EUROPEAN HEMATOLOGY ASSOCIATION

# EHA-TSH Hematology Tutorial

## Self-assessment Case – Session 2: How I Treat PTCL-NOS

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# Case study (1)

- 29-year-old male
- Admitted to gastroenterology outpatient clinic with complaints of diarrhea
- FBC:
  - WBC: 21.11 × $10^9$/L
  - Neutrophils: 7.58 × $10^9$/L
  - Lymphocytes: 3.18 × $10^9$/L
  - Eosinophils: 9.23 × $10^9$/L
  - Hb: 140 g/L
  - Platelets: 298 × $10^9$/L

FBC, full blood count; Hb, hemoglobin; WBC, white blood cell.

# Case study (2)

- Upper and lower GI endoscopic evaluation reveals a polyp in the colon
- Excised polyp pathology shows no malignancy
- Stool culture reveals enteropathogenic *Escherichia coli* infection

- 2 months later, patient starts to lose weight; reports night sweats (B symptoms)
- Patient is referred to the hematology department

GI, gastrointestinal

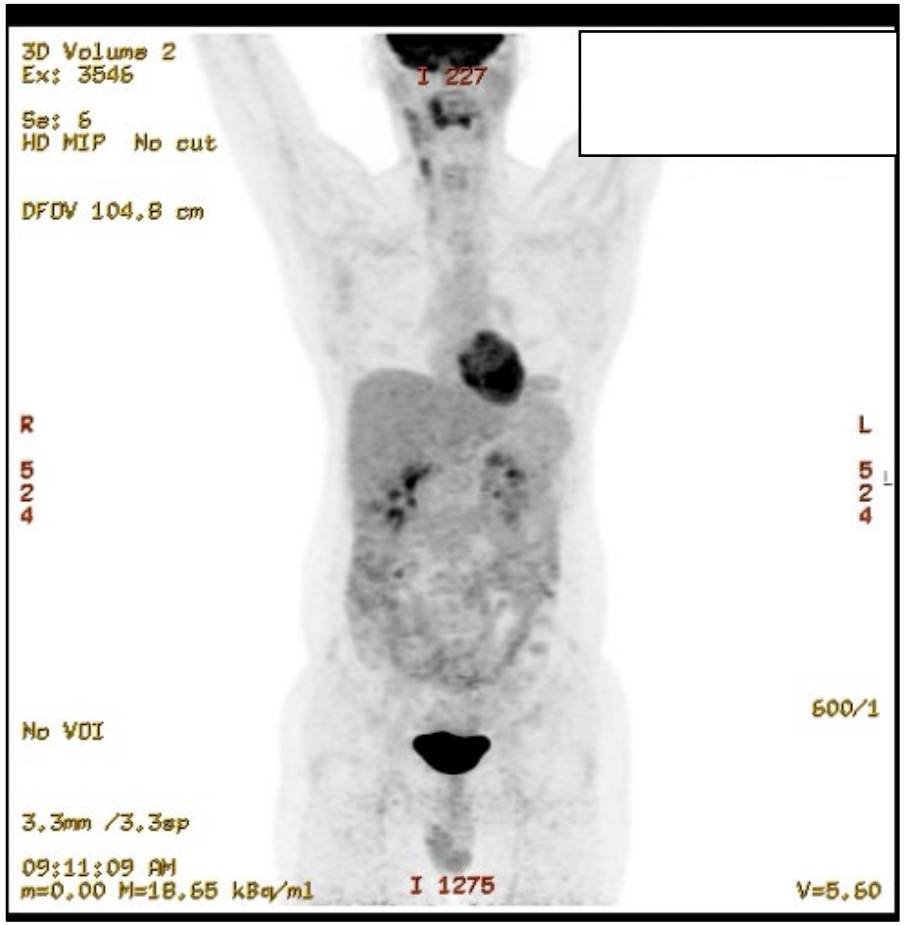
# Case study (3)

- Hematology department repeats FBC
  - WBC: 18.35 × $10^9$/L
  - Neutrophils: 5.39 × $10^9$/L
  - Lymphocytes: 2.91 × $10^9$/L
  - Eosinophils: 8.85 × $10^9$/L
  - Hb: 142 g/L
  - Platelets: 390 × $10^9$/L
- Physical examination reveals right-cervical lymph node of 2 cm

# Case study (4)

- FDG uptake at right tonsil: $SUV_{max}$ 6.9
- FDG uptake at right-cervical lymph node: $SUV_{max}$ 4.6
- Tonsillectomy and bone marrow biopsy performed

**PET–CT at diagnosis**



# Case study (5)

- Bone marrow biopsy reveals $CD2^+$, $CD3^+$, $CD5^+$, and $CD7^+$ lymphoid aggregates
  - Reactive?
  - Lymphoproliferative disease?
- *JAK2* mutation negative
- *BCR::ABL1* mutation negative
- Cervical lymph node excisional biopsy reveals medium-sized cells:
  - $CD2^+$, $CD3^+$, $CD5^+$, $CD7^+$, $CD4^+$, $CD30^+$
  - $CD8^-$, $CD10^-$, $CD20^-$
  - Negative for BCL6, PD-1, and granzyme expression

# Question 1: What is the most likely diagnosis?

1. Angioimmunoblastic T-cell lymphoma
2. Anaplastic large cell lymphoma
3. Follicular helper T-cell lymphoma, NOS
4. Peripheral T-cell lymphoma, NOS
5. Follicular helper T-cell lymphoma, follicular type

NOS, not otherwise specified.

