Health Organization (WHO) histological classification system is used to distinguish between thymomas, TCs, and thymic carcinoids and to distinguish between different histological types of thymomas (i.e., A, AB, B1, B2, and B3). Revised in 2021, this classification system categorizes TCs into the following larger subtype groups: squamous, adenocarcinomas, adenosquamous, and carcinomas not otherwise specified. Histology plays an important role in disease biology because poor differentiation is correlated with shorter disease-free survival and overall survival (OS) (3).

The Masaoka-Koga staging system has been widely accepted for the management and determination of the prognosis of thymomas and TCs (4). Patients with stages I, II, and III thymomas have 5-year survival rates of 100%, 98%, and 85%, respectively. On the other hand, patients diagnosed with stage IVa or IVb thymoma exhibit 5-year survival rates of 55% and 77%, respectively (4). The chances of survival for patients with TC vary based on the stage of diagnosis: the higher the Masaoka stage is, the lower the OS rate. Patients with stage IVb disease have a 5-year OS of only 17%, whereas those with stage I disease have a 5-year OS of 100%, demonstrating a statistically significant difference (P<0.001) (5). To achieve a positive prognosis, thorough removal of tumors is crucial, especially in patients with advanced stage III or IV tumors (6,7). Unfortunately, a considerable proportion of these tumors fall under the Masaoka-Koga III–IVa category, which indicates that R0 resection is difficult owing to extensive spread of the disease in the surrounding area. In stage III tumors, mediastinal and intrathoracic structures, including the pericardium, heart, major blood vessels, and lungs, are invaded. In stage IVa tumors, there are pleural and/or pericardial implants as well. Therefore, for treating TETs, complete resection is essential to ensure a positive outcome (8).

It is strongly recommended in the European Society for Medical Oncology (ESMO) guidelines that complete resection be conducted and that all patients be discussed with a multidisciplinary cancer board comprising medical oncologists, radiation oncologists, and thoracic surgeons (1,9). The decision to pursue additional treatments is based on factors such as histology, stage, and degree of radicality achieved during surgery (R1 *vs.* R0) (1).

Objectives

In cases where complete removal of a tumor is not possible because of advanced-stage involvement in areas such as the lung, vessels, or heart, induction therapy may be administered to downstage the tumor and achieve clear surgical margins. This therapy can include chemotherapy, radiotherapy, or chemoradiotherapy. The best treatment for locally advanced TETs is still under debate, but recent advancements in various therapies, such as immunotherapy and targeted drugs, have shown promise. Therefore, we conducted this narrative review to evaluate the current progress in induction treatment for locally advanced TETs. We present this article in accordance with the Narrative Review reporting checklist (available at https://med.amegroups.com/article/view/10.21037/med-23-30/rc).

Table 1 Search strategy summary

Items	Specification
Date of search	5/1/2023–6/6/2023
Databases and other sources searched	PubMed, Web of Science
Search terms used	"thymic epithelial tumors", "thymoma", "thymic carcinoma", "locally advanced", "neoadjuvant", "preoperative", "chemotherapy", "radiotherapy", "chemoradiotherapy", "immunotherapy", and "target therapy"
Timeframe	Up to 2023
Inclusion and exclusion criteria	Inclusion: retrospective studies, case studies, clinical trial
	Exclusion: case report, no mention of stage of disease, no mention of clinical data, no mention of TETs treatment details
Selection process	One author compiled a list of eligible studies followed by review by the other author to determine suitability

TETs, thymic epithelial tumors.

Methods

The literature search was performed using PubMed and Web of Science in June 2023. The keywords used for the research were "thymic epithelial tumors", "thymoma", "thymic carcinoma", "locally advanced", "neoadjuvant", "preoperative", "chemotherapy", "radiotherapy", "chemoradiotherapy", "immunotherapy", and "target therapy". Prospective and retrospective published trials, systemic and narrative reviews, and meta-analyses were included. No limits regarding the years of publication were applied, and only papers written in English were accepted (*Table 1*). Sixty-two articles were selected according to the inclusion criteria and exclusion criteria from 1,091 PubMed references identified by keywords and 431 Web of Science references identified by keywords; case reports were excluded by keywords.

Results

Induction chemotherapy

Recent studies have yielded promising results regarding surgical resection after induction therapy for advanced TETs. According to a meta-analysis by Hamaji *et al.* of 12 trials involving 266 patients, the pooled rate of response to induction therapy was 59%, with a pooled rate of complete resection of 73% and pooled 5- and 10-year OS rates of 87% and 76%, respectively (10). Park *et al.* (11) investigated the efficacy of neoadjuvant chemotherapy in 1,486 patients with surgically resected thymic tumors and reported that 110 patients (7.4%) underwent surgery after neoadjuvant chemotherapy, whereas 1,376 patients (92.6%) underwent upfront surgery. Propensity score matching was used to minimize differences in preoperative and intraoperative variables, and the two groups were compared for postoperative outcomes and survival.

The matched cohort analysis did not reveal significant differences in postoperative mortality (P value not calculated), postoperative complications (P=0.405), or length of hospital stay (P=0.821) between the neoadjuvant chemotherapy and upfront surgery groups. However, compared with those in the upfront surgery group, the patients in the neoadjuvant chemotherapy group exhibited significantly greater transfusion rates (P=0.003) and longer operation times (P<0.001). The pathological complete resection rate (P=0.382) and tumor size (P=0.286) were similar between the two groups. The 5-year OS rates were 77.4% and 76.7% (P=0.596) and the 3-year recurrence-free survival rates were 62.9% and 71.5% (P=0.070) in the neoadjuvant chemotherapy and upfront surgery groups, respectively (11).

