Safety and efficacy of chimeric antigen receptor T-cell therapy for acute myeloid leukemia: A subgroup based meta-analysis

Mahmoud M. Morsy, Ahmed Y. Azzam, Osman Elamin, Adam Elswedy, Abdulqadir J. Nashwan

Leukemia Research 140 (2024) 107498

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Research Paper

Safety and efficacy of chimeric antigen receptor T-cell therapy for acute myeloid leukemia: A subgroup based meta-analysis

Mahmoud M. Morsy [a], Ahmed Y. Azzam [a], Osman Elamin [b], Adam Elswedy [a], Abdulqadir J. Nashwan [c,*]

[a] Faculty of Medicine, October 6 University, Giza, Egypt
[b] Department of Neurosurgery, Jordan Hospital, Amman, Jordan
[c] Nursing & Midwifery Research Department (NMRD), Hamad Medical Corporation, Doha, Qatar

ARTICLE INFO

Keywords:
Acute myeloid leukemia
CAR-T cell therapy
Hematology
Oncology

ABSTRACT

Introduction: Acute myeloid leukemia (AML) is a significant hematological malignancy in the United States, with a high mortality rate and limited treatment options. CAR T-cell therapy, a new and promising treatment, is being investigated for its efficacy and safety in AML. This meta-analysis aims to assess the safety and efficacy of CAR T-cell therapy in AML, considering various subgroups such as study location, study design, prior transplantation status, conditioning regimen, and CAR T-cell source.

Methods: We conducted a comprehensive literature review across multiple databases, adhering to PRISMA guidelines and focusing on studies concerning CAR T-cell therapy in AML. We included original articles in English and excluded non-original reviews, abstracts, and non-English studies. The risk of bias was assessed using the Cochrane ROBINS-I tool. Statistical analysis involved meta-analysis with Cochrane's Q-test and I^2 statistic, using both fixed-effect and random-effects models, and assessed for publication bias.

Results: Our search yielded studies encompassing 57 AML patients treated with CAR T-cell therapy. The meta-analysis revealed a 48% incidence of complete remission with CAR T-cell therapy, varying significantly across subgroups based on study design, location, prior transplantation, conditioning regimen, and CAR T-cell source. The highest complete remission rates were observed in patients from China, those who had undergone prior hematopoietic cell transplantation, and those treated with fludarabine and cyclophosphamide conditioning regimen. Adverse events included graft-versus-host disease (7%) and cytokine release syndrome (53%).

Conclusions: This meta-analysis highlights the potential of CAR T-cell therapy in AML treatment, especially when integrated with certain prior treatments and conditioning regimens. The findings suggest a higher efficacy in patients with previous hematopoietic cell transplantation and specific conditioning regimens. Further large-scale, randomized trials are essential to confirm these findings and establish CAR T-cell therapy as a standard treatment for AML.

1. Introduction

Acute myeloid leukemia (AML) comprises around 1% of all recent cancers in the United States and still the most dangerous one regarding hematological malignancy with 5-year survival of 31.7% [1]. Being of poor prognosis with a cure rate of 5%-15% of patients above age of 60-years, and 35%-40% in patient younger than 60-years [2]. AML is primarily treated with chemotherapy [3]. However 10–40% are from the start refractory to chemotherapy [2]. Introducing Hematopoietic stem cell therapy (HSCT) is the only treatment for those patients as it makes long lasting complete remission (CR) [4]. Although 50% of patients are eligible to receive HSCT [5]. The current therapeutic protocols for AML have several limitations in controlling the disease progression and survival, therefore there is an unmet need for other treatment options to be added to the current regimens [6].

Chimeric antigen receptor (CAR) T-cell therapy is a new promising treatment which is currently being trialed in the treatment of chemotherapy refractory B cell malignancies as well as for multiple myeloma [7–10]. The use of CAR T-cell therapy is still under investigation for AML patients [11].

