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Differences in lymphoma patients between chimeric antigen receptor T-cell therapy trials and the general population

Eric A. Apaydin[1,2], **Andrea S. Richardson**[3], **Sangita Baxi**[1], **Jerry Vockley**[4], **Olamigoke Akinniranye**[1], **Jody Larkin**[1], **Aneesa Motala**[1,5], **Susanne Hempel**[1,5]

[1]Southern California Evidence-Based Practice Center, RAND Corporation, 1776 Main St, Santa Monica, CA 90401-3208, USA

[2]Center for the Study of Healthcare Innovation, Implementation and Policy, VA Greater Los Angeles Healthcare System, Los Angeles, CA, USA

[3]Southern California Evidence-Based Practice Center, RAND Corporation, Pittsburgh, PA, USA

[4]Children's Hospital of Pittsburgh, Pittsburgh, PA, USA

[5]Southern California Evidence Review Center, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

Abstract

Chimeric antigen receptor (CAR)-T cell therapies appear to be promising treatments for non-Hodgkin's and B-cell lymphoma. However, several CAR-T therapies approved by the US Food and Drug Administration have only been tested for efficacy in relatively few single-arm clinical trials with small sample sizes. We sought to examine the differences between patients in these trials and the general population of patients with non-Hodgkin's and B-cell lymphoma. Five hundred and twenty-two patients from 15 CAR-T trials found in a systematic review and 417,492 patients from the Surveillance, Epidemiology, and End Results (SEER) Program database were compared. CAR-T study participants appeared to be younger (46.7% under 70 years old vs. 42.2%), more male (68.0% vs. 55.7%), and followed for a shorter period of time compared to patients in the SEER population (mean [M] 45.6 months, 95% confidence interval [CI] 17.7 to 63.3 months follow-up vs. M 57.1 months, 95% CI 57.0 to 57.3 months survival). CAR-T study participants may differ significantly from the general population of patients with non-Hodgkin's and B-cell lymphoma. Effectiveness of CAR-T therapies in the general population of lymphoma patients may differ from effectiveness demonstrated in trials. Newly created CAR-T patient registries are essential to establishing population-level effectiveness of the therapies.

✉Eric A. Apaydin, eapaydin@rand.org.

Keywords

Genetic therapy; CAR-T; Lymphoma; Non-Hodgkin's

Introduction

Genetic therapies are a rapidly evolving treatment modality for many cancers. One promising therapy, chimeric antigen receptor T-cells (CAR-T), involves genetically modifying T-cells ex vivo and injecting these cells into a cancer patient to therapeutically recognize and attack cancers [1, 2]. Non-Hodgkin's lymphoma, a disease which accounted for over 3% of all cancer deaths in 2020 [3], is a target for several CAR-T therapies. In our recent systematic reviews of the effectiveness of genetic therapies [4, 5], we identified two Food and Drug Administration (FDA)-approved CAR-T therapies, Yescarta (axicabtagene ciloleucel) and Kymriah (tisagenlecleucel), and one therapy seeking FDA approval, JCAR017 (lisocabtagene maraleucel), to treat adults with non-Hodgkin's lymphoma and B-cell lymphoma. Due to the severity of the disease these treatments target, the FDA did not require randomized control trials for Yescarta and Kymriah before approving them. The best available evidence for these treatments does not include untreated control groups. Given the lack of controlled comparison groups, as well as the limited duration of patient follow-up and small sample sizes characteristic of such studies, it is unclear whether treatment response among the general population with the same diagnosis would be as robust as it was for those enrolled in the trials. To understand these differences, we compared participants in the CAR-T research studies for the treatment of non-Hodgkin's and B-cell lymphoma with adults in the general population with these diseases.

This analysis examines two sources: studies of CAR-T interventions for the adult treatment of non-Hodgkin's or B-cell lymphoma found in our previous reviews [4, 5], and in an updated literature search; and the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) SEER data files.