The optimal neoadjuvant therapy regimen for minimizing operative morbidity and mortality and maximizing resectability and survival has not been established. *Table 2* provides a comprehensive overview of the induction chemotherapy regimens, complete resection rates, and response rates for patients with locally advanced TETs (8,12-31). Platinum- and anthracycline-based chemotherapy are the most commonly used regimens in clinical practice, with response rates ranging from 37% to 100%. In patients for whom radical surgery (R0 resection) is feasible, a surgical approach is pursued, and complete resection is achieved in approximately 50–80% of patients. However,

Table 2 Induction chemotherapy for locally advanced thymoma and TC

Author, year	Reference	Study design	Regimen	Stage	Tumor type (No. of locally advanced pts)	Response rate (%)	No. of R0/ No. of surgery
Rea, 2011	(8)	Retrospective analysis	ADOC	III–IV	T [32]/TC [6]	68 (T)/50 (TC)	28/38 (74%)
Shin, 1998	(12)	Prospective cohort study	PAC + predonisone	III–IVa	T [12]	91	9/11 (82%)
Kim, 2004	(13)	Prospective single arm phase II trial	PAC + predonisone	III–IV	T [22]	77	16/21 (76%)
Rea, 1993	(14)	Prospective interventional study	ADOC	III–IVa	T [16]	100	11/16 (69%)
Yokoi, 2007	(15)	Prospective interventional study	CAMP	III–IV	T [14]	92	2/9 (22%)
Hassan, 2009	(16)	Prospective cohort study	PE	III–IVA	T [9]	77	5/8 (63%)
Mineo, 2010	(17)	Retrospective analysis	PE	III	T [33]	37	17/33 (52%)
Furugen, 2011	(18)	Retrospective analysis	CP	IVa–IVb	TC [16]	37	1/16
Hirai, 2015	(19)	Prospective single arm phase II trial	CP	III–IVB	TC [39]	39	NA
Lemma, 2011	(20)	Prospective single arm phase II trial	CP	III–IVb	T [21]/TC [23]	42 (T)/21 (TC)	NA
Park, 2013	(21)	Prospective single arm phase II trial	TP	III–IV	T [9]/TC [18]	55 (T)/66 (TC)	15/19 (79%)
Macchiarini, 1991	(22)	Prospective interventional study	PAE	IA-IIIA	T [7]	100	4/7 (57%)
Lucchi, 2006	(23)	Prospective interventional study	PAE	III–IVA	T [30]	73	23/30 (77%)
Venuta, 2003	(24)	Prospective interventional study	PAE	III	T [9]/TC [6]	66 (T + TC)	13/15 (87%)
Kunitoh, 2010	(25)	Prospective single arm phase II trial	CODE	III	T [23]	62	9/13 (69%)
Berruti, 1993	(26)	Prospective interventional study	ADOC	III–IVa	T [6]	83	–/5
Berruti, 1999	(27)	Prospective interventional study	ADOC	III–IVa	T [16]	81	–/9
Bretti, 2004	(28)	Prospective interventional study	ADOC or PE	III–IVa	T + TC [25]	72 (T + TC)	11/14 (79%)
Cardillo, 2010	(29)	Retrospective analysis	PAC + predonisone	III–IVa	T [21]/TC [10]	61 (T)/50 (TC) Reduction >50%	NA
Ishikawa, 2009	(30)	Retrospective analysis	CAMP	IVa–IVb	T [11]	85	5/10 (50%)
Nakamura, 2019	(31)	Retrospective analysis	CAMP	IV	T [19]	78	NA

TC, thymic carcinoma; pts, patients; ADOC, cisplatin + adriamycin + cyclophosphamide + vincristine; T, thymoma; PAC, cisplatin + doxorubicin + cyclophosphamide; CAMP, cisplatin + doxorubicin + methylprednisolone; PE, cisplatin + etoposide; CP, carboplatin + paclitaxel; NA, not available; TP, docetaxel + cisplatin; PAE, cisplatin + etoposide + epirubicin; CODE, cisplatin + adriamycin + vincristine + etoposide.

only limited data are provided by prospective randomized trials comparing chemotherapy with chemoradiotherapy in this specific setting and previous reports do not include sufficient information. In cases where there is substantial tumor shrinkage or transition from an unresectable tumor to a potentially resectable tumor occurs, extensive surgery should be offered, and postoperative radiotherapy should be considered. The most commonly prescribed platinum and anthracycline-based regimens in clinical practice are cisplatin + doxorubicin + cyclophosphamide (PAC), cisplatin + adriamycin + cyclophosphamide + vincristine (ADOC), and cisplatin + doxorubicin + methylprednisolone (CAMP). In a study by Shin *et al.*, 12 patients with unresectable stage III–IVA thymoma received three courses of PAC + prednisolone; three patients achieved a complete response, while eight achieved a partial response. Of the 11 patients

who underwent subsequent surgical intervention, nine achieved R0 resection (12). Similarly, in a study by Kim *et al.*, 22 patients with stage III–IVb invasive thymoma received three courses of PAC + prednisolone; 17 exhibited major responses (complete responses, n=3; partial responses, n=14), and 21 were surgically treated (16 achieved R0 resection) (13). In a study by Rea *et al.*, 16 patients with stage III–IVA invasive thymomas were treated with the ADOC regimen; 100% (seven complete and nine partial) of the patients achieved a response, followed by surgery, and 11 patients (68%) achieved complete resection (14). CAMP is also frequently used in clinical trials. In a study by Yokoi *et al.*, the CAMP regimen was administered to 14 patients with invasive III–IVb stage thymoma in a neoadjuvant setting; 13 (92.9%) patients achieved a good response to this regimen, and nine underwent surgical treatment, with 2 (22.2%) achieving R0 resection (15).

Among these phase II trials or retrospective studies with a small number of patients, a pattern in the use of anthracyclines emerges when comparing platinum-based and anthracycline-based combination therapy with platinum-based and non-anthracycline-based combination therapy. In combination therapy with cisplatin and etoposide, the overall response rate (ORR) in both thymoma and TC patients were 51–62% (16,17). Carboplatin and paclitaxel have also shown promising results, with an ORR of 22–36% in patients with both thymoma and TC (18-20). Park *et al.* explored the impact of induction chemotherapy using docetaxel and cisplatin (TP) (21). In nine patients with thymomas (one with stage III disease and eight with stage IVA), five (55.6%) achieved a partial response, and four achieved a complete response. Moreover, seven patients were eligible for surgery, and all patients ultimately achieved R0 resection. For patients with thymoma who cannot tolerate anthracycline combination regimens, nonanthracycline regimens such as cisplatin + etoposide (EP), carboplatin + paclitaxel, or docetaxel and cisplatin (TP) can be used.

