Impact of Increasing Wait Times on the Cost-Effectiveness of Chimeric Antigen Receptor (CAR) T-Cell Therapy in large B-cell lymphoma: A Discrete Event Simulation Model

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Overview

- Background
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  - Methods
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- Limitation and Conclusion
Background
The development of chimeric antigen receptor (CAR) T-cells has transformed oncology treatment, offering the potential to cure certain cancers.

CAR T-cell therapy genetically engineers a patient’s own T-cells by transforming the cell surface to incorporate a new protein capable of targeting the CD19 antigen exclusively found on B-cells, including the cancer cells in diffuse large B-cell lymphoma (DLBCL).

Treatment begins with leukapheresis, in which white blood cells, containing T-cells, are separated from a patient’s blood.

These cells are then transported to a facility that genetically engineers these T-cells into CAR T-cells.

Retroviruses are used to insert the DNA of the chimeric antigen receptor protein into the DNA of the patient’s cells.

These cells are amplified by several million-fold, before they are transfused back into the patient.
# Background – Clinical Trials for DLBCL

<table>
<thead>
<tr>
<th></th>
<th>ZUMA-1 PHASE 2 TRIAL (N=101) Neelapu S et al. NEJM 2017</th>
<th>JULIET PHASE 2 TRIAL (N= 93) Schuster et al. NEJM 2018</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td>101 adults w DLBCL, PMBCL, or transformed FL</td>
<td>93 adults with relapsed/refractory DLBCL</td>
</tr>
<tr>
<td></td>
<td>Median age 58 yrs (23-76)</td>
<td>Median age 56 years (22-76)</td>
</tr>
<tr>
<td></td>
<td>Median follow up 15 months</td>
<td>Median follow up 14 months</td>
</tr>
<tr>
<td><strong>Product</strong></td>
<td>Axicabtagene Ciloleucel Gamma-retrovirus; CD28 co-stim domain</td>
<td>Tisagenlecleucel CTL019</td>
</tr>
<tr>
<td><strong>CAR T-Cell Therapy</strong></td>
<td>Fludarabine 30 mg/m^2 daily x 3 Cylophosphamide 500 mg/m^2 daily x 3 Axi-cel (target 2.0x10^8 cells/kg) Maximum 2.0 x 10^8 total cells</td>
<td>Fludarabine 25 mg/m^2 daily x 3 Cylophosphamide 250 mg/m^2 daily x 3 Or Bendamustine 90 mg/m^2/day × 2 days CAR-positive viable T-cells Median dose 3.0 x 10^8 cells</td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td>ORR 82%; CR 54%; PFS 44% at 12 months; OS 59% at 12 months</td>
<td>ORR 52%; CR 40%; PR 12%</td>
</tr>
<tr>
<td><strong>Toxicity</strong></td>
<td>Grade 3 or 4 AEs: 95%; CRS: 93% (13% Grade 3 or higher) Neurotoxicity: 64% (28% Grade 3 or higher) TRM: 2 pts</td>
<td>Grade 3 or 4 AEs: 86%; CRS: 58% (22% Grade 3 or higher) Neurotoxicity: 21% (12% Grade 3 or higher) TRM: 0 pts</td>
</tr>
</tbody>
</table>
Background – ZUMA-1

- In this Phase 2 trial, axi-cel was successfully manufactured in 110 patients (99%) and 101 patients received axi-cel (91%).

- Median time from leukapheresis to delivery of axi-cel to the treating facility was 17 days.

- Response was evaluated one month after infusion, with objective response (complete and partial response) as the primary outcome.

- At the updated data cut-off at a median of 15.4 months of follow-up, 42% remained in response, including 40% with a complete response.

- Common adverse events included cytokine release syndrome of 93% of patients with most cases being Grade 1 or 2 severity (80%), and neurologic events in 64% of patients, with 28% being Grade 3 or higher.
Background - Hypothesis

- CAR T-cell therapy is resource intensive and potentially limited to centers of excellence when firstly funded.

- Demand will be high in the beginning, limited capacity may prolong wait-times.

- Currently, there is lack of data to inform the limits of an acceptable CAR-T wait-time.
Objective

- Using mathematical simulation models to estimate the hypothetical effectiveness of CAR T-cell therapy with increasing wait-times.

