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# Association of bridging therapy utilization with clinical outcomes in patients receiving chimeric antigen receptor (CAR) T-cell therapy

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## ABSTRACT

**Background** Chimeric antigen receptor (CAR) T-cell therapy recipients may receive bridging therapy while awaiting product manufacturing to control disease. Yet, data are lacking regarding the impact of bridging therapy use on clinical outcomes.

**Methods** We conducted a retrospective analysis of 235 patients who received CAR T-cell therapy at two tertiary care centers from February 2016 to December 2019. We abstracted clinical outcomes from review of the electronic health record including (1) overall response; (2) complete response (CR); (3) progression-free survival (PFS); (4) overall survival (OS); and (5) toxicity (cytokine release syndrome (CRS) and neurotoxicity). We assessed the association of bridging therapy use with overall response rate (ORR) and CR rate using multivariable logistic regression and with PFS and OS using multivariable Cox regression controlling for covariates. We analyzed the association of bridging therapy use with CRS and neurotoxicity using Fisher's exact test.

**Results** Patients' median age was 63.1 years (range: 19–82), and the majority were men (144/235, 61.3%). Most patients received axicabtagene ciloleucel (192/235, 81.7%), and the most common lymphoma subtype was diffuse large B-cell lymphoma or grade 3B follicular lymphoma (107/235, 45.5%). Overall, 39.4% (93/236) received bridging therapy. Bridging therapy regimens included systemic chemotherapy (48/92, 52.2%), corticosteroids (25/92, 27.2%), radiation (9/92, 9.8%), and other systemic therapies (10/92, 10.9%). In multivariable Cox regression, bridging therapy use was associated with OS (HR: 1.97, p=0.004) but not PFS (HR: 1.18, p=0.449). In multivariable logistic regression, bridging therapy use was not associated with ORR (OR: 0.69, p=0.391) or CR rate (OR: 0.96, p=0.901). We did not identify an association of bridging therapy use with grade 3+ CRS (p=0.574) or grade 3+ neurotoxicity (p=0.748).

**Conclusions** We identified that bridging therapy use is not associated with differences in ORR, CR rate, or PFS but is associated with worse OS. These data suggest bridging therapy may be a surrogate for additional poor prognostic factors leading to inferior OS and underscore the need for novel bridging therapy regimens to optimize outcomes in this patient population.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Prior studies have shown mixed results when examining bridging therapy use and its association with clinical outcomes. Moreover, prior work has focused primarily on the cellular therapy product axicabtagene ciloleucel.

### WHAT THIS STUDY ADDS

⇒ This study examines the association of bridging therapy use with clinical outcomes and includes patients receiving one of multiple different cellular therapy products. Bridging therapy use was associated with worse overall survival but not with differences in response rates or progression-free survival. This data identifies bridging therapy use as a surrogate for additional poor prognostic factors leading to inferior overall survival.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings highlight an unmet need for more effective bridging therapy regimens to optimize outcomes in patients with lymphoma receiving CAR T-cell therapies.

## INTRODUCTION

Chimeric antigen receptor (CAR) T-cell therapy is a novel treatment that involves collecting and altering the patient's autologous T- cells to target a cell surface antigen on the tumor and then re-infusing the genetically modified CAR T-cells into the patient.[1 2] CAR T-cell therapy has transformed the treatment of relapsed/refractory B-cell lymphomas and multiple myeloma.[3–5] However, patients receiving this treatment must wait 17–24 days for manufacturing of the autologous cellular therapy product, during which time bridging therapy may be utilized for disease control.[4–8] Moreover, patients receiving CAR T-cell therapy are at risk for unique toxicities, such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), which can also result in intensive healthcare utilization.[4–8]

Despite the revolutionary nature of CAR T-cell therapy, we lack data to guide the utilization of bridging therapy in this patient population.[9] In prior studies, bridging therapy was associated with worse long-term overall survival (OS); yet, these analyses were limited by an inability to control for confounding factors.[10 11] Bridging therapy could theoretically reduce tumor burden and thus mitigate risk of treatment toxicity and improve clinical outcomes or potentially have negative consequences on patient fitness, performance status, and overall treatment toxicity. It remains unclear which populations derive the most benefit from bridging therapy and if certain bridging therapies are favored. Unfortunately, the majority of patients will ultimately relapse or fail to respond to CAR T-cell therapy.[12] Thus, bridging therapy represents one of many potential avenues for improving clinical outcomes in this unique population.

In the present study, we sought to depict the survival of CAR T-cell therapy recipients by use of bridging therapy. We also aimed to examine the association of bridging therapy use with important clinical outcomes, including response rates and toxicities. Data describing the association of bridging therapy with important clinical outcomes could provide insights into the design of prospective clinical trials aimed at optimizing the use of bridging therapy in CAR T-cell therapy recipients. We hypothesized that bridging therapy use would be associated with worse OS, progression-free survival (PFS), and response rates.

