Physician Preferences for CAR T Therapy: Trading off Benefits, Risks, and Time to Infusion in the Treatment of Diffuse Large B-Cell Lymphoma

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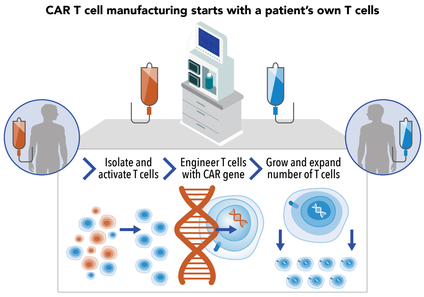
BACKGROUND

- Approximately 74,000 Americans are diagnosed with non-Hodgkin lymphoma (NHL) each year. Diffuse large B-cell lymphoma (DLBCL) is the most common form of NHL in adults, representing 33% of all NHL in the United States (US).[1]
- First-line treatment for DLBCL is usually a combination of intravenous and oral treatments referred to as R-CHOP (rituximab, cyclophosphamide, Oncovin, doxorubicin hydrochloride, and prednisone).
- Historically, limited treatment options (including stem cell transplants) have been available for patients with DLBCL who relapse or have refractory disease.
- Recently, autologous anti-CD19 chimeric antigen receptor T-cell (CAR T) therapies were approved for the treatment of patients with relapsed or refractory large B cell lymphoma with ≥ 2 prior systemic therapies.
- CAR T therapy carries additional risks and requires manufacturing time between leukapheresis (collection of patient's T-cells) and infusion.
- Several steps are involved in CAR T therapy (see Figure 1).

Figure 1. Steps Involved in CAR T Therapy



Source: Wang et al.[2]

- Currently, there are 2 CAR T options available to treat DLBCL. These options differ regarding time to infusion and risk of adverse events.[3,4]
- Currently, little quantitative information is available about how physicians make decisions when choosing among CAR T treatments for patients with DLBCL.

OBJECTIVES

- Quantify physician preferences for efficacy, time from leukapheresis to infusion, and risk of complications associated with CAR T treatments for adult patients with DLBCL
- Determine whether physicians' treatment preferences vary systematically between a patient profile with average disease progression and a patient profile with rapid disease progression
- Quantify the tradeoffs that physicians are willing to accept between risks, benefits, and specific improvements in time from initial cell collection to infusion

METHODS

Study Design

- A discrete-choice experiment (DCE) was administered to US oncologists and hematologists who treated at least 10 patients with DLBCL in the past year.
- Physicians were shown two hypothetical patient profiles, one with average and one with rapid disease progression.
- For each patient profile, physicians chose between two hypothetical CAR T treatments in 12 experimentally designed choice questions and one direct-comparison question in which CAR T Treatment A was similar to Yescarta© and CAR T Treatment B was similar to Kymriah©.
- The hypothetical CAR T alternatives in each choice question were defined by 6 attributes shown in Table 1.
- The survey instrument was pre-tested in 10 physician interviews in May 2019.

Table 1. CAR T Treatment Attributes and Levels

Attribute Label	Attribute Definitions	Levels
Probability of complete response achieved at 6 months	Different CAR T therapies result in different probabilities of achieving complete response (CR) as assessed according to the International Working Group (IWG) Response Criteria for Malignant Lymphoma. In this survey, we will ask you to consider treatments with different rates of CR at 6 months ranging from 40% to 60%.	40% 52% 60%
Probability of overall survival at 12 months	Different CAR T treatments result in different probabilities of overall survival (OS) at 12 months. In this survey, we will ask you to consider treatments with different rates of OS at 12 months ranging from 40% to 60%.	40% 52% 60%
Probability of overall survival at 24 months	Different CAR T treatments result in different rates of OS at 24 months. In this survey, we will ask you to consider treatments with different rates of OS at 24 months ranging from 40% to 55%.	40% 48% 55%
Time from initial collection (leukapheresis) to infusion	CAR T therapy uses the patient's own immune cells to seek and destroy cancerous cells. After blood is taken from the patient, the T cells are removed from the sample, genetically modified to create chimeric antigen receptors, and then infused back into the patient. This process requires time from initial collection (leukapheresis) and manufacturing to reinfusing a patient's individual T cells. In this survey, we will ask you to consider different treatments that take between 16 and 113 days to manufacture and get to the patient.	16 days 24 days 47 days 73 days 113 days
Risk of severe cytokine release syndrome	Patients receiving CAR T treatment are at risk for severe (grade 3 or 4) cytokine release syndrome (CRS). Symptoms of CRS may include pyrexia, hypotension, hypoxia, arrythmia, chills, and sinus tachycardia. Please note that CRS is transient and that the median time to resolution is approximately 7-8 days; however, some patients will experience severe or life-threatening complications from CRS. In this survey, we will ask you to consider treatments with a risk of severe CRS ranging from 5% to 25%.	5% 10% 25%
Risk of a severe neurological event	Patients receiving CAR T treatment are at risk of experiencing severe (grade 3 or 4) neurological events (NEs). These NEs may include encephalopathy, confusion, tremor, aphasia, somnolence, agitation, memory impairment, and mental-status changes. Please note that the severe NEs described above are transient and that the median time to resolution is approximately 2 weeks. In this survey, we will ask you to consider treatments with a risk of NEs ranging from 10% to 32% of patients.	10% 20% 32%

