Outpatient vs. inpatient administration of CAR-T cell therapy in cancer patients: A systematic literature review

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INTRODUCTION

- Chimeric antigen receptor (CAR)-T cell therapies have revolutionized the treatment landscape in several hematological cancers, demonstrating effective and long-lasting clinical responses[1,2]
- CAR-T therapies are usually administered in the inpatient setting, with patients being closely monitored following infusion to watch out for CAR-T related side effects like cytokine release syndrome (CRS) and neurotoxicity[3]
- Nevertheless, outpatient administration of CAR-T therapies is rapidly expanding and has the potential to reduce the long-term treatment burden on patients and caregivers, as well as to reduce the overall cost burden on the healthcare system[3]
- While there are some standalone studies which have presented a case for outpatient administration of CAR-T therapies, there is no known systematic literature review (SLR) which has compared the clinical efficacy, healthcare resource utilization (HCRU), and economic implications of outpatient management versus the inpatient management of CAR-T therapies

OBJECTIVES

- The objective of this exercise was to carry out an SLR to compile clinical efficacy, safety, quality of life (QoL), HCRU, and cost outcomes of patients treated with CAR-T in the outpatient setting and compare these to treatment in the inpatient setting where available

METHODS

Study design and search process

- An SLR was conducted in three electronic databases (Medline, Embase, and the Cochrane Library) to identify the publications of interest
- This was supplemented by manual searches of conference proceedings, bibliography of published studies and grey literature
- The search was limited to articles published between January 1, 2016, and January 4, 2023, and that reported relevant outcomes of CAR-T therapy administration in both outpatient and inpatient settings, or only the outpatient setting
- This SLR was conducted following the PRISMA guidelines and the Cochrane Handbook for Systematic Reviews of Interventions, version 6.3[4,5]

Eligibility criteria and study selection

- No restrictions were placed on the type of cancer or the CAR-T therapy administered
- No restrictions were placed on study design; the search included clinical trials, and observational studies (retrospective or prospective)
- Studies that did not specify the setting of CAR-T administration were excluded
- The relevant outcomes considered were clinical efficacy (response rates, survival etc.), safety, QoL, HCRU, and costs
- Literature screening and data extraction were conducted by two independent reviewers, with any disagreements being resolved by a third reviewer

Data analysis

- Evidence gathered for the studies were synthesized qualitatively
- Common themes and patterns were identified and summarized for the outcomes of interest

RESULTS

- Of 7,701 records retrieved, 1208 met the inclusion criteria. Of these, 38 records from 21 distinct studies were selected for qualitative analysis
- These studies focused on patients diagnosed with leukemias and lymphomas. Most studies were carried out in the United States
- Eleven studies, including five clinical trials reported data on CAR-T administration in both the outpatient and the inpatient settings
- However, none of the identified studies randomized patients to the outpatient and the inpatient settings

Efficacy outcomes – Response rate

- The overall response rate among patients treated in the outpatient setting was found to be comparable to those treated in the inpatient setting **(Table 1)**
- Real-world studies generally reported numerically lower response rates than in clinical trials for patients managed in the outpatient setting (43-77% vs. 80-100%)[7-11] **(Table 1)**

TABLE 1: Summary of response rates

CR PR

Study	Patient Population	Treatment	Follow-up	Outpatient N	Outpatient CR, PR, ORR	Inpatient N	Inpatient CR, PR, ORR
OUTREACH (Ph 2)[6]	R/R LBCL (3L+)	Liso-cel	NA	25	58% 25% 82%	57	44% 32% 76%
PILOT (Ph 2)[7]	R/R LBCL (2L+)	Liso-cel	24 mos.	41	50% 30% 80%	20	56% 24% 80%
TRANSCEND NHL 001 (Ph 3)[8]	R/R LBCL (2L+)	Liso-cel	NA	231	56% 24% 89%	25	53% 19% 72%
NCT03277729 (Ph 1/2)[9]	R/R FL	CAR-T cells	13 mos.	18	78% 17% 94%	NR	
	Others[a]			7	57% 43% 100%	NR	
Borogovac 2022 (RW)[10]	DLBCL and ALL	Axi-cel	1 mos.	13	69% 8% 77%	NR	
		Others[b]		8	75% 13% 88%	NR	
Nasta 2022 (RW)[11]	Lymphoma	Tisa-cel	39.5 wks.	72	35% 8% 43%	NR	
Shao 2021 (RW)[12]	DLBCL	Tisa-cel	29.1 wks.	12	25% 33% 58%	NR	