## METHODS

### Study design

We conducted a retrospective analysis of adult patients treated with CAR T-cell therapy at the Dana-Farber Cancer Institute (DFCI) or Massachusetts General Hospital (MGH) between February 2016 and December 2019. We excluded patients who were seen for consultation but did not receive CAR T-cell therapy at either institution. We identified the eligible cohort through the MGH and DFCI CAR-T therapy database, which includes all patients receiving CAR T-cell therapy at our institutions.

### Clinical information

We abstracted information from the electronic health record (EHR) through a comprehensive chart review about patients' demographics, Eastern Cooperative Oncology Group (ECOG) performance status (determined within 2 weeks of CAR T-cell infusion), diagnosis, date of relapse, date of apheresis, and date of CAR T-cell infusion (defined as day 0), therapies received, CAR T-cell product, pretreatment lactate dehydrogenase (LDH), ferritin, C-reactive protein (CRP), and platelet count (all on day −5, day 0 if no day −5 value was available, or date closest to but before day −5 if neither day −5 nor day 0 values were available), Charlson Comorbidity Index score (calculated from EHR review excluding patients' lymphoma diagnosis),[13] bridging therapy use (yes or no and regimen received), presence and grade of toxicities including CRS and neurotoxicity, receipt of tocilizumab and/or corticosteroids (calculated total equivalent dexamethasone dose in decigram from days 0–31), response to treatment, and duration of follow-up. CRS was graded according to Lee criteria,[14] and neurotoxicity was graded according to Common Terminology Criteria for Adverse Events V.5.0.[5] CRS and ICANS management followed institutional guidelines.

### Clinical outcomes

We reviewed the EHR to determine patients' best overall response as assessed by the clinician and recorded in the EHR (complete response (CR), partial response (PR), stable disease, or progressive disease). We defined overall response as a CR or PR as recorded in the EHR. We determined patients' date and cause of death using the EHR and the Social Security Death Index. We classified cause of death as secondary to cancer progression, CAR T-cell therapy complication, late (>3 months post CAR T-cell infusion) infection, other cause, or unknown. We defined CAR T-cell therapy complication as grade 5 CRS or neurotoxicity, an early (≤3 months from infusion) infectious death, death from lymphodepleting chemotherapy complication, or death caused by persistent cytopenias. The majority of patients receiving CAR-T therapy received their healthcare within our system. Additionally, the clinical team maintaining the CAR-T database obtains information regarding healthcare outcomes at other institutions and those are scanned into the EHR to maintain high data quality.

### Statistical analysis

We used descriptive statistics to summarize patients' sociodemographic and clinical characteristics, and rates of toxicities and response. We used descriptive statistics to characterize cause of death for patients who died in the cohort. We defined OS as the time from the date of CAR T-cell infusion until the date of death from any cause. We censored OS data from patients who were alive on the date last recorded having a medical visit in the EHR. We defined PFS as the time from the date of CAR T-cell infusion to the earlier of progression or death due to any cause. We censored PFS data from patients alive without disease progression at the date last recorded having a medical visit in the EHR. We calculated median follow-up with the reverse Kaplan-Meier method.[15] We utilized multivariable Cox regression to examine the association of bridging therapy with OS and PFS. We first conducted univariate Cox regression analyses to assess the association between patient demographic (age, sex, marital status), and clinical factors (bridging therapy use, Charlson Comorbidity Index, lymphoma diagnosis, number of prior therapies, history of autologous stem cell transplant (SCT), time from relapse to CAR T-cell therapy, vein-to-vein time, ECOG performance status (closest to day 0), LDH


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(>500 U/L vs ≤500),[16] CRP (<30 mg/L vs ≥30),[11] ferritin (<411 µg/L vs ≥411[17]) and platelet count (<100 K/µL vs ≥100), prior to CAR T-cell infusion, CAR T-cell product, total dose of steroids received (days 0–31), and receipt of tocilizumab) with OS and PFS. Variables with a p value<0.05 in the univariate analyses were included in the multivariable models.[18] We conducted univariate Cox regression analyses to assess the association of bridging therapy response with OS and PFS.

We utilized multivariable logistic regression to examine the association between bridging therapy and binary outcomes of interest (overall response, CR). We first conducted univariate analyses utilizing the same factors as described above. We utilized Fisher's exact test to examine the association between bridging therapy and toxicities of interest (grade 3+ CRS and grade 3+ neurotoxicity) given the small number of toxicity events, we did not adjust these analyses for multiple covariates. All reported p values are two-sided with a p value<0.05 considered statistically significant. We performed statistical analyses using Stata V.14.2.