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# Rationale

- Peripheral T-cell lymphoma (PTCL), NOS: a diagnosis of exclusion for those cases of PTCL lacking specific features that qualify for other specific PTCL subtypes
- Morphology (medium-sized cells) excludes anaplastic large cell lymphoma
- Lack of follicular helper T-cell lymphoma immunophenotype (PD-1, ICOS, CXCL13, CD10, and BCL6) excludes follicular helper T-cell lymphoma

PTCL, peripheral T-cell lymphoma.

Bisig B, et al. Haematologica. 2023;108:3227-43.

# Question 2: What is the expected 5-year OS in a patient with PTCL-NOS?

1. 10–15%
2. 20–25%
3. 30–35%
4. 50–55%
5. 60–65%

OS, overall survival.

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# Rationale

- 3 largest retrospective series including nodal PTCL have demonstrated a 5-year OS rate of 30–35% for PTCL, NOS

Brink M, et al. Blood. 2022;140:1009-19. Ellin F, et al. Blood. 2014;124:1570-7. Vose J, et al. J Clin Oncol. 2008;26:4124-30.

# Question 3: Which is NOT a marker used in the immunohistochemical algorithm for molecular classification of PTCL-NOS?

1. TBX21
2. ICOS
3. CXCR3
4. GATA3
5. CCR4

CCR4, chemokine receptor 4; CXCR3, C-X-C chemokine receptor type 3; GATA3, GATA binding protein 3; TBX21, transcription box factor 21.

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# Rationale

- An immunohistochemical algorithm has been developed as a surrogate to gene expression profiling-based classification
- The algorithm uses antibodies specific to TBX21, CXCR3 (a TBX21 transcriptional target), GATA3, and CCR4 (a GATA3 transcriptional target), which are interpreted sequentially
- Positivity for TBX21 or CXCR3 in 20% or more of the neoplastic cells defines the TBX21 subgroup
- Lymphomas negative or below the threshold for TBX21 markers are classified as GATA3 if 50% or more of the neoplastic cells are $GATA3^+$ or $CCR4^+$



Amador C, et al. Blood. 2019;134:2159-70.

# Case study (6)

- At follow-up visit, 1 month after the results of the biopsies
  - Patient reports B symptoms and difficulty in breathing
  - On physical examination:
    - New right-cervical peripheral lymphadenopathy (4 cm in diameter)
    - Splenomegaly (6 cm; palpable below costal margin)
    - Signs of pleural effusion in right lung
  - PET–CT:
    - FDG uptake in right-pleural effusion
    - Splenomegaly of 22 cm
    - New peripheral lymphadenopathy in right-cervical region
  - ECOG PS of 2
  - LDH: 550 U/L (normal: < 254U/L)
  - 2 extranodal sites (pleural effusion + bone marrow)
  - Clinical stage IV
  - IPI score of 4 (high risk)

ECOG PS, Eastern Cooperative Oncology Group (ECOG) Performance Status; IPI, International Prognostic Index; LDH, lactate dehydrogenase.

# Question 4: What will be your choice of firstline treatment?

1. Brentuximab vedotin monotherapy
2. Anthracycline-based regimen
3. Gemcitabine-based regimen
4. Platinum-based regimen
5. Pralatrexate

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# Feedback

- According to both ESMO and NCCN guidelines, anthracycline-based regimens should be the choice for firstline treatment of PTCL-NOS

ESMO, European Society for Medical Oncology; NCCN, National Comprehensive Cancer Network.
d'Amore F, et al. Ann Oncol. 2015;26 Suppl 5:v108-v115. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) T-Cell Lymphomas Version 4.2024 — May 28, 2024. Available from: www.nccn.org/professionals/physician_gls/pdf/t-cell.pdf. Accessed June 27, 2024.