Unlike in patients with thymoma, in patients with TC, the ORR did not significantly differ between anthracycline and nonanthracycline regimens, and the key therapy was a platinum-containing regimen. Carboplatin + paclitaxel is the preferred choice for treating locally advanced TC. Anthracycline regimens, including CAP and ADOC, are also effective, but these regimens have greater toxicity.

Overall, neoadjuvant chemotherapy has proven to be effective in prospective and retrospective studies, with most regimens being well tolerated and resulting in a reasonable response rate in patients with locally advanced tumors. Thus, all available options must be discussed with patients and their medical team to make an informed decision regarding the ideal treatment plan.

Induction radiotherapy

Radiation therapy as a preoperative treatment for locally advanced thymic tumors has attracted considerable interest and research. However, most institutions currently favor chemotherapy as the preferred induction treatment. Radiation therapy poses a considerable challenge because of the potential damage it can inflict on adjacent tissues, particularly in patients where mediastinum radiation is involved. When administering radiation to this area, it is crucial to safeguard vital organs such as the heart, lungs, and esophagus. In addition, postoperative radiation therapy is generally considered for locally advanced thymic tumors. In cases where preoperative radiation therapy is considered, the risk of additional postoperative radiation therapy should also be considered.

In several studies, scholars have investigated the use of radiation therapy alone as an induction treatment for thymic tumors. In a multi-institutional study using the European Society of Thoracic Surgeons database, only 1% of patients (12 out of 2,030) received radiation monotherapy as induction therapy (32). Similarly, a review of the International Thymic Malignancy Interest Group database showed that only 6% of TC patients (48 out of 1,042) received induction radiation as the sole treatment (2).

Ribet *et al.* described a series of 113 patients, 19 of whom received preoperative radiation (33). Within this cohort, ten patients achieved complete resection, for a 5-year OS rate of 44%. Akaogi *et al.* reported 12 patients with thymic tumors that invaded the great vessels who underwent preoperative radiation. The cohort showed a 75% rate of complete resection, and ten patients also received adjuvant radiation, resulting in 5- and 10-year OS rates of 72% and 48%, respectively (34). The findings from various radiation experiences are summarized in *Table 3*.

In summary, radiation therapy as a preoperative induction treatment for locally advanced thymic tumors is not widely practiced. Most institutions prefer chemotherapy as the primary induction therapy. Based on the literature, radiotherapy may be effective to some extent. However, these previous studies involved a small number of patients; thus, there is little evidence that this treatment is more effective than preoperative chemotherapy

Table 3 Induction radiotherapy for locally advanced thymoma and TC

Author, year	Reference	Study design	Stage	Tumor type [No. of pts]	RT dose	Response rate (%)	No. of R0/No. of surgery
Yagi, 1996	(7)	Retrospective analysis	III–IV	T [11]	20–66 Gy	NA	NA
Bretti, 2004	(28)	Prospective interventional study	III–IVA	T + TC [8]	24–30 Gy	37	1/3 (33%)
Akaogi, 1996	(34)	Retrospective analysis	III–IV	T [12]	12–21 Gy	91	9/12 (75%)

TC, thymic carcinoma; pts, patients; RT, radiation therapy; T, thymoma; R0, complete resection; NA, not available.

Table 4 Induction chemoradiotherapy for locally advanced thymoma and TC

Author, year	Reference	Study design	Regimen	Stage	Tumor type [No. of pts]	RT dose	Response rate (%)	No. of R0/ No. of surgery
Korst, 2014	(35)	Prospective single-arm phase II trial	PE	I–IV	T [13]/TC [7]/ metaplastic [1]	40–45 Gy	47 (T + TC)	17/21 (77%)
Chu, 2020	(36)	Retrospective analysis	PAC or CP (with Radiotherapy)	III–IV	T [5]/TC [3]/ other [4]	60–70 Gy	NA	NA/1
Wright, 2008	(37)	Retrospective analysis	PE	III–VA	T [9]/TC [1]	33–45 Gy	40 (T + TC)	8/10 (80%)

TC, thymic carcinoma; pts, patients; RT, radiation therapy; R0, complete resection; PE, cisplatin + etoposide; T, thymoma; PAC, cisplatin + doxorubicin + cyclophosphamide; CP, carboplatin + paclitaxel; NA, not available.

or chemoradiotherapy. It should be used only in limited circumstances, such as severe organ dysfunction, where chemotherapy cannot be administered. In cases where radiation therapy is considered, the risk of additional postoperative radiation therapy should also be considered. Further research and well-designed studies are necessary to address these challenges and determine the optimal radiation therapy for the management of locally advanced thymic tumors.

Induction chemoradiotherapy

Preoperative chemoradiotherapy has emerged as a treatment strategy for TETs to increase the chances of complete tumor removal and improve response rates compared with chemotherapy alone. However, prospective randomized trials that directly compare chemotherapy with chemoradiotherapy in TET patients are rare, leading to inconclusive data (*Table 4*) (35-37). Concurrent chemoradiotherapy with 40–50 Gy radiation is often considered the optimal induction therapy for patients with TC (38). Several studies have reported encouraging results in investigating neoadjuvant chemoradiotherapy for locally advanced TETs. Korst *et al.* reported a phase 2 trial involving patients with thymoma or TC who underwent induction therapy with a combination of two cycles of cisplatin and etoposide combined with 45 Gy of thoracic radiotherapy. After induction therapy, computed tomography (CT) and positron emission tomography (PET) were performed, followed by attempted resection. The primary goal was to assess the pathologic response to induction therapy, while secondary endpoints included toxicity, surgical complications, radiographic response, and the rate of complete resection. Of the 22 patients enrolled, 21 completed induction therapy, and nine experienced severe toxicity. A partial radiographic response was observed in ten patients, while stable disease was detected in 11 patients. Approximately 77% of the patients underwent complete resection, 36% experienced surgical complications, and two died after the procedure. Although no patient achieved a pathological complete response, 24% of the specimens had <10% viable tumors (35). Chu *et al.* reported 114 TET patients who received chemotherapy or chemoradiotherapy as initial treatment and pre- and post-treatment scans at a tertiary academic cancer center between 2007 and July 2018. Of the 114 patients, 12 patients were in the chemotherapy group (ten with thymoma, one with TC, and one with an unclassifiable thymic tumor), and 12 were in the radiation therapy group (5 with thymoma, three with TC, and four with unclassifiable thymic tumors). All patients in both groups were in stage III–IV. After a median imaging follow-up of 15 months, chemoradiation