Note: To ensure the presentation of efficacy in each hypothetical CAR T treatment profile was realistic, the DCE experimental design was constrained so that CR at 6 months was always greater than or equal to OS at 12 months and that OS at 12 months was always greater than or equal to OS at 24 months.

Data Analysis

- Choice data were analyzed using random-parameters logit to generate preference weights for all attribute levels.
- Physicians' preferences did not vary systematically between two patient profiles. Therefore, the data were pooled for analysis.
- Random-parameters logit results were used to calculate maximum percentage-point increases in treatment-related risks for reductions in time to infusion and to predict the share in the direct elicitation question (i.e., for validation) by simulating the distributions estimated for each coefficient with 10,000 random draws.
- The results from the DCE were used to predict the share in the direct elicitation question (i.e., for validation).

RESULTS: PRIMARY ANALYSIS

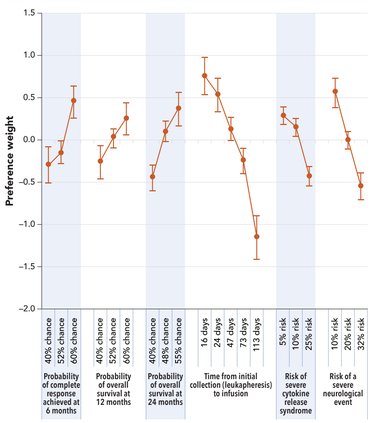
Sample

- 150 physicians completed the online survey:
  - 17% report 1 to 5 years of experience treating adult patients with DLBCL, 26% report 6 to 10 years, 19% report 11 to 15 years, and 38% report more than 15 years of experience.
  - 79% are male, 47% work in academic hospitals, and 63% work at hospitals where CAR T therapy is commercially available.
    - Among 94 physicians whose institution uses commercial CAR T, 65% have both Yescarta© and Kymriah©, 15% have only Yescarta©, 14% have only Kymriah©, and 6% did not know or were not sure.
    - Among these 94 physicians, 90% used commercial CAR T to treat patients with relapsed/refractory DLBCL during the past 12 months. More than 68% of them used CAR T for 6 or more patients.
  - 8% have been an investigator in a clinical trial for CAR T treatment, and 33% of their institutions are currently running a clinical trial using CAR T therapy.

Preference Weights

- Figure 2 shows the preference-weight estimate for each attribute level.
- The change in utility associated with a change in the levels of each attribute is represented by the difference between the preference weights for any two levels of that attribute in Figure 2.
  - Decreasing time to infusion from 113 to 16 days yields the highest utility gain.
  - Shifts from the least- to most-preferred levels of the other attributes yielded lower utility gains, with risk of severe NEs generating slightly higher utility gains than the rest.

Figure 2. Preference Weights (N = 150)



Notes: A higher preference weight indicates that a level is more preferred. The vertical bars surrounding each mean preference weight denote the 95% confidence interval of the point estimate.

RESULTS: SECONDARY ANALYSIS

Maximum Acceptable Risk Increase

- The preference weights (Figure 2) were used to calculate the maximum acceptable risk increase (MARI) by percentage point of severe CRS from 5% and of a severe NE from 10% (the lowest levels included in the DCE) that physicians would be willing to accept for increases in the probability of a CR, increases in the probability of OS, and reductions in time from initial collection to infusion (see Table 3).
- The percentage-point difference between the highest and lowest levels presented in the survey is 20% and 22% for risk of CRS and severe NE, respectively.
- Greater MARI requires the strong assumption that the disutility of each unit increase in risk remains constant beyond the highest level of risk presented. For simplicity, these MARI estimates are reported as greater than 20 or 22.
- To gain improvements in CR at 6 months and OS at 12 months, physicians were generally willing to accept increases in the risk of severe CRS and severe NE.
- To reduce time to infusion from 113 to 47 days (or lower), physicians were willing to accept increases in risk of > 20 percentage points for severe cytokine release syndrome and > 22 percentage points for severe NEs.