# Case study (7)

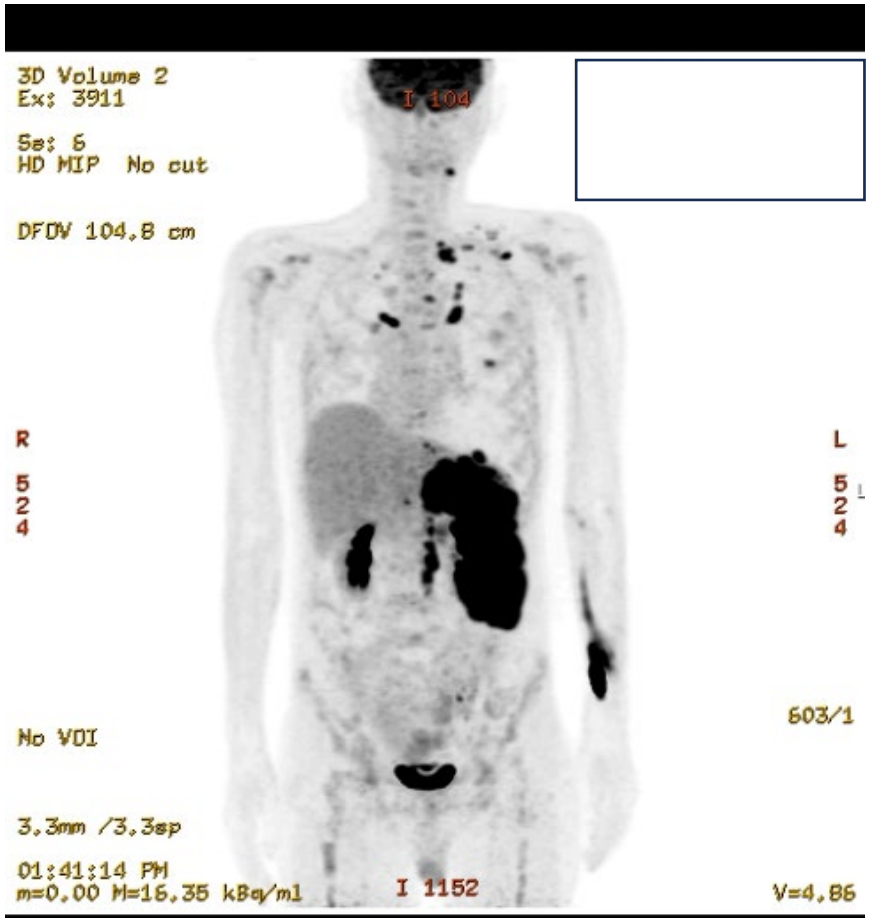
- BV-CHP is started, with intention to proceed to autologous stem cell transplantation
- After 3 cycles of BV-CHP, PET–CT reveals progression of disease
- Change of treatment to GemOx

BV-CHP, brentuximab vedotin, cyclophosphamide, doxorubicin, prednisolone; GemOx, gemcitabine, oxaloplatin.

# Case study (8)

- Progression of disease is noted following 2 cycles of GemOx
- HLA typing
  - HLA-matched sibling
- Change of treatment to pralatrexate
  - Patient starts his first cycle

**PET–CT imaging**



# Question 5: What is the expected median DOR with pralatrexate?

1. 5 months
2. 10 months
3. 18 months
4. 24 months
5. 36 months

DOR, duration of response.

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# Rationale

- In the pivotal PROPEL study, in which pralatrexate was tested in patients with relapsed/refractory PTCL, the median DOR was 10.1 months

O'Connor OA, et al. J Clin Oncol. 2011;29:1182-9.

# Question 6: If the patient responds well to pralatrexate, what will be your treatment plan?

1. Continue with pralatrexate
2. Autologous stem cell transplantation
3. Allogeneic stem cell transplantation
4. CAR-T treatment
5. Brentuximab vedotin maintenance

CAR-T, chimeric antigen receptor T cell.

# Question 6: If the patient responds well to pralatrexate, what will be your treatment plan?

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CAR-T, chimeric antigen receptor T cell.

# Feedback

- Salvage therapy should be considered as palliative therapy, or as a bridge to transplantation
- Combined retrospective registry study from the EBMT and CIBMTR, which evaluated 1,942 patients with PTCL (AITL, PTCL-NOS, ALCL) undergoing allogeneic stem cell transplantation between 2008 and 2018 (primarily for relapsed/refractory disease [70%])
- Overall, 3-year PFS was 50% and 3-year OS 60%, highlighting better outcomes with more advanced therapies
- Allogeneic stem cell transplantation should be favored in patients with transplant-eligible PTCL-NOS

AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; CIBMTR, Center for International Blood and Marrow Transplant Research; EBMT, European Society for Blood and Marrow Transplantation; PFS, progression-free survival.

Ngu HS, et al. Haematologica 2023;108:3211-26. Smith SM, et al. J Clin Oncol. 2013;31:3100-9.

# Discussion

- Despite advances in the frontline setting, a large proportion of patients with PTCL have lymphoma relapse or primary refractory disease
- No standard firstline salvage therapy for patients with relapsed/refractory PTCL
- Median OS from first relapse/progression is typically < 6 months in patients who do not undergo transplantation
- The only established curative treatment is stem cell transplantation
- Most evidence supports the use of allogeneic stem cell transplantation in relapsed, and especially refractory, PTCL, if the patient is fit enough
- Novel agents have been increasingly used as a bridge to transplantation

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