## RESULTS

### Study participants

Table 1 describes the sociodemographic and clinical characteristics of the patients (N=235) in this study. The median age was 63.1 years (range: 19–82), and the majority of patients were men (144/235, 61.3%), white (217/235, 92.3%), and married/had a life partner (163/235, 69.4%). Most patients (82.1%, 193/235) had an ECOG performance status of 0 or 1. The most common lymphoma subtype was diffuse large B-cell lymphoma or grade 3B follicular lymphoma (107/235, 45.5%), and the median prior lines of therapy was 3 (range: 0–10). Overall, 81.7% of patients received axicabtagene ciloleucel (192/235), 27.7% (65/235) had a prior autologous SCT, and 39.2% received bridging therapy (92/235). In respect to types of bridging therapy, 52.2% (48/92) received chemotherapy with or without additional agents, 27.2% (25/92) received steroids, 9.8% (9/92) received radiation therapy, and 10.9% (10/92) received other systemic bridging therapies without chemotherapy (online supplemental table 1). The most common systemic chemotherapy regimens utilized as bridging therapy were rituximab, gemcitabine, and oxaliplatin; rituximab, gemcitabine, dexamethasone, and cisplatin; and rituximab, ifosfamide, carboplatin, and etoposide. Patients had a median Charlson Comorbidity Index score of 0 (range: 0–3) and a median time from apheresis to CAR T-cell infusion of 26 days (range: 14–330). The median pretreatment LDH was 231 U/L (range: 85–1722), the median pretreatment CRP was 17.0 mg/L (range: 0.2–300), and the median pretreatment ferritin was 642 µg/L (range: 1–29,541). The median follow-up time was 11.4 months (range: 0.17–44.7).

### Clinical outcomes by receipt of bridging therapy

Table 2 depicts clinical outcomes by use of bridging therapy. The overall response rate (ORR) was 88.8% (127/143) in those without bridging therapy use versus 79.4% (73/92) in those with bridging therapy use. The CR rate was 65.7% (94/143) in those without bridging therapy use versus 63.0% (58/92) in those with bridging therapy use. Median OS was not reached (NR) (95% CI: NR to NR) in patients without bridging therapy use versus 22.9 months (95% CI: 8.6 to NR) in patients with bridging therapy use (figure 1). Median PFS was NR (95% CI: 13.3 to NR) in patients without bridging therapy use versus 6.03 months (95% CI: 4.00 to NR) in patients with bridging therapy use (figure 2). CRS occurred in 79.0% (113/143) of patients without bridging therapy use, with 7.0% (10/143) being grade 3+, whereas CRS occurred in 76.1% (70/92) of patients with bridging therapy use, with 4.4% (4/92) being grade 3+. Neurotoxicity occurred in 52.5% (75/143) of patients without bridging therapy use, with 23.1% (33/143) being grade 3+, and in 54.4% (50/92) of patients with bridging therapy use, with 20.7% (19/92) being grade 3+. There was one event of grade 5 CRS and one event of grade 5 neurotoxicity.

### Association of bridging therapy with OS

Among 235 patients, 81 died, and 154 were censored. In a univariate Cox regression model, high pretreatment CRP (HR: 2.11, 95% CI: 1.36 to 3.27, p=0.001), worse ECOG performance status (HR: 1.47, 95% CI: 1.16 to 1.87, p=0.002), bridging therapy use (HR: 1.86, 95% CI: 1.20 to 2.89, p=0.005), higher steroid dose received from days 0–31 (HR: 1.17, 95% CI: 1.07 to 1.28, p<0.001), and high pretreatment LDH (HR 2.06, 95% CI: 1.24 to 3.42, p=0.005) were all associated with worse OS. Longer time from relapse to CAR T-cell therapy infusion was associated with better OS (HR: 0.75, 95% CI: 0.57 to 0.99, p=0.041) (table 3).

In a multivariable Cox regression model adjusting for covariates (N=225, 78 deaths), bridging therapy use was associated with worse OS (HR: 1.97, 95% CI: 1.24 to 3.14, p=0.004) (table 4). In addition, higher pretreatment CRP (HR: 1.78, 95% CI: 1.11 to 2.86, p=0.017) and higher steroid dose from days 0–31 (HR: 1.12, 95% CI: 1.01 to 1.24, p=0.028) were both associated with worse OS, whereas a longer time from relapse to CAR T-cell infusion (HR: 0.71, 95% CI: 0.53 to 0.95, p=0.019 was associated with better OS.

### Association of bridging therapy with PFS

Among 235 patients, 2 had missing data for date of progression and were not included. Among 233 patients, 106 had an event, and 127 were censored. In a univariate Cox regression model, high pretreatment CRP (HR: 2.11, 95% CI: 1.36 to 3.27, p=0.001), worse ECOG performance status (HR: 1.47, 95% CI: 1.16 to 1.87, p=0.002), bridging therapy use (HR: 1.50, 95% CI: 1.02 to 2.20, p=0.041), and high pretreatment LDH (HR 2.06, 95% CI: 1.24 to 3.42, p=0.005) were all associated with worse PFS. Prior

