Practical Management Pearls for Immunotherapy for the Treatment of Lymphoma

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4 – 5 p.m. EST

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Webinar faculty

David L. Porter, MD – University of Pennsylvania

Justin P. Kline, MD – University of Chicago

Koen van Besien, MD, PhD – Weill Cornell Medicine
Outline

• Prioritizing therapies in lymphoma
  • Current options
  • Role of CAR T and stem cell transplant
  • Sequencing ICIs and stem cell transplant

• CAR T in lymphoma
  • Curative potential
  • Predicting success or failure
  • Earlier use of CAR T
  • Toxicities of CAR T
Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the treatment of lymphoma

Sattva S Neelapu,1 Sherry Adkins,1 Stephen M Ansell,2 Joshua Brody,3 Mitchell S Cairo,4 Jonathan W Friedberg,5 Justin P Kline,6 Ronald Levy,7 David L Porter,8 Koen van Besien,9 Michael Werner,10 Michael R Bishop6
Guideline development

• *The Institute of Medicine’s Standards for Developing Trustworthy Practice Guidelines* were used to develop these recommendations

• Panel consisted of 12 participants, including medical oncologists, a pediatric oncologist, a nurse practitioner, and a patient advocate

• Recommendations come from literature evidence, supplemented with clinical experience of the panel members where necessary

• Consensus defined as ≥75% agreement
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Approved immunotherapies for non-Hodgkin lymphoma

Immunotherapy options include:

• Monoclonal antibodies
  • Rituximab (CD20)
  • Obinutuzumab (CD20)
  • Mogamulizumab-kpkc (CCR4)
  • Tafasitamab-cxix (CD19)

• Antibody-drug conjugates
  • Ibritumomab tiuxetan (CD20)
  • Brentuximab vedotin (CD30)
  • Polatuzumab vedotin-piiq (CD79)
  • Loncastuximab tesirine (CD19)

• Cellular therapies
  • Axicabtagene ciloleucel (CD19)
  • Tisagenlecleucel (CD19)
  • Brexucabtagene autoleucel (CD19)
  • Lisocabtagene maraleucel (CD19)

• Immunomodulators
  • Lenalidomide

• Immune checkpoint inhibitors
  • Pembrolizumab (PD-1)
## Approved immunotherapies for Hodgkin lymphoma

<table>
<thead>
<tr>
<th>Agent</th>
<th>Therapy type</th>
<th>Target</th>
<th>Indication(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brentuximab vedotin</td>
<td>ADC</td>
<td>CD30</td>
<td>First-line stage III-IV cHL (combination with doxorubicin, vinblastine and dacarbazine)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Consolidation therapy for cHL after autoSCT and high risk of relapse</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>R/R cHL after autoSCT</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>ICI</td>
<td>PD-1</td>
<td>R/R cHL after autoSCT and brentuximab vedotin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>R/R cHL after 3+ prior therapies</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>ICI</td>
<td>PD-1</td>
<td>R/R cHL after 3+ prior therapies</td>
</tr>
</tbody>
</table>
Sequencing therapies in lymphoma

• Even among the Expert Panel, the question of how to sequence therapies for lymphoma remains largely debatable.
  • Example: “The panel did not reach consensus on second-line or later lines of treatment for patients with MCL. Treatment options include brexucabtagene autoleucel, proteasome inhibitors, BTK inhibitors, BTK inhibitors+rituximab, or lenalidomide+rituximab.”

• Choice of therapy sequence may depend on patient characteristics, disease characteristics and response to prior therapies.
Stem cell transplant vs CAR T

• There is debate as to the potential of CAR T to be used in conjunction with or to replace traditional autoSCT.

• Here, 29 patients receiving anti-CD19 CART are compared with contemporaneous 27 patients who underwent autologous transplant.

• Larger studies are ongoing (i.e. ZUMA-7, BELINDA, TRANSFORM).
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
Immune checkpoint inhibitors (ICIs) and SCT

• There is limited data on ICI use prior to autoSCT.
  • This study included 78 patients with prior ICI treatment who then underwent autoSCT.

• There is a theoretical risk of GVHD exacerbation with ICIs used before/after alloSCT.

• ICIs appear to be safe after autoSCT.