led to a greater radiological response than chemotherapy alone (volume: –47.0 cm^3 more, P<0.001; diameter: –0.8 cm more, P=0.03). Eight patients who received chemotherapy also experienced significant tumor shrinkage with additional radiation or chemoradiation. The median survival time was significantly longer for patients who ultimately underwent surgery than for patients who did not (46 *vs.* 14 months) (36).

Wright *et al.* reported the therapeutic effect of concurrent induction chemoradiotherapy in ten patients with initially unresectable locally advanced thymic tumors (including 9 with thymomas and 1 with TC). The therapeutic protocol consisted of two cycles of EP chemotherapy with concurrent radiotherapy (33–49 Gy) before surgery. Adjuvant EP chemotherapy was administered for patients with incomplete resection and a high risk of recurrence. After completion of induction chemoradiotherapy, 4 (40%) patients achieved a partial response, while the remaining 6 (60%) patients presented no changes. All ten patients were directed toward surgery, and R0 resection was achieved in 8 (80%) patients. The examination of resected specimens revealed substantial (>90%) tumor necrosis in four (40%) patients. No postoperative deaths were observed, and the estimated 5-year survival was 69% (37).

Based on these reports, chemoradiotherapy as induction treatment for unresectable locally advanced TETs may be as effective as preoperative chemotherapy. However, there are only a few reports on the vagueness of the definition of "unresectable" and the regimen to be used. The indication for additional radiation should be carefully considered in terms of the stage and histology of the target tumor, as additional radiation may increase toxicity.

Yamada *et al.* analyzed the extracted data of a total of 310 stage III thymoma patients from the Japanese National Database. Among the thymoma tumors in these cases, 194 (62.6%) involved the lungs, 151 (48.7%) involved the pericardium, 1,236 (40.6%) involved the great vessels, and 247 (79.7%) were completely resected. The complete resection rate was significantly lower in patients with invasion of the great vessels than in the other patients (73.8% *vs.* 83.7%, respectively; P=0.011) (39). Hassan *et al.* explored the function of induction chemotherapy in nine patients with locally advanced thymoma who underwent three cycles of EP before surgery (16). In three patients (37.5%) with confirmed invasion of the great vessels, including the ascending aorta, main pulmonary artery, superior vena cava, and heart, via anterior mediastinotomy and radiology, there was incomplete resection after induction chemotherapy; extended full-thickness tumor invasion of the vessels remained during surgery, causing incomplete resection. Therefore, in TET patients with great vessel invasion, chemotherapy alone may be insufficient, while chemoradiotherapy may enhance antitumor activity and the possibility of total resection.

In summary, the use of chemoradiotherapy as a preoperative induction treatment for TETs may improve the likelihood of complete tumor removal and enhance response rates. However, further research, including prospective randomized trials, is necessary to determine the optimal treatment approach for different histological subtypes and to assess the long-term outcomes of induction chemoradiotherapy in TET patients.

Induction immunotherapy

Immunotherapy, specifically programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) immune therapy, has emerged as a revolutionary approach for the treatment of TETs. PD-L1 expression is commonly used as a predictor of PD-1/PD-L1 immune therapy efficacy, and high PD-L1 expression is associated with aggressive histological type, advanced disease stage, and worse prognosis (40-45). Padda *et al.* examined PD-L1 expression in tissue microarrays (TMAs) of TETs. TMAs were generated from 69 TETs and 17 thymic controls, and the PD-L1 scores of the epithelial cells were evaluated. A high PDL1 score was more frequent in patients with TETs than in controls (68.1% *vs.* 17.6%; P=0.0036). Histology and PD-L1 expression were significantly correlated, with higher intensity staining according to the WHO classification B2/B3/C TETs. According to an adjusted analysis (for age and sex), patients with PD-L1-high TETs had a markedly worse OS than patients with PD-L1-low TETs [hazard ratio: 5.40, 95% confidence interval (CI): 1.13–25.89; P=0.035] and had a trend toward worse event-free survival (hazard ratio: 2.94, 95% CI: 0.94–9.24; P=0.064) (46). Tumor-infiltrating lymphocytes, which are crucial for immune system activation, are abundantly present in patients with TETs (47). These factors support the potential efficacy of PD-1/PD-L1 therapy for TETs.

