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Autologous Transplant versus Chimeric Antigen Receptor T-cell Therapy for Relapsed DLBCL in Partial Remission

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Disclosures

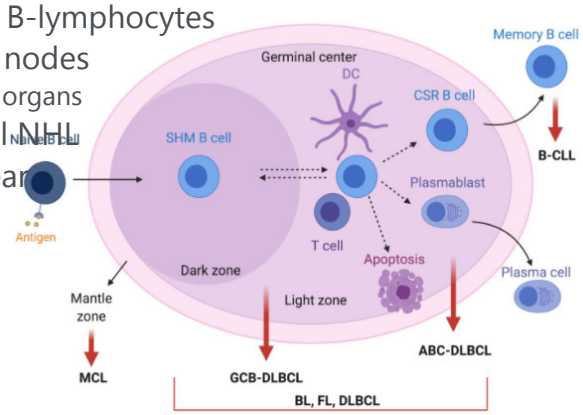
Neither myself nor any of my affiliates have any conflicts of interest regarding this presentation.

Objective

Evaluate the role of autologous transplant versus treatment with chimeric antigen receptor t-cell therapy in patients with relapsed DLBCL in partial remission.

Background

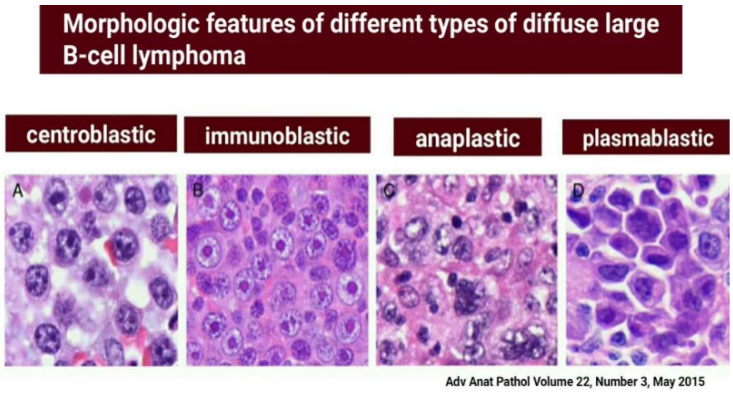
- Diffuse Large B Cell Lymphoma (DLBCL)
  - Most common form of non-Hodgkin lymphoma (NHL)
  - Aggressive form of NHL affecting B-lymphocytes
  - B-cells quickly grow in the lymph nodes
    - Spleen, liver, bone marrow, or other organs
  - 25-30% of newly diagnosed B-cell NHL
  - 18,000 people diagnosed each year
  - Incidence increases with age
  - More common in Caucasian
  - Curable in ~60% of cases



Padala SA, Kallam A. DLBCL In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan

Pathophysiology

- DLBCL derived from mature B cells
  - Centroblasts or immunoblasts
- Pathogenesis
  - BCL 6
  - Shared molecular alterations
  - Richter's transformation
  - Transformation from other lymphomas



https://lymphomahub.com/medical-information/genetic-dysregulation-of-b-cell-lymphoma-a-focus-on-epigenetic-modifiers-in-dlbcl-and-fl-from-esh-2020

Prognosis

- Dependent on staging, histopathology, extranodal involvement, age and performance status
- Decreased overall survival correlated with
  - Age >60 years of age
  - Eastern Cooperative Oncology Group (ECOG) >2
  - LDH elevation
  - Clinical stage III or IV
  - >1 extranodal involvement
- Relapse rate of 40%
  - Patients who relapse within 2 years reported 1.4-year median survival

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Koh, et al Predictors of ER vs LR in DLBCL relapses in the rituximab era Journal of Clinical Oncology 2018 36:15_suppl, e19553-e19553

Standard-of-care

- Current standard-of-care for relapsed disease
  - Fit patients
    - Alternative salvage therapy
    - Followed by high-dose chemotherapy
  - Patient achieves a complete remission (CR)
    - Autologous hematopoietic cell transplant (Auto-HCT)
  - Patient achieves a partial remission (PR)
    - Autologous hematopoietic cell transplant (Auto-HCT)
    - Chimeric antigen receptor T-cell (CAR-T)

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Definitions

Deauville Score	
1	No uptake
2	Uptake ≤ mediastinum
3	Uptake ≥ mediastinum < liver
4	Uptake moderately increased above liver at any site
5	Markedly increased uptake at any site including new sites of disease

