Case 1

- 27-year-old man presents with 6 months of diffuse pruritus, 25 lb weight loss, progressive dry cough, dyspnea, and orthopnea.
- On exam, he is ill-appearing, unable to speak in complete sentences or lie flat, with expiratory wheezing and decreased breath sounds at the right lung base.
- Labs: WBC 20.4, 88% PMNs, 5% lymphs, Hgb 11.8, Plt 420, Alb 3.1, ESR 65
- Imaging: CXR shows a large anterior mediastinal mass and right hilar adenopathy. CT shows confluent mediastinal and right hilar adenopathy measuring 13 x 11 x 5 cm with mass effect on the lower trachea and bronchus intermedius.
- EBUS-guided biopsy of mediastinal mass: mixed inflammatory infiltrate of lymphocytes, histiocytes, neutrophils, eosinophils, and scattered Reed-Sternberg cells positive for CD30, CD15, and PAX5 (dim) and negative for CD20, EBER, and ALK, consistent with classic Hodgkin lymphoma (cHL).
- Intraoperatively, noted to have 95% occlusion of the bronchus intermedius by the mediastinal/hilar mass and a metallic stent is placed.
- PET-CT: hypermetabolic adenopathy above and below the diaphragm
- Stage IIIIBX cHL, IPS 4/7 (male, leukocytosis, lymphopenia, low albumin)
Case 1

How would you treat this patient?

A. ABVD x 2 cycles, de-escalating to AVD x 4 cycles if PET2 negative (Deauville 1-3)
B. Esc BEACOPP x 2 cycles, de-escalating to ABVD x 4 cycles if PET2 negative (Deauville 1-3)
C. Esc BEACOPP x 2 cycles, continuing for 2 additional cycles if PET2 negative (Deauville 1-3)
D. Brentuximab vedotin (BV) + AVD x 6 cycles
E. ABVD x 6 cycles + 30 Gy ISRT

Case 1

How would you proceed now?

A. Continue with BV-AVD for 4 additional cycles
B. Switch to escalated BEACOPP for 4 cycles
C. Switch to AVD for 4 cycles

He is started on BV-AVD with rapid resolution of B symptoms, pruritus, and dyspnea. PET2: favorable response to therapy with decrease in size and metabolic activity of mediastinal mass, now measuring 7 x 3 cm with max SUV 3.8. **Deauville score 4.**

He receives 4 additional cycles of BV-AVD. End of therapy PET-CT after cycle 6: stable size and FDG avidity of the anterior mediastinal mass with max SUV 3.8. **Deauville score 4.**
**Case 1**

How would you proceed now?

A. Observation with repeat PET-CT in 6 weeks
B. Referral for radiotherapy
C. Biopsy of mediastinal mass
D. Salvage ICE and autologous stem cell transplant (ASCT)

19th Multidisciplinary Management of Cancers: A Case-based Approach

- He receives 30 Gy ISRT to the mediastinum
- Follow up PET-CT 8 weeks post-radiotherapy shows a complete metabolic response (Deauville score 2)

**Treatment options for advanced stage cHL in 2019**

- **RATHL**
  - IIB-IV or IA unfavorable
  - PET- (84%) PET+ (16%)
  - 2 x ABVD or 2 x AVD or 4 x BEACOPP-14
  - 82% (3 yrs) 68% (3 yrs) 97% (3 yrs) 86% (3 yrs) 41 months

- **LYSA**
  - IIB-IV
  - PET- (88%) PET+ (12%)
  - 2 x EB + 4 x ABVD 6 x EB
  - 88.9% (5 yrs) 70.7% (5 yrs)

- **HD18**
  - IIB-IV PET- (52%)* PET+ (48%)
  - 4 x EB 6 x EB
  - 92.2% (5 yrs) 89.7% (5 yrs)

- **ECHELON-1**
  - III-IV
  - PET- (89%) PET+ (11%)
  - 6 x BV-AVD 6 x BV-AVD
  - 85.2% (2 yrs) 57.5% (2 yrs)