Several trials have explored the efficacy and safety of immunotherapy for advanced or recurrent thymomas. For example, a phase II study by Cho *et al.* evaluated the role of pembrolizumab in 26 patients with TC and seven patients with refractory thymoma and reported partial responses in two thymoma patients and 5 TC patients (48). In addition to efficacy, toxicity is also an important consideration for

Table 5 Immunotherapy for advanced thymoma and TC

Author, year	Reference	Study design	Regimen	Stage	Tumor type [No. of pts]	Response rate (%)	No. of R0/ No. of surgery
Cho, 2019	(48)	Prospective single-arm phase II trial	Pembrolizumab	IV	T [7]/TC [26]	28 (T)/19 (TC)	NA
Giaccone, 2018	(50)	Prospective single-arm phase II trial	Pembrolizumab	III–IVb	TC [40]	22	NA
Rajan, 2019	(51)	Prospective single-arm phase I trial	Avelumab	IV	T [7]/TC [1]	57 (T)/0 (TC)	NA

TC, thymic carcinoma; pts, patients; RT, radiation therapy; R0, complete resection; T, thymoma; NA, not available.

treatment. Five of seven (71.4%) patients with thymoma and four of 26 (15.4%) patients with TC reported grade 3 immune-related adverse events (irAEs), including myocarditis, hepatitis, myasthenia gravis, colitis, thyroiditis, and glomerulonephritis. Moreover, in another study, the administration of anti-PD-1 therapy resulted in a storm of irAEs (including myasthenia gravis, myositis, myocarditis, and death) after the administration of the first treatment cycle (49). Patients with TC and type B3 thymoma, characterized by mature T lymphocyte infiltration, have lower risks of irAEs during immune checkpoint inhibitor therapy. These entities should be preferred when considering the use of these agents. Pembrolizumab has been included as a possible therapeutic option for refractory TC in the National Comprehensive Cancer Network (NCCN) guidelines. However, caution is warranted when using immune checkpoint inhibitors in thymomas due to the increased risk of irAEs. Clinical trials are warranted to determine the exact role of induction immunotherapy in patients with TETs. A notable ongoing Korean phase II study (NCT03858582) is evaluating the efficacy and safety of neoadjuvant therapy with pembrolizumab plus chemotherapy (docetaxel and cisplatin) for three cycles every 3 weeks. Patients who undergo R0 resection are receiving pembrolizumab, while those who undergo R1 or R2 resection are receiving radiation therapy and pembrolizumab.

Immunotherapy studies for TETs are presented in *Table 5*. Clinical trials should be conducted to assess the exact effect of induction immunotherapy in patients with TETs. Currently, studies on the efficacy and safety of immunotherapy as a preoperative option are limited. Toxicity must be avoided during preoperative treatment, as it could hinder or delay surgery. Prospective clinical trials, including safety studies, are necessary to provide more comprehensive data on the potential benefits and risks of induction immunotherapy in patients with TETs.

Induction-targeted therapy

The advances in the research of the molecular biology of TETs have increased the number of targeted therapies in clinical trials (52). However, in the neoadjuvant setting for TETs, the use of targeted treatment is supported by limited evidence. One ongoing clinical trial is investigating the effects of combining cetuximab with traditional platinum and anthracycline-based chemotherapy as neoadjuvant therapy for locally advanced thymoma (Clinical Trials. gov NCT01025089). This phase II study was designed to evaluate the combination of cetuximab and the PAC regimen as neoadjuvant chemotherapy for locally advanced thymoma. Initially, patients receive cetuximab weekly for up to 4 weeks to evaluate the tumor response to cetuximab alone. Subsequently, the continue to receive weekly cetuximab along with concurrent PAC for four cycles before surgery. The primary endpoint of the trial is the frequency of complete pathological response, with secondary endpoints including toxicity, treatment response, and R0 resection.

The activation of the PI3K/AKT pathway in TETs (53) led to the investigation of the mammalian target of rapamycin (mTOR) inhibitor everolimus in a phase II trial, which demonstrated a median progression-free survival (PFS) of 10.1 months and OS of 25.7 months in advanced, treatment-refractory thymoma and TC (54). Although epidermal growth factor receptors are often overexpressed in TETs, activating mutations are rarely observed (55). A phase II study using gefitinib showed poor response rates in patients with chemorefractory TETs (56). *KIT* overexpression has been reported in TCs; however, under 10% of tumors harbor a *KIT* mutation, and no response has been reported with the use of imatinib to date (57). Thymic tumors exhibit insulin-like growth factor receptor overexpression (58). A phase II study of cixutumumab enrolled 49 patients (37 with thymomas and 12 with TCs) with recurrent or refractory disease, five with thymoma and

Table 6 Targeted therapy for advanced thymoma and TC

Author, year	Reference	Study design	Regimen	Stage	Tumor type [No. of pts]	Response rate (%)	No. of R0/ No. of surgery
Zucali, 2018	(54)	Prospective single-arm phase II trial	Everolimus	III–IVb	T [32]/TC [18]	9 (T)/16 (TC)	NA
Giaccone, 2009	(57)	Prospective single-arm phase II trial	Imatinib	IV*	T [2]/TC [5]	0	NA
Rajan, 2014	(59)	Prospective single-arm phase II trial	Cixutumumab	Recurrent or chemotherapy refractory	T [37]/TC [12]	14 (T)/0 (TC)	NA
Thomas, 2015	(61)	Prospective single-arm phase II trial	Sunitinib	Chemotherapy refractory	T [16]/TC [24]	6 (T)/26 (TC)	NA
Remon, 2016	(62)	Retrospective analysis	Sunitinib	III–IV	T [7]/TC [20]	28 (T)/20 (TC)	NA
Sato, 2020	(63)	Prospective single-arm phase II trial	Lenvatinib	III–IV	TC [42]	38	NA

*, not stated whether the stage classification is based on Masaoka Classification. TC, thymic carcinoma; pts, patients; RT, radiation therapy; R0, complete resection; T, thymoma; NA, not available.

a partial tumor response, 28 with stable disease, and four with progressive disease. Among the 12 TC patients who received treatment, none responded, five had stable disease, and seven had progressive disease (59).

Vascular endothelial growth factor (VEGF) and VEGF receptors have been identified as possible targets in high-risk thymomas and TCs (60), suggesting the potential use of antiangiogenic agents such as sunitinib. An open-label phase II study of sunitinib in patients with chemorefractory TETs demonstrated a partial response in 6 patients and stable disease in 15 patients among 23 TC patients. Among the 16 thymoma patients, 1 had a partial response, while 12 had stable disease (61). A retrospective review of 28 patients (20 with TCs and eight with thymomas) of sunitinib in the off-label cohort study showed a response rate of 22% and a disease control rate (DCR) of 63%, with a median PFS of 3.7 months and a median OS of 14.5 months (62). A phase II trial of lenvatinib, an oral multitargeted kinase inhibitor for VEGFR, FGFR, and c-Kit, enrolled 42 patients with advanced TC who had progressed after at least one platinum-based chemotherapy (63). The ORR was 38%, the DCR was 95%, and the median PFS was 9.3 months. Of the 42 patients, 30 (71%) had squamous cell carcinoma, and 14 out of these 30 (47%) had a partial response. Two ongoing clinical trials of lenvatinib were identified.

