Thymomas and Thymic Carcinomas

Clinical Trials: The NCCN recommends cancer patient participation in clinical trials as the gold standard for treatment.

Cancer therapy selection, dosing, administration, and the management of related adverse events can be a complex process that should be handled by an experienced healthcare team. Clinicians must choose and verify treatment options based on the individual patient; drug dose modifications and supportive care interventions should be administered accordingly. The cancer treatment regimens below may include both U.S. Food and Drug Administration-approved and unapproved indications/regimens. These regimens are only provided to supplement the latest treatment strategies.

These Guidelines are a work in progress that may be refined as often as new significant data becomes available. The National Comprehensive Cancer Network Guidelines® are a consensus statement of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

Note: All recommendations are category 2A unless otherwise indicated.

▶First-line Combination Chemotherapy Regimens for Thymoma[1,a,b]

REGIMEN	DOSING
Preferred Regimen	
CAP (Cyclophosphamide/ Doxorubicin/Cisplatin)[2-5,c-e]	**Day 1:** Cyclophosphamide 500mg/m^2 IV over 30 minutes **Day 1:** Doxorubicin 50mg/m^2 IV push **Day 1:** Cisplatin 50mg/m^2 IV over 1 hour. Repeat cycle every 3 weeks for up to 8 cycles.
Other Recommended Regimens	
ADOC (Doxorubicin/Cisplatin/ Vincristine/ Cyclophosphamide)[2-4,6-9,c-e]	**Day 1:** Doxorubicin 40mg/m^2 IV push **Day 1:** Cisplatin 50mg/m^2 IV over 1 hour **Day 3:** Vincristine 0.6mg/m^2 (maximum 2mg) IV over 5-10 minutes **Day 4:** Cyclophosphamide 700mg/m^2 IV over 30 minutes. Repeat cycle every 3 or 4 weeks for a maximum of 8 cycles.
CAP (Cyclophosphamide/ Doxorubicin/Cisplatin) + Prednisone[2-4,10,11,c-e]	**Day 1:** Cyclophosphamide 500mg/m^2 IV over 30 minutes **Days 1-3:** Doxorubicin 20mg/m^2 IV continuous infusion over 24 hours daily **Days 1-3:** Cisplatin 30mg/m^2 IV over 1 hour daily **Days 1-5:** Prednisone 100mg orally once daily. Repeat cycle every 3 or 4 weeks for a maximum of 8 cycles.
Carboplatin/Paclitaxel[12-15,f] *Premedication is required.*	**Day 1:** Paclitaxel 200mg/m^2 IV over 3 hours, **followed by:** **Day 1:** Carboplatin AUC 6 IV over 30 minutes. Repeat cycle every 3 weeks for up to 6 cycles.
Etoposide + Ifosfamide + Cisplatin[4,16-18,c,g,h]	**Days 1-4:** Etoposide 75mg/m^2 IV over 1 hour daily **Days 1-4:** Mesna 240mg/m^2 IV over 15 minutes 3 times daily (one dose before Ifosfamide, then at 4 and 8 hours from the start of each Ifosfamide dose). **Days 1-4:** Ifosfamide 1,200mg/m^2 IV over 3 hours daily **Days 1-4:** Cisplatin 20mg/m^2 IV over 1 hour daily. Repeat cycle every 3 weeks for 4 cycles.
PE (Cisplatin/Etoposide)[4,16,19,c]	**Day 1:** Cisplatin 60mg/m^2 IV over 1 hour **Days 1-3:** Etoposide 120mg/m^2 IV over 1 hour daily. Repeat cycle every 3 weeks for 8 cycles.

