Systemic treatments for thymic tumors: a narrative review

Paolo Andrea Zucali\textsuperscript{1,2}, Fabio De Vincenzo\textsuperscript{2}, Matteo Perrino\textsuperscript{2}, Nunzio Digiacomo\textsuperscript{3}, Nadia Cordua\textsuperscript{1}, Federica D’Antonio\textsuperscript{1}, Federica Borea\textsuperscript{1}, Armando Santoro\textsuperscript{1,2}

\textsuperscript{1}Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy; \textsuperscript{2}Department of Oncology, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy

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Correspondence to: Paolo Andrea Zucali, MD. Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy; Department of Oncology, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy. Email: paolo.zucali@hunimed.eu.

Abstract: Thymic epithelial tumours (TETs) are rare tumours originating from the thymus. Considering the rarity of this disease, the management of TETs is still challenging and difficult. In fact, all the worldwide clinical practice guidelines are based on data from retrospective analyses, prospective single arm trials or experts’ opinions. The results of combined modality therapy (chemotherapy, surgery, radiotherapy) in thymic malignancies are reasonably good in less advanced cases whereas in case of advanced (unsuitable for surgery) or metastatic disease, a platinum-based chemotherapy is considered standard of care. Unfortunately, chemotherapy in the palliative setting has modest efficacy. Moreover, due to the lack of known oncogenic molecular alterations, no targeted therapy has been shown to be efficient for these tumours. In order to offer the best diagnostic and therapeutic tools, patients with TETs should be managed with a continuous and specific multidisciplinary expertise at any step of the disease, especially in the era of a novel coronavirus disease (COVID-19). Current evidences show that cancer patients might have more severe symptoms and poorer outcomes from COVID-19 infection than general population. With the exception of the patients carrying a Good’s syndrome, there is no evidence that patients with TETs present a higher risk of infection compared with other cancer patients and their management should be the same. The aim of this review is to summarize the existing literature about systemic treatments for TETs in all clinical setting (local and locally advanced/metastatic disease) exploring how these therapeutic strategies have been managed in the COVID-19 era.

Keywords: Thymic epithelial tumours (TETs); systemic therapy; COVID-19

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Introduction

Thymic malignancies are rare tumours originating from the thymus (world annual incidence ranges from 1.3 to 3.2 per million), but they are the most common anterior mediastinal tumours in adults (50% of anterior mediastinal masses) (1). The mean age at diagnosis is 50–60 years even if TETs may be diagnosed in elderly patients as well as children.

According to the World Health Organization (WHO) histopathological classification, thymic epithelial tumours (TETs) are classified in thymoma, further classified into types A, AB, B1, B2 and B3, and thymic carcinoma (TC) (2). Compared to thymoma (incidence rate 2.8 per million), TC are extremely rare (incidence <0.1 per million). Moreover, TC are the most aggressive TETs characterised by common lymphatic and haematogenous spread and are commonly diagnosed in an advanced stage.

If the Masaoka Koga staging system has been the mostly widely used for routinely staging of TETs, from 2014 it was...
replaced by the TNM staging system and a node map based on overall survival (OS) analyses of an International Thymic Malignancies Interest Group (ITMIG) retrospective international database of more than 10,000 cases from 105 institution worldwide (3-9).

The most important independent prognostic factors are stage, histology, and completeness of surgical resection. The 5-year survival of completely resected patients was 90%, 90%, 60%, and 25% for stages I, II, III, and IV, respectively (10). However, a combination of stage and histological subtype should be considered in predicting survival. Types A, AB, and B1 have an excellent OS rate of more than 90–95% at 10 years whereas the five-year survivals for types B2, B3, and C are 75%, 70%, and 48%, respectively (11,12). Last but not least, the completeness of resection is very important for prognosis, even for stages III and IV tumours (13,14).

The results of combined modality therapy (chemotherapy, surgery, radiotherapy) in thymic malignancies are reasonably good in less advanced cases (15-19). In case of advanced (unsuitable for surgery) or metastatic TETs, a platinum-based chemotherapy is considered standard of care. However, chemotherapy in the palliative setting has modest efficacy (20,21). No targeted therapy has been shown to be efficient for these tumours due to the lack of known oncogenic molecular alterations. Anti-angiogenic agents (22-24), cKIT inhibitors (25), mTOR inhibitors (26), and immunotherapy with anti-PD-1 inhibitors (27,28) have been tested in limited series of stage IV diseases, showing interesting results. Of course, the rarity of these tumours has precluded the development of large phase II and III clinical trials, delaying the investigation of new drugs. Moreover, a better understanding of the biology of these rare tumours may allow the development of better therapies, especially for the more aggressive tumour types. In fact, in contrast to many other solid tumours, the genetic background of TETs remains unknown so far.

All the most important worldwide clinical practice guidelines on thymic cancers, give recommendations on diagnosis, staging, risk assessment, and therapeutic management of disease. Nevertheless, all these guidelines are based on data from retrospective analyses, prospective single arm trials or experts’ opinions. For these reasons, the management of TETs is still very complex and challenging. In order to offer the best diagnostic and therapeutic tools, a specific expertise and a multidisciplinary approach is mandatory and several national and international networks to coordinate the work among centres involved in the treatment of these diseases have been created (21). The aim of this manuscript is to present an overview of the existing literature about the role and appropriate use of systemic treatments for thymoma and TC in all clinical setting (local and locally advanced/metastatic disease) and to explore how these strategies have been managed in the COVID-19 era in order to identify in the future any corrective measures for the management of TETs in clinical practice in the context of pandemic. We present the following article in accordance with the Narrative Review reporting checklist (available at: https://dx.doi.org/10.21037/med-21-11).

**Methods**

Literature search was done via the PubMed® database from origin until January 15, 2021. We included all types of articles and study design, including original research, meta-analyses, reviews, and abstracts. Only studies published in English were considered. The keywords were used during the research: thymic epithelial tumours, thymoma, thymic carcinoma, unresectable local advance disease, metastatic disease, chemotherapy, target therapy, immunotherapy.