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Lugano Classification

Modality	Complete Response	Partial Response	Stable Disease	Progressive Disease
CT	Lymph nodes ≤ 1.5 cm in LDI Complete disappearance of radiologic evidence of disease	Single lesion: ↓ > 50% in SPD of up to six lymph nodes or extra nodal sites	↓ ≤50% in SPD of up to 6 lymph nodes or extra nodal sites (no criteria for progressive disease are met)	1) New lymphadenopathy or ↑; single node must be abnormal with: a) Ldi > 1.5 cm and b) PPD ≥ 50% and c) LDI or Sdi ↑ 0.5 cm if ≤ 2.0 cm and ↑ 1.0 cm if > 2.0 cm 2) ↑ splenic volume (several criteria)
FDG PET-CT	Scores 1, 2, 3 in nodal or extra nodal sites with or without a residual mass	Scores 4 or 5 with ↓ uptake compared with baseline And residual mass(es)	Scores 4 or 5 with no obvious change in FDG uptake	Scores 4 or 5 in any lesion with ↑ uptake from baseline and/or new FDG-avid foci

Abbreviations
LDI: longest transverse diameter
SPD: sum of the product of the perpendicular diameter of multiple lesions
PPD: product of perpendicular diameters
SDI: shortest transverse diameter
FDG: fluorodeoxyglucose

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Cheson BD. Staging and response assessment in lymphomas: the new Lugano classification. Chin Clin Oncol. 2015 Mar;4(1):5.

Previous literature in relapsed/refractory DLBCL

Trial	Population	Intervention	Outcome
Mills, W 1995	• 107 participants	• BEAM then Auto-HCT	• ORR 73% (41% CR and 32% PR) • 5-year OS 41% • 5-year PFS 35%
TRANSCEND NHL 001	• 269 participants	• Lisocabtagene maraleucel (Breyanzi)	• 73% ORR (CI 66.8-78) • 53% CR (CI 46.8-59.4)
JULIET	• 93 participants	• Tisagenlecleucel (Kymriah)	• Best ORR 52% (CI 41-62) • CR 40% • PR 12% • 1-year RFS 65%
ZUMA-1	• 111 participants	• Axicabtagene ciloleucel (Yescarta)	• OR 82% • CR 54% • 18-month survival 52%

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Mills W, et al. BEAM chemo and autoHCT for R/R nHL J Clin Oncol. 1995 Mar;13(3):588-95
Abramson JS, et al (TRANSCEND NHL 001). Lancet. 2020 Sep 19;396(10254):839-852.
Schuster SJ, et al. Tisagenlecleucel in Adult R/R DLBCL. N Engl J Med. 2019 Jan 3;380(1):45-56.
Neelapu SS, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy rBCL N Engl J Med. 2017 Dec

Currently Ongoing Trials

Trial	Population	Intervention	Comparison	Outcome
BELINDA	• 355 participants • Phase 3 randomized, open-label study	• Investigator's choice (R-ICE, R-GemOx, R-GDP, R-DHAP) + cyclophosphamide and fludarabine or bendamustine and tisagenlecleucel	• Investigator's choice (R-ICE, R-GemOx, R-GDP, R-DHAP) + BEAM and Auto-HCT	• **EFS** • OS • ORR • DOR • Others
TRANSFORM	• 175 participants • Phase 3 randomized, open-label study	• Conditioning regimen of cyclophosphamide and fludarabine followed by lisocabtagene maraleucel	• Standard of Care (R-DHAP, R-ICE, or R-GDP) + BEAM and Auto-HCT	• **EFS** • CRR • PFS • OS • Others
ZUMA-7	• 359 participants • Phase 3 randomized, open-label study	• Conditioning regimen of cyclophosphamide and fludarabine followed by axicabtagene ciloleucel	• Standard Therapy (R-ICE) + BEAM and Auto-HCT	• **EFS** • ORR • OS • mEFS • Others

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clinicaltrial.gov/NCT03570892
clinicaltrial.gov/NCT03575351
clinicaltrial.gov/NCT03391466

Polling Question #1

- What is the preferred CAR-T product for DLBCL at your institution?
  A. Axicabtagene ciloleucel (Yescarta™)
  B. Tisagenlecleucel (Kymriah™)
  C. Lisocabtagene maraleucel (Breyanzi™)
  D. Clinical Trial

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Background

Purpose

- Currently no consensus for subsequent treatment of patients with a partial remission (PR)

Objectives

- Primary endpoint was progression free survival (PFS)
- Secondary endpoints
  - Overall survival (OS)
  - Cumulative incidence of relapse/progression

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Study Design & Methods

- **Design**
  - Retrospective analysis of patients with DLBCL who achieved a PR as the best response to therapy who received either auto-HCT or CAR-T.
- **Methods**
  - Patients were identified via the Center for International Blood & Marrow Transplant Research (CIBMTR) registry database.