Methods

We searched for empirical published literature in the research databases PubMed, EMBASE, and the Web of Science from inception to April 2020. Searches were executed by an Evidence-based Practice Center librarian experienced in transparent and comprehensive literature searches. Search outputs were screened by two independent reviewers. All citations deemed potentially relevant by at least one reviewer were obtained as full text. Full-text publications were screened against the eligibility criteria. We documented the reasons for exclusion in a citation management database. Publications were abstracted and appraised by one reviewer, and summaries were checked by content and methodological experts. We applied explicit inclusion and exclusion criteria as designated below:

- Participants: Human adults (age 18+ years).

- Interventions: Axicabtagene ciloleucel (Axi-cel, Yescarta,), tisagenlecleucel (Kymriah), lisocabtagene maraleucel (JCAR017, Liso-cel), and unnamed CAR-T interventions.

- Comparator: Any comparator or no comparator studies were eligible.

- Outcomes: Disease-related effectiveness/benefit indicators such as complete response (e.g., remission), partial response, disease recurrence, mortality, patient-centered outcomes including psychosocial outcomes such as anxiety and worry, and treatment-associated adverse events/harms (e.g., cytokine release syndrome).

- Timing: Any treatment duration and follow-up of included studies were eligible.

- Setting: Any geographic location and medical setting was eligible.

- Study design: Primary research studies in English since 1989 were eligible. Studies published only as a conference abstract without trial record or full text publication were excluded.

We used a standardized form with explicit and pilot-tested categorization rules to extract data. All reports of the same participants were consolidated into one study entry. The search strategy, PRISMA literature flow diagram (Supplementary Fig. 1) and evidence table (Supplementary Table 1) are included in online-only supplementary material.

We analyzed data from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) 18 1975–2016 Research Data full data files (https://seer.cancer.gov/data/). Incidence data from all regions in the data files containing leukemia and lymphoma cases was included, with some exception. We excluded the Louisiana cases in 2005 because Hurricane Katrina disrupted reporting. We limited diagnosis dates to 2000–2015, since the values for the 2016 lymphoma subgroup variable were missing. Data were processed by a research programmer experienced in using SEER data.

Frequencies for all patients with non-Hodgkin's lymphomas contain subtypes 7–45 and frequencies for patients with large B-cell lymphoma contain all subtypes 8–26. After limiting to non-Hodgkin's lymphomas, we deduplicated records by patient. We kept the first diagnosis for each patient, unless a later diagnosis was for a higher "priority" subtype because it was a more specific diagnosis.

Lymphomas were categorized into primary mediastinal B-cell, follicular, mantle-cell, diffuse large B-cell, large B-cell, or non-Hodgkin's, based on the lymphoma subtype. Since some of the cancer types of interest were subtypes of larger groups, we used a hierarchy to categorize patients according to cancer type by prioritizing the most specific level of cancer type for which they received a diagnosis, as shown in Supplementary Table 1. In the cases where a patient was diagnosed with multiple cancers we prioritized as level 2, we categorized them as the cancer type that was first diagnosed.

Prior to deduplication of reports, we limited the sample to current age of 18 years or older. We calculated current age using birth year, date of diagnosis, and survival months. SEER provides survival months calculated as number of months from diagnosis to date of last contact or study cutoff date and vital status. Since only the birth year is recorded, current age is not exact and is calculated as of the end of the date of last contact or study cutoff.

To capture disease progression, we report the Ann Arbor stage, which is a classification system developed by the American Joint Committee on Cancer (AJCC) [6] for describing the extent of disease progression in cancer patients. Comorbidity data were not available.

CAR-T trials found in the systematic review are listed in Supplementary Table 2. SEER data is available at https://seer.cancer.gov/data/.