**Discussion**

**Thymoma**

**Resectable disease**

The main goal of the treatment strategy of TETs is the completeness of surgical resection. Therefore, therapeutic strategy is based on the resectability of the tumor. In case of resectable thymic tumor at the moment of the diagnosis (stage Masaoka I, II and III or IASLC/ITMIG TNM I, II and IIIA/T3), surgery represents the first step of treatment (20,21,29). In order to define the need for adjuvant treatments, three factors are usually considered: complete surgical resection, stage of disease, and histology (30). Unfortunately, there are not randomized studies evaluating the role of post-operative radiotherapy and/or chemotherapy. The available trials were mainly retrospective or institutional reports and despite the high sensitivity to chemotherapy of thymomas, current data do not support post-operative chemotherapy as a sole adjuvant treatment in advanced stages of thymoma (15,31-39). Several chemotherapeutic regimens have been delivered in this setting, consisting of anthracycline and/or platinum-based multi-agent combinations. A retrospective analysis on 1,320 patients with TETs showed that patients with
Masaoka stage I thymoma were treated with surgery only, patients with Masaoka stage II and III underwent surgery and post-operative chemo/radiotherapy, and patients with stage IV mainly received radiotherapy or chemotherapy (15). In this series, the 5-year survival rates of patients with total resection and subtotal resection were 93% and 64%, respectively. However, adjuvant therapy including radiation or chemotherapy did not improve the prognosis in patients with totally resected stage III and IV tumors. Ströbel and colleagues, in a retrospective analysis of 228 patients with TETs, showed that adjuvant chemotherapy did not influence the outcome of patients with WHO type A, AB and B1 thymomas and of patients with completely resected type B2 or B3 tumors in Masaoka stage II (32). A single institution retrospective analysis on 100 patients who received surgery, Kim and colleagues showed no differences in the 5-year survival in Masaoka stage II and IV thymomas between patients who received post-operative chemo/ radiotherapy compared with those with post-operative radiotherapy only (36).

In conclusion, adjuvant chemotherapy treatment in combination with radiotherapy should be discussed only in case of R2 resected thymoma and in case of R1 resected thymoma B3 (20,21,29,40). Adjuvant treatments should be administered within 8–12 weeks from surgery.

Unresectable local advance disease
In case of locally advanced unresectable disease (Masaoka stage III and IASLC/ITMIG TNM stage IIIA/IIIB), the primary therapeutic endpoint still remains the achievement of a complete surgical resection to obtain long-term survival. Therefore, a multimodality treatment with curative intent is usually proposed after discussion about specific therapeutic choices in a multidisciplinary board. In the largest trials including TETs (Table 1), the response rate to chemotherapy in neo-adjuvant setting ranged from 70% to 80% and patients for whom radical surgery (R0) was considered to be feasible received surgical approach and complete resection is achieved in approximately 50% of cases (45). Unfortunately, there are no data from prospective randomized trials comparing chemotherapy with chemo-radiotherapy also in this specific setting and the few available literature data do not settle this point (15,31,38,41-43, 46-57). In general, an induction chemotherapy (alone or combined with radiotherapy) is administered to obtain a tumor shrinkage. In this setting, several chemotherapeutic regimens have been delivered, consisting of Adriamycin and/or platinum-based multi-agents and the regimen with cisplatin, adriamycin, and cyclophosphamide (PAC) have been recommended, based on historical trials (58). Combination chemotherapy with carboplatin/paclitaxel may be considered for patients anthracycline non eligible. Usually, 2–4 cycles of chemotherapy (up to a maximum of 6) are administered, with a radiological reevaluation after 2–3 cycles (20,21,29). In case of significant tumor shrinkage leading from unresectable tumor to potentially complete resectable tumor, an extensive surgery should be offered and post-operative radiotherapy should be considered. On the other hand, in patients with unresectable disease after induction systemic treatment, concomitant chemoradiotherapy should be also considered (20,21,29,47).

Table 1 Main systemic therapies for locally advanced thymoma and TC.

| Regimen   | Author (year) | Stage | Tumor type | No. of pts | RR (%) | mPFS     | mOS (months) | Subsequent surgery (no of pts) |
|-----------|---------------|-------|------------|------------|--------|----------|--------------|--------------------------------|
| ADOC      | Berruti et al. [1999] (41) | III, IVa | T          | 16         | 81     | 33.2 months | 47.5 months | 9                              |
| CODE      | Kunitoh et al. [2010] (42) | III    | T          | 21         | 62     | 4.5 years | NR; OS rate at 8 years 69% | 11                             |
| CAP       | Kim et al. [2004] (38) | III, IVa-b | T          | 22         | 77     | NR; PFS rate at 7 years 77% | NR; OS rate at 7 years 79% | 21                             |
| CDDP-DTX  | Jacot et al. [2005] (43) | III, IVa-b | T/TC       | 8          | 75     | NA       | NR           | 3                              |
|           | Park et al. [2013] (44) | III, IVa-b | T/TC       | 27         | 63     | NR; PFS rate at 4 years 40.6% | NR; OS rate at 4 years 79.4% | 19                             |

No., number; Pts, patients; RR, response rate; mPFS, median progression free survival; mOS, median overall survival; ADOC, doxorubicin, cisplatin, vincristine, cyclophosphamide; T, thymoma; CODE, cisplatin, vincristine, doxorubicin, etoposide; CAP, cisplatin, doxorubicin, cyclophosphamide; TC, thymic carcinoma; CDDP-DTX, cisplatin, docetaxel; NA, not available; NR, median not reached at time of data publication.
Chemotherapy is the primary treatment for unresectable or metastatic thymoma (Masaoka stage IV or IASLC/ITMIG TNM stage IV). No randomized studies have been conducted and which regimen should be considered standard remains unknown. In case of unresectable recurrence, the rechallenge of a previous effective regimen should be considered, particularly in case of previous response and late occurring of recurrence. In general, a platinum-based chemotherapy in combination with anthracycline has been suggested as the optimal regimen (Table 2) for the treatment of advanced thymomas (20,21,29). A pooled analysis of 314 patients from 15 studies with advanced thymoma, including both prospective and retrospective data, demonstrated that a platinum-based chemotherapy in combination with anthracycline is better than platinum-based chemotherapy without anthracycline. In fact, the response rate (RR) was 69.4% (95% CI: 63.1–75.0%) for platinum with anthracycline-based chemotherapy and 37.8% (95% CI: 28.1–48.6%) for platinum with non-anthracycline-based chemotherapy (62). Several chemotherapy regimens containing a combination of platinum with anthracyclines have been evaluated in patients with thymoma. In a retrospective analysis, the combination of cisplatin, doxorubicin, vincristine and cyclophosphamide (ADOC) achieved an overall RR (ORR) of 92% and an OS of 15 months as first line therapy (59). Based on the results (in terms of efficacy and toxicity profile) of an intergroup trial from ECOG, Southwest Oncology Group and South-eastern Cancer Study Group, the regimen with cisplatin, doxorubicin and cyclophosphamide (PAC) represents the favorite choice as first line treatment in thymoma (60). This combination yielded an ORR of 50% [12 partial responses (PRs) and 3 complete responses (CRs)] with a median duration of response of 11.8 months, a time to treatment failure of 18.4 months, and a median OS of 37.7 months. Several multiagent platinum-based chemotherapy anthracyclines have been also evaluated in patients with thymoma (55-57). In a small prospective trial of 16 previously untreated patients with thymoma, the combination cisplatin and etoposide (PE) showed an ORR of 56% (55). The combination with carboplatin and paclitaxel achieved an ORR of 42.9% in patients with thymoma (56). Therefore, the combination of platinum and etoposide or platinum and paclitaxel should be considered as valid options in case of contraindications to anthracyclines or unfit patients.