An open-label, single-arm phase II study will evaluate the efficacy and safety of the combination treatment of pembrolizumab and lenvatinib in pretreated type B3 thymoma or TC patients who have progressed after at least one course of platinum-based chemotherapy for advanced disease without any previous immunotherapy (previous bevacizumab allowed but not sunitinib) and who are not suitable for curative-intent radical surgery and/or radiotherapy regardless of PD-L1 status (Clinical Trials.gov NCT04710628). Another phase II, investigator-initiated, nonrandomized, open-label, single-arm, multicenter study will evaluate the efficacy and safety of carboplatin, paclitaxel, lenvatinib, and pembrolizumab in combination for previously untreated advanced or recurrent TCs that are judged to be incapable of radical resection (Clinical Trials.gov NCT05832827).

A list of the major molecularly targeted agents reported for TETs is shown in *Table 6*. Targeted therapy may be an option for heavily pretreated patients in clinical practice, and some agents have shown promising effects with tolerable side effects. However, no previous study has shown more pronounced responses compared to chemotherapy or chemoradiotherapy. However, further studies are needed to investigate the benefits of incorporating targeted therapy into preoperative chemotherapy for TETs.

Discussion

The management of locally advanced TETs remains challenging. Complete resection is crucial for improving the

prognosis of these tumors, but achieving R0 resection can be difficult due to the invasion of surrounding structures and distant metastasis. In such cases, induction therapy plays an important role in downstaging the tumor and making it amenable to surgical resection. Currently, chemotherapy is the most widely used induction therapy for locally advanced thymomas, with platinum and anthracycline-based regimens being the standard approach; for TCs, chemotherapy with either platinum and anthracycline-based regimens or carboplatin and paclitaxel is favored. Furthermore, the emergence of immunotherapy and targeted therapies may provide additional options for the treatment of TETs.

Due to concerns about potential damage to surrounding tissues, radiation therapy as the sole induction treatment for locally advanced TETs is less common. However, combining modern radiation techniques with surgery has shown promising outcomes in some cases.

Preoperative chemoradiotherapy may be an emerging approach that is intended to improve the chances of complete tumor removal compared with chemotherapy in more advanced special situations, such as severe vessel invasion.

Neoadjuvant chemotherapy or chemoradiotherapy has shown promising results in terms of response rates and complete resection rates, although there are no prospective randomized trials comparing chemotherapy with chemoradiotherapy.

There is still insufficient evidence for the use of preoperative immunotherapy and preoperative targeted therapy. Close attention should be given to the emergence of irAEs during immunotherapy.

Since TETs are rare tumors, in most studies, there is clear selection bias with a shrinking denominator. Moreover, the level of evidence is limited in most publications. A multidisciplinary approach involving thoracic surgeons, medical oncologists, radiation oncologists, radiologists, immunologists, neurologists and pathologists is crucial for the comprehensive management of patients with TETs. Treatment decisions should be individualized based on factors such as histology, stage, and the feasibility of radical surgery. Close collaboration among medical teams and informed discussions with patients are essential for determining the most appropriate treatment plan.

Conclusions

In conclusion, the use of induction treatment for locally advanced TETs is evolving, highlighted by ongoing advancements in chemical regimens, radiotherapy technologies, immunotherapy, and targeted therapies. However, further research and well-designed studies are needed to address the remaining challenges and optimize the management of these rare tumors, ultimately improving patient outcomes.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Masatsugu Hamaji) for the series "Locally Advanced Thymic Epithelial Tumors" published in *Mediastinum*. The article has undergone external peer review.

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://med.amegroups.com/article/view/10.21037/med-23-30/rc

Peer Review File: Available at https://med.amegroups.com/article/view/10.21037/med-23-30/prf

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://med.amegroups.com/article/view/10.21037/med-23-30/coif). The series "Locally Advanced Thymic Epithelial Tumors" was commissioned by the editorial office without any funding or sponsorship. Y.S. reports payment or honoraria from Chugai Pharmaceutical Co. Ltd. The authors have no other 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.