1. Stephens et al, 2018 ASH abstract #928
3. Casasnovas et al, Lancet Oncol 2019
5. Connors et al, NEJM 2018

*PET- defined as Deauville 1-2 in HD18 study
When to consider frontline therapy with BV-AVD

- Patients with stage III-IV cHL ineligible for bleomycin or with high risk disease
- PFS benefit is greatest for patients with stage IV disease, IPS 4-7, and extranodal involvement

Hutchings et al, 2018 EHA abstract #S112
Connors et al, NEJM 2018
Connors et al, 2018 ASH abstract #2904

Case 2

- 60-year-old man presents to his PCP after noting a lump in his left neck, which increased in size over the past month
- Exam: 3 x 2 cm left anterior cervical node, several smaller 1-1.5 cm anterior cervical nodes bilaterally
- Labs: WBC 8.3, ANC 4.7, ALC 2.1, Hgb 14.3, Plt 280, LDH 190
- CT neck: bilateral left > right cervical adenopathy involving levels 1b and 2 with largest node measuring 3.5 x 2.1 cm

Case 2

- FNA left cervical node: atypical population of intermediate to large lymphocytes with prominent nucleoli, strongly positive for CD3 and CD30 and negative for ALK, PAX5, and PD-1
- Flow cytometry: distinct population of T cells expressing CD30, bright CD52, CD3, CD4, CD5, and dim CD2 with partial loss of CD7
- Excisional biopsy: anaplastic large cell lymphoma (ALCL), ALK-negative, Ki67 >90%
- PET-CT: bilateral cervical, axillary, and upper abdominal adenopathy, 1.5-3.0 cm nodes, SUV 5-8
- Bone marrow biopsy: negative
- Final diagnosis: Stage IIIA ALCL, ALK-negative, IPI 2/5 (age, stage)
Case 2

Which chemotherapy regimen would you recommend?

A. CHOP
B. CHOEP
C. BV + CHOP
D. BV + CHP
E. BV alone

Case 2

He receives 3 cycles of CHOEP with resolution of palpable lymphadenopathy. How would you proceed now?

A. Interim PET-CT
B. Interim CT
C. Continue with 3 additional cycles of CHOEP
D. Proceed to ASCT

Case 2

He completes an additional 3 cycles of CHOEP with end of therapy PET-CT showing an ongoing CR (Deauville score 2).

How would you proceed now?

A. Observation
B. BV maintenance
C. Referral for consolidative ASCT
D. Test for DUSP22 rearrangement
DUSP22 rearrangements

- Present in 30% of patients with ALK- ALCL, associated with a more favorable prognosis akin to ALK+ ALCL
- ALK- ALCL patients with DUSP22 rearrangements do not appear to benefit from consolidative ASCT in CR1

Peripheral T-cell lymphoma outcomes with CHOEP

<table>
<thead>
<tr>
<th>ALK- ALCL</th>
<th>5-year OS</th>
<th>5-year PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALK+ ALCL</td>
<td>78%</td>
<td>64%</td>
</tr>
<tr>
<td>AITL</td>
<td>52%</td>
<td>47%</td>
</tr>
<tr>
<td>PTCL-NOS</td>
<td>47%</td>
<td>48%</td>
</tr>
<tr>
<td>EATL</td>
<td>48%</td>
<td>52%</td>
</tr>
</tbody>
</table>

5-year OS 78% 5-year PFS 64%

Cederleuf et al, BJH 2017

d’Amore JCO 2012

BV-CHP is FDA-approved for frontline treatment of CD30+ PTCL

- ECHELON-2 trial demonstrated superior PFS and OS with 6-8 cycles of BV-CHP compared to CHOP
- BV is substituted for vincristine given overlapping toxicities (peripheral neuropathy)

CD30+ defined as CD30 expression >10%

Horowitz et al, Lancet 2018
**Pre-planned subset analysis from the ECHELON-2 trial**

- Greatest benefit of BV-CHP observed in patients with ALCL
- No clear PFS benefit seen in patients with CD30+ AITL