### Table 2 Main systemic therapies for thymoma (first line)

| Regimen  | Author (year) | Stage     | No. of pts | RR (%) | mPFS (months) | mOS (months) |
|----------|---------------|-----------|------------|--------|--------------|--------------|
| ADOC     | Fornasiero et al. [1991] (59) | III, IV   | 37         | 92     | 12.0         | 15.0         |
|          | Rea et al. [1993] (50)          | III, Iva  | 16         | 75     | NA           | 66.0         |
|          | Berruti et al. [1999] (41)     | III, Iva  | 16         | 81     | 33.2         | 47.5         |
| Dose-dense CODE | Kunitoh et al. [2010] (42) | Iva-b     | 27         | 59     | 0.79 years   | 6.1 years    |
| CAP      | Loehrert et al. [1997] (47)    | IV         | 29         | 52     | 11.8         | 37.7         |
|          | Loehrert et al. [1994] (60)    | III, Iva-b| 22         | 77     | NA           | NA           |
| CAMP     | Yokoi et al. [2007] (53)       | Iva-b     | 14         | 93     | NA           | NA           |
| Anthracycline-free regimens |
| PE       | Giaccone et al. [1996] (55)    | III, IV   | 16         | 56     | 26.0         | 51.0         |
| CBDCA-PTX| Lemma et al. [2011] (56)       | III, Iva-b| 21         | 43     | 16.7         | NR           |
| VIP      | Loehrert et al. [2001] (57)    | Iii-b, Iva-b| 20     | 35     | 11.9         | 31.6         |
|          | Grassin et al. [2010] (61)     | III, Iva-b| 16         | 25     | 13.1         | NR           |

No., number; Pts, patients; RR, response rate; mPFS, median progression free survival; mOS, median overall survival; ADOC, doxorubicin, cisplatin, vincristine, cyclophosphamide; CODE, cisplatin, vincristine, doxorubicin, etoposide; CAP, cisplatin, doxorubicin, cyclophosphamide; CAMP, cisplatin, doxorubicin, methylprednisolone; PE, cisplatin, etoposide; CBDCA-PTX, carboplatin, paclitaxel; VIP, etoposide, ifosfamide, cisplatin; NA, not available; NR, median not reached at time of data publication.
It is estimated that 50% to 70% of patients with thymoma recurrence receive a second line chemotherapy. Unfortunately, there are very poor data on treatment choice in this setting and there is not a standard of care in second line for TETs. In general, after failure of platinum and/or anthracycline based chemotherapy, in patients with a good medical condition, a second line chemotherapy may include doublets such as carboplatin plus paclitaxel, platinum plus etoposide, and capecitabine plus gemcitabine or single agents such as pemetrexed, 5-FU or analogues, gemcitabine, ifosfamide, etoposide, and paclitaxel (Table 3). If available, it is important to enroll patients in clinical trials. The available trials have shown ORR from 15% to 40% (63-66,69). In particular, the combination of gemcitabine and capecitabine showed an ORR of 40% with 1- and 2-year survival rates of 80% and 67%, respectively (65). Etoposide as single agent achieved a disease control rate (DCR) of about 100% of patients with thymoma (66,71). In patients not eligible to receive additional chemotherapy with octreoscan-positive thymoma, octreotide alone or with prednisone may represent a valid option (67,68).

### Target therapy

Although targeted therapies have become standard of care in many malignancies, no targeted therapy has been shown to be efficient for TETs due to the lack of known oncogenic molecular alterations.

Based on the modest antitumor activity reported in the phase II studies (i.e., ORR<10-15%), treatments with anti-EGFR/anti-IGFR drugs (i.e., erlotinib, gefitinib, cetuximab, cixutumumab), anti-angiogenic agents (i.e., bevacizumab, sunitinib), cKIT inhibitors, and epigenetic drugs are not indicated in patients with thymoma (22,23,25,72-77). Mechanistic target of rapamycin (mTOR) is emerging as a potential target in TETs. In a phase II trial, Everolimus has shown a DCR of 93.8% with a median progression free survival (PFS) of 16.6 months in 32 patients with cisplatin pre-treated thymoma (26). Therefore, Everolimus may represent an off-label option for refractory thymomas. Milciclib, an inhibitor of cyclin D-dependent kinases, showed promising preliminary activity in thymoma B3 and a well-tolerated safety profile. Oral treatment with milciclib met PFS-3 as primary endpoint and OS as a secondary