ALL, Acute lymphoblastic leukemia; Axi-cel, Axicabtagene ciloleucel; Brexu-cel, Brexucabtagene autoleucel; CLL, Chronic lymphocytic leukemia; CR, Complete response; DLBCL, Diffuse large B-cell lymphoma; FL, Follicular lymphoma; inpatient; LBCL, Large B-cell lymphoma; Liso-cel, Lisocabtagene maraleucel; MCL, Mantle cell lymphoma; mos, Months; N/A, Not available; NHL, Non-Hodgkin lymphoma; NR, Not relevant; OP, Outpatient; ORR, Overall response rate; Ph, Phase; PR, Partial response; R/R, Relapsed/refractory; RW, Real-world; Tisa-cel, Tisagenlecleucel; wks., Weeks; WM/LPL, Waldenström macroglobulinemia/lymphoplasmacytic lymphoma a. R/R MCL, CLL, DLBCL, WM/ LPL; b. Tisa-cel, brexu-cel, liso-cel

Efficacy outcomes – Survival

- Survival outcomes, including overall survival (OS), progression-free survival (PFS), and event-free survival, were reported in a limited number of studies
- Median PFS was reported to be 6.1 months and 4.1 months in the outpatient and inpatient groups, respectively in the OUTREACH trial,[6] 12-month PFS was similar in both the groups (41% vs. 39% in OUTREACH trial and 60% vs. 70% in ELARA trial)[6,13]
- OS at 12 months was reported as 60% for both the outpatient (median OS: not reached) and inpatient groups (median OS: 22.2 months) in the OUTREACH trial[6]

Safety outcomes

- Patients who received CAR-T in the outpatient setting generally experienced comparable frequencies of adverse events (AEs)[6-8, 13, 14] **(Table 2)**
- In studies focusing only on outpatient administration of CAR-T, CRS-related toxicities and neurologic toxicities were reported in 40%-92% and 6%-57% patients, respectively [9-12, 17-21]

QoL outcomes

- Only OUTREACH trial reported QoL outcomes. No difference was observed in change in QoL, assessed by EORTC-QLQ-C30 and EQ-5D-5L, between patients managed in the outpatient setting and the inpatient setting[15]

TABLE 2: Safety outcomes of included studies

Outpatient Inpatient

Study	Patient population	Treatment	Follow up	N IP, OP	CRS	Neurotoxicity
OUTREACH[6]	R/R LBCL (3L+)	Liso-cel	NA	54, 25	37% 44%	30% 32%
ELARA[13]	R/R FL (3L+)	Tisa-cel	20 mos.	17, 80	53% 48%	6% 11%
PILOT[7]	R/R LBCL (2L+)	Liso-cel	12.3 mos	20, 41	15% 48%	10% 41%
TRANSCEND NHL 001[8]	R/R LBCL (2L+)	Liso-cel	18.8 mos	25, 244	40% 42%	44% 28%
Denlinger 2022[14]	BCL	Tisa-cel	NA	NR,18	44%	22%
		Axi-cel	NA	45, NR	96%	73%

Axi-cel, Axicabtagene ciloleucel; BCL, B-cell lymphoma; CRS, Cytokine release syndrome; FL, Follicular lymphoma; LBCL, Large B-cell lymphoma; IP, Inpatient; Liso-cel, Lisocabtagene maraleucel; mos, Months; NA, Not available; NHL, Non-Hodgkin lymphoma; NR, Not relevant; OP, Outpatient; Ph, Phase; R/R, Relapsed/refractory; Tisa-cel, Tisagenlecleucel

Cost outcomes

- Costs for patients who received CAR-T in an outpatient setting were lower compared to those who received it in an inpatient setting **(Table 3)**
- Total costs in the 6 month post-infusion period when administered in the inpatient setting were 2 to 4 times greater ($61,772-$96,297), driven by higher hospitalization expenses[22,23] **(Table 3)**