<table>
<thead>
<tr>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Horowitz et al, *Lancet* 2018

---

**Case 3**

- 54-year-old man presents with enlarged lymph nodes in his left neck and right groin up to 2 cm. He feels well and has no B symptoms.
- Labs: WBC 7.6, ANC 4.7, ALC 2.1, Hgb 15.1, Pr 293, LDH 172
- Excisional biopsy of left cervical node: **grade 1-2 follicular lymphoma**
- PET-CT: left cervical, axillary, and right external iliac and inguinal adenopathy with largest node measuring 2.0 x 2.2 cm, max SUV 6.5. No splenomegaly or effusions.
- Bone marrow biopsy: normal trilineage hematopoiesis
- Final diagnosis: **stage IIIA grade 1-2 follicular lymphoma, FLIPI score 1**

---

**What treatment would you recommend?**

A. Watchful waiting
B. Rituximab
C. Rituximab + Lenalidomide
D. Rituximab + Bendamustine
E. Obinutuzumab + Bendamustine

- Kahl et al, *JCO* 2014
- Morschhauser et al, *NEJM* 2018
- Rummel et al, *JCO* 2017
- Marcus et al, *NEJM* 2017

---

**END OF CASE 2**
Case 3

- Therapy is deferred and he is followed with observation.
- Two years later, he notes enlarging lymph nodes in his left neck. He is anxious and has mild fatigue. Labs are normal.
- PET-CT: increased adenopathy above and below the diaphragm. Largest node (right external iliac node) measures 3.1 x 2.2 cm, max SUV 7.2.
- He receives 4 doses of weekly rituximab.
- Repeat PET-CT: most lymph nodes have resolved. Right external iliac node now measures 2.0 x 1.5 cm, max SUV 3.5 (Deauville score 4).

Case 3

How would you proceed now?

A. Observation
B. Rituximab maintenance every 2 months for 2 years
C. Rituximab + Bendamustine
D. Referral for ISRT
E. Referral for ASCT

Case 3

How would you treat him?

A. R-CHOP
B. DA-EPOCH-R
C. R-HyperCVAD
D. R-CHOP + Lenalidomide
E. R-CHOP + Ibrutinib

Case 3

- He continues to be observed.
- Three years later, he presents with new severe low back pain radiating down the right leg with MRI of the L-spine showing a T1 hypointense infiltrative mass replacing the L3 vertebral body.
- PET-CT: right psoas mass measuring 7.3 x 5.3 cm, SUV max 45.6 with extensive erosion and hypermetabolic activity of the adjacent L3 vertebral body. Hypermetabolic sternal mass with SUV max 35.8. Mild increase in adenopathy above and below the diaphragm.
- Core biopsy of right psoas mass: diffuse large B-cell lymphoma, GCB subtype, double expressor with MYC >40% and BCL2 >50%, negative for MYC translocation, Ki67 90%.
- IPI 4/5 (stage, PS, LDH, extranodal sites).

Case 3

- IPI 4/5 (stage, PS, LDH, extranodal sites).
Case 3

Is CNS prophylaxis warranted?

A. Yes
B. No

He receives 6 cycles of DA-EPOCH-R with 4 doses of IT methotrexate

Interim and end of therapy PET imaging show a metabolic CR (Deauville score 2)

6 x DA-EPOCH-R

Case 3

How would you proceed now?

A. Observation
B. Rituximab maintenance
C. Consolidative radiotherapy to right psoas
D. Referral for ASCT

Double Hit vs. Double Expressor Lymphomas

**Double Hit**
- Genetic diagnosis by FISH
- Separate entity in the 2016 WHO classification (High-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangement)
- ~8% of DLBCL
- Typically GCB
- Very poor outcomes with R-CHOP (4-year OS 26%)

**Double Expressor**
- Refers to protein not DNA
- Diagnosis by IHC with expression of both MYC (>40%) and BCL2 (>50%)
- Not a separate entity in the 2016 WHO classification
- ~30% of DLBCL
- Typically ABC > GCB
- Poor outcomes with R-CHOP (4-year OS 54%)