Results

Fifteen studies of CAR-T therapies for 522 participants with non-Hodgkin's and B-cell lymphoma were included: two studies of Yescarta, one study of Kymriah, and 12 of an experimental CD19- or CD20-type CAR-T intervention (Supplementary Table 2). Most studies (Table 1) were single-arm trials (12 studies; 80%) and specified the following criteria for inclusion: no comorbidity that would interfere with treatment/assessment (14 studies; 93%), refractory disease/prior treatment (13 studies; 87%), age (12 studies; 80%), no pregnancy or lack of contraception use (10 studies; 67%), CD19 or 20 expression (9 studies; 60%), a given life expectancy (8 studies; 53%), an adequate understanding of treatment (5 studies; 33%), no prior CAR-T or gene therapy (4 studies; 27%), and no prior stem cell transplant (4 studies; 27%).

Compared to the SEER population 417,492 patients, participants in the CAR-T studies were younger and more male (Table 2). Follow-up time in the CAR-T studies (mean [M] 45.6 months; 95% confidence interval [CI] 17.7 to 63.3 months) was shorter than survival time in the SEER population (M 57.1 months; 95% CI 57.0 to 57.3 months). Over half of the studies reported durable improvement (see Supplementary Material for detailed effectiveness categories). Treatment effectiveness was not reported in the SEER database.

Discussion

Participants in the CAR-T studies differed from the SEER population. Study participants appeared to be younger, more male, and most were followed for a shorter period of time.

Over three quarters of studies reported reduced symptoms for over a year among patients treated with CAR-T. However, participants were not followed in these studies for as long as the population's average expected survival duration, as reported in the SEER database. The length of study follow-up was 46 months on average, compared to the average survival of 57 months in the SEER population. Study follow-up duration may have been sufficient to demonstrate safety and efficacy, but to establish evidence that the treatment cured the disease would require following patients longer than their expected lifetime.

In the general population, non-Hodgkins and B-cell lymphoma patients may have a different response to CAR-T treatment than trial participants. Most identified research studies required that participants have relapsed disease refractory to prior treatment. Patients with more severe disease have higher mortality, although it is easier to show intervention improvement in this group. Study participants also did not have any treatment interfering comorbidities that are present in the general population, although SEER did not report these

comorbidities. Given these differences, it may be that treatment effectiveness differs in the "real-world" outside of research trials.

It is possible that real-world CAR-T patients are younger and have less severe disease than the general population of non-Hodgkin's lymphoma and B-cell patients, given the invasiveness of the treatment and the length of time required to modify T cells. However, a recent worldwide survey of physicians who administer CAR-T therapy indicated that most did not consider older age to be contraindication to treatment [7]. Poor performance, not disease progression, was agreed to be an exclusion criterion for treatment by most of those surveyed. Therefore, it is still likely that CAR-T trial participants do not reflect non-Hodgkin's lymphoma and B-cell patients who would be offered the treatment in the real world.

Assessing the potential success of CAR-T treatment for adults with non-Hodgkin's and B-cell lymphoma in general practice will require long-term observational studies and registries. The Center for International Blood & Marrow Transplant Research recently announced collaborations between Kite Pharma and Novartis to track long-term outcomes of patients treated with Yescarta (Axicabtagene ciloleucel) and Kymriah (Tisagenlecleucel), respectively [8–11]. Research from this registry has not yet been published, but data from this and future registries will be an important tool in comparing the effectiveness of CAR-T between trials and the real world.

In summary, we found that study participants differed demographically and clinically from adults in the general population with the same diagnosis. Treatment effectiveness in the general population may vary from initial efficacy estimates from trials due to these patient-level differences. Newly established CAR-T patient registries aim to follow patients in the general population and resolve this discrepancy in data. At present, understanding the differences between trial populations and the comparable SEER population may provide some insight into how these therapies will function in general practice.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Availability of data and material

Included studies are listed in Supplementary Material. SEER data is available at https:// seer.cancer.gov/data/.