### Table 3 Main systemic therapies for thymoma (second line)

| Regimen                  | Author (year) | Stage       | No. of pts | RR (%) | mPFS (months) | mOS (months) |
|--------------------------|---------------|-------------|------------|--------|---------------|--------------|
| Chemotherapy             |               |             |            |        |               |              |
| Pemetrexed               | Loehrer et al. [2006] (63) | IVa-b     | 23         | 17     | 11.2          | NA           |
|                          | Gbolahan et al. [2018] (64) | IVa-b    | 16         | 25     | 12.1          | 46.4         |
| Capecitabine + Gemcitabine | Palmieri et al. [2009] (65) | IVb       | 12         | 41     | 11.0          | NA           |
| Etoposide                | Bluthgen et al. [2016] (66) | IVb       | 5          | 20     | 21.0          | 99.0         |
| Octreotide + Prednisone  | Palmieri et al. [2002] (67) | III, IV a-b | 13        | 38     | 14.0          | 15.0         |
|                          | Loehrer et al. [2004] (68) | III, IV   | 32         | 31.6   | 8.8           | NR           |
| Ifosfamide               | Highley et al. [1999] (69) | III, IV   | 15         | 40     | NA            | NR           |
| Target therapy           |               |             |            |        |               |              |
| Everolimus               | Zucali et al. [2018] (26) | III, IV    | 32         | 9      | 16.6          | NR           |
| Sunitinib                | Thomas et al. [2015] (22) | IV          | 16         | 6      | 8.5           | 15.5         |
|                          | Remon et al. [2016] (23) | IV          | 8          | 29     | 5.4           | NR           |
| Imatinib                 | Giaccone et al. [2009] (25) | IV          | 2          | 0      | NA            | 4.0          |
| Immunotherapy            |               |             |            |        |               |              |
| Pembrolizumab            | Cho et al. [2019] (28) | IV          | 7          | 29     | 6.1           | NR           |
| Avelumab                 | Rajan et al. [2019] (70) | IV          | 7          | 29     | NA            | NA           |

No., number; Pts, patients; RR, response rate; mPFS, median progression free survival; mOS, median overall survival; NA, not available; NR, median not reached at time of data publication.
endpoint in two phase 2 trials (78). However, more mature follow-up and the availability of definitive drug efficacy and toxicity results and the need for definitive drug efficacy and toxicity results are needed before mibliclib can be suggested as a therapeutic option outside of clinical trials. Table 3 summarizes the more active targeted drugs in thymoma.

**Immunotherapy**

Immune checkpoint inhibitors (ICIs) are in nascent stages of development for treatment of TETs. PD-L1 is commonly expressed in thymomas from 23% to 92% and this result provides a rationale for using PD-1/PD-L1 inhibitors to treat TETs (79-82). However, the thymus plays a key role in the development of immune tolerance and thymic tumors have a unique biology which can influence the risk-benefit balance of immunotherapy. Moreover, autoimmune diseases are frequently associated with thymoma, especially with B1 and B2 subtypes. The most frequent autoimmune diseases associated with thymoma are myasthenia gravis, in up to 44% of the patients, pure red cell aplasia, systemic lupus erythematosus, polymyositis, paraneoplastic neurological disorders, thyroid disorders, and Good’s syndrome (83-85). Early results from clinical trials have demonstrated clinical activity of immunotherapy in thymomas, albeit at a cost of a higher incidence of immune-related adverse events, which seem to particularly affect skeletal and cardiac muscle and the neuromuscular junction. Cho and colleagues evaluated pembrolizumab in 7 patients with recurrent thymoma and reported an ORR of 28.6% (tumors with high PD-L1 expression were more likely to respond to treatment). Median PFS was 6.1 months and median OS was not reached (28). Another early report on a phase 1 study of avelumab, a fully human IgG1 anti-PD-L1 antibody, in patients with advanced T found that in a cohort of 7 thymomas, 4 patients achieved PR (70). In both trials, 15–62.5% of patients developed uncommon immune-related adverse events, including polymyositis/myocarditis, asthenia, myalgia/myositis, and hyperglycemia. Besides published trials of ICIs in thymomas, there are three ongoing clinical trials that are evaluating (avelumab, nivolumab or pembrolizumab) in thymoma patients (www.clinicaltrials.gov). Results of these trials are awaited and will provide further information about the risks and benefits of using PD-1/PD-L1 inhibitors, either alone or as part of a combination strategy in patients with thymomas. Table 3 summarizes the immunotherapeutic drugs tested in patients with thymoma.

**Conclusions**

To sum up, for localized thymoma radical surgery is the cornerstone of treatment. In locally advanced disease, a multimodality approach with neoadjuvant chemotherapy or chemoradiotherapy should be proposed to obtain a tumor shrinkage and consequently, if feasible, a radical surgery. For unresectable or metastatic disease a systemic therapy is the primary choice. A clear standard of care has not been identified yet, but usually a platinum-based chemotherapy in combination with anthracycline is proposed and in this context PAC (containing cisplatin, doxorubicin and cyclophosphamide) is currently the favorite first-line chemotherapeutic regimen. Unfortunately, only poor data are available about treatment choice in subsequent line of treatment, also considering that in thymomas target therapy has not shown to be particularly effective and immunotherapy use is limited by the high incidence percentage of autoimmune disease.

**TC**

**Resectable disease**

As for thymoma, completely resectable TC (Masaoka stage I, II, III or IASLC/ITMIG TNM stage I, II, IIIA/T3) should undergo to upfront surgery (20,21,29). After a radical surgery, post-operative radiotherapy, starting within three months, is optional for stage I, should be considered for stage II, and is recommended for stage III-IVa disease and for non-radical (R1-R2) surgery (20). Adjuvant chemotherapy is not recommended for stage I completely resected tumours (20,21,29,86). On the other hand, the role of adjuvant chemotherapy for higher stage of disease is not clear. In the literature there are no randomized controlled trials to clarify its role and the optimal chemotherapeutic regimen and schedule are not yet defined. Kondo and Mondon, in a multi-institutional retrospective analysis of 186 TC cases, have found that adjuvant chemotherapy (administered in various regimens, cycles and doses) seems not bringing any survival benefit in patients with Masaoka stage III and stage IV TC treated with radical surgery (R0) (15). In another retrospective data analysis of 632 patients with Masaoka stage IIB and III TC, Kim and colleagues observed similar results for R0 Masaoka stage IIB patients, while they found a benefit of post-operative systemic treatment (with or without radiotherapy) for R1 and R2 resection Masaoka stage IIB patients and for all Masaoka stage III patients (87). Ahmad et al., in another retrospective, international analysis on 1,042 cases of TC, noticed an association of adjuvant chemotherapy (administered in 237 patients) with a better OS in a univariate analysis, but this finding was
not confirmed in the multivariate analysis (88). Despite the contradictory data, in clinical practice adjuvant chemotherapy consisting of platinum-based multi-agent combinations is usually proposed to fit patients, especially after non-radical surgery (R1–R2), but also after a radical resection (R0), from stage II or higher, if an induction treatment was not delivered and/or a high grade tumor was found (20,21,29).