▶First-line Combination Chemotherapy Regimens for Thymic Carcinoma[1,a,b]

Preferred Regimen	
Carboplatin + Paclitaxel[12-15,f] *Premedication is required.*	**Day 1:** Paclitaxel 200mg/m^2 IV over 3 hours, **followed by:** **Day 1:** Carboplatin AUC 6 IV over 30 minutes. Repeat cycle every 3 weeks for up to 6 cycles.
Other Recommended Regimens	
ADOC (Doxorubicin/Cisplatin/ Vincristine/ Cyclophosphamide)[2-4,6-9,c-e]	**Day 1:** Doxorubicin 40mg/m^2 IV push **Day 1:** Cisplatin 50mg/m^2 IV over 1 hour **Day 3:** Vincristine 0.6mg/m^2 (maximum 2mg) IV over 5-10 minutes **Day 4:** Cyclophosphamide 700mg/m^2 IV over 30 minutes. Repeat cycle every 3 or 4 weeks for a maximum of 8 cycles.

continued

▶First-line Combination Chemotherapy Regimens for Thymic Carcinoma[1,a] (continued)

REGIMEN	DOSING
Other Recommended Regimens (continued)	
CAP (Cyclophosphamide/ Doxorubicin/Cisplatin)[2-5,c-e]	**Day 1:** Cisplatin 50mg/m^2 IV over 1 hour **Day 1:** Doxorubicin 50mg/m^2 IV push **Day 1:** Cyclophosphamide 500mg/m^2 IV over 30 minutes. Repeat cycle every 3 weeks for up to 8 cycles.
CAP (Cyclophosphamide/ Doxorubicin/Cisplatin) + Prednisone[2-4,10-11,c-e]	**Day 1:** Cyclophosphamide 500mg/m^2 IV over 30 minutes **Days 1-3:** Doxorubicin 20mg/m^2 IV continuous infusion over 24 hours daily **Days 1-3:** Cisplatin 30mg/m^2 IV over 1 hour daily **Days 1-5:** Prednisone 100mg orally once daily. Repeat cycle every 3 or 4 weeks for a maximum of 8 cycles.
Etoposide + Ifosfamide + Cisplatin[4,16-18,c,g,h]	**Days 1-4:** Etoposide 75mg/m^2 IV over 1 hour daily **Days 1-4:** Mesna 240mg/m^2 IV over 15 minutes 3 times daily (one dose before Ifosfamide, then at 4 and 8 hours from the start of each Ifosfamide dose). **Days 1-4:** Ifosfamide 1,200mg/m^2 IV over 3 hours daily **Days 1-4:** Cisplatin 20mg/m^2 IV over 1 hour daily. Repeat cycle every 3 weeks for 4 cycles.
PE (Cisplatin/Etoposide)[4,16,19,c]	**Day 1:** Cisplatin 60mg/m^2 IV over 1 hour **Days 1-3:** Etoposide 120mg/m^2 IV over 1 hour daily. Repeat cycle every 3 weeks for 8 cycles.

▶Second-Line Systemic Therapy for Thymoma[1,b]

Other Recommended Regimens	
Etoposide[16,19-22]	**Days 1-21:** Etoposide 50mg/m^2 orally once daily. Repeat cycle every 4 or 5 weeks. **OR** **Days 1-3:** Etoposide 120mg/m^2 IV over 1 hour daily. Repeat cycle every 3 weeks.
Everolimus[23,24,i]	**Days 1-28:** Everolimus 10mg orally once daily. Repeat cycle every 4 weeks.
Fluorouracil (continuous infusion) + Leucovorin[25-29,j,k]	**Day 1:** Leucovorin 400mg/m^2 IV over 2 hours, **followed by:** **Day 1:** Fluorouracil 400mg/m^2 IV push, **followed by:** **Days 1-2:** Fluorouracil 1,200mg/m^2 IV continuous infusion daily (2,400mg/m^2 IV over 46-48 hours). Repeat cycle every 2 weeks.
Gemcitabine[30-32]	**Days 1,8:** Gemcitabine 1,000mg/m^2 IV over 30 minutes. Repeat cycle every 3 weeks.
Gemcitabine + Capecitabine[30-33]	**Days 1-14:** Capecitabine 650mg/m^2 orally twice daily **Days 1,8:** Gemcitabine 1,000mg/m^2 IV over 30 minutes. Repeat cycle every 3 weeks.
Ifosfamide[17,34,g]	**Days 1-5:** Ifosfamide 1,500mg/m^2 IV over 3 hours daily **Days 1-5:** Mesna 300mg/m^2 IV over 15 minutes 3 times daily (one dose before Ifosfamide, then at 4 and 8 hours from the start of each Ifosfamide dose). Repeat cycle every 3 weeks.
Octreotide and Octreotide LAR [35-37,l,m]	**Days 1-28:** Octreotide Acetate 500mcg subcutaneous three times daily Once patient stabilized on subcutaenous Octreotide, may change to: **Day 1:** Octreotide Acetate (LAR) 20-30mg IM. Repeat cycle every 4 weeks.
Paclitaxel[13,38,f] ***Premedication is required.***	**Days 1,8:** Paclitaxel 80mg/m^2 IV over 1 hour. Repeat cycle every 3 weeks.
Pemetrexed[39,40,n] ***Premedication is required.***	**Day 1:** Pemetrexed 500mg/m^2 IV over 10 minutes. Repeat cycle every 3 weeks for 6 cycles.

