Management of Thymomas and Thymic Carcinomas

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Outline

- Classification and staging.
- Epidemiology and paraneoplastic syndromes in thymomas.
- Initial treatment of thymomas.
- Treatment of unresectable or metastatic disease.

- Background information on thymic carcinomas.
- Chemotherapy combinations for treatment of metastatic thymic carcinomas.
- Novel agents in the second line treatment for thymic carcinomas.

Thymic epithelial tumors.

- The WHO classifies TET into thymomas, thymic carcinomas, and thymic carcinoids.
- Thymomas have different histologic types (i.e. A, AB, B1, B2, B3, etc.).
- Thymic carcinomas subtype groups (i.e. squamous carcinomas, adenocarcinomas, adenosquamous carcinomas, and carcinomas not otherwise specified (NOS).)
- Thymic carcinoids.

Marx A, et al. WHO 5th ed;(7):2021.

WHO classification of Thymomas

Thymoma subtype	Obligatory criteria	Optional criteria
Type A	Occurrence of bland, spindle shaped epithelial cells (at least focally); paucity[a] or absence of immature (TdT+) T cells throughout the tumor	Polygonal epithelial cells CD20+ epithelial cells
Atypical type A variant	Criteria of type A thymoma; in addition: comedo-type tumor necrosis; increased mitotic count (>4/2mm^2); nuclear crowding	Polygonal epithelial cells CD20+ epithelial cells
Type AB	Occurrence of bland, spindle shaped epithelial cells (at least focally); abundance[a] of immature (TdT+) T cells focally or throughout tumor	Polygonal epithelial cells CD20+epithelial cells
Type B1	Thymus-like architecture and cytology: abundance of immature T cells, areas of medullary differentiation (medullary islands); paucity of polygonal or dendritic epithelia cells without clustering (i.e.<3 contiguous epithelial cells)	Hassall's corpuscles; perivascular spaces
Type B2	Increased numbers of single or clustered polygonal or dendritic epithelial cells intermingled with abundant immature T cells	Medullary islands; Hassall's corpuscles; perivascular spaces
Type B3	Sheets of polygonal slightly to moderately atypical epithelial cells; absent or rare intercellular bridges; paucity or absence of intermingled TdT+ T cells	Hassall's corpuscles; perivascular spaces
MNT[b]	Nodules of bland spindle or oval epithelial cells surrounded by an epithelial cell-free lymphoid stroma	Lymphoid follicles; monoclonal B cells and/or plasma cells (rare)
Metaplastic thymoma	Biphasic tumor composed of solid areas of epithelial cells in a background of bland-looking spindle cells; absence of immature T cells	Pleomorphism of epithelial cells; actin, keratin, or EMA-positive spindle cells
Rare others[c]		

Marx A, et al. WHO 5th ed;(7):2021.

Table 1 Masaoka staging system

Stage	Description
I	Macroscopically encapsulated and no microscopic capsular invasion
II	Macroscopic invasion into adjacent tissues (fatty or mediastinal pleura) or microscopic capsular invasion
III	Macroscopic invasion into adjacent organ(s)
IVA	Pleural or pericardial dissemination
IVB	Lymphogenous or hematogenous metastasis

Masaoka A., J Thorac Oncol 2010;5:S304-312.

Table 9 The relationship between the IASLC/ITMIG TNM proposal staging categories and Masaoka-Koga staging system

The 8th edition TNM stage	TNM	Definition (involvement of)	Masaoka-Koga
Stage I	T1aN0M0	Encapsulated or unencapsulated, with or without extension into mediastinal fat	Stage I and II
	T1bN0M0	Extension into mediastinal pleura	Stage III (partial-pleura)
Stage II	T2N0M0	Pericardium	Stage III (partial-pericardium)
Stage IIIa	T3N0M0	Lung, brachiocephalic vein, superior vena cava, chest wall, phrenic nerve, hilar (extrapericardial) pulmonary vessels	Stage III (partial-completeness of resection)
Stage IIIb	T4N0M0	Aorta, arch vessels, main pulmonary artery, myocardium, trachea, or esophagus	Stage III (partial-incompleteness of resection)
Stage IVa	TxN1M0	Anterior (perithymic) nodes	Stage IVb
	TxN0M1a	Separate pleural or pericardial nodule(s)	Stage IVa
	TxN1M1a	Anterior (perithymic) nodes, Separate pleural or pericardial nodule(s)	Stage IVb
Stage IVb	TxN2M0	Deep intrathoracic or cervical nodes	Stage IVb
	TxN2M1a	Deep intrathoracic or cervical nodes, Separate pleural or pericardial nodule(s)	Stage IVb
	TxNxM1b	Pulmonary intraparenchymal nodule or distant organ metastasis	Stage IVb

IASLC, the International Association for the Study of Lung Cancer; ITMIG, the International Thymic Malignancies Interest Group.