Locally advanced unresectable disease
Up to 80% of TC, at diagnosis, shows invasion of contiguous mediastinal structures (89). As stated for thymoma, the ultimate aim of the treatment of invasive TC, including stage III (Masaoka stage III or IASLC/ITMIG TNM stage IIIA/IIIB) and IV tumors that are unresectable at the time of diagnosis, is to achieve complete resection to obtain long-term survival. Therefore, a multimodality treatment with curative intent is usually proposed after discussion in a multidisciplinary board also in case of TC. An induction chemotherapy (alone or combined with radiotherapy) should be administered to reduce the tumor volume and several chemotherapy regimens have been tested, consisting of Adriamycin and/or platinum-based multi-agent combinations (45). Usually, 2–4 cycles of chemotherapy (up to a maximum of 6) are administered, with a radiological reevaluation after 2–3 cycles (20,21,29).

In the largest trials including TETs (Table 1), the response rate to chemotherapy in neo-adjuvant setting ranged from 70% to 80% and for whom radical surgery (R0) was thought to be feasible received surgical approach and complete resection is achieved in approximately 50% of cases (31,38,41-43,46-57). Chemotherapy may be combined with radiotherapy with the aim to increase the RR of chemotherapy. As for thymoma, there are no data from prospective randomized trials comparing chemotherapy with chemo-radiotherapy in this specific setting and the few available literature data are not conclusive (46,47,90,91). In a phase II trial evaluating neo-adjuvant chemo-radiotherapy for locally advanced TETs, 20 out of 21 patients achieved tumor shrinkage (90). In a retrospective analysis, chemo-radiotherapy achieved a greater response (volume: −47.0 cc more, P<0.001; diameter: −0.8 cm more, P=0.03) compared to chemotherapy alone in 24 patients not suitable for upfront resection (91). Moreover, in 8 patients who received chemotherapy, 33% saw further tumor shrinkage (median volume: −42.3%, P=0.03; diameter: −3.0%, P=0.049) with additional radiation/chemoradiation and median survival increased for patients ultimately receiving surgery versus those who did not (46 months, range: 16–127 vs. 14 months, range: 6–82; P<0.01). After neoadjuvant chemotherapy, if surgery or radiotherapy are not feasible, chemotherapy alone is initiated with a palliative intent. Approximately 10–20% of patients with locally advanced TETs treated with upfront chemotherapy did not receive local therapy (either surgery or radiotherapy or other local treatments) achieving a very modest survival outcomes (45). In general, the major criticism in interpreting data about neoadjuvant chemotherapy in TETs is the extremely wide variation in the number of patients subsequently treated with surgery, radiotherapy or chemotherapy alone, suggesting significant heterogeneity in the inclusion criteria among trials. Moreover, newly diagnosed and recurrent tumors, as well as thymoma and TC, were not analyzed separately and the majority of trials are retrospective with an uncontrolled design.

Metastatic disease
Chemotherapy
At diagnosis, a significant percentage (ranging from 15% to 40%) of TC shows metastatic spread (Masaoka stage IV or IASLC/ITMIG TNM stage IV), commonly to bones, lung, pleura, liver, and lymph nodes (92,93). In metastatic setting, systemic treatment with chemotherapy represents the main therapeutical approach (20,21,29).

Unfortunately, no randomized trials have been performed also in this setting and which regimen should be considered standard for patients with metastatic TC remains unknown. In fact, main evidence is based on retrospective series, involving small numbers of patients or grouping both types of TETs together, making difficult to extrapolate specific data about TC. As first line systemic treatment, a multi-agent chemotherapy is generally used, conventionally with a cisplatin- +/− anthracycline-containing regimen, mostly based on the available evidence for thymoma (Table 4). The ADOC regimen (using cisplatin, doxorubicin, vincristine and cyclophosphamide, intravenously administered) showed to be effective both in thymoma and in TC (59). In a small trial, Koizumi and colleagues treated with this regimen eight patients diagnosed with unresectable or metastatic TC (Masaoka IVa or IVb stage) (94). Five out of eight patients received ADOC as first line chemotherapy: four of them achieved PR whereas one stable disease (SD). Two patients obtaining a PR were also able to receive subsequent radiotherapy on residual thoracic tissue. In a retrospective analysis of 34 patients with untreated and unresectable TC, the ADOC regimen (with cis- or carbo-platinum)
showed a RR of 50% (PR: 17 patients) after a median of four treatment cycles (95). Only four patients experimented a progressive disease (PD) whereas 13 patients achieved SD. Median OS was 21.3 months. Main toxicity was hematological with neutropenia, while non-hematological adverse events were mild. In a retrospective analysis, Yoh and colleagues evaluated the efficacy of cisplatin, vincristine, doxorubicin and etoposide (CODE) regimen with a weekly schedule for a maximum of nine cycles (96). Among 12 patients with locally advanced or metastatic TC treated with a median of seven chemotherapy cycles, five obtained a PR (with an ORR of 42%) and six had a SD. Among five patients obtaining a PR, three received a subsequent local treatment (surgery or radiotherapy). Median PFS was 5.6 months and median OS was 46 months. Most relevant toxicity was hematological. Also the combination with cisplatin, doxorubicin and cyclophosphamide (PAC) has shown to be effective for TC. In a retrospective analysis of 117 patients with TC, this regimen achieved RR up to 74% when administered as induction chemotherapy in unresectable upfront, locally advanced disease (with a median PFS of 23.2 months) and up to 37% when administered as first line treatment for metastatic disease (with a median PFS of 6.2 months) (97).