continued

▶Second-Line Systemic Therapy for Thymic Carcinoma[1,b]

REGIMEN	DOSING
Other Recommended Regimens	
Everolimus[23,24,i]	**Days 1-28:** Everolimus 10mg orally once daily. Repeat cycle every 4 weeks.
Fluorouracil (continuous infusion) + Leucovorin[25-29,j,k]	**Day 1:** Leucovorin 400mg/m^2 IV over 2 hours, **followed by:** **Day 1:** Fluorouracil 400mg/m^2 IV push, **followed by:** **Days 1-2:** Fluorouracil 1,200mg/m^2 IV continuous infusion daily (2,400mg/m^2 IV over 46-48 hours). Repeat cycle every 2 weeks.
Gemcitabine[30-32]	**Days 1,8:** Gemcitabine 1,000mg/m^2 IV over 30 minutes. Repeat cycle every 3 weeks.
Gemcitabine + Capecitabine[30-33]	**Days 1-14:** Capecitabine 650mg/m^2 orally twice daily **Days 1,8:** Gemcitabine 1,000mg/m^2 IV over 30 minutes. Repeat cycle every 3 weeks.
Lenvatinib[41,42,i]	**Days 1-28:** Lenvatinib 24mg orally once daily. Repeat cycle every 4 weeks.
Paclitaxel[13,38,f] ***Premedication is required.***	**Days 1,8:** Paclitaxel 80mg/m^2 IV over 1 hour. Repeat cycle every 3 weeks.
Pembrolizumab[43-46,o]	**Day 1:** Pembrolizumab 200mg IV over 30 minutes. Repeat cycle every 3 weeks for up to 2 years. **OR** **Day 1:** Pembrolizumab 400mg IV over 30 minutes. Repeat cycle every 6 weeks for up to 2 years.
Pemetrexed[39,40,n] ***Premedication is required.***	**Day 1:** Pemetrexed 500mg/m^2 IV over 10 minutes. Repeat cycle every 3 weeks for 6 cycles.
Sunitinib[47,48,i]	**Days 1-28:** Sunitinib 50mg orally once daily. Repeat cycle every 6 weeks (4 weeks on followed by 2 weeks off treatment).
Useful in Certain Circumstances	
Etoposide[16,19-22]	**Days 1-21:** Etoposide 50mg/m^2 orally once daily. Repeat cycle every 4 or 5 weeks until disease progression or unacceptable toxicity. **OR** **Days 1-3:** Etoposide 120mg/m^2 IV over 1 hour daily. Repeat cycle every 3 weeks.
Ifosfamide[17,34,g]	**Days 1-5:** Ifosfamide 1,500mg/m^2 IV over 3 hours daily **Days 1-5:** Mesna 300mg/m^2 IV over 15 minutes 3 times daily (one dose before Ifosfamide, then at 4 and 8 hours from the start of each Ifosfamide dose). Repeat cycle every 3 weeks.