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Eligibility

Inclusion Criteria

- Adult patients (≥18 years of age)
- DLBCL high grade B-cell lymphoma
  - MYC and BCL2 and/or BCL6 rearrangements
- Primary Mediastinal large B-cell Lymphoma
- Achieved a partial remission
- Underwent either auto-HCT or CAR-T with axi-cel

Exclusion Criteria

- Patients with available negative PET scan
- Patients in CAR-T cohort with prior auto-HCT

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Statistical Analysis

- Baseline characteristics
  - Kruskal-Wallis test for continuous variables
  - Pearson chi-square test for categorical variables
- Kaplan-Meier and log-rank test used to compare OS and PFS
- Gray's test for competing events
  - Hemopoietic recovery
  - Non-relapse mortality (NRM)
  - Relapse/progression rates
- Cox proportional hazard model for PFS and OS
- Proportional cause-specific hazard model for NRM and relapse or progression

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Population

- 411 patients with DLBCL
  - 266 who received auto-HCT
  - 145 who received CAR-T
- Significant differences between race, prior lines of therapy, and largest node prior to treatment
- Fewer patients in the auto-HCT group had largest pretreatment residual node
- 14 patients received CAR-T after post auto-HCT relapse

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Baseline Characteristics	Auto-HCT	CAR-T
Median age (range) ≥60 years (%)	58 (18-80) 118 (63)	60 (24-91) 89 (61)
Male	167 (63)	89 (61)
Stage at diagnosis Stage III-IV (%) Missing	 163 (61) 42 (16)	 80 (55) 35 (24)
Refractory to first line (%) Missing	160 (60) 6 (2)	79 (55) 22 (15)
Time from diagnosis ≤ 12 months > 12 months Missing	 103 (39) 162 (61) 1 (0)	 64 (44) 81 (56) 0
Lines of therapy Median (range) More than 2 lines- no (%)	 2 (1-6) 89 (33)	 3 (2-11) 97 (67)

Univariable Analysis

	Auto-HCT (N=266)	CAR-T (N=145)	
Outcomes	Prob (95% CI)	Prob (95% CI)	p-value
Non-relapse Mortality			0.2
100-day	4% (2-7)	2% (0-5)	0.3
1-year	7% (4-11)	3% (1-6)	0.05
3-year	9% (5-13)	6% (1-16)	0.6
Progression/relapse			0.01
1-year	34% (28-40)	45% (37-54)	0.03
2-year	40% (33-46)	52% (41-63)	0.05
Progression-free survival			0.1
1-year	59% (53-65)	52% (43-61)	0.2
2-year	52% (46-58)	42% (30-53)	0.1
Overall survival			0.01
1-year	76% (70-81)	67% (59-75)	0.1
2-year	69% (63-74)	47% (33-60)	0.004

Abbreviations:
N eval: number evaluated Auto-HCT: autologous hematopoietic cell transplantation
Prob: probability
CAR-T: chimeric antigen receptor T-cells

Subgroup Univariable Analysis

	Auto-HCT (N=222)	CAR-T (N=126)	
Outcomes	Prob (95% CI)	Prob (95% CI)	p-value
Non-relapse Mortality			0.2
100-day	3% (1-5)	2% (0-5)	0.5
1-year	6% (3-9)	3% (1-6)	0.1
3-year	7% (4-11)	3% (1-6)	0.04
Progression/relapse			0.007
1-year	33% (27-39)	46% (36-55)	0.03
2-year	39% (32-46)	54% (42-66)	0.03
Progression-free survival			0.04
1-year	61% (55-68)	52% (42-61)	0.1
2-year	54% (47-61)	43% (32-55)	0.1
Overall survival			0.005
1-year	79% (73-84)	69% (60-77)	0.06
2-year	71% (65-77)	49% (34-63)	0.006