- This will provide valuable information to both clinicians and health policy decision-makers to account for resource allocation
Methods:

Impact of Increasing Wait Times on 1-year Mortality
Methods: Population and Inception time

- Our study population represents the individuals who underwent the ZUMA-1 study. (i.e. patients who are relapsed or refractory diffuse large B-cell lymphoma (DLBCL).
- These are patients who’ve already received second-line chemotherapy and are preparing to undergo CAR T-cell Therapy.
- The average age is 58 years.
- Inception time point:
  - We begin our model with the patient having completed all necessary diagnostic tests and deemed appropriate to begin CAR T-cell Therapy.
- The delay in time for treatment represents the amount of time the CAR T-cell Therapy population must wait to receive their therapy, and the corresponding one-year outcomes were based on the one-year period from the inception point.
- Important assumption:
  - The model assumes that patients will undergo chemotherapy treatment while they wait for their CAR T-cell therapy and will follow the OS and PFS chemotherapy curves while awaiting CAR T-cell Therapy treatment.
Methods: Decision Model

- Discrete event simulation (DES) is a form of computer-based modeling that provides an intuitive and flexible approach to represent a complex system.
  - It can represent complex relationships among individuals, populations and their environment.
- Most early applications involved analyses of systems with constrained resources, where the general aim was to improve the organization of delivered services.
  - DES models are used widely in service facilities, production and material handling systems when congestion or competition for scarce resources can occur.
- More recently, DES has increasingly been applied to evaluate specific technologies in the context of health technology assessment.
  - DES models can simulate individual patients as they transit through the health care system, with transitions dependent on both patient characteristics and the availability of resources.
  - Models can determine if queues will develop due to resource constraints, and can also evaluate the impact of wait-time strategies.
Methods: DES

Eligible Patient

CAR T-Cell Therapy

Queue for CAR T-cell Therapy

Wait time death

Yes

CAR T-cell Therapy All cause mortality

No

1 year death

Yes

CAR T-Cell Therapy Survival

No

1 year death

Yes

Chemotherapy All cause mortality

No

Chemotherapy Survival

see Figure 1b

Salvage Chemotherapy
Methods: Wait time contributors

Approval and Leukapheresis
• Average reimbursement approval time
• Average wait time for facilities
• Facility capacity (Personnel/Equipment)
• Patient travel time
• Leukapheresis time
• Centres available

Manufacturing Parameters
• Time to engineer cells.
• Facility capacity (Personnel/Equipment)
• Manufacturing Failure rate
• Delivery time receive from clinic
• Centres available

Infusion Centre and Monitoring
• Delivery time receive from manufacturing centre
• Duration during patient monitoring
• Wait time for infusion
• Facility capacity (Personnel/Equipment)

Parameters impacting delay of treatment
Patient uses standard chemotherapy treatment until end of delay

ZUMA-1: From Leukapheresis to time engineered cells are ready to be infused: 2-3 weeks
Methods: Input Parameters

- **Main Input parameters:**
  - CAR-T-cell Therapy arm: ZUMA-1
  - Chemotherapy arm: SCHOLAR-1
    - SCHOLAR-1: Retrospective Study contains relapsed or refractory DLBCL (N = 424)

- **Digitalization and Reconstructing the KM curves:** Survival curves of the ZUMA-1 and SCHOLAR-1 were digitized and Kaplan-Meier curves were reconstructed using an algorithm designed by Guyot et. al.

- **Extrapolation:** Parametric fits
  - OS and PFS curves of the ZUMA-1
  - OS curve of the SCHOLAR-1
  - Based on the best model fit using AIC/BIC information.
Methods: Analysis

- Fully probabilistic individual level model
  - For each CAR-T-cell Therapy wait-time:
    - 10,000 1st order Monte-Carlo simulations.
    - 100 2nd order Monte-Carlo simulations for parameter uncertainty.
  - Acceptability Curve
    - Proportion of 100 2nd order simulations in which CAR-T vs. chemotherapy had lower mortality.

- For mortality illustration
  - 1-year time horizon
  - Wait-times ranging between 1 to 9 months
Results - Validation

Overall Survival

- DES
- ZUMA-1
- Distribution

OS (%) vs. Time (months)
Results:

Impact of Increasing Wait Times on 1-year Mortality
## Results – 1 year mortality