[a] If patients cannot tolerate first-line combination regimens, consider second-line systemic therapy options.

[b] Pembrolizumab is not recommended for patients with thymoma. In patients with thymic carcinoma, there is concern for a higher rate of immune-related adverse events than seen in most other malignancies treated with PD-1/PD-L1inhibitor therapy. For example, grade 3-4 myocarditis has been reported in 5%-9% of patients receiving pembrolizumab.

[c] Hydration is required with supplemental electrolytes pre- and post-administration of cisplatin.

[d] Oral hydration is strongly encouraged with cyclophosphamide; poorly hydrated patients may need supplemental IV hydration. Patients should attain combined oral and IV hydration of 2,000 -3,000mL/day on day of chemotherapy.

[e] Doxorubicin is an anthracycline. Cumulative anthracycline dosage should be monitored.

[f] For Paclitaxel: Premedication for hypersensitivity is required. H2 antagonist – famolidine 20mg IV or orally (or equivalent H2 blocker) 30-60 minutes pre-Paclitaxel AND H2 antagonist – diphenhydramine 12.5-50mg IV or orally 30-60 minutes pre-Paclitaxel AND dexamethasone (for 21-day regimen) – dexamethasone 20mg orally approximately 12 and 6 hours pre-Paclitaxel OR dexamethasone 20mg IV 30 minutes pre-Paclitaxel OR dexamethasone (for weekly regimen) – dexamethasone 10mg IV 30 minutes pre-Paclitaxel. In the absence of infusion reactions for Doses 1-3, may consider dexamethasone 4mg IV 30 minutes pre-Paclitaxel starting with Dose 4.

[g] Hydration is required pre- and post-administration of Ifosfamide.

[h] Filgrastim (or clinically appropriate G-CSF agent) 5mcg/kg subcutaneously daily, recommended to start the day following or up to 3-4 days after completion of chemotherapy and to continue until post-nadir ANC recovery to normal or near-normal levels by laboratory standards. Same-day administration is not recommended. OR Pegfilgrastim (or clinically appropriate biosimilar) 6mg subcutaneously once, recommended to e given the day following or up to 3-4 days after completion of chemotherapy. There are insufficient data to support use of pegfilgrastim for cytotoxic chemotherapy regimens administered less frequently than every 2 weeks. Same-day administration is not recommended.

[i] This agent has multiple potential drug-drug and drug-food interactions.

[j] For Leucovorin: the dose listed above is based on racemic leucovorin product. Levoleucovorin is not interchangeable and the product doses are not equivalent.

continued

[k] For Fluorouracil: patients with dihydropyrimidine dehydrogenase (DPD) deficiency are unable to metabolize this agent normally and may have severe unexpected toxicity.

[l] Dose and frequency of Octreotide Acetate may be further increased for symptom control as needed. Octreotide Acetate (LAR) would not be expected to be therapeutic for 10-14 days. Short-acting Octreotide can be added to Octreotide Acetate (LAR) for rapid relief of symptoms or breakthrough.

[m] This regimen may also be administered with prednisone.

[n] For Pemetrexed: Premedication and supplemental medications to reduce the incidence of severity of hematologic, gastrointestinal and cutaneous toxicities are required. The recommended dosing is: Vitamin B12 (cyanocobalamin) 1,000mcg IM during the week preceding the first cycle of Pemetrexed and every 3 cycles thereafter AND fofic acid 400-1,000mcg orally daily starting 7 days before the first cycle and continuing 21 days after the last dose of Pemetrexed AND dexamethasone 4mg orally twice daily for 3 days starting the day prior to Pemetrexed.

[o] Early and late-onset immune-related adverse events affecting multiple organ systems can occur in patients receiving immune checkpoint inhibitors. Patients with neurologic or life-threatening autoimmune disorders as well as those receiving high levels of immunosuppression for underlying disease should be approached with caution when considering immunotherapy. All patients will require extensive resources including ongoing intensive monitoring and supportive care.

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