* Correspondence to: Hamad Medical Corporation, Doha 3050, Qatar
E-mail address: anashwan@hamad.qa (A.J. Nashwan).

https://doi.org/10.1016/j.leukres.2024.107498
Received 11 February 2024; Received in revised form 22 March 2024; Accepted 30 March 2024
Available online 1 April 2024

The aim of this systematic review and meta-analysis is to estimate the safety and efficacy of CAR T-cell therapy for AML patients based on the current evidence from the literature. We aim to perform the analysis on different subgroup levels according to the study location, study design, prior transplantation status, conditioning regimen, and CAR T-cell source. To our knowledge, this is the first meta-analysis to perform this subgroup analysis to address the therapeutic concerns of CAR T-cell therapy for AML.

2. Methods

2.1. Literature review

We performed the search strategy for the literature through PubMed/Medline, Scopus, Web of Science, and Google Scholar. We followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines. Our keywords strategy included: "Acute Myeloid Leukemia", "AML", "Chimeric Antigen Receptor T-cell Therapy", "CAR T-cell Therapy", "Immunotherapy". We included original articles, and English language articles which targeted the CAR T-cell therapy for AML. We excluded non-original review articles such as review articles, systematic reviews, meta-analysis. We also excluded abstracts, and non-English language articles. We have searched the literature up to 15th of December 2023, we did not include an upper limit for publication inclusion.

2.2. Risk of bias assessment

Two reviewers independently utilized the Cochrane Risk of Bias in the non-randomized studies of interventions (ROBINS-I) tool to evaluate the quality and risk of bias among included studies. Two authors independently evaluated the risk of bias. The reviewers settled the discrepancies by discussion.

2.3. Statistical analysis

We performed a meta-analysis of the included studies to estimate the cumulative incidence (event rate), and 95% confidence interval (CI).