Carter BW, et al. Radiographics 2017;37:758-776.
Masaoka A., J Thorac Oncol 2010;5:S304-312.

Epidemiology and demographics of thymomas

- Account for 20% of mediastinal neoplasms.
- Most patients are between 40 and 60 years old.
- Similar incidence between males and females.
- No known risk factors.
- Strong association between myasthenia gravis and other paraneoplastic syndromes.

Safieddine N, et al. J Thorac Oncol 2014;9:1018.

Paraneoplastic disorders of thymomas.

- Myasthenia gravis: diplopia, ptosis, dysphagia, weakness, fatigue, etc.
- Pure red-cell aplasia.
- Immunodeficiency.
- Thymoma-associated multiorgan autoimmunity.

Nakagiri T, et al. J Thorac Oncol 2007;2:1130.

Initial treatment of thymomas

- Surgical resection.
- Radiation is recommended for residual disease after surgery or for patients with unresectable disease.
- Neoadjuvant chemotherapy for locally advanced borderline resectable disease yields the same 5-year OS compared to surgery alone (77.4% vs. 76.7%).
- No role for adjuvant chemotherapy.

Park S, et al. Ann Thorac Surg 2019;107:355-362.

Treatment for unresectable or metastatic disease

- 1st line chemo: Cisplatin/Adriamycin/Cyclophosphamide (CAP)

  Adriamycin/Cisplatin/Vincristine/Cyclophosphamide (ADOC)

  Cisplatin/Etoposide (PE)
  Etoposide/Ifosfamide/Cisplatin
  Carboplatin/Paclitaxel.

- 2nd line chemo: Pemetrexed/Everolimus/Paclitaxel

  Gemcitabine/Capecitabine

  5-FU/Etoposide/Ifosfamide.

NCCN guidelines version 1.2023;MS-7.

Sunitinib for previously treated advanced thymoma.

- **Phase 2 single-arm.**

Patients with previously treated thymoma. (n:16)

Sunitinib 50mg PO QD for 4 wks then 2 weeks off

- PR: 6%
- DCR: 81%
- PFS: 8.5 months
- OS: 15.5 months

Remon J, et al. Lan Onc 2016;(97):99-104.

Pemetrexed in patients with recurrent thymoma.

- **Phase 2 single-arm.**

- Patients with previously treated thymoma.

(n:16)

Pemetrexed 500mg/m2 iv every 21 days for up to 6 cycles

- ORR:27%
- 2 patients with PR
- 2 patients with CR
- PFS: 12.1 months
- mOS: 46.4 months

Gbolahan OB, et al. J Thorac Oncol 2018;33(12):1940-1948.

Everolimus for advanced thymoma previously treated with cisplatin.

- **Phase 2 single-arm.**

Patients with previously treated thymoma. (n:32)

→ Everolimus 10mg PO QD

- DCR: 94%
- TTF: 11.3 months
- RR: 9%
- PFS: 16.6 months
- 1 –year PFS 56%
- 1-year OS 81%

*36% incidence of pneumonitis. 3 deaths pneumonitis.

Zucali PA, et al. JCO 2018;36(4):342-349.

Pembrolizumab for treatment of thymoma.

- **Phase 2 single-arm.**

Pts with previously treated thymoma (n:7)

Pembrolizumab 200mg iv q 3wks

*72% of ≥ grade 3 irAEs: -hepatitis 12%
-myocarditis 9%
-myasthenia gravis 6%
-thyroiditis 3%
-glomerulonephritis 3%
-colitis 3%

Cho J, et al. JCO 2019;37:2162-2170.

Thymic carcinomas

- Very rare and aggressive tumors. Approx. 1.5 cases/ 1 million.
- Squamous and undifferentiated carcinomas.
- Unknown etiology.
- No clear identifiable risk factors.
- Worst prognosis than thymomas.
- Not associated with paraneoplastic syndromes.
- Surgical resection for localized disease.
- Postoperative radiation is recommended.
- Adjuvant chemotherapy should be considered.

Metastatic Thymic carcinomas

*Anthracycline and platinum based chemotherapy combinations.

- Cis/dox/vin/cyclophos (ADOC)
- Cis/adria/cyclophos (PAC)
- Cis/adria/etoposide (PAE)
- Adria/cis/vinc/etoposide (CODE)
- Carbo/paclitaxel
- Cis/etoposide (PE)
- Vinc/ifos/cis (VIP)

Sunitinib for previously treated advanced thymic carcinoma.

- **Phase 2 single-arm.**

Patients with previously treated thymic carcinoma. (n:20)

Sunitinib 50mg PO QD for 4 wks then 2 weeks off (n:20)

- RR: 26%
- PFS: 7.2 months
- OS at 1 year: 78%
- Median duration of response 16.4 months.