**Table 1** Patient characteristics

| Characteristic | Bridging therapy (N=92) | No bridging therapy (N=143) | P value |
|---|---|---|---|
| Age (years)—median (range) | 63.1 (19–82) | 63.2 (19–82) | 0.900 |
| Female sex | 36 (39.1%) | 55 (38.5%) | 0.918 |
| White race‡ | 79 (88.8%) | 138 (96.5%) | **0.027** |
| Married/life partner | 65 (70.7%) | 98 (68.5%) | 0.731 |
| CAR T-cell product | | | **<0.001** |
| Axicabtagene ciloleucel | 60 (65.2%) | 123 (86.0%) | |
| Tisagenlecleucel | 29 (31.5%) | 6 (4.2%) | |
| Axicabtagene ciloleucel combined with immunotherapy | 1 (1.1%) | 8 (5.6%) | |
| Brexucabtagene autoleucel | 2 (2.2%) | 5 (3.5%) | |
| Lisocabtagene maraleucel | 0 (0%) | 1 (0.7%) | |
| Lymphoma subtype | | | **0.011** |
| DLBCL/grade 3B follicular lymphoma | 46 (50.0%) | 61 (42.7%) | |
| Indolent lymphoma transformed to DLBCL§ | 15 (15.3%) | 25 (17.5%) | |
| HGBCL with *MYC* and *BCL2* and/or *BCL6* rearrangements | 17 (18.5%) | 23 (16.1%) | |
| Follicular lymphoma | 2 (2.2%) | 20 (14.0%) | |
| Primary mediastinal large B-cell lymphoma | 3 (3.3%) | 9 (6.3%) | |
| Other | 9 (9.8%) | 5 (3.5%) | |
| ECOG performance status¶ | | | 0.943 |
| 0–1 | 75 (83.3%) | 118 (83.7%) | |
| 2–4 | 15 (16.7%) | 23 (16.3%) | |
| Bridging therapy regimen | | | N/A |
| Steroids | 25 (27.2%) | N/A | |
| Chemotherapy | 48 (52.2%) | N/A | |
| Other systemic therapy** | 10 (10.9%) | N/A | |
| Radiation | 9 (9.8%) | N/A | |
| Pretreatment lactate dehydrogenase (U/L)—median (range) | 275 (122–1722) | 205 (85–1272) | **0.004** |
| Pretreatment platelet count (K/μL)—median (range) | 133 (10–548) | 165 (15–576) | 0.112 |
| Pretreatment CRP (mg/L)—median (range)* | 16.2 (0.2–300) | 17.2 (0.3–300) | 0.438 |
| Pretreatment ferritin (μg/L)—median (range)† | 741.5 (1–7965) | 560 (13.4–29,541) | 0.985 |
| Charlson Comorbidity Index score—median (range) | 0 (0–3) | 0 (0–3) | 0.625 |
| Prior lines of therapy—median (range) | 3 (0–8) | 2 (0–10) | 0.533 |
| Prior autologous stem cell transplant | 29 (31.5%) | 36 (25.2%) | 0.288 |
| Days from apheresis to CAR T-cell therapy—median (range) | 27 (14–60) | 26 (17–330) | 0.604 |
| Days from relapse to CAR T-cell therapy—median (range) | 60.5 (13–224) | 55.5 (11–166) | 0.055 |

*1 patient with missing data
†15 patients with missing data
‡3 patients either had missing data or declined to report for race
§Richter's transformation was classified under other
¶4 patients with missing data
**Other systemic therapies included lenalidomide, ibrutinib, pembrolizumab, venetoclax, venetoclax plus ibrutinib, and polatuzumab vedotin (with steroids)
CAR, chimeric antigen receptor; CRP, C-reactive protein; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group.

autologous SCT (HR: 0.53, 95% CI: 0.32 to 0.88, p=0.013) and receipt of tocilizumab (HR: 0.63, 95% CI: 0.43 to 0.92, p=0.018) were associated with better PFS (table 5). ECOG performance status (HR: 1.23, 95% CI: 0.98 to 1.54, p=0.078) and CD28 co-stimulatory domain CAR T-cell product (HR: 0.64, 95% CI: 0.39 to 1.04, p=0.072)

**Table 2** Clinical outcomes by receipt of bridging therapy

| Outcome | Bridging therapy (N=92) | No bridging therapy (N=143) | P value |
|---|---|---|---|
| ORR | 79.4% | 88.8% | 0.047 |
| CR rate | 63.0% | 65.7% | 0.674 |
| Median OS (months) | 22.9 | Not reached | 0.005 |
| Median PFS (months) | 6.03 | Not reached | 0.039 |
| CRS (all grades) | 76.1% | 79.0% | 0.597 |
| CRS (grade 3+) | 4.4% | 7.0% | 0.574 |
| ICANS (all grades) | 54.4% | 52.5% | 0.776 |
| ICANS (grade 3+) | 20.7% | 23.1% | 0.748 |