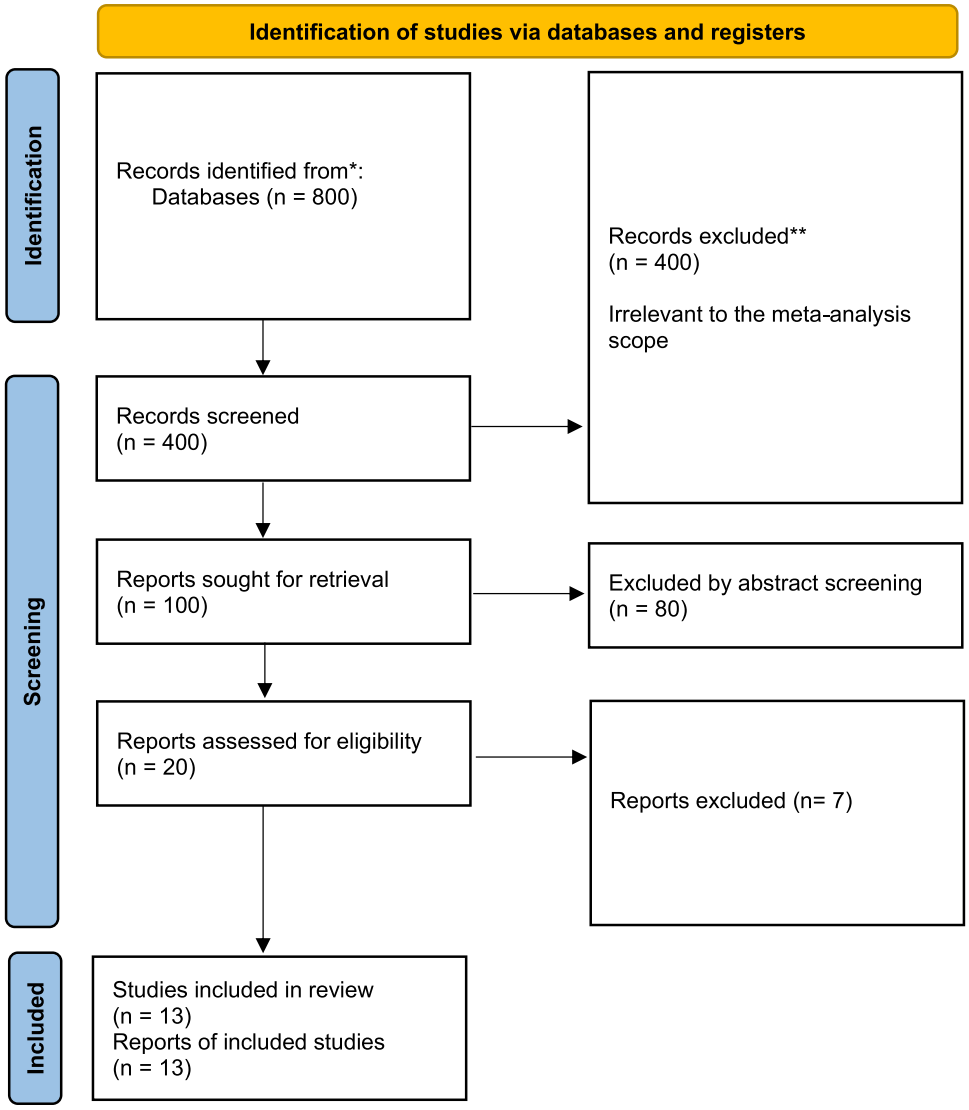

Fig. 1. PRISMA flow chart for the included studies. **PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only** *Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers). **If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools. *From:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.

The heterogeneity of results among the included studies was examined using Cochrane's Q-test and the I^2 statistic. The common-effects (fixed-effect) model was indicated for outcomes without significant heterogeneity, while random-effects model was indicated for outcomes with significant heterogeneity. Heterogeneity was assessed through visual inspection of the forest plots and measured using the I^2 and chi-square ($\chi 2$) tests. The $\chi 2$ test was employed to determine the presence of significant heterogeneity, while the I^2 test was utilized to quantify the magnitude of heterogeneity, if present. The interpretation of the I^2 test followed the recommendations provided by the Cochrane Handbook (Part 2, Chapter 9). For testing statistical heterogeneity, a significance level (α) below 0.1 was considered indicative of significant heterogeneity, as recommended by the Cochrane Handbook. Publication bias was visually assessed with a funnel plot and confirmed by Egger's test if possible. All p-values were two-sided, and a p-value < 0.05 was considered statistically significant. Also, statistical significance was assessed in alliance with confidence interval range. The analysis was conducted using the R version 4.3.0. In addition, an individual patient meta-analysis was conducted to assess predictors of outcomes and complications.

3. Results

3.1. Search strategy and risk of bias assessment

The PRISMA flow chart results are listed in Fig. 1. The results of ROBINS-I risk of bias assessment were listed in Fig. 2. We performed the assessment for the clinical trials only, we were not able to assess the case reports and case series due to their limited nature of assessment.

3.2. Baseline characteristics of included studies

57 patients were included from the eligible studies, the included studies had different study designs (three case reports and ten clinical trials) who received CAR-T cell therapy from different sources (Allogeneic, Autologous, or both) for AML. The median age of patients was 41 years with a range of 7–80 years. The included trials were in different countries (Australia, China, USA, and Germany). 29% received prior hematopoietic cell transplantation (HCT) before CAR-T cell therapy. In five studies the patients received Fludarabine and Cyclophosphamide (FC) as a conditioning regimen [12–16] while Qu et al. used decitabine with FC as condition regimen [17]. Four studies did not use a conditioning regimen for their patients[18–21], while two studies did not report whether they have used a conditioning regimen or not [22, 23] (Table 1).

We listed the overall response rate, complete remission, partial response, follow up, response duration and overall survival, cytokine release syndrome, neurotoxicity, and graft versus host disease related information from the included studies in (Table 2).

3.3. Complete remission

22 patients who received CAR-T cell therapy had complete remission with an incidence of 48% (95% CI= 34%-62%) with no statistically significant heterogeneity (I^2=0%, P-value= 0.94) (Supplementary File 1). We conducted subgroup analysis according to the study design, location, prior hematopoietic cell transplantation (HCT), Conditioning regimen, and the source of CAR-T cell therapy. As for study design subgroup analysis.