References

1. Girard N, Ruffini E, Marx A, et al. Thymic epithelial tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015;26 Suppl 5:v40-55.
2. Ahmad U, Yao X, Detterbeck F, et al. Thymic carcinoma outcomes and prognosis: results of an international analysis. J Thorac Cardiovasc Surg 2015;149:95-100, 101.e1-2.
3. Marx A, Chan JKC, Chalabreysse L, et al. The 2021 WHO Classification of Tumors of the Thymus and Mediastinum: What Is New in Thymic Epithelial, Germ Cell, and Mesenchymal Tumors? J Thorac Oncol 2022;17:200-13.
4. Masaoka A. Staging system of thymoma. J Thorac Oncol 2010;5:S304-12.
5. Litvak AM, Woo K, Hayes S, et al. Clinical characteristics and outcomes for patients with thymic carcinoma: evaluation of Masaoka staging. J Thorac Oncol 2014;9:1810-5.
6. Nakahara K, Ohno K, Hashimoto J, et al. Thymoma: results with complete resection and adjuvant postoperative irradiation in 141 consecutive patients. J Thorac Cardiovasc Surg 1988;95:1041-7.
7. Yagi K, Hirata T, Fukuse T, et al. Surgical treatment for invasive thymoma, especially when the superior vena cava is invaded. Ann Thorac Surg 1996;61:521-4.
8. Rea F, Marulli G, Di Chiara F, et al. Multidisciplinary approach for advanced stage thymic tumors: long-term outcome. Lung Cancer 2011;72:68-72.
9. Falkson CB, Vella ET, Ellis PM, et al. Surgical, Radiation, and Systemic Treatments of Patients With Thymic Epithelial Tumors: A Clinical Practice Guideline. J Thorac Oncol 2022;17:1258-75.
10. Hamaji M, Ali SO, Burt BM, et al. A meta-analysis of induction therapy for advanced thymic epithelial tumors. Ann Thorac Surg 2015;99:1848-56.
11. Park S, Park IK, Kim YT, et al. Comparison of Neoadjuvant Chemotherapy Followed by Surgery to Upfront Surgery for Thymic Malignancy. Ann Thorac Surg 2019;107:355-62.
12. Shin DM, Walsh GL, Komaki R, et al. A multidisciplinary approach to therapy for unresectable malignant thymoma. Ann Intern Med 1998;129:100-4.
13. Kim ES, Putnam JB, Komaki R, et al. Phase II study of a multidisciplinary approach with induction chemotherapy, followed by surgical resection, radiation therapy, and consolidation chemotherapy for unresectable malignant thymomas: final report. Lung Cancer 2004;44:369-79.
14. Rea F, Sartori F, Loy M, et al. Chemotherapy and operation for invasive thymoma. J Thorac Cardiovasc Surg 1993;106:543-9.
15. Yokoi K, Matsuguma H, Nakahara R, et al. Multidisciplinary treatment for advanced invasive thymoma with cisplatin, doxorubicin, and methylprednisolone. J Thorac Oncol 2007;2:73-8.
16. Hassan M, Seoud DE. Multimodality treatments in locally advanced stage thymomas. Hematol Oncol Stem Cell Ther 2009;2:340-4.
17. Mineo TC, Mineo D, Onorati I, et al. New predictors of response to neoadjuvant chemotherapy and survival for invasive thymoma: a retrospective analysis. Ann Surg Oncol 2010;17:3022-9.
18. Furugen M, Sekine I, Tsuta K, et al. Combination chemotherapy with carboplatin and paclitaxel for advanced thymic cancer. Jpn J Clin Oncol 2011;41:1013-6.
19. Hirai F, Yamanaka T, Taguchi K, et al. A multicenter phase II study of carboplatin and paclitaxel for advanced thymic carcinoma: WJOG4207L. Ann Oncol 2015;26:363-8.
20. Lemma GL, Lee JW, Aisner SC, et al. Phase II study of carboplatin and paclitaxel in advanced thymoma and thymic carcinoma. J Clin Oncol 2011;29:2060-5.
21. Park S, Ahn MJ, Ahn JS, et al. A prospective phase II trial of induction chemotherapy with docetaxel/cisplatin for Masaoka stage III/IV thymic epithelial tumors. J Thorac Oncol 2013;8:959-66.
22. Macchiarini P, Chella A, Ducci F, et al. Neoadjuvant chemotherapy, surgery, and postoperative radiation therapy for invasive thymoma. Cancer 1991;68:706-13.
23. Lucchi M, Melfi F, Dini P, et al. Neoadjuvant chemotherapy for stage III and IVA thymomas: a single-institution experience with a long follow-up. J Thorac Oncol 2006;1:308-13.
24. Venuta F, Rendina EA, Longo F, et al. Long-term outcome after multimodality treatment for stage III thymic tumors. Ann Thorac Surg 2003;76:1866-72; discussion 1872.
25. Kunitoh H, Tamura T, Shibata T, et al. A phase II trial of dose-dense chemotherapy, followed by surgical resection and/or thoracic radiotherapy, in locally advanced thymoma: report of a Japan Clinical Oncology Group trial (JCOG 9606). Br J Cancer 2010;103:6-11.
26. Berruti A, Borasio P, Roncari A, et al. Neoadjuvant chemotherapy with adriamycin, cisplatin, vincristine and cyclophosphamide (ADOC) in invasive thymomas: results in six patients. Ann Oncol 1993;4:429-31.