CR, complete response; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

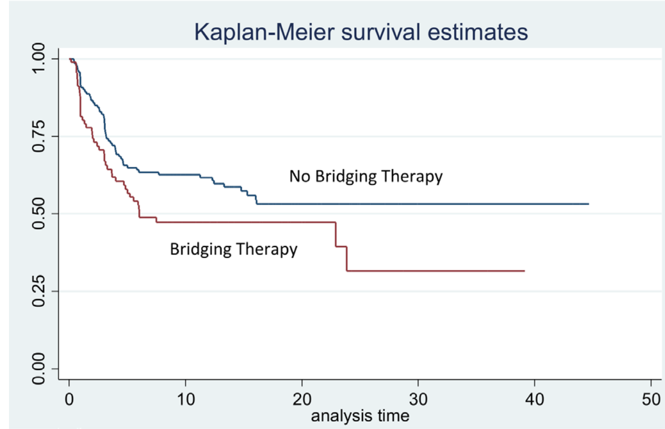


**Figure 2** Kaplan-Meier progression-free survival curve by receipt of bridging therapy (months).

were not associated with PFS but were included in the multivariable model for PFS given their known association with bridging therapy and/or PFS.[4 5 19]

In a multivariable Cox regression model adjusting for covariates (N=228, 104 events), bridging therapy use was not associated with PFS (HR: 1.18, 95% CI: 0.77 to 1.82, p=0.449) (table 6). Higher pretreatment CRP (HR: 2.01, 95% CI: 1.32 to 3.07, p=0.001) was associated with worse PFS, whereas prior autologous SCT (HR: 0.56, 95% CI: 0.34 to 0.94, p=0.029) and receipt of tocilizumab (HR: 0.52, 95% CI: 0.34 to 0.80, p=0.003) were associated with better PFS.

## Association of the response to bridging therapy with OS and PFS

Of patients receiving bridging therapy (N=92), response data were available for 42 patients (45.7%). In a univariate Cox regression analysis with patients without bridging therapy use as a reference group, a response of stable disease or progressive disease was associated with worse OS (HR=3.36, 95% CI: 1.89 to 6.00, p<0.001) and worse PFS (HR=2.94, 95% CI: 1.74 to 4.95, p<0.001), whereas a CR or PR was not associated with OS (HR=1.20, 95% CI: 0.43 to 3.35, p=0.727) or PFS (HR=1.17, 95% CI: 0.51 to 2.72, p=0.710). Patients receiving bridging therapy but without data on response also did not have a statistically significant difference in OS (HR=1.47, 95% CI: 0.85 to 2.55, p=0.172) or PFS (HR=1.10, 95% CI: 0.67 to 1.81, p=0.704).

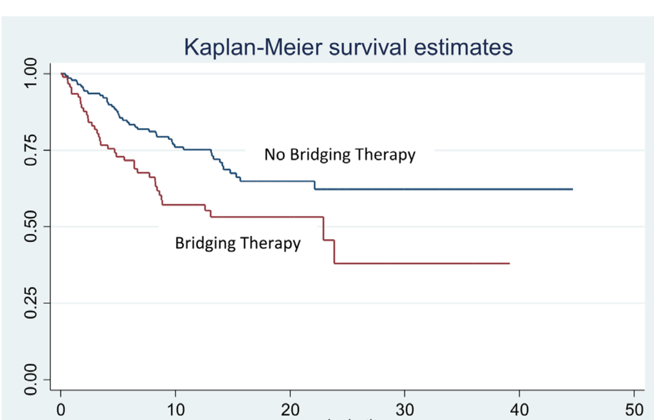


**Figure 1** Kaplan-Meier overall survival curve by receipt of bridging therapy (months).

## Cause of death by receipt of bridging therapy

Among 143 patients not receiving bridging therapy, 35 (24.5%) died of cancer progression, 1 (0.7%) died of CAR T-cell therapy complication, 4 (2.8%) died of late infection, 2 (1.4%) died of other causes, and 1 (0.7%) had an unknown cause of death. Among 92 patients receiving bridging therapy, 32 (34.8%) died of cancer progression, 4 (4.3%) died of CAR T-cell therapy complication, 1 (1.1%) died of other causes, and 1 (1.1%) had an unknown cause of death.

## Association of bridging therapy with response and toxicity

In a univariate Cox regression model, ECOG performance status (OR 0.53, 95% CI: 0.35 to 0.80, p=0.003) and bridging therapy (OR 0.48, 95% CI: 0.23 to 1.00, p=0.050) were associated with a lower likelihood of an overall response, whereas prior autologous SCT (OR 3.40, 95% CI: 1.15 to 10.1, p=0.027), and CD28 co-stimulation CAR T-cell product (OR 3.21, 95% CI: 1.40 to 7.34, p=0.006) were associated with a higher likelihood of an overall response. In a multivariable logistic regression model (N=231), bridging therapy use was not associated with overall response (OR: 0.69, 95% CI: 0.29 to 1.62, p=0.391). Worse pretreatment ECOG performance status (OR: 0.56, 95% CI: 0.36 to 0.86, p=0.008) was associated with a lower likelihood of an overall response, whereas prior autologous SCT (OR: 3.39, 95% CI: 1.11 to 10.4, p=0.032) was associated with a greater likelihood of an overall response.