The incidence of complete remission in phase I trials was 43% (95% CI 29%-58%), with no statistically significant heterogeneity (I^2=0%, P-value=0.77), and for case reports it was found that the estimated completed remission is 100% (95% CI= 0–100%), with no statistically significant heterogeneity (I^2=0% P-value=1.00). However, there was no statistically significant difference in the effect according to the test for subgroup differences between both subgroups (P-value= 1.00) (Supplementary File 1).

According to the location (country of study) subgrouping, there were four countries included (Australia, China, USA, Germany) there was only one study only in Australia with an incidence of complete remission

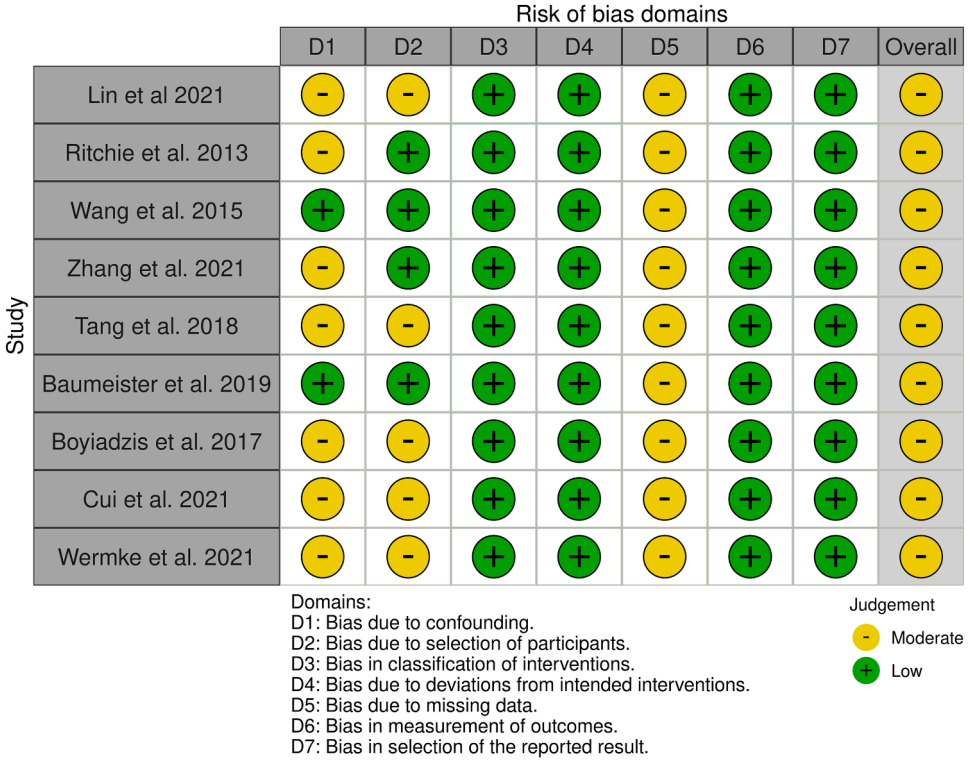

Fig. 2. Risk of bias assessment figure according to ROBINS-I Scale.

Table 1
Baseline Characteristics of the Included Studies.