Friedberg et al., Blood 2017
Double hit and double expressor lymphomas have inferior outcomes with R-CHOP

- Several retrospective studies and one trial suggest improved outcomes with intensive chemotherapy for double hit lymphomas:
  - Petrich et al, Blood 2014
  - Oki et al, Br J Haematol 2014
  - Dunleavy et al, Lancet Haematol 2018

- No standard of care for double expressor lymphomas

- Consider DA-EPOCH-R for high-risk double expressor lymphomas (e.g. high IPI, advanced stage disease, extranodal involvement)

Double expressor DLBCLs have a higher risk of CNS relapse independent of CNS-IPI

- Our patient had a CNS-IPI of 3, cumulative incidence of CNS relapse of 11% at 2 years

Our patient had a CNS-IPI of 3, cumulative incidence of CNS relapse of 11% at 2 years

END OF CASE 3

Case 4

- A fit 64-year-old man presents with enlarging lumps in his bilateral neck and groin

- Exam: multiple 1 cm cervical nodes bilaterally, 2 cm right supraclavicular node, multiple 1-2 cm inguinal nodes bilaterally, spleen edge palpable 3 cm below LCM

- Labs: WBC 8.4, ANC 3.6, ALC 3.1, Hgb 13.8, Plt 136, LDH 198

- CT NCAP: bilateral cervical, mediastinal, hilar, axillary, retroperitoneal, mesenteric, porta hepatis, iliac, and inguinal lymphadenopathy, and mild splenomegaly
Case 4

- Excisional biopsy, right supraclavicular node: vaguely nodular proliferation of small to medium sized lymphocytes expressing CD19, bright CD20, dim CD5, and BCL1 and negative for CD10 and CD23, consistent with mantle cell lymphoma. Ki67 60%.

- Bone marrow biopsy: 10% involvement by mantle cell lymphoma

- PET-CT: hypermetabolic adenopathy above and below the diaphragm and mild splenomegaly with SUV of the spleen greater than that of the liver. The largest node (subcarinal) measures 3.4 x 1.3 cm with SUV max 7.1.

- Final diagnosis: stage IVAS mantle cell lymphoma, MIPI score 6.9 (high risk)

Which chemotherapy regimen would you recommend?

A. R-CHOP
B. R-CHOP alternating with R-DHAP
C. R-HyperCVAD
D. R-Bendamustine
E. R-Bendamustine alternating with R-Cytarabaine

You now recommend:

A. Observation
B. ClonoSEQ molecular testing for MRD
C. Molecular testing for TP53 mutation
D. Both B and C
Case 4

- He has no detectable MRD by ClonoSEQ
- Molecular testing is negative for TP53 mutation or deletion

How would you proceed now?

A. Observation
B. Consolidative ASCT
C. Consolidative ASCT followed by rituximab maintenance
D. Ibrutinib maintenance

How would you monitor the patient for relapse?

A. ClonoSEQ testing for MRD every 6 months
B. PET-CT every 6 months for 2 years
C. CT NCAP every 6 months for 2 years
D. Physical exam and routine labs every 6 months for 2 years
E. A and C
Case 4

- He is followed with CT imaging and ClonoSEQ testing for MRD every 6 months
- Two years after ASCT, he is found to have detectable MRD by ClonoSEQ at 165 clones per million, subsequently rising to 1,260 clones per million
- PET-CT shows recurrent hypermetabolic adenopathy above and below the diaphragm with largest node measuring 2.2 x 2.1 cm
- Biopsy of a right inguinal node confirms relapsed mantle cell lymphoma, Ki67 40%

You now recommend:

A. R-Bendamustine
B. R-Lenalidomide
C. Ibrutinib
D. Acalabrutinib
E. Venetoclax

Case 4

- He starts on ibrutinib 560 mg daily, achieving CR2, MRD negative

Approach to the young, fit patient with mantle cell lymphoma

- Consolidation with ASCT in CR1, except for patients with TP53 mutations (Eskelund et al, Blood 2017)
- Rituximab maintenance post-ASCT improves PFS and OS (Le Gouill et al, NEJM 2017)
MRD monitoring in mantle cell lymphoma patients in clinical remission

