Case Studies in Immunotherapy for the Treatment of Lymphoma

Wednesday, July 7, 2021
5:30-6:30 p.m. EDT

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Webinar faculty

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Case #1 – presentation and diagnosis

- 31 year-old woman, presenting with persistent cough, 30 lb weight loss, drenching night sweats, pleural effusion, and bulky anterior mediastinal mass in March, 2017.
- Core needle biopsy of mass revealed cHL, nodular sclerosis subtype
- PET scan was consistent with stage IV, bulky disease with osseous involvement. Initial stage: IVBX
- IPS was 3/7
Case #1 – first-line therapy

• Patient was treated with 6 cycles of ABVD
• Interim PET scan after 3 cycles showed complete response
• Post-therapy PET scan in October, 2017 confirmed complete response
• Observation was recommended
Case #1 - recurrence

• Patient presented with acute shortness of breath in February, 2018
• Chest CT scan revealed extensive soft tissue nodularity
• Patient underwent numerous thoracenteses for recurrent pleural effusion. Pleural fluid cytology revealed no evidence of malignancy
• PET/CT revealed hypermetabolic lesions in mediastinum, pericardium, hilium, and paratracheal nodes
• Patient underwent VATS and biopsy, which revealed recurrent cHL
Case #1 – second-line treatment

• Patient underwent salvage therapy with ICE followed by planned ASCT
• Patient achieved a likely CR (with mild residual FDG activity in the chest) after cycle 2
• Cycle 3 of ICE was administered and autologous stem cells were collected
• PET/CT after cycle 3 of ICE demonstrated disease progression
Case #1 – Question 1

What treatment would have the highest likelihood of improved PFS at this time?

A. Pembrolizumab
B. Brentuximab vedotin
C. ASCT
D. Bendamustine and brentuximab vedotin
E. Conventional salvage chemotherapy (GND, GDP, etc)
Case #1 – third-line treatment

- Patient enrolled onto study of pembrolizumab vs BV (KEYNOTE-204) and was randomized to pembrolizumab arm
- After 4 cycles of therapy, PET/CT revealed a complete metabolic response
KEYNOTE-204: Pembrolizumab vs brentuximab vedotin

Key Eligibility Criteria
- Relapsed or Refractory cHL
- Relapse post-auto-SCT or ineligible for auto-SCT and failed one prior line of therapy
- Measurable disease per IWG 2007 criteria
- ECOG PS 0-1
- BV-naive and BV-exposed patients eligible

Stratification Factors
- Prior auto-SCT (yes vs no)
- Status after 1L therapy (primary refractory vs relapsed <12 months vs relapsed ≥12 months after end of 1L therapy)

Primary End Point: PFS per blinded independent central review (BICR) by IWG 2007 criteria including clinical and imaging data following auto-SCT or allogeneic stem cell transplant (allo-SCT); OS

Secondary End Points: PFS per BICR by IWG 2007 criteria excluding clinical and imaging data following auto-SCT or allo-SCT; ORR by BICR per IWG 2007; PFS per investigator review; DOR; safety
KEYNOTE-204: Pembrolizumab vs brentuximab vedotin

PFS per blinded independent central review
Including clinical and imaging data following auto-SCT or allo-SCT

**ORR**
Pembrolizumab: 65.6%
Brentuximab vedotin: 54.2%

**mDOR**
Pembrolizumab: 20.7 mo
Brentuximab vedotin: 13.8 mo
Nivolumab + brentuximab vedotin

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Grade 1-2</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>49%</td>
<td>0%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>40%</td>
<td>2%</td>
</tr>
<tr>
<td>IRRs</td>
<td>41%</td>
<td>3%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>29%</td>
<td>2%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>25%</td>
<td>2%</td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>15%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Herrera, Blood 2018
Case #1 – Question 2

What treatment approach(es) can be considered at this point in treatment?