Anthracycline-free chemotherapy regimens have also been studied. Two prospective trials have evaluated carboplatin and paclitaxel as palliative-intent chemotherapy for advanced TC, and one trial as induction chemotherapy (44,56). In general, carboplatin and paclitaxel achieved a RR of 30–40% in metastatic setting whereas cisplatin and docetaxel combination showed a RR of 66.7% as induction chemotherapy, suggesting a highest efficacy of cisplatinum compared to carboplatinum (44). In particular, in a prospective multicentric phase II trial, Lemma and colleagues evaluated the role of carboplatin plus paclitaxel intravenously administered every three weeks in 46 patients with TETs (56,98). Among 23 patients affected by TC, five patients had a PR (21.7%), 12 had a SD, and 6 had PD. Median PFS was 5 months and median OS was 20 months. The same schedule was administered to 39 naïve-treatment patients with TC in another single-arm multicentric phase II trial. The ORR was 36% (CR: 1; PR: 13). In this study, which is one of the largest clinical trials limiting to TC, median PFS was 7.5 months and 1- and 2-year OS rates were 85% and 71%, respectively. Main adverse event observed with carboplatin plus paclitaxel in these two studies was grade 3–4 neutropenia.

For patients not eligible to receive taxanes and/or anthracycline, the combination of PE could be considered as a valid option. This regimen, with evidence mainly derived from advanced thymoma treatment, achieved an ORR of 50% in TC (55).

The regimen with etoposide, ifosfamide and cisplatin (VIP) is another anthracycline-free option tested in patients

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**Table 4 Main systemic therapies for TC (first line)**

| Regimen    | Author (year) | Stage      | No. of pts | RR (%) | mPFS (months) | mOS (months) |
|------------|---------------|------------|------------|--------|---------------|--------------|
| Anthracycline-containing regimens | | | | | | |
| ADOC       | Koizumi et al. [2002] (94) | IVA-b      | 5          | 80     | 9.4           | 19.0         |
|            | Agatsuma et al. [2011] (95) | IVA-b      | 34         | 50     | NA            | 21.3         |
| CODE       | Yoh et al. [2003] (96) | III, IVA-b | 12         | 42     | 5.6           | 46.0         |
| CAP        | Merveilleux du Vigneaux et al. [2018] (97) | II, III, IV | 36       | 37     | 6.2           | NR           |
|             |               |            |            |        |               |              |
| Anthracycline-free regimens | | | | | | |
| CBDCA-PTX  | Lemma et al. [2011] (56) | III, IVA-b | 23         | 21.7   | 5.0           | 20.0         |
|            | Hirai et al. [2015] (98) | III, IVA-b | 39         | 36     | 7.5           | OS rates at 1 year 85% |
| VIP        | Loherer et al. [2001] (57) | III, IVA-b | 8          | 25     | NA            | OS rates at 1 year 75% |
|            | Grassin et al. [2010] (61) | III, IVA-b | 4          | 25     | NA            | NA           |

TC, thymic carcinoma; No., number; Pts, patients; RR, response rate; mPFS, median progression free survival; mOS, median overall survival; ADOC, doxorubicin, cisplatin, vincristine, cyclophosphamide; CODE, cisplatin, vincristine, doxorubicin, etoposide; CAP, cisplatin, doxorubicin, cyclophosphamide; CBDCA-PTX, carboplatin, paclitaxel; VIP, etoposide, ifosfamide, cisplatin; NA, not available; NR, median not reached at time of data publication.
with TC. In a prospective phase II trial, two out of eight patients (25%) achieved PR and the 1- and 2-year OS rates were 75% and 50%, respectively (57). In another phase II trial of 16 patients with TETs, among four patients with TC, one had a PR and three achieved SD (61).

In a pooled analysis encompassing 15 studies involving a total of 314 patients with advanced or recurrent TETs who were treated using platinum with or without anthracycline chemotherapy, Okuma and colleagues observed a not significant difference in response rate between anthracycline-containing regimens (41.8%, 95% CI: 31.5–52.8%) and non-anthracycline-containing regimens using platinum-based chemotherapies (40.9%, 95% CI: 32.8–49.6%; P<0.82) in TC patients, suggesting a different spectrum of responsiveness to chemotherapy between thymoma and TC (62). Therefore, considering the activity and the better toxicity profile of the anthracycline-free regimens, carboplatin plus paclitaxel is usually the preferred regimen for first line treatment in patients with TC (20,21,29).

In patients progressing to first-line polychemotherapy treatment, and with a good medical condition, second-line treatment should be considered (20,21,29). As for thymoma, there are very poor data on treatment choice in this setting and there is not a standard of care in second line for TC. In general, after failure of platinum based chemotherapy, a second line chemotherapy may include doublets such as platin plus etoposide and capetcitabine plus gemcitabine or single agents such as pemetrexed, 5-FU or analogues, gemcitabine, ifosfamide, etoposide, irinotecan, and paclitaxel (Table 5). If available, it is mandatory to enroll patients in clinical trials. In general, phase II studies conducted in the second or later lines of therapy, with mono or poly-chemotherapy, report rates of objective disease responses ranging from 5% to 26% (63-66,69,99,100). A recent retrospective analyses on 191 patients with advanced TC treated with second line chemotherapy from 1995 to 2014 at 40 institutions in the North East Japan Study Group, showed not statistically significant difference in terms of RR and OS among chemotherapy regimens, including platinum-based doublet and monotherapy (102). Even if patients received platinum-based doublet or other multidrug platinum-based chemotherapy as the first-line treatment, platinum-based doublets were often selected again as second-line chemotherapy. Second-line chemotherapy included platinum-based doublets (carboplatin plus paclitaxel, followed by cisplatin plus etoposide and cisplatin plus irinotecan) in 57.6% of cases, other multidrug chemotherapy (e.g., ADOC regimen) in 13.6%, and monotherapy in 28.8%. The median RR 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 (the ORR in all population was 20%). The median OS from the start of second-line chemotherapy was 22.4 months 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). One hundred four patients (54.5%) were treated with third-line or higher chemotherapy. Considering that the toxicities of platinum-based doublets or other multidrug regimens, especially bone marrow suppression and gastrointestinal toxicities, were reportedly more severe than those of monotherapies, these data support the use of monotherapy as second-line chemotherapy for patients with previously treated advanced TC.