Direct-Comparison Question

- Direct comparisons between hypothetical CAR T treatments A and B predicted physician preferences 79% of the time for CAR T A, with higher response rate and adverse event rate attributes but lower time from collection to infusion (see Table 2).

Table 2. Direct-Comparison Question (N = 150)

Attribute	CAR T Treatment A	CAR T Treatment B
Profiles		
Probability of complete response achieved at 6 months of treatment	58% chance	40% chance
Probability of OS at 12 months	60% chance	49% chance
Probability of OS at 24 months	50% chance	40% chance
Time from initial collection (leukapheresis) to infusion	24 days	113 days
Risk of severe cytokine release syndrome	11% risk	22% risk
Risk of a severe NE	32% risk	12% risk
Response summaries		
Observed Choice Patient Profile 1, N (%)	116 (77.33%)	34 (22.67%)
Observed Choice Patient Profile 2, N (%)	119 (79.33%)	31 (20.67%)
Combined Observed Choices, N (%)	235 (78.33%)	65 (21.67%)
Predicted Preference Share	78.56%	21.44%

Table 3. Maximum Acceptable Risk Increase (by Percentage Point) in Adverse Event Risks in Exchange for Different Treatment Improvements (N = 150)

			Severe Cytokine Release Syndrome			Severe Neurological Event		
Attribute	From Level	To Level	Mean	95% Confidence Interval		Mean	95% Confidence Interval	
Time from initial collection (leukapheresis) to infusion	113 days	16 days	> 20.00	33.45	68.19	> 22.00	24.93	54.62
	113 days	24 days	> 20.00	29.99	60.52	> 22.00	21.87	48.08
	113 days	47 days	> 20.00	22.92	46.41	> 22.00	15.71	36.00
	113 days	73 days	> 20.00	15.55	34.54	17.57	8.80	26.34
	73 days	16 days	> 20.00	17.35	37.47	19.61	10.74	28.48
	73 days	24 days	> 20.00	13.35	30.34	14.81	7.20	22.43
	73 days	47 days	11.25	4.55	17.96	6.58	1.77	11.39
	47 days	24 days	17.79	9.38	26.20	11.32	3.27	19.38
	47 days	16 days	12.23	4.41	20.04	7.24	2.02	12.47
	24 days	16 days	7.20	−1.82	16.23	3.81	−2.00	9.61
Probability of complete response achieved at 6 months of treatment	40% chance	52% chance	5.59	−3.38	14.56	2.70	−2.69	8.10
	40% chance	60% chance	> 20.00	10.36	31.75	14.13	4.53	23.73
	52% chance	60% chance	17.10	9.90	24.30	10.73	3.78	17.67
Probability of OS at 12 months	40% chance	52% chance	8.97	1.49	16.44	5.01	0.20	9.83
	40% chance	60% chance	14.80	4.34	25.26	9.00	1.23	16.78
	52% chance	60% chance	7.47	−0.07	15.01	3.99	−0.72	8.70
Probability of OS at 24 months	40% chance	48% chance	15.51	9.22	21.80	9.49	4.49	14.49
	40% chance	55% chance	> 20.00	12.80	32.22	15.38	6.85	23.91
	48% chance	55% chance	8.63	0.58	16.69	4.79	−0.47	10.04

DISCUSSION

- While there are serious risks associated with CAR T—including severe CRS and NEs—CAR T is a promising therapy for patients with an otherwise poor prognosis.
- Treatment requires waiting during the time it takes for a patient's individual treatment to be manufactured, which can be an added risk for patients whose disease is progressing rapidly.
- This study elicited physicians' preferences for time to infusion, efficacy, and risk of complications associated with CAR T treatments for adult patients with DLBCL and explored their willingness to make trade offs between these attributes.
- Physicians demonstrated a strong preference for avoiding the longest wait times and treating a patient as quickly as possible. Physicians were willing to accept increases in adverse event risk to gain reductions in time spent waiting for an infusion.
- Physicians also demonstrated a strong preference for 60% CR at 6 months and 52%-60% OS at 12 months. Physicians were willing to accept higher risks of CRS and NEs for higher CRs and survival rates.

Limitations

- The survey presents hypothetical scenarios to respondents. Decisions made in the survey may not fully predict decisions made in a clinical setting.
- The sample of physicians is a convenience sample recruited through opt-in panels of individuals who choose to participate in research. The study sample may not be representative of the broader population of physicians who treat patients with DLBCL.
- The final survey was administered online. Research has shown that results from online stated-preference surveys are, in general, not statistically significantly different from those elicited through face-to-face interviews.[5,6] However, the online setting of the survey may also have influenced the choices physicians made.

CONCLUSIONS

- Physicians were willing to trade risks for the benefits of CAR T.
- Reducing time from leukapheresis to infusion and higher OS at 24 months were the most important drivers of their choices.

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