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Table 1

Eligibility criteria in CAR-T studies treating adults with non-Hodgkin's lymphoma or B-cell lymphoma ($N =$ 15)

Intervention	N (%)
Yescarta (Axicabtagene ciloleucel)	2 (13.3)
Kymriah (Tisagenlecleucel)	1 (6.7)
CD19- or CD20-type CAR-T cell intervention	12 (80.0)
Study type	
Single-arm trial of one intervention	12 (80.0)
Multi-arm trial with multiple doses of same intervention	3 (20.0)
Demographic eligibility criteria	
Specified an age criteria	12 (80.0)
Clinical eligibility criteria	
No comorbidity that would interfere with treatment/assessment	14 (93.3)
Refractory/prior treatment	13 (86.7)
Not pregnant/contraception use	10 (66.7)
CD19 or 20 expression	9 (60.0)
Given life expectancy	8 (53.3)
Adequate cognition/understanding of treatment	5 (33.3)
No prior CAR-T or gene therapy	4 (26.7)
No prior stem cell transplant	4 (26.7)

Table 2

Participants in CAR-T studies with non-Hodgkin's lymphoma or B-cell lymphoma and SEER adult population

Descriptors	CAR-T Studies[a] (N = 522 participants in 15 studies) (%)	SEER Population (N=417,492) (%)
Proportion of population by age group[b] (95% CI for SEER)		
Age < 70 years	46.7	42.2 (42.0–42.3)
Age 70+ years	46.7	57.8 (57.7–58.0)
Not reported	6.7	NA
Age of population	NA	70.4 (70.4–70.5)
Proportion of female participants[c] (95% CI)	31.9 (25.1–38.7)	44.3 (44.1–44.4)
Range of proportions of female participants [min-max]	[11–53]	NA
Proportion of male participants[c] (95% CI)	68.1 (61.3–74.9)	55.7 (55.6–55.9)
Range of proportions of male participants [min-max]	[47–89]	NA
Proportion of studies/population by non-Hodgkins indication[d] (95% CI for SEER)		
Diffuse large B-cell lymphoma	6.7	23.0 (22.9–23.2)
Large B-cell lymphoma	13.3	52.5 (52.4–52.7)
Mantle-cell lymphoma	6.7	2.5 (2.5–2.5)
Non-Hodgkin's lymphoma	6.7	10.3 (10.2–10.4)
Primary mediastinal B-cell lymphoma	6.7	0.2 (0.1–0.2)
Follicular lymphoma	NA	11.5 (11.4–11.6)
At least two of the above	60.0	NA
Months of follow-up mean (95% CI) [min-max]	45.6 (17.7–63.3) [12–180]	NA
Months of survival mean (95% CI) [min-max][e]	NA	57.1 (57.0–57.3) [0–203]
Proportion Ann Arbor stage[f] (95% CI for SEER)		
Stage I or II	11–43	23.7 (23.6–23.8)
Stage III or IV	11–88	28.4 (28.2–28.5)
Proportion treatment effect		
Durable improvement	53.3	NA
Sustained improvement	26.7	NA
Improvement	6.7	NA

Descriptors	CAR-T Studies[a] (N = 522 participants in 15 studies) (%)	SEER Population (N=417,492) (%)
Unclear	13.3	NA

[a]Treating non-Hodgkin's/B-cell lymphoma in 522 participants;

[b]CAR-T studies: using range reported; SEER: using age at last contact by end of 2015;

[c]CAR-T studies: average percentage, SEER: percentage;

[d]CAR-T studies: percentage of studies; SEER: percentage;

[e]N=414,181 for survival data in SEER;

[f]CAR-T studies: range of percentages reported in 5 studies, SEER: 43.7% NA, 4.3% unknown

CAR-T, chimeric antigen receptor T cells; min, minimum; max, maximum; NA, not applicable; SD, standard deviation; SEER, surveillance, epidemiology, and end results program