Target therapy

As for thymoma, no targeted therapy has been shown to be efficient for TCs due to the lack of known oncogenic molecular alterations. Based on the modest antitumor activity reported in the phase II studies (i.e., overall response rate <10–15%), treatments with anti-EGFR/anti-IGFR drugs (i.e., erlotinib, gefitinib, cetuximab, cixutumumab) and epigenetic drugs (i.e., belinostat) are not indicated in patients with TCs (72-77). The c-KIT overexpression has been reported in 73–86% of TC, while c-KIT mutations have been found in 9% of cases, consisting of mutations observed in other malignancies (V560del, L576P) or mutations unique to TC (H697Y, D820E) (103). Multiple case reports have described responses to imatinib or other multikinase inhibitors (ie sorafenib and sunitinib) in patients with TC carrying c-KIT mutations whereas two phase II trials evaluating imatinib in patients with TC unselected for c-KIT mutations resulted negative (25,104-107).

Mechanistic target of rapamycin (mTOR) is a potential target also in TC. In a phase II trial, Everolimus has shown a DCR of 61.1% (one CR) with a median PFS of 5.6 months in 18 patients with cisplatin pre-treated TC (26). Therefore, Everolimus may represent an off label option also for refractory TC.

Angiogenesis is thought to play an important role in the genesis of TETs. In fact, vascular endothelial growth factor (VEGF)-A and VEGF receptor 1 (VEGFR-1) and VEGFR-2 are overexpressed in both thymoma and TC (108,109). The microvessels density and VEGF expression
levels have been shown to correlate with tumor invasion, aggressive histology and clinical stage (110). Moreover, patients with TC have increased levels of VEGF in the serum, which is not observed in patients with thymoma (111).

Despite this encouraging biological background, the results of anti-angiogenic therapy in patients with TC are discordant. In a phase II trial, bevacizumab combined with erlotinib was tested in 7 TC and no tumor response was observed (73). In a phase II trial, sunitinib as second line therapy achieved an overall RR of 26% with a median PFS of 7.2 months in 23 patients with TC (22). Sunitinib therapy is the currently viable treatment with the highest rate of objective responses reported in patients pretreated with platinum-containing polychemotherapy, and therefore represents the treatment of choice in this setting.

In the REMORA phase II trial, the activity of Lenvatinib, an orally multi targeted kinase inhibitor for VEGFR, FGFR, c-Kit, was assessed in 42 patients with advanced TC that progressed after at least one platinum-based chemotherapy (24). The ORR was 38%, the DCR 95%, and the median PFS 9.3 months. Interestingly, a significant proportion of patients (30 of 42, 71%) had squamous carcinoma and 14 out of these 30 (47%) showed PR. These findings suggested that lenvatinib may have an important potential activity in the treatment of squamous cell TC. Table 5 summarizes the more active targeted drugs in TC.

**Table 5** Main systemic therapies for TC (second line)

| Regimen                      | Author (year) | Stage | No. of pts | RR  | mPFS (months) | mOS (months) |
|------------------------------|---------------|-------|------------|-----|---------------|--------------|
| **Chemotherapy**             |               |       |            |     |               |              |
| Pemetrexed                   | Loehrer et al. [2006] (63) | IV    | 11         | 0%  | 5.1 weeks     | NR           |
| Gbolahan et al. [2018] (64) | IV 11         | 9%    | 2.9        |     |               | 9.8          |
| Capecitabine + Gemcitabine   | Palmieri et al. [2009] (65) | IV    | 3          | 33% | 6.0           | NR; OS rate at 1 year: 80% |
| Oral Etoposide               | Bluthgen et al. [2016] (66) | IV    | 15         | 13% | 4.0           | 13.0         |
| Carbo- or Cisplatin + Irinotecan | Kanda et al. [2007] (99) | IV    | 7          | 28.6% | NA        | 17.5         |
| Docetaxel                    | Song et al. [2013] (100)  | IV    | 15         | 26.7% | 4.0        | 22.0         |
| Octreotide                   | Palmieri et al. [2002] (67) | IV    | 3          | 33%  | 14.0         | 15.0         |
|                              | Loeherer et al. [2004] (68) | IV    | 6          | 0%   | 4.5          | 23.4         |
| **Target therapy**           |               |       |            |     |               |              |
| Gefitinb                     | Kurup et al. [2005] (72)  | IV    | 7          | NA  | 4.0           | NA           |
| Erlotinib + bevacizumab      | Bedano et al. [2008] (73) | IV    | 7          | 0%; DCR 60% | NA        | NA           |
| Cixutumumab                  | Rajan et al. [2014] (74)  | IV    | 12         | 0%; DCR 41.6% | 1.7     | 8.4          |
| Imatinib                     | Palmieri et al. [2012] (75) | IV    | 3          | 0% | 3.0          | NR           |
| Lenvatinib                   | Sato et al. [2020] (24)   | IV    | 42         | 38%  | 9.3          | NR           |
| Belinostat                   | Giaccone et al. [2011] (76) | IV    | 16         | 0%; DCR 50% | 2.7     | 12.4         |
| **Immunotherapy**            |               |       |            |     |               |              |
| Pembrolizumab                | Giaccone et al. [2018] (27) | IV    | 40         | 22.5% | 4.2     | 24.9         |
|                              | Cho et al. [2019] (28)  | IV    | 26         | 19.2% | 6.1     | 14.5         |
| Nivolumab                    | Katsuya et al. [2019] (101) | IV    | 15         | 0%; DCR 73.3% | 3.8     | 14.1         |
| Avelumab                     | Rajan et al. [2016] (70) | IV    | 1          | 0% | NA           | NA           |

TC, thymic carcinoma; No., number; Pts, patients; RR, response rate; mPFS, median progression free survival; mOS, median overall survival; NR, median not reached at time of data publication; NA, not available; DCR, disease control rate.
88% as reported by series of retrospective analyses. Based on these data, PD-1-targeting antibodies have been evaluated in patients with TC. In a phase II trial of 41 patients with advanced refractory or recurrent TC, pembrolizumab achieved an ORR of 22.5% (CR: 1; PR: 8) and SD in 21 patients (53%) (27). High PD-L1 expression (defined as PD-L1 more than 50% of tumor cell) was related with longer PFS (24 months) compared to low or no PD-L1 expression (2.9 months). Cho and colleagues tested pembrolizumab in 26 Asian patients with TC, reporting an ORR and DCR of 19.2% and 73%, respectively. High PD-L1 levels (i.e., ≥50%) were associated with better response (28). The PRIMER first phase II trial tested nivolumab as second line in patients with TC. The RR was 0% and 11 out of 15 total patients had SD, so patients accrual was interrupted at a preplanned futility interim analyses, because nivolumab was unable to produce tumor shrinkage by RECIST (101). In a phase I, dose-escalation trial on efficacy and tolerability of avelumab, one patient with TC achieved SD (70).