Merryman, Blood Adv 2021
Use of ICIs before alloSCT

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients</th>
<th>No CPI</th>
<th>CPI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>59</td>
<td>30 (51%)</td>
<td>29 (49%)</td>
<td>0.896</td>
</tr>
<tr>
<td>Median age</td>
<td>30 (19-64)</td>
<td>31 (19-64)</td>
<td>30 (21-61)</td>
<td>0.181</td>
</tr>
<tr>
<td>Previous auto-SCT</td>
<td>49 (83%)</td>
<td>27 (90%)</td>
<td>22 (76%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous lines of therapy (median)</td>
<td>5 (2-11)</td>
<td>4 (2-11)</td>
<td>6 (3-9)</td>
<td>0.355</td>
</tr>
<tr>
<td>Disease status at Naplo-SCT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>40 (68%)</td>
<td>22 (73%)</td>
<td>18 (62%)</td>
<td>0.345</td>
</tr>
<tr>
<td>PR</td>
<td>14 (24%)</td>
<td>5 (17%)</td>
<td>9 (31%)</td>
<td>0.358</td>
</tr>
<tr>
<td>SD/PD</td>
<td>5 (8%)</td>
<td>3 (10%)</td>
<td>2 (7%)</td>
<td></td>
</tr>
<tr>
<td>Stem cells source</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BM</td>
<td>17 (29%)</td>
<td>7 (23%)</td>
<td>10 (36%)</td>
<td>0.495</td>
</tr>
<tr>
<td>PBSC</td>
<td>42 (71%)</td>
<td>23 (77%)</td>
<td>19 (64%)</td>
<td></td>
</tr>
<tr>
<td>Conditioning regimen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non myeloablatative Reduced toxicity</td>
<td>45 (76%)</td>
<td>24 (80%)</td>
<td>21 (72%)</td>
<td>0.358</td>
</tr>
<tr>
<td>0-2</td>
<td>31 (52%)</td>
<td>14 (47%)</td>
<td>17 (59%)</td>
<td></td>
</tr>
<tr>
<td>3-5</td>
<td>28 (48%)</td>
<td>16 (53%)</td>
<td>12 (41%)</td>
<td></td>
</tr>
</tbody>
</table>

De Philippis, Blood Adv 2020
Use of ICIs after alloSCT (1)

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>47</td>
<td>25</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>Male</td>
<td>Male</td>
</tr>
<tr>
<td><strong>Prior therapies (no.)</strong></td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td><strong>Stem cell source</strong></td>
<td>Matched-related</td>
<td>Matched-related</td>
</tr>
<tr>
<td><strong>Conditioning regimen</strong></td>
<td>Reduced intensity</td>
<td>Reduced intensity</td>
</tr>
<tr>
<td><strong>T cell depleted graft</strong></td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Prior GVHD</strong></td>
<td>No</td>
<td>Chronic GVHD of gut</td>
</tr>
<tr>
<td><strong>Days to relapse following AlloHSCT (no.)</strong></td>
<td>181</td>
<td>2456</td>
</tr>
<tr>
<td><strong>Localization and size of relapse</strong></td>
<td>Diffuse bone and splenic involvement</td>
<td>Multifocal adenopathy in mediastinum, retroperitoneum and pelvis. Largest lymph node 2.3 x 1.5 cm in mediastinum</td>
</tr>
<tr>
<td><strong>Prior DLI</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Immune-related adverse events</strong></td>
<td>Grade 2 Keratoconjunctivitis</td>
<td>Grade 3 Inflammatory polyarthritis and grade 2 keratoconjunctivitis</td>
</tr>
<tr>
<td><strong>Response to nivolumab</strong></td>
<td>Partial response</td>
<td>Partial response</td>
</tr>
<tr>
<td><strong>Duration of response</strong></td>
<td>6 Months+</td>
<td>10 Months+</td>
</tr>
<tr>
<td><em><em>Donor CD3</em> chimerism before and after treatment</em>*</td>
<td>18 to 49%</td>
<td>Not available</td>
</tr>
</tbody>
</table>

Godfrey, J Immunother Cancer 2017
Use of ICIs after alloSCT (2)

- 31 patients treated with PD-1 therapy for relapsed disease after allo-SCT
- ORR: 77%
- mPFS: 591 days
- mOS: not achieved
- Associated with risk of GVHD
Panel recommendations for sequencing of therapies with SCT

• There was consensus that ICI and CAR T cell therapy are both acceptable after a patient has received autoSCT. The panel did not reach consensus on the subject of whether ICIs or CAR T cell therapy should be administered prior to autoSCT.

• There was consensus that CAR T cell therapy is safe and could be considered following alloSCT, if the patient does not have active GVHD or require immunosuppression. Caution should also be exercised for patients with a history of severe GVHD.