A. Autologous stem cell transplant
B. Continued treatment with pembrolizumab
C. Observation
D. Allogeneic stem cell transplant
ASCT after checkpoint inhibitors

• ASCT in cHL traditionally requires demonstration of chemosensitivity with salvage therapy

• Study question: What is the role of immune checkpoint inhibitors prior to ASCT?
ASCT after checkpoint inhibition

Merryman, Blood Adv 2021
Case #1 – stem cell transplant

• Decision was made to proceed to ASCT in CR2 after pembrolizumab
• Patient received BEAM conditioning and was infused with her autologous stem cells
• Day 30 PET/CT was consistent with ongoing CR
• Patient received 16 cycles of maintenance BV
• Ongoing clinical remission since that time
Case #1 - conclusions

- Standard of care therapy for relapsed or primary refractory cHL remains second-line therapy and ASCT
- Negative PET/CT prior to ASCT is highly predictive of a favorable outcome following ASCT
- Approach to salvage therapy prior to ASCT has classically been to use chemotherapy (ICE, GND)
- Newer options include BV/bendamustine, BV/nivolumab
- Patients with relapsed/refractory cHL who enter remission with PD-1 blockade therapy appear to do well after ASCT
Case #2 – presentation and diagnosis

- 62 year old woman with history of hypertension, diabetes, and obesity
- Patient noticed right axillary swelling in 12/2017
- Core needle biopsy revealed follicular lymphoma (diffuse type) grade 2
- PET/CT demonstrated lesions above and below the diaphragm, indicating stage 3A disease
Case #2 – transformed FL

• Biopsy in 12/2018 revealed DLBCL (50%) arising from FL
  • Grade 3B
  • With sclerosis, and areas with necrosis
  • Positive for: CD20, CD79a, CD10, BCL2, BCL6, M1B1/Ki67 = 70-80%
  • Negative for: CD30, CD3, CD5, CD43, MYC, BCL1, MUM1, Kappa, Lambda, CD23
Case #2 – Initial treatments

• Patient treated with 6 cycles of R-CHOP, which she tolerated well
• PET/CT in 3/2019 indicated resolution of axillary, abdominal, RP and pleural base nodules (Deauville 2)
• PET/CT in 4/2020 indicated new hypermetabolic nodules in subcutaneous tissue of right chest
• Axillary biopsy showed FL grade 2
• PET/CT in 12/2020 revealed increased nodules (Deauville 5)
• Chest mass biopsy indicated DLBCL, GC type
Case #2 – next treatments

- Patient treated with 3 cycles of RICE
- PET/CT revealed some responding lesions (Deauville 2) and some non-responding lesions (Deauville 4)
Case #2 – Question #1

What treatment would you consider next for this patient?
A. ASCT
B. CD20xCD3 bispecific agent
C. CD30 antibody-drug conjugate
D. Chemotherapy
Case #2 – bispecific treatment

• Patient was treated with gemcitabine + oxaliplatin + epcoritamab, with epcoritamab step-up dosing
• Following first full dose, patient exhibits fever, hypotension and tachycardia, consistent with Grade 2 cytokine release syndrome
Case #2 – Question 2

What management approaches would you use for this patient’s Grade 2 CRS?

A. IV fluids + acetaminophen + ibuprofen
B. Steroids
C. Tocilizumab
D. Vasopressors
E. More than one of above
Case #2 – Question 3

What management approaches would you use if a patient developed Grade 3 CRS?

A. IV fluids + acetaminophen + ibuprofen
B. Steroids
C. Tocilizumab
D. Vasopressors
E. More than one of above
## Grading and management of CRS

<table>
<thead>
<tr>
<th>CRS parameter</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever &gt; 38°C</td>
<td>&gt; 38°C</td>
<td>&gt; 38°C</td>
<td>&gt; 38°C</td>
<td>&gt; 38°C</td>
</tr>
<tr>
<td>Hypotension</td>
<td>None</td>
<td>Not requiring vasopressors</td>
<td>Requiring a vasopressor with or without vasopressin</td>
<td>Requiring multiple vasopressors (excluding vasopressin)</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>None</td>
<td>Requiring low-flow nasal cannula or blow-by</td>
<td>Requiring high-flow nasal cannula, face mask, non-rebreather mask or venturi mask</td>
<td>Requiring positive pressure (e.g. CPAP, BiPAP, intubation and mechanical ventilation)</td>
</tr>
</tbody>
</table>