In a univariate logistic regression, bridging therapy use was not associated with likelihood of CR (OR 0.89, 95% CI: 0.51 to 1.54, p=0.674). Older age (OR: 1.03, 95% CI: 1.01 to 1.05, p=0.009), prior autologous SCT (OR: 3.17, 95% CI: 1.58 to 6.36, p=0.001), and having a spouse/partner (OR: 2.08, 95% CI: 1.18 to 3.68, p=0.012)

**Table 3** Univariate Cox regression analysis of bridging therapy use and overall survival

| Variable | HR (95% CI) | SE | P value |
|---|---|---|---|
| Age | 1.01 (0.99 to 1.03) | 0.01 | 0.484 |
| Female sex | 0.68 (0.43 to 1.08) | 0.16 | 0.104 |
| Married/with a life partner | 0.77 (0.49 to 1.23) | 0.18 | 0.279 |
| Charlson Comorbidity Index score | 1.00 (0.71 to 1.39) | 0.17 | 0.973 |
| Double hit lymphoma diagnosis | 1.54 (0.93 to 2.56) | 0.40 | 0.092 |
| Number of prior therapies | 1.02 (0.89 to 1.17) | 0.07 | 0.762 |
| Prior autologous stem cell transplant | 0.62 (0.35 to 1.08) | 0.18 | 0.093 |
| Months from relapse to CAR T-cell infusion | 0.75 (0.57 to 0.99) | 0.11 | 0.041 |
| Vein-to-vein time (months) | 0.74 (0.33 to 1.66) | 0.30 | 0.462 |
| ECOG performance status | 1.47 (1.16 to 1.87) | 0.18 | 0.002 |
| LDH >500 (U/L, prior to CAR T-cell infusion) | 2.06 (1.24 to 3.42) | 0.53 | 0.005 |
| CRP >30 (mg/L, prior to CAR T-cell infusion) | 2.11 (1.36 to 3.27) | 0.47 | 0.001 |
| Ferritin ≥411 (µg/L, prior to CAR T-cell infusion) | 1.65 (0.98 to 2.78) | 0.44 | 0.058 |
| Platelet count <100 K/µL | 1.41 (0.86 to 2.30) | 0.35 | 0.171 |
| Bridging therapy use | 1.86 (1.20 to 2.89) | 0.42 | 0.005 |
| CD28 co-stimulatory domain CAR T-cell product | 0.65 (0.37 to 1.17) | 0.19 | 0.152 |
| Dexamethasone dose (dg) from days 0–31 | 1.17 (1.07 to 1.28) | 0.05 | <0.001 |
| Receipt of tocilizumab | 0.89 (0.57 to 1.37) | 0.20 | 0.584 |

CAR, chimeric antigen receptor; CRP, C-reactive protein; dg, decigram; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase.

were associated with a greater likelihood of a CR, whereas elevated LDH (OR: 0.32, 95% CI: 0.16 to 0.67, p=0.002) and elevated CRP (OR 0.37, 95% CI: 0.21 to 0.64, p<0.001) were associated with a lower likelihood of a CR. ECOG performance status was not associated with CR (OR: 0.72, 95% CI: 0.51 to 1.00, p=0.052) but was included in the multivariable model given its known association with the outcome,[11 19] and receipt of tocilizumab (OR: 1.61, 95% CI: 0.94 to 2.77, p=0.082) was not associated with CR but was included in the multivariable model given its association with PFS.

In a multivariable logistic regression model (N=234), bridging therapy use was not associated with CR (OR: 0.96, 95% CI: 0.51 to 1.82, p=0.901). Worse pretreatment ECOG performance status (OR: 0.67, 95% CI: 0.45 to 0.98, p=0.041) and elevated CRP (OR: 0.42, 95% CI: 0.22 to 0.81, p=0.009) were associated with a lower likelihood of CR, whereas prior autologous SCT (OR: 3.25, 95% CI: 1.50 to 7.03, p=0.003), older age (OR: 1.03, 95% CI: 1.01 to 1.06, p=0.007), and receipt of tocilizumab (OR: 2.26, 95% CI: 1.17 to 4.35, p=0.015) were associated with a greater likelihood of CR.

Using Fisher's exact test, we did not identify an association of bridging therapy use with grade 3+ CRS (p=0.574), or grade 3+ neurotoxicity (p=0.748).

### Association of bridging therapy type with OS and PFS

Online supplemental table 1 summarizes the bridging therapies administered. In a multivariable Cox regression model controlling for covariates, use of systemic bridging therapy was not significantly associated with OS (HR=1.02, 95% CI: 0.51 to 2.07, p=0.946) or PFS (HR=1.23, 95% CI:

**Table 4** Multivariable Cox regression analyzing the association of bridging therapy use with overall survival (N=225)

| Variable | HR (95% CI) | SE | P value |
|---|---|---|---|
| Months from relapse to CAR T-cell infusion | 0.71 (0.53 to 0.95) | 0.10 | 0.019 |
| ECOG performance status | 1.25 (0.97 to 1.61) | 0.16 | 0.082 |
| LDH >500 (U/L, prior to CAR T-cell infusion) | 1.04 (0.58 to 1.87) | 0.31 | 0.901 |
| CRP >30 (mg/L, prior to CAR T-cell infusion) | 1.78 (1.11 to 2.86) | 0.43 | 0.017 |
| Bridging therapy use | 1.97 (1.24 to 3.14) | 0.47 | 0.004 |
| Dexamethasone dose (dg) from days 0–31 | 1.12 (1.01 to 1.24) | 0.06 | 0.028 |

.CAR, chimeric antigen receptor; CRP, C-reactive protein; dg, decigram; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase.