• The panel did not reach consensus on the subject of whether ICIs should be considered contraindicated before or after alloSCT.
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# CAR T in lymphoma

## CD19 CAR T therapies

<table>
<thead>
<tr>
<th>Agent</th>
<th>Approved indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axicabtagene ciloleucel</td>
<td>R/R large B cell lymphomas after 2+ prior therapies</td>
</tr>
<tr>
<td></td>
<td>R/R follicular lymphoma after 2+ prior therapies</td>
</tr>
<tr>
<td>Tisagenlecleucel</td>
<td>R/R large B cell lymphomas after 2+ prior therapies</td>
</tr>
<tr>
<td>Lisocabtagene maraleucel</td>
<td>R/R large B cell lymphomas after 2+ prior therapies</td>
</tr>
<tr>
<td>Brexucabtagene autoleucel</td>
<td>R/R MCL</td>
</tr>
</tbody>
</table>

Axi-cel and brexu-cel have the same CAR construct; however, the manufacturing of brexu-cel involves enrichment of specific lymphocytes to improve therapeutic potential.
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*
Predictors of success vs failure: early experience (JULIET)
Predictors of success vs failure: emerging evidence

- Response to CAR T therapy is impacted by:
  - **Disease** characteristics (LDH, tumor volume, metabolic activity)
  - **Patient** characteristics (performance status, prior therapies)
  - **CAR T product** characteristics (persistence, expansion)

### Low risk:
- Pre-lymphodepletion LDH < ULN; platelet count ≥ 100,000/uL; and use of fludarabine in lymphodepletion regimen

### High risk:
- Pre-lymphodepletion LDH > ULN; platelet count < 100,000/uL; and no fludarabine in lymphodepletion regimen

*Hay, Blood 2019*
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.*
Common CAR T toxicities: cytopenias

- Short-term cytopenias are expected with lymphodepletion
- Timing and persistence of cytopenias may vary by product
- Important to consider myelodysplastic syndromes in differential diagnosis
- Risk factors include high disease burden, prior HSCT and high-grade CRS

Infection precautions and prophylaxis

• Any bacterial or fungal infections should be treated, and CAR T held until infections are controlled
• All patients should undergo pneumocystis pneumonia prophylaxis
• The decision for antibacterial, antiviral and/or antifungal prophylaxis should be risk-adjusted by patient characteristics
• For patients with high-risk historical features, antibacterial/antifungal prophylaxis should be strongly considered
• Patients with persistent neutropenia should receive antibacterial/antifungal prophylaxis
Common CAR T toxicities: B cell aplasia and hypogammaglobulinemia

• Due to on-target killing of CD19-positive B cells
• Occurs in most patients who respond to CD19 CAR T therapy
• Can be long-lasting
• Managed with immunoglobulin replacement therapy
Uncommon CAR T toxicities: HLH/MAS

- CRS and HLH/MAS substantially overlap.
- Late-onset, tocilizumab-refractory HLH/MAS-like symptoms may represent a distinct and separate pathology from conventional CRS.
- Delayed coagulopathy may be one hallmark of delayed onset HLH/MAS-like toxicity.
- Etoposide should only be administered to patients experiencing late-onset, tocilizumab-refractory HLH/MAS-like symptoms after CAR T cell therapy as a last resort.
- For treatment of late-onset, HLH/MAS-like pathology, which may be tocilzumab-refractory, third-line CRS agents such as anakinra and steroids may be considered.
Conclusions

• SITC Clinical Practice Guideline panel consisted of 12 participants, including medical oncologists, a pediatric oncologist, a nurse practitioner, and a patient advocate.

• Discussed numerous immunotherapies for lymphoma.

• Many options are available, consensus often reached on best practices and safe use of immunotherapy.

• Lack of consensus did not mean “disagreement” or “controversy”, but rather lack of data or multiple reasonable options and opinions.

• CAR T cells represent an exciting potent new approach to immunotherapy in lymphoma.

• Associated with significant and unique toxicities.

• New information is allowing physicians to better predict which patients are most likely to benefit from CAR T cells.

• CAR T cells have curative potential in lymphoma.
Case Studies in Immunotherapy for the Treatment of Lymphoma

July 7, 2021, 5:30-6:30 pm ET

Learn more and register at: https://www.sitcancer.org/research/cancer-immunotherapy-guidelines/webinars
Targets for Cancer Immunotherapy: A Deep Dive Seminar Series

Eight online seminars will address key questions in the field of cancer immunotherapy drug development

SEMINAR 2 – THE TIGIT PATHWAY: A DEEP DIVE IN CANCER IMMUNOTHERAPY TARGETS – June 29, 2021, 2-4 p.m. EDT

SEMINAR 3 – IL-2 VARIANTS AND IL-15: A DEEP DIVE IN CANCER IMMUNOTHERAPY TARGETS – July 19, 2021, 4:30-6:30 p.m. EDT

Learn more and register at: https://www.sitcancer.org/education/deepdive
Clinical Updates from ESMO Immuno-Oncology Virtual Congress 2020

July 16, 2021, 12 – 1 PM ET

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Questions or comments: connectED@sitcancer.org

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