### Management of CRS (one algorithm):
- **Grade 1** *Tocilizumab*: No. *Steroids*: No.
- **Grade 2** *Tocilizumab*: No (yes, if comorbidities). *Steroids*: No (consider, if comorbidities).
- **Grade 3** *Tocilizumab*: Yes. *Steroids*: Consider.
- **Grade 4** *Tocilizumab*: Yes. *Steroids*: Yes

*Lee, Santomasso, Biol Blood Marrow Transpl 2018*
## Bispecifics in NHL - Epcoritamab

### Clinical Efficacy of Epcoritamab in DLBCL/HGBCL

**Table 1: Efficacy of Epcoritamab in DLBCL/HGBCL**

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>DLBCL ≥12 mg</th>
<th>De novo*</th>
<th>Transformed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Evaluatable patients, n†</strong></td>
<td>14</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td><strong>Overall response rate, n (%)</strong></td>
<td>7 (50.0%)</td>
<td>5 (62.5%)</td>
<td>2 (33.3%)</td>
</tr>
<tr>
<td>Complete response</td>
<td>3 (21.4%)</td>
<td>2 (25.0%)</td>
<td>1 (16.7%)</td>
</tr>
<tr>
<td>Partial response</td>
<td>4 (28.6%)</td>
<td>3 (37.5%)</td>
<td>1 (16.7%)†</td>
</tr>
<tr>
<td>Stable disease, n (%)</td>
<td>2 (14.3%)††</td>
<td>1 (12.5%)</td>
<td>1 (16.7%)</td>
</tr>
<tr>
<td>Progressive disease, n (%)</td>
<td>5 (35.7%)</td>
<td>2 (25.0%)</td>
<td>3 (50.0%)</td>
</tr>
</tbody>
</table>

*Hutchings, ASCO 2020*
Bispecifics in NHL - Glofitamab
Bispecifics in NHL - safety

<table>
<thead>
<tr>
<th>Epcoritamab</th>
<th>All patients (N=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRS, n (%)</td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>17 (29.3%)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>16 (27.3%)</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Symptoms of CRS (≥10%)</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>33 (56.9%)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>12 (20.7%)</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>9 (16.5%)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>8 (14.5%)</td>
</tr>
<tr>
<td>Chills</td>
<td>6 (10.3%)</td>
</tr>
<tr>
<td>Neurotoxicity, n (%)</td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>2 (3.4%)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>2 (3.6%)</td>
</tr>
</tbody>
</table>

Image of safety profile for Epcoritamab showing adverse events (AEs) and grades for CRS and other symptoms.

Hutchings, ASCO 2020; Hutchings, J Clin Oncol 2021
Case #2 - conclusions

• Standard of care therapy for 3rd line DLBCL is undefined
• CAR-T, tafastiamab + lenalidomide, loncastuximab tesirine, polatuzumab+rituximab+bendamustine, selinexor, all recently approved for these patients
• Possibly, bispecific mAb will be approved in the near-term, off-the-shelf T cell-based therapy targeting different antigen than current CAR-T options
• Multiple agents (glofitamab, epcoritamab, mosunetuzumab, odronestamab) all with high ORR and CR rates, a majority of CRs appears to be durable, e.g. > 2 years
Case #3 – presentation and diagnosis

• 67 year old woman with hepatitis C
• 9/2017: PET/CT showed extensive lymph node uptake – mediastinal, gastrohepatic, peri-pancreatic, aortocaval, RP, mesenteric
• Biopsy of RP LN showed DLBCL, GCB
• Ureteral stent placed for hydroureter due to RP mass compression
Case #3 – first treatments

• 10/2017-2/2018: Patient received DA-REPOCH x 6 cycles
• 11/2018: PET/CT showed relapse with diffuse LN uptake
• Patient recommended for second-line chemotherapy
• Deferred chemotherapy due to history of low platelets and poor tolerance of REPOCH
• 9/2019: progression
• 11/2019: treated with R-DHAP x 2 cycles
• R-DHAP was tolerated poorly, with two hospitalizations for febrile neutropenia
Case #3 – next treatment

• 4/2020: Partial response (Deauville 4)
• 6/2020: Disease progression with ~70% increase in tumor bulk
Case #3 – Question 1

What treatment would be appropriate at this point?