<table>
<thead>
<tr>
<th>CAR-T wait time</th>
<th>CAR-T 1 year death (%) (95% C.I)</th>
<th>Chemotherapy 1 year death(%) (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No delay</td>
<td>33.65 (33.15-34.13)</td>
<td>74.69(74.26-75.1)</td>
</tr>
<tr>
<td>1 month</td>
<td>35.61(35.05-36.17)</td>
<td>74.69(74.26-75.1)</td>
</tr>
<tr>
<td>2 months</td>
<td>38.59(38.2-38.97)</td>
<td>74.69(74.26-75.1)</td>
</tr>
<tr>
<td>3 months</td>
<td>44.47(44.28-44.65)</td>
<td>74.69(74.26-75.1)</td>
</tr>
<tr>
<td>4 months</td>
<td>51.00 (50.79-51.19)</td>
<td>74.69(74.26-75.1)</td>
</tr>
<tr>
<td>5 months</td>
<td>57.35(57.13-57.57)</td>
<td>74.69(74.26-75.1)</td>
</tr>
<tr>
<td>6 months</td>
<td>62.99(62.64-63.32)</td>
<td>74.69(74.26-75.1)</td>
</tr>
<tr>
<td>7 months</td>
<td>67.99(67.33-68.64)</td>
<td>74.69(74.26-75.1)</td>
</tr>
<tr>
<td>8 months</td>
<td>72.05(71.33-72.76)</td>
<td>74.69(74.26-75.1)</td>
</tr>
<tr>
<td>9 months</td>
<td>75.66(75.11-76.19)</td>
<td>74.69(74.26-75.1)</td>
</tr>
</tbody>
</table>
Results – 1 year mortality

![Graph showing the comparison of 1 year mortality between CAR T cell therapy and chemotherapy over wait time (in months). The graph displays a higher mortality rate for CAR T cell therapy compared to chemotherapy as wait time increases.](image)
Results – Acceptability Curves

Proportion of 100 2\textsuperscript{nd} order simulations in which CAR-T vs. chemotherapy had lower mortality

Acceptability Curves for CAR T-cell Therapy and Chemotherapy

Delay of CAR T-cell Therapy treatment (Months)

- CAR T-cell Therapy
- Chemotherapy
Methods:

Impact of Increasing Wait Times on System-level Cost-Effectiveness
Methods: System-level Cost-effectiveness Analysis

- Model: Same DES
- Main Input parameters:
  - CAR-T-cell Therapy arm: ZUMA-1
  - Chemotherapy arm: SCHOLAR-1
    - SCHOLAR-1: Retrospective Study contains relapsed or refractory DLBCL (N = 424)
- Cost and QALY:
  - Based on Institute for Clinical and Economic Review Report:
    - https://icer-review.org/material/car-t-final-report/
  - Using the same assumptions as indicated in the report:
    - Assumptions of “cured” on PFS and OS
    - US perspective
    - Discount rate 3%
    - Life-time horizon
Preliminary Results:

Impact of Increasing Wait Times on CEA
Preliminary Results - CEA

<table>
<thead>
<tr>
<th>CAR-T wait time</th>
<th>Δ Cost (CAR-T vs Chemo)</th>
<th>Δ QALY (CAR-T vs Chemo)</th>
<th>ICER (CAR-T vs Chemo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No delay</td>
<td>$392,230</td>
<td>3.54</td>
<td>$110,799</td>
</tr>
<tr>
<td>1 month</td>
<td>$352,015</td>
<td>2.97</td>
<td>$118,524</td>
</tr>
<tr>
<td>2 months</td>
<td>$315,469</td>
<td>2.34</td>
<td>$134,816</td>
</tr>
<tr>
<td>3 months</td>
<td>$282,015</td>
<td>1.56</td>
<td>$180,779</td>
</tr>
<tr>
<td>4 months</td>
<td>$232,043</td>
<td>0.91</td>
<td>$254,992</td>
</tr>
<tr>
<td>5 months</td>
<td>$183,463</td>
<td>0.36</td>
<td>$509,619</td>
</tr>
<tr>
<td>6 months</td>
<td>$142,033</td>
<td>-0.02</td>
<td>Dominated</td>
</tr>
</tbody>
</table>

ICER (CAR-T vs chemotherapy)
Limitations

- ZUMA-1 and SCHOLAR-1 trials are both single arm studies, with the ZUMA-1 containing a relatively small population.
  - Direct comparative and long-term evidence is lacking.

- No wait-time specific data currently available. We make the best-case scenario assumption on wait-time mortality that a patient who will experience a delay before receiving CAR T-cell Therapy, will immediately begin chemotherapy treatment without any additional delays.

- This research was a modelling exercise, and does not incorporate many of the distinctions of clinical decision-making.
  - Our model should therefore be considered hypothesis-generating and not conclusive
Conclusion

- CAR T-cell Therapy treatment delay has a significant impact on survival outcomes, and that even modest delays in CAR T-cell Therapy significantly hinder its efficacy and system-level cost-effectiveness.

- Wait-time strategies that minimize delays in access to CAR T-cell Therapy will be associated with a reduction of complications during waiting, and improvement of clinical outcomes.

- When policy makers decide to implement CAR T-cell Therapy, information pertaining to the wait-time of treatment must factor into their decision.
Next step

Phase 1: Qualitative Study
- Implementation challenges
- System capacity
- Inform unknown parameters

Phase 2: System-level DES
- Projected health and economic burden
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