Study	Number of Patients	Age, year (Range)	Number of Males (%)	Study Design	Location	AML Status	Prior HCT	Conditioning regimen	Post CAR-T Allo-HCT	Source of CAR-T cell Therapy	Manufacturing time in days	Target Antigen	Transduction Mechanism	Costimulatory Domain
Lin et al. 2021 [18]	10	27 (8–56)	7 (70)	Clinical Trial	China	Refractory=1 Relapsed=9	No	None	No	Autologus and Allogenic	14	CLL-1	Lentiviral vector	CD-3 and CD-28
Ritchie et al. 2013 [24]	4	71 (64–78)	2 (50)	Phase I clinical trial	Australia	Refractory=3 Relapsed= 1	No	FC	No	Autologus	12	LeY Ag	Retroviral	CD28 and the TCR-zeta chain
Wang et al.2015 [20]	1	41	1 (100)	Clinical Trial	China	Relapsed&Refractory	No	None	No	Autologus	13	CD33	Lentiviral vector	4–1BBzeta-GFP
Zhang et al. 2021 [13]	4	8.4 (7.3–9.6)	2 (50)	Phase I/II clinical trial	China	All relapsed &Refractory	No	FC	1 patient at day 90	Autologus	N/A	CLL-1	Lentiviral vector	CD28-CD27-CD3zeta
Tang et al. 2018 [22]	3	24 (14–49)	1 (33)	Phase I clinical trial	China	All relapsed	1 patient	N/A	1 patient at day60	Allogenic (NK-92 cells)	N/A	CD33	Lentiviral	CD-28/4–1BB
Baumeister et al. 2019 [19]	7	70 (44–79)	NA	Phase I clinical trial	USA	Refractor=4 Relapsed=3	N/A	None	1 patient at day 120	Autologus	9	NKG2D	Retroviral	Dap10
Boyiadzis et al. 2017 [23]	6	71 (56–80)	6 (100)	Phase I clinical trial	USA	All relapsed &Refractory	No	N/A	No	Allogenic (aNK cell)	10	CD33, CD34, CD45, CD117	N/A	N/A
Qu et al. 2019 [17]	2	15,18	2 (100)	Case Report	China	Refractory=1 Relapsed=1	1 patient	Decitaine&FC	No	Auto (1)Allo (1 from sibiling donor)	Case 1 (8) Case 2 (14)	CD19	N/A	N/A
Sallman et al. 2018 [21]	1	52	1 (100)	Case Report	USA	Relapsed&Refractory	Yes	None	Yes at day 97	Autologus	N/A	NKG2D	Retroviral	CD3zeta
Yao et al. 2019 [25]	1	25	1 (100)	Case Report	China	relapsed	Yes	RIC regimen of TVFB	Yes	allogenic (Donor drived)	8–12 days	CD123	Retroviral	41BB
Cui et al. 2021 [15]	6	34.5 (7–52)	5 (83)	Clinical Trial	china	Relapsed&Refractory	6 patients	FC	No	Autologous 4, Allogeneic donor 2 (donor derived)	N/A	CD38	N/A	41BB-CD3zeta
Wermke et al. 2021 [14]	3	66 (54–80)	3(100)	Clinical Trial	Germany	relapsed and refractory	2 patients	FC	No	Autologus	N/A	CD123	N/A	CD-28
Fang et al. 2020 [16]	9 Seven were de novo AML, one was JMML transformed AML, one was CML in accelerated phrase	32 (6–48)	1 (11)	Phase I clinical trial	China	relapsed and refractory	N/A	FC	6	Autologus8, MSD 1	N/A	CLL-1 -CD33	N/A	N/A

Table 2
Adverse Events in the Included Studies.

Study	ORR, n (%)	CR, n (%)	PR, n (%)	CRS, n (%, Grade)	Neurotoxicity, n (%)	GVHD, n (%)
Lin et al. 2021 [18]	NA	NA	NA	NA	NA	NA
Ritchie et al. 2013 [24]	2 (50)	1 (25)	1 (25)	0	0	0
Wang et al.2015 [20]	1 (100)	0	1 (100)	1 (100, IV)	NA	NA
Zhang et al. 2021 [13]	3 (75)	3(75)	0	3 (75, I-II)	1 (25)	NA
Tang et al. 2018 [22]	2 (67)	1 (33)	1 (33)	2 (66, I-II)	NA	1 (33)
Baumeister et al. 2019 [19]	0	0	0	0	0	0
Boyiadzis et al. 2017 [23]	1 (17)	0	1(17)	0 (Grade II fever and Chills)	0	0
Qu et al. 2019 [17]	2 (100)	2 (100)	0	2 (100, I-IV)	NA	NA
Sallman et al. 2018 [21]	1 (100)	1 (100)	0	0	0	NA
Yao et al. 2019 [25]	1 (100)	1 (100)	0	1 (100, III-IV)	NA	1 (100)
Cui et al. 2021 [15]	4 (67)	4 (67)	1 (17)	5 (83, I-II), 1 (17, III)	0	0
Wermke et al. 2021 [14]	3 (100)	2 (67)	1 (33)	2 (67, I)	0	NA
Fang et al. 2020 [16]	7 (78)	7 (78)	0	8(89) 3 I,3II,2III	4 (44)	NA