- Persistence or reappearance of MRD in the peripheral blood is highly predictive for shorter PFS and OS
- Ongoing trials are evaluating MRD-guided treatment strategies such as maintenance lenalidomide (NCT02354313) or maintenance obinutuzumab (NCT02896582) for MRD+ patients

Trials evaluating chemotherapy-free regimens for relapsed/refractory mantle cell lymphoma

<table>
<thead>
<tr>
<th>Regimen</th>
<th>N</th>
<th>ORR</th>
<th>CR rate</th>
<th>Median PFS</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib</td>
<td>141</td>
<td>32%</td>
<td>8%</td>
<td>6.7 months</td>
<td>Goy et al, Ann Oncol 2009</td>
</tr>
<tr>
<td>Temsirolimus + rituximab</td>
<td>71</td>
<td>59%</td>
<td>19%</td>
<td>9.7 months</td>
<td>Ansell et al, Lancet Oncol 2011</td>
</tr>
<tr>
<td>Lenalidomide + rituximab</td>
<td>52</td>
<td>57%</td>
<td>36%</td>
<td>11.1 months</td>
<td>Wang et al, Lancet Oncol 2013</td>
</tr>
<tr>
<td>Ibrutinib</td>
<td>111</td>
<td>68%</td>
<td>21%</td>
<td>13.9 months</td>
<td>Wang et al, NEJM 2013</td>
</tr>
<tr>
<td>Ibrutinib + rituximab</td>
<td>50</td>
<td>88%</td>
<td>44%</td>
<td>NR (15-month PFS 69%)</td>
<td>Wang et al, Lancet Oncol 2016</td>
</tr>
<tr>
<td>Ibrutinib + venetoclax</td>
<td>24</td>
<td>71%</td>
<td>71%*</td>
<td>NR (18-month PFS 57%)</td>
<td>Tam et al, NEJM 2018</td>
</tr>
<tr>
<td>Acalabrutinib</td>
<td>124</td>
<td>81%</td>
<td>40%</td>
<td>NR (12-month PFS 67%)</td>
<td>Wang et al, Lancet 2018</td>
</tr>
</tbody>
</table>

*67% MRD-negative

19th Multidisciplinary Management of Cancers: A Case-based Approach

Case 5

- 31-year-old female presents with progressive cough and dyspnea on exertion
- Exam: no palpable nodes, prominent veins over anterior chest wall
- Labs: WBC 7.7, ANC 6.0, ALC 1.0, Hgb 14.0, Plt 299, LDH 306
- CXR: bulky anterior mediastinal mass
- CT chest: 12.6 x 9.8 cm mediastinal mass extending to the subcarinal and right hilar stations
Case 5

- PET-CT: bulky anterior mediastinal mass with max SUV 24.1 along with subcarinal and right hilar adenopathy. There is no evidence of disease below the diaphragm.
- Mediastinoscopy with biopsy of the mass shows a diffuse lymphoid proliferation of intermediate size atypical cells expressing CD20, CD79A, PAX5, CD30 (dim), MUM1, BCL2, and BCL6, and negative for CD10, BCL1, and EBER. FISH was negative for MYC, BCL2, and BCL6 rearrangements.
- Final diagnosis: primary mediastinal B-cell lymphoma, stage IIAX.

Which treatment regimen would you recommend?

A. R-CHOP
B. R-CHOP + ISRT
C. R-CHOP + Lenalidomide
D. DA-EPOCH-R

How would you now proceed?

A. Observation with repeat PET-CT in 6-8 weeks
B. Refer for ISRT
C. Biopsy area of residual metabolic activity
D. Salvage therapy with a platinum-based regimen and ASCT
Case 5

- She is observed with repeat PET-CT 6 weeks later showing stable size and metabolic activity of the mediastinal mass. **Deauville 4.**
- Four months after completing therapy: develops fevers and cough
- PET-CT: increase in the size and FDG uptake of the mediastinal mass, now 9.4 x 6.3 cm, SUV max 12.7
- Biopsy of the mediastinal mass confirms relapsed PMBCL.