27. Berruti A, Borasio P, Gerbino A, et al. Primary chemotherapy with adriamycin, cisplatin, vincristine and cyclophosphamide in locally advanced thymomas: a single institution experience. Br J Cancer 1999;81:841-5.
28. Bretti S, Berruti A, Loddo C, et al. Multimodal management of stages III-IVa malignant thymoma. Lung Cancer 2004;44:69-77.
29. Cardillo G, Carleo F, Giunti R, et al. Predictors of survival in patients with locally advanced thymoma and thymic carcinoma (Masaoka stages III and IVa). Eur J Cardiothorac Surg 2010;37:819-23.
30. Ishikawa Y, Matsuguma H, Nakahara R, et al. Multimodality therapy for patients with invasive thymoma disseminated into the pleural cavity: the potential role of extrapleural pneumonectomy. Ann Thorac Surg 2009;88:952-7.
31. Nakamura S, Kawaguchi K, Fukui T, et al. Multimodality therapy for thymoma patients with pleural dissemination. Gen Thorac Cardiovasc Surg 2019;67:524-9.
32. Ruffini E, Detterbeck F, Van Raemdonck D, et al. Tumours of the thymus: a cohort study of prognostic factors from the European Society of Thoracic Surgeons database. Eur J Cardiothorac Surg 2014;46:361-8.
33. Ribet M, Voisin C, Gosselin B, Pruvot FR, Ramon P, Wallaert B, et al. [Lympho-epithelial thymoma. Anatomo-clinical and therapeutic study of 113 cases]. Rev Mal Respir. 1988;5(1):53-60.
34. Akaogi E, Ohara K, Mitsui K, et al. Preoperative radiotherapy and surgery for advanced thymoma with invasion to the great vessels. J Surg Oncol 1996;63:17-22.
35. Korst RJ, Bezjak A, Blackmon S, et al. Neoadjuvant chemoradiotherapy for locally advanced thymic tumors: a phase II, multi-institutional clinical trial. J Thorac Cardiovasc Surg 2014;147:36-44, 46.e1.
36. Chu RF, Hussien A, Li QK, et al. Radiologic response of chemotherapy alone versus radiation and chemotherapy in the treatment of locally-advanced or advanced thymic epithelial tumors. Thorac Cancer 2020;11:2924-31.
37. Wright CD, Choi NC, Wain JC, et al. Induction chemoradiotherapy followed by resection for locally advanced Masaoka stage III and IVA thymic tumors. Ann Thorac Surg 2008;85:385-9.
38. Shintani Y, Inoue M, Kawamura T, et al. Multimodality treatment for advanced thymic carcinoma: outcomes of induction therapy followed by surgical resection in 16 cases at a single institution. Gen Thorac Cardiovasc Surg 2015;63:159-63.
39. Yamada Y, Yoshino I, Nakajima J, et al. Surgical Outcomes of Patients With Stage III Thymoma in the Japanese Nationwide Database. Ann Thorac Surg 2015;100:961-7.
40. Herbst RS, Soria JC, Kowanetz M, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature 2014;515:563-7.
41. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med 2016;375:1823-33.
42. Song JS, Kim D, Kwon JH, et al. Clinicopathologic Significance and Immunogenomic Analysis of Programmed Death-Ligand 1 (PD-L1) and Programmed Death 1 (PD-1) Expression in Thymic Epithelial Tumors. Front Oncol 2019;9:1055.
43. Yokoyama S, Miyoshi H, Nishi T, et al. Clinicopathologic and Prognostic Implications of Programmed Death Ligand 1 Expression in Thymoma. Ann Thorac Surg 2016;101:1361-9.
44. Ishihara S, Okada S, Ogi H, et al. Programmed death-ligand 1 expression profiling in thymic epithelial cell tumors: Clinicopathological features and quantitative digital image analyses. Lung Cancer 2020;145:40-7.
45. Hakiri S, Fukui T, Mori S, et al. Clinicopathologic Features of Thymoma With the Expression of Programmed Death Ligand 1. Ann Thorac Surg 2019;107:418-24.
46. Padda SK, Riess JW, Schwartz EJ, et al. Diffuse high intensity PD-L1 staining in thymic epithelial tumors. J Thorac Oncol 2015;10:500-8.
47. Higuchi R, Goto T, Hirotsu Y, et al. PD-L1 Expression and Tumor-Infiltrating Lymphocytes in Thymic Epithelial Neoplasms. J Clin Med 2019;8:1833.
48. Cho J, Kim HS, Ku BM, et al. Pembrolizumab for Patients With Refractory or Relapsed Thymic Epithelial Tumor: An Open-Label Phase II Trial. J Clin Oncol 2019;37:2162-70.
49. Konstantina T, Konstantinos R, Anastasios K, et al. Fatal adverse events in two thymoma patients treated with anti-PD-1 immune check point inhibitor and literature review. Lung Cancer 2019;135:29-32.
50. Giaccone G, Kim C, Thompson J, et al. Pembrolizumab in patients with thymic carcinoma: a single-arm, single-centre, phase 2 study. Lancet Oncol 2018;19:347-55.
51. Rajan A, Heery CR, Thomas A, et al. Efficacy and tolerability of anti-programmed death-ligand 1 (PD-L1) antibody (Avelumab) treatment in advanced thymoma. J Immunother Cancer 2019;7:269.
52. Lamarca A, Moreno V, Feliu J. Thymoma and thymic carcinoma in the target therapies era. Cancer Treat Rev

2013;39:413-20.
53. Alberobello AT, Wang Y, Beerkens FJ, et al. PI3K as a Potential Therapeutic Target in Thymic Epithelial Tumors. J Thorac Oncol 2016;11:1345-56.
54. Zucali PA, De Pas T, Palmieri G, et al. Phase II Study of Everolimus in Patients With Thymoma and Thymic Carcinoma Previously Treated With Cisplatin-Based Chemotherapy. J Clin Oncol 2018;36:342-9.
55. Henley JD, Koukoulis GK, Loehrer PJ Sr. Epidermal growth factor receptor expression in invasive thymoma. J Cancer Res Clin Oncol 2002;128:167-70.
56. Inoue A, Suzuki T, Fukuhara T, et al. Prospective phase II study of gefitinib for chemotherapy-naive patients with advanced non-small-cell lung cancer with epidermal growth factor receptor gene mutations. J Clin Oncol 2006;24:3340-6.
57. Giaccone G, Rajan A, Ruijter R, et al. Imatinib mesylate in patients with WHO B3 thymomas and thymic carcinomas. J Thorac Oncol 2009;4:1270-3.
58. Girard N, Teruya-Feldstein J, Payabyab EC, et al. Insulin-like growth factor-1 receptor expression in thymic malignancies. J Thorac Oncol 2010;5:1439-46.
59. Rajan A, Carter CA, Berman A, et al. Cixutumumab for patients with recurrent or refractory advanced thymic epithelial tumours: a multicentre, open-label, phase 2 trial. Lancet Oncol 2014;15:191-200.
60. Lattanzio R, La Sorda R, Facciolo F, et al. Thymic epithelial tumors express vascular endothelial growth factors and their receptors as potential targets of antiangiogenic therapy: a tissue micro array-based multicenter study. Lung Cancer 2014;85:191-6.
61. Thomas A, Rajan A, Berman A, et al. Sunitinib in patients with chemotherapy-refractory thymoma and thymic carcinoma: an open-label phase 2 trial. Lancet Oncol 2015;16:177-86.
62. Remon J, Girard N, Mazieres J, et al. Sunitinib in patients with advanced thymic malignancies: Cohort from the French RYTHMIC network. Lung Cancer 2016;97:99-104.
63. Sato J, Satouchi M, Itoh S, et al. Lenvatinib in patients with advanced or metastatic thymic carcinoma (REMORA): a multicentre, phase 2 trial. Lancet Oncol 2020;21:843-50.

doi: 10.21037/med-23-30
Cite this article as: Ajimizu H, Sakamori Y. Narrative review of indication and management of induction therapy for thymic epithelial tumors. Mediastinum 2024;8:44.