These data demonstrate the clinical activity of PD-1/PD-L1 inhibitors in patients with recurrent TC with toxicity profile better than tried out in patients with thymoma. As observed for thymoma, high PD-L1 expression appears to be associated with a greater likelihood of response and a subset of patients achieve durable responses. Table 5 summarizes the immunotherapeutic drugs tested in patients with TC.

**Conclusions**

In conclusions, for localized and locally advanced TC a radical surgery should be the therapeutic goal, also using neoadjuvant chemotherapy or chemoradiotherapy if an upfront removal of the primary tumor is not feasible at the moment of diagnosis. Moreover, in clinical practice, adjuvant radiotherapy is proposed in case of non-radical surgery or stage II/III. In metastatic disease a multi-agent chemotherapy is the main initial therapeutic approach, but which is the best regimen to use has not been clarified yet. In this context, anthracycline-free regimens showed a similar efficacy compared with anthracycline-containing ones, with less cardiological toxicity, so, currently, carboplatin plus paclitaxel is usually the preferred first line systemic treatment. Second line treatment is not yet standard of care. Chemotherapy regimens, including platinum-based doublet and monotherapy or, as target therapy, sunitinib could be considered, due to the good rate of objective response obtained in patients pretreated with platinum-based chemotherapy. Finally, immunotherapy in TC has showed an interesting clinical activity and good toxicity profile, especially in patients with a high PD-L1 expression, representing a potential therapeutic option in second or further line of treatment.

**COVID-19 and systemic treatment of thymic epithelial tumors**

The novel coronavirus disease (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the most common symptoms are fever (98.6%), fatigue (69.6%), dry cough (59.4%), myalgia (34.8%), and dyspnea (31.2%) (112). Less common symptoms are headache, dizziness, abdominal pain, diarrhea, nausea, and vomiting. Some cases may be asymptomatic, whereas others can experience acute respiratory distress syndrome (ARDS) and death. Severity appears to be related to older age and concomitant comorbidities.

Current evidences show that cancer patients might have more severe symptoms and poorer outcomes from COVID-19 infection than general population, including hospitalization, respiratory failure and death. It is well established that cancer patients are more susceptible to infections (113). In fact, they often present multiple risk factors as well as older age and immunosuppressive state caused by anticancer treatments and several comorbidities. In addition, they need frequent hospital admissions and visits that represent a recognized potential risk factors for COVID-19 infection (114).

It is well known that TETs and the immune system are strongly correlated with each other but it is not clear if this could have an implication on the infectious risk. The organ of thymus is crucial for the immune system development. Auto-immune diseases are frequently associated with thymoma, especially with B1 and B2 subtypes, and the most frequent are myasthenia gravis, in up to 44% of the patients, pure red cell aplasia, systemic lupus erythematosus, polymyositis, paraneoplastic neurological disorders, thyroid disorders, and Good’s syndrome. On the other hand, patients with TC rarely develop autoantibody-induced phenomena (83-85).

With the exception of the patients carrying a Good’s syndrome, also known as thymoma-immunodeficiency, a very rare acquired immunodeficiency syndrome characterized by the association of thymoma and combined B-cell and T-cell immunodeficiency of adult onset with increased susceptibility to infections, there is no evidence that patients with TETs present a higher risk of viral...
infection compared with other cancer patients.

To our knowledge there are no specific recommendations concerning thymic neoplasms in the COVID-19 era. Some indications can be taken from the numerous management reports from the scientific societies of thoracic oncology, but these are mainly focused on lung cancer and COVID-19 (115,116). There is obviously a common anatomical site with thymic neoplasms and the importance in both types of cancer of a multidisciplinary team to choose the best options available for treatment of patients. However, the biological characteristics of the disease, the type of patients, and part of treatments are different from each other. Thymic neoplasms have an incidence at a younger age than lung cancer (average age at diagnosis 59 versus 70 years old), determining the presence of fewer comorbidities. Moreover, there are no known risk factors for the development of TETs and they are not always related to a history of smoking. Finally, the prognosis of TETs is generally better than lung cancer, particularly in case of thymoma.

Considering that the main goal of the treatment strategy of TETs is the completeness of surgical resection, surgery is mandatory and not postponable in case of resectable tumor whereas multimodality treatment with curative intent must be timely in case of locally advanced unresectable disease, also in the COVID-19 era, in order not to lose the window for a complete surgical resectability. As suggested by several oncology societies, we discussed case by case, evaluating the possibility of postponing a treatment, considering the biological aspects of cancer, the clinical features of a patient, from age to ECOG performance status and life expectancy (117-120). In particular, regarding patients receiving active treatment, we maintained all regimens with a survival benefit whenever possible. Palliative treatments, which have less impact on survival or patient's quality of life, have been discussed with patients and balanced against the risk of their exposure to Sars-Cov-2 and the potential morbidity or mortality from COVID-19 disease.

**Conclusions**

Considering the rarity of this disease, the management of systemic therapy for TETs is still arduous. If combined modality therapy (chemotherapy, surgery, radiotherapy) in thymic malignancies achieves reasonably good results in less advanced cases, in case of advanced (unsuitable for surgery) or metastatic TETs, a platinum-based chemotherapy is considered standard of care but with a modest efficacy and therefore with a palliative role. No targeted therapy has been shown to be efficient for these tumors due to the lack of known oncogenic molecular alterations. Anti-angiogenic agents, cKIT inhibitors, mTOR inhibitors, and immunotherapy with anti-PD-1 inhibitors have been tested in limited series of stage IV diseases, showing interesting results. A better understanding of the biology of these rare tumours may allow the development of better therapies, especially for the more aggressive tumour types. In order to offer the best diagnostic and therapeutic tools, patients with advanced TETs should be managed with a continuous and specific multidisciplinary expertise at any step of the disease. This attitude must be persevered especially in the COVID-19 era, with the aim to activate or to maintain active all therapeutic strategies with a survival benefit whenever possible.

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