**Table 5** Univariate Cox regression analysis of bridging therapy use with progression-free survival

| Variable | HR (95% CI) | SE | P value |
|---|---|---|---|
| Age | 1.00 (0.98 to 1.01) | 0.01 | 0.556 |
| Female sex | 0.87 (0.58 to 1.29) | 0.17 | 0.475 |
| Married/with a life partner | 0.80 (0.53 to 1.20) | 0.17 | 0.276 |
| Charlson Comorbidity Index score | 1.04 (0.78 to 1.37) | 0.15 | 0.800 |
| Double hit lymphoma diagnosis | 1.39 (0.87 to 2.22) | 0.33 | 0.171 |
| Number of prior therapies | 1.05 (0.94 to 1.18) | 0.06 | 0.397 |
| Prior autologous stem cell transplant | 0.53 (0.32 to 0.88) | 0.14 | 0.013 |
| Months from relapse to CAR T-cell infusion | 0.86 (0.68 to 1.07) | 0.10 | 0.180 |
| Vein-to-vein time (months) | 0.85 (0.54 to 1.33) | 0.19 | 0.471 |
| ECOG performance status | 1.23 (0.98 to 1.54) | 0.14 | 0.078 |
| LDH >500 (U/L, prior to CAR T-cell infusion) | 2.04 (1.28 to 3.24) | 0.48 | 0.003 |
| CRP >30 (mg/L, prior to CAR T-cell infusion) | 2.10 (1.43 to 3.08) | 0.41 | <0.001 |
| Ferritin ≥411 (µg/L, prior to CAR T-cell infusion) | 1.10 (0.73 to 1.68) | 0.24 | 0.645 |
| Platelet count <100 K/µL | 1.31 (0.84 to 2.03) | 0.29 | 0.228 |
| Bridging therapy use | 1.50 (1.02 to 2.20) | 0.29 | 0.041 |
| CD28 co-stimulatory domain CAR T-cell product | 0.64 (0.39 to 1.04) | 0.16 | 0.072 |
| Dexamethasone dose (dg) from days 0–31 | 1.08 (1.00 to 1.18) | 0.05 | 0.081 |
| Receipt of tocilizumab | 0.63 (0.43 to 0.92) | 0.12 | 0.018 |

CAR, chimeric antigen receptor; CRP, C-reactive protein; dg, decigram; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase.

0.65 to 2.32, p=0.525) when compared with use of corticosteroids and/or radiation bridging therapy.

## DISCUSSION

In this study, we demonstrate that patients receiving bridging therapy for CAR T-cell therapy experienced worse OS. However, they experienced no difference in PFS, grade 3+ CRS or grade 3+ neurotoxicity, or response to therapy. Nearly 40% of the patients received bridging therapy, reflecting the frequent need for disease control in CAR T-cell therapy. Among those patients, almost 80% received corticosteroids or systemic chemotherapy as bridging therapy. These findings underscore the unmet need for novel bridging therapies in this population.

Interestingly, we identified an association of bridging therapy use with OS but not with PFS, ORR, or CR rate. Prior studies have shown mixed results when examining bridging therapy and its association with clinical outcomes. In a univariate analysis of axicabtagene ciloleucel (axi-cel) recipients in the non-trial setting, patients who received bridging therapy experienced worse PFS and OS.[11] In contrast, another study showed no association of bridging therapy with 1-year OS or PFS, but the sample size included 75 patients and did not incorporate multivariable analysis.[20] A recent study examining bridging therapy in 148 axi-cel recipients found on univariate analysis an association of bridging therapy with OS and PFS, but this was driven primarily by the group of

**Table 6** Multivariable Cox regression analyzing the association of bridging therapy use with progression-free survival (N=228)

| Variable | HR (95% CI) | SE | P value |
|---|---|---|---|
| Prior autologous stem cell transplant | 0.56 (0.34 to 0.94) | 0.15 | 0.029 |
| ECOG performance status | 1.23 (0.97 to 1.55) | 0.15 | 0.084 |
| LDH >500 (U/L, prior to CAR T-cell infusion) | 1.52 (0.89 to 2.59) | 0.41 | 0.122 |
| CRP >30 (mg/L, prior to CAR T-cell infusion) | 2.01 (1.32 to 3.07) | 0.43 | 0.001 |
| Bridging therapy use | 1.18 (0.77 to 1.82) | 0.26 | 0.449 |
| Receipt of tocilizumab | 0.52 (0.34 to 0.80) | 0.11 | 0.003 |
| CD28 co-stimulatory domain CAR T-cell product | 0.66 (0.37 to 1.17) | 0.19 | 0.158 |