Abbreviations:
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Prob: probability
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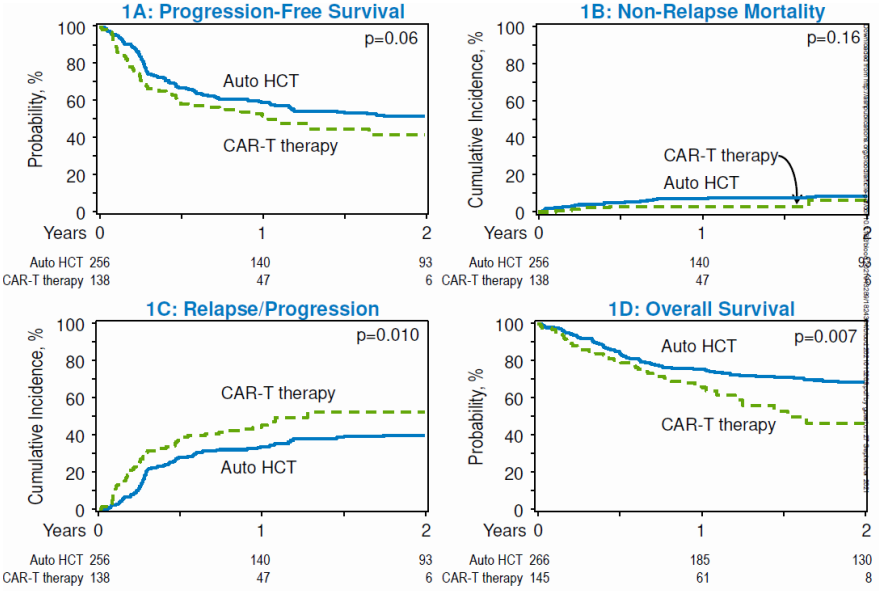
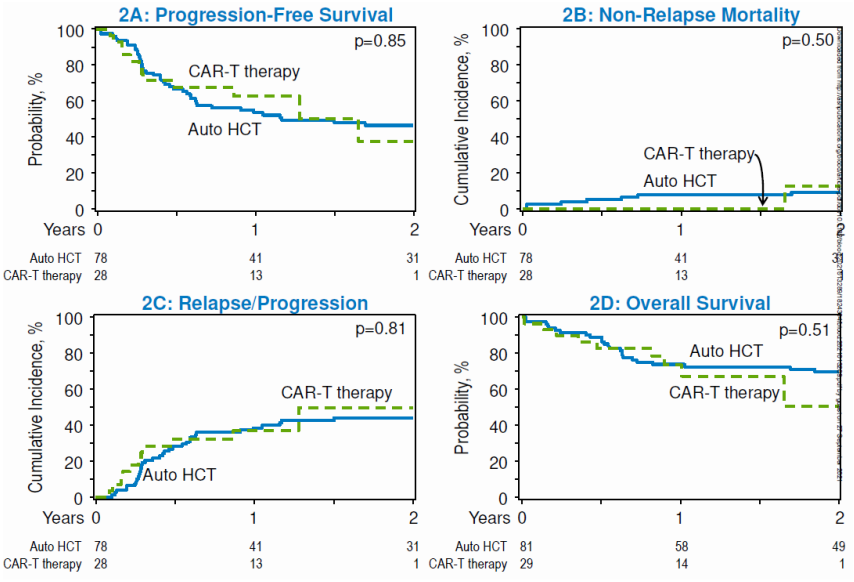
All Patient Outcomes for Patients in PR



Outcomes for Patients in PR after ≤ 2 Prior Lines of Therapy



Author's Conclusions

- Auto-HCT does not improve progression free survival but does have a lower incidence of relapse and improved overall survival
- Results of future randomized phase III trials help determine optimal second-line therapy
- Some patients may still receive chemotherapy despite potential for CAR-T to provide superiority
  - Patients may not meet eligibility criteria
  - Lack of immediate access to CAR-T
  - Patient or physician preferences

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Evaluation

Strengths

- Limited studies on optimal treatment sequence in relapsed patients
- Currently no NCCN guideline recommendation for sequence

Weaknesses

- Retrospective analysis
- Unable to determine clinical decisions behind treatment modality selection
- Partial remission criteria not standardized
- Limited subgroup analyses
  - Small sample size

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Reviewer's Conclusions

- Further evaluate the impact of multiple lines of therapy prior to auto-HCT or CAR-T
- Patients received auto-HCT prior to CAR-T approval
- Future directions
  - Prospective randomized- controlled trials
  - Cost analysis versus outcomes
  - Results of current ongoing studies
    - BELINDA
    - TRANSFORM
      ZUMA-7

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Polling Question #2

- What is the standard of practice at your institution for patients with relapsed DLBCL?
  A. Proceed to CAR-T
  B. Proceed to auto-HCT
  C. No standard of practice currently in place

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