A. Allogeneic Stem Cell Transplantation
B. CD30 x CD3 Bispecific Agent
C. CD19 CAR-T cells
D. Chemotherapy
Curative potential of CAR T

ZUMA-1: axicabtagene ciloleucel in large B cell lymphoma

JULIET: tisagenlecleucel

Chong, NEJM 2021
Jacobson, ASH 2020
Potential of CAR T: real-world evidence

<table>
<thead>
<tr>
<th></th>
<th>ZUMA-1</th>
<th>Real-world use*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>83%</td>
<td>70%</td>
</tr>
<tr>
<td>CRR</td>
<td>58%</td>
<td>50%</td>
</tr>
<tr>
<td>mDOR</td>
<td>11.1 months</td>
<td>11.0 months</td>
</tr>
<tr>
<td>mPFS</td>
<td>5.9 months</td>
<td>4.5 months</td>
</tr>
<tr>
<td>mOS</td>
<td>NR (f/u 27.1 months)</td>
<td>NR (f/u 10.4 months)</td>
</tr>
<tr>
<td>CRS G3+</td>
<td>11%</td>
<td>16%</td>
</tr>
<tr>
<td>ICANS G3+</td>
<td>32%</td>
<td>35%</td>
</tr>
<tr>
<td>Treatment-related deaths</td>
<td>1.9% (2/108)</td>
<td>6%</td>
</tr>
</tbody>
</table>

*62% of patients in this study were ZUMA-1-eligible*
Emerging data for CD19 CAR T in LBCL

• TRANSFORM trial (NCT03575351): randomized, multicenter Phase 3 trial evaluating lisocabtagene maraleucel compared to current standard of care regimens in second line

• Press release in June 2021: study met its primary endpoint of demonstrating a clinically meaningful and statistically significant improvement in event-free survival

• Peer-reviewed report pending

• Implications: CD19 CAR T may move to second line therapy for R/R DLBCL, replacing autologous stem cell transplant
Case #3 – CAR T treatment

• Patient received flu-cy lymphodepletion
• Treated with axicabtagene ciloleucel
• Patient developed Grade 3 cytokine release syndrome and Grade 3 neurotoxicity
Case #3 – Question 2

What treatment approach is appropriate for managing the patient’s Grade 3 CRS and Grade 3 ICANS?
A. High-dose corticosteroids
B. Tocilizumab
C. Anti-pyretics and vasopressors
D. Both A and B
Common CAR T toxicities: CRS and ICANS

Cytokine release syndrome
• Fever, hypotension, hypoxia
• Manage with tocilizumab and steroids
• Supportive care as needed: vasopressors, oxygen support

Immune effector cell-associated neurotoxicity syndrome
• Confusion, delirium, aphasia, headache, tremors, seizures
• Manage with steroids
• Monitor patients daily for mental status changes

SITC recommends the ASTCT grading systems for CRS and ICANS.

Check out the SITC clinical practice guideline on immune effector cell-related adverse events for more guidance.
Case #3 - post-CAR T

• 8/2020: 1 month post-CAR T, PET/CT showed complete response (Deauville 2)
• 11/2020: PET/CT shows external iliac LNs, biopsy indicates DLBCL
Case #3 – Question 3

What treatment would you consider for this patient with progression after CAR T?
A. Allogeneic Stem Cell Transplantation
B. Radiation Therapy
C. Anti CD20xCD3 Bispecific T-Cell Engager
D. Chemotherapy
Case #3 - Conclusions

• CD19 CAR T-Cells are safe and effective in patients with DLBCL as third care treatment

• Emerging data suggests CD19 CAR T-cells may become the treatment of choice in patients with DLBCL requiring 2\textsuperscript{nd} line therapy

• Grade III/IV complications such as CRS and ICANS can occur in patients with DLBCL treated with CD19 CAR T-cells
Practical Management Pearls for Immune Effector Cell-related Adverse Events
August 12, 2021, 5:30-6:30 p.m. EDT

Immune Checkpoint Inhibitor-related Adverse Events
August 13, 2021, 10-11 a.m. EDT

Learn more and register at:
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SEMINAR 4: ADENOSINE – August 24, 2021, 11:30 a.m.-1:30 p.m. EDT

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