Remon J, et al. Lan Onc 2016;(97):99-104.

Everolimus for advanced thymic carcinoma previously treated with cisplatin.

- **Phase 2 single-arm.**

Patients with previously treated thymic carcinoma. (n:18)

Everolimus 10mg PO QD (n:18)

- RR: 20%
- PFS: 5.6 months
- OS: 14.7 months

*36% incidence of pneumonitis. 3 deaths pneumonitis.

Zucali PA, et al. JCO 2018;36(4):342-349.

Pemetrexed in patients with recurrent thymic carcinomas.

- **Phase 2 single-arm.**

- Patients with previously treated thymic carcinomas.

(n:11)

Pemetrexed 500mg/m2 iv every 21 days for up to 6 cycles

- ORR: 9%
- 1 patient had a PR
- PFS: 2.9 months
- mOS: 9.8 months

Gbolahan OB, et al. J Thorac Oncol 2018;33(12):1940-1948.

Regorafenib for previously treated advanced thymic carcinoma.

- **Phase 2 single-arm.**

Pts with previously treated TET.

(n:19): -12 thymic carcinomas

-11 thymoma

Regorafenib 160mg daily for 21 days then 7 days off.

- PR: 5%
- SD: 73%
- PD: 10%
- DCR: 78%
- mPFS: 9 months

Perrino M, et al. JCO 2018;36:abstr 8579.

Pembrolizumab for advanced thymic carcinoma previously treated with cisplatin.

- **Phase 2 single-arm.**

Patients with previously treated thymic carcinoma. (n:26)

Pembrolizumab 200mg iv q 3wks (n:26)

- RR: 19%
- PFS: 6.1 months
- OS: 14.5 months

*High rate of irAEs

Cho J, et al. JCO 2019;37:2162-2170.

Pembrolizumab for recurrent metastatic thymic carcinoma.

- **Phase 2 single-arm.**

Patients with previously treated thymic carcinoma. (n:40)

Pembrolizumab 200mg iv q 3wks (n:26)

- RR: 22%

*High rate of irAEs

Giaccone G, et al. Lancet Oncol 2018;19(3):347-355.

Lenvatinib for treatment of thymic epithelial tumors.

- **Phase 2 single-arm.**

Pts with previously treated TET. (n:29): -18 thymic carcinomas -11 thymoma

Lenvatinib 24mg daily.

- ORR: 38%
- DCR: 76%
- PFS at 6m 64%
- PFS at 12m 30%

*Grade 3 hypertension 64%

Benitez JC, et al. ASCO 2022;PS8585.

Palbociclib for treatment of thymic epithelial tumors.

- **Phase 2 single-arm.**

Pts with previously treated TET. (n:48): -23 thymic carcinomas
-25 thymoma

Palbociclib 125mg daily for 21 days then 7 days off.

- PR: 12%
- PFS at 6 months: 60%
- mPFS: 11 months
- mOS: 26 months

*AEs:-neutropenia 62%
-anemia 37%
-thrombocytopenia 29%

Ahn MJ, et al. ASCO 2022;PS8576.

PT-112 for treatment of thymic epithelial tumors.

- **Phase 2 single-arm.**

Pts with previously treated TET.
(n:9): -5 thymic carcinomas
-4 thymoma

PT-112 360mg/m2 iv on days 1, 8, and 15 of a 28-day cycle.

- SD: 89%
- PD: 11%
- mPFS: 6.2 months

*AEs:-peripheral neuropathy 60%
- myalgias 50%
-anemia 50%

McAdams M, et al. ASCO 2023;e20647.

Conclusions

Thymomas

- Anthracycline and platinum based chemotherapy combinations remain the standard treatment of choice for metastatic thymomas.
- Single agent pemetrexed is a good second line treatment option.
- Everolimus is an effective treatment option albeit with a high-risk of pneumonitis.
- Sunitinib is not recommended due to the lack of c-Kit mutations.
- Immune check point inhibitors should not be used in patients with thymomas due to the high incidence of irAEs.

Thymic carcinomas

- Anthracycline and platinum based chemotherapy combinations remain the standard treatment of choice for metastatic thymic carcinomas.
- Pemetrexed has minimal activity in thymic carcinomas. Presumably due to their high expression of thymidylate synthase.
- Sunitinib, everolimus, regorafenib, lenvatinib, and palbociclib are treatment options in second-line. Everolimus has a high incidence of pneumonitis.
- Pembrolizumab demonstrates activity second line but it is associated with a high rate of severe immune related adverse events.

Thymic epithelial neoplasms

- There are remarkable differences between thymomas and thymic carcinomas.
- These thymic malignancies represent histologically, molecular, and genomically distinct neoplasms.
- We should not lump both histologic subtypes into one category and as such treatment should be tailored as separate entities.