CAR, chimeric antigen receptor; CRP, C-reactive protein; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase.

patients who underwent apheresis and never received axi-cel.[9] A multicenter study of 298 patients receiving axi-cel found an association of bridging therapy use with OS but not PFS.[19] Our results are consistent with the latter study, as we detected an association of bridging therapy with OS but not with ORR, CR rate, or PFS on multivariable analysis when controlling for patient-related and disease-related factors. It is possible that discordant findings in these studies are explained by selection bias, with utilization of bridging therapy being more common in high-risk disease. Our work adds to the literature by demonstrating an association of bridging therapy use with worse OS in a patient population receiving multiple CAR T-cell therapy products despite controlling for myriad other factors through detailed medical record review. Therefore, patients receiving bridging therapy for CAR T-cell therapy constitute a high-risk patient population for poor survival outcomes.

In contrast to our hypothesis, we did not demonstrate an association of bridging therapy use with PFS or CR rate. Thus, our findings suggest that at least part of the association of bridging therapy use with worse OS may be related to non-relapse mortality with ineffective bridging. Unfortunately, we did not have adequate power in this analysis to specifically examine the association of bridging therapy use with non-relapse mortality. When examining cause of death by manual review of discharge summaries and the Social Security Death Index, four out of five patients who died of CAR T-cell therapy complications had received bridging therapy, and two of the four CAR T-cell therapy complication deaths in those receiving bridging therapy were due to early infection or cytopenias with an infection. Moreover, we identified that a response to bridging therapy of stable or progressive disease was associated with worse OS and PFS, suggesting that ineffective bridging therapies may augment mortality risk, whereas effective bridging strategies may hold the potential to improve clinical outcomes. These findings are merely hypothesis generating given we lacked adequate power to examine response to bridging therapy in a multivariable model, but raises the possibility that myelosuppressive therapies with limited debulking of disease may augment non-relapse mortality and suggests that future studies should evaluate the association of bridging therapy response with non-relapse and relapse mortality in CAR T-cell therapy recipients.

Our results also underscore the unmet need for novel bridging therapies with the capability to control disease without augmenting mortality risk and the need for prospective clinical trials evaluating bridging therapies. Notably, a paucity of patients in our analysis received either radiation therapy or novel systemic therapies without chemotherapy; thus, we were limited in our ability to compare outcomes among different bridging therapy strategies and did not identify any differences in outcomes by type of bridging therapy. Future work should evaluate clinical outcomes with those receiving radiation therapy and/or novel systemic therapies without chemotherapy as a bridging therapy strategy. In fact, a prior study reported that bridging therapy utilizing radiation was associated with improved PFS compared with systemic therapy,[9] and recent data has suggested polatuzumab vedotin, a CD79b-binding monoclonal antibody conjugated to monomethyl auristatin E, may hold promise as a novel bridging therapy agent.[21]

We also demonstrated that patients receiving bridging therapy for CAR T-cell therapy experienced no differences in grade 3+ CRS or neurotoxicity. This finding is consistent with multiple prior studies, all of which did not detect an association of bridging therapy use with likelihood of CRS or neurotoxicity.[9 11 19 20] The number of grade 5 toxicities overall was small, with one grade 5 CRS and one grade 5 neurotoxicity; therefore, we could not evaluate specifically for risk of grade 5 CRS or neurotoxicity. Notably, the incidence of grade 5 CRS or neurotoxicity was rare, occurring in fewer than 1% of patients.

Our study has several limitations worth considering. First, this study is a retrospective study of patients at two large academic sites, and thus our findings could certainly be impacted by selection bias, as patients receiving bridging therapy may be more likely to experience clinical deterioration. Moreover, the bridging therapies used in this study may not reflect modern options with the emergence of additional targeted therapies. Thus, there remains a critical unmet need for randomized controlled trials to further clarify optimal bridging strategies. Second, we were limited to information about patients' clinical and toxicity outcomes that were available in the medical record, and therefore our data may not have fully captured all clinical and toxicity outcomes. Finally, our sample size limited the number of covariates we could analyze in multivariable logistic regression for clinical outcomes and prohibited analyzing non-relapse mortality; thus, our model may not fully account for all possible confounders. Future research studies should assess bridging therapy use prospectively and examine the association of bridging therapy use with non-relapse mortality.

## CONCLUSION

We demonstrated that bridging therapy use is common in CAR T-cell therapy recipients, with nearly 40% of patients receiving bridging therapy. We also identified that bridging therapy use is associated with worse OS but is not associated with PFS, ORR, CR rate, or grade 3+ CRS or neurotoxicity. These data suggest that bridging therapy may be a surrogate for additional poor prognostic factors leading to inferior OS. Our findings underscore the need to develop novel bridging therapy strategies to improve the outcomes for patients receiving CAR T-cell therapy.

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