1. Refer for ISRT
2. Salvage therapy with a platinum-based regimen and ASCT
3. Brentuximab vedotin
4. Pembrolizumab
5. Axicabtagene ciloleucel

How would you now proceed?

A. Refer for ISRT
B. Salvage therapy with a platinum-based regimen and ASCT
C. Brentuximab vedotin
D. Pembrolizumab
E. Axicabtagene ciloleucel

She receives 2 cycles of salvage R-DHAP with repeat PET-CT showing stable disease (**Deauville score 5**). How would you now proceed?

A. Refer for ISRT
B. Brentuximab vedotin
C. Pembrolizumab
D. Axicabtagene ciloleucel
E. Allogeneic transplantation

She receives 36 Gy ISRT to the mediastinum

PET-CT 3 months post-ISRT shows a metabolic CR (**Deauville score 3**)

16 months later, she develops new chest pressure with repeat PET-CT showing progressive disease in the mediastinum (**Deauville score 5**).
**Case 5**

**How would you now proceed?**

A. Brentuximab vedotin  
B. Pembrolizumab  
C. Axicabtagene ciloleucel  
D. Allogeneic transplantation

---

**Excellent long-term outcomes with DA-EPOCH-R in primary mediastinal B-cell lymphoma**

A. Event-free Survival (Total Cohort)

- N = 93 patients
- 59% with bulky disease
- Median follow-up 8.4 years
- 8-year EFS = 91%
- 8-year OS = 95%

Melani et al, Haematologica 2018

**Excellent outcomes in PMBCL patients with Deauville 1-4 on end of therapy PET**

Melani et al, Haematologica 2018

---

• She receives 3 cycles of pembrolizumab with repeat PET-CT demonstrating a CR (Deauville score 3)
Approach to relapsed/refractory PMBCL

- If local recurrence, ISRT alone may be curative
- If systemic recurrence, consider salvage chemotherapy and ASCT
- FDA-approved third-line options:
  - Pembrolizumab (Armand et al, 2018 ASH abstract #228)
  - Axicabtagene ciloleucel (Neelapu et al, NEJM 2017)
  - BV has poor activity, ORR 13%, no CRs (Zinzani et al, Blood 2017)

Outcomes of relapsed/refractory PMBCL following autologous SCT

- Relapsed, stage I-II
  - Vardhana et al, BBMT 2018
  - 5-year PFS 62%

- Refractory or stage III-IV
  - Avivi et al, BMT 2018
  - 5-year PFS 62%

Pembrolizumab is active in relapsed/refractory PMBCL

- ZUMA-1 trial included only 8 patients with PMBCL

Limited data with CD19 CAR T-cell therapy for relapsed/refractory PMBCL

<table>
<thead>
<tr>
<th>Trial</th>
<th>CAR T-cell product</th>
<th>N with PMBCL</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kochenderfer et al, Mol Ther 2017</td>
<td>Axicabtagene ciloleucel</td>
<td>3</td>
<td>67% (2/3 with durable CRs)</td>
</tr>
<tr>
<td>Neelapu et al, NEJM 2017 (ZUMA-1)</td>
<td>Axicabtagene ciloleucel</td>
<td>8</td>
<td>Not reported*</td>
</tr>
<tr>
<td>Abramson et al, 2018 ASCO #7505 (TRANSCEND)</td>
<td>Lisoctagene maraleucel</td>
<td>2</td>
<td>Not reported</td>
</tr>
<tr>
<td>Schuster et al, NEJM 2019 (JULIET)</td>
<td>Tisagenlecleucel</td>
<td>0</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*ORR specifically for PMBCL not reported. ORR for PMBCL (N=8) + transformed FL (N=16) was 83% (CR 71%).
END OF CASE 5