TABLE 3: Cost outcomes of included studies

Study	Patient population, Tx	Follow-up	Outpatient N	Outpatient Total costs	Outpatient Hosp. costs	Inpatient N	Inpatient Total costs	Inpatient Hosp. costs
Palomba 2020[16]	R/R LBCL (3L+), Liso-cel	6 mos.	47	6-mos: $36,702, 1st mos: $19,837[a]	NA	256	6-mos: $89,535, 1st mos: $50,369[a]	NA
Denlinger 2022[14]	BCL, Tisa-cel; axi-cel	Median: Axi-cel: 31.4 mos, Tisa-cel: 23.8 mos	18	Tisa-cel[b]: $64,834	NA	45	Axi-cel[b]: $176,535	NA
McGarvey 2022[22]	R/R LBCL (2L+), Liso-cel	NA	20	6-mos: $16,172 1st mos: $13,261[a]	$9,455	41	6-mos: $61,772 1st mos: $46,947[a]	$49,495
McGarvey 2022[23]	R/R LBCL (2L+), Liso-cel	NA	19	6-mos: $38,314 1st mos: $18,774[a]	$20,867	71	6-mos: $96,297 1st mos: $49,111[a]	$69,153
Fowler 2022[13]	R/R FL (3L+), Tisa-cel	Median: 20 mos.	17	NA	$7,477	80	NA	$40,054
Maziarz 2022[24]	R/R DLBCL, Tisa-cel, Axi-cel	Mean: 5 mos.	Tisa-cel: 8	For FU period: Tisa-cel: $13,389 For Infusion encounter: Tisa-cel: $4,741	Tisa-cel: $4,753	Tisa-cel: 25 Axi-cel: 86	For FU period: Axi-cel: $46,575; Tisa-cel: $33,701; Infusion encounter: Axi-cel: $51,378 Tisa-cel: $34,908	For FU period: Axi-cel: $44,561 Tisa-cel: $29,953
Yang 2022[25]	R/R DLBCL, Tisa-cel, Axi-cel	IP: 6.6 mos, OP: 6 mos.	50	1st mos: $371,839, Mos 2-7: $48,056[c,d]	NA	380	1st mos: $348,364, mos 2-7: $44,874[c,d]	NA

Axi-cel, Axicabtagene ciloleucel; DLBCL, Diffuse large B-cell lymphoma; BCL, B-cell lymphoma; FL, Follicular lymphoma; FU, Follow-up; Hosp., Hospitalization; IP, Inpatient; LBCL, Large B-Cell lymphoma; Liso-cel, Lisocabtagene maraleucel; mos, Months; NA, Not available; OP, Outpatient; Ph, Phase; R/R, Relapsed/refractory; Tisa-cel, Tisagenlecleucel; Tx, Treatment

HCRU

- Among patients receiving CAR-T infusion in outpatient setting, 33-78% patients were hospitalized within 30 days of infusion.[26,27] Median time to hospitalization was reported as 4-9 days, and the most common reason for outpatient group hospitalizations was CRS[12,26,28]
- Unplanned hospitalizations, defined as those occurring post-CAR-T infusion in the outpatient setting and re-hospitalisations in the inpatient setting, were found to be generally higher in the outpatient group (33%-42%) compared to inpatient group (26%-29%)[27,29]
- Most studies reported higher mean length of overall hospitalization stay (2-3x higher)[6,7,13,16, 24, 25] and of ICU stay (2-3x higher)[13,16,25] for the inpatient cohort

KEY TAKEAWAYS

- Outpatient administration of CAR-T results in comparable clinical outcomes relative to inpatient administration
- While CAR-Ts are typically administered in the inpatient setting, outpatient administration of CAR-Ts can reduce the economic burden without adversely impacting clinical effectiveness and QoL

CONCLUSIONS

- Outpatient administration of CAR-T therapies appears to result in comparable overall outcomes in effectiveness, safety, and quality of life, compared with inpatient administration
- Costs associated with outpatient administration of CAR-T are substantially less compared with inpatient administration

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