ORR: Overall Response Rate; CR: Complete Response; PR: Partial Response; CRS: Cytokine Release Syndrome; GVHD: Graft-versus-host Disease

of 25%, for China the incidence was 72% (95% CI= 52%-86%), with no statistically significant heterogeneity (I^2=0% P=0.87), USA subgroup the incidence was 7% (95% CI 1%-37%) with no statistically significant heterogeneity (I^2=0%, p=1.00). There was only one study in Germany with a complete remission incidence of 67%. According to the test of subgroup differences, there was a statistically significant difference according to the location and country of study (P-value= 0.01). There was a significantly higher incidence in China compared to other countries, which may raise a concern for a geographical or racial bias for treatment response (Supplementary File 1).

For prior HCT subgrouping, the incidence of complete remission in patients who did not undergo HCT prior to CAR-T cell therapy was 37% (95% CI= 22%-55%) with no statistically significant heterogeneity (I^2=0% P-value =0.56), however for patients who received prior HCT the incidence was 69% (95% CI 43%-86%) with no statistically significant heterogeneity (I^2=0% P-value =0.97). There was a statistically significant difference between subgroups according to the test of subgroup differences (P-value= 0.01), denoting that patients who received HCT before CAR-T cell therapy had a 32% higher chance of undergoing complete remission compared to patients who did not receive prior HCT (Supplementary File 1).

For conditioning regimen subgrouping, the incidence of complete remission in patients who received a combination of FC as conditioning regimen was 68% (95% CI 49%-82%), with no statistically significant heterogeneity (I^2=0% P-value =0.70). For those who did not get any of the conditioning regimen protocols the incidence was 12% (95% CI= 3%-37%) with no statistically significant heterogeneity (I^2=0% P-value =1.00). There was one study which reported therarbucin, teniposide, fludarabine and busulfan (TVFB) as a conditioning regimen with an incidence of 100% (95% CI= 2%-100%). There was a statistically significant difference between subgroups (P-value < 0.01), resulting that patients who received FC conditioning regimen had the highest incidence of achieving complete remission compared to patients which did not receive any conditioning regimen protocols or received TVFB. The FC group had a 5% higher incidence in achieving complete remission compared to patients who did not receive any conditioning protocols (Supplementary File 1).

Regarding the source of CAR-T cell therapy (autologous, allogeneic or both) subgrouping, the incidence in autologous group was 37% (95% CI= 19%-60%), with no statistically significant heterogeneity (I^2=0% P-value= 0.73). For the allogeneic group the incidence was 20% (95% CI= 5%-54%) with no statistically significant heterogeneity (I^2=0% P-value= 1.00). For the group which received both allogeneic and autologous cells the incidence was 76% (95% CI= 51%-91%), with no statistically significant heterogeneity (I^2=0%, P-value= 0.89). There was a statistically significant difference between the subgroups (P-value= 0.01), favoring that the group which received both autologous and allogeneic cells had the highest incidence of achieving complete remission compared to receiving a single source of cells (Supplementary File 1).

3.4. Partial response

Six patients who received CAR-T cell therapy had a partial response with an incidence of 13% (95% CI=6%-26%) with no statistically significant heterogeneity (I^2=0%, P-value= 1.00) (Supplementary File 1). As for study design subgroup analysis, there were three different categories included: phase I clinical trials, phase I/II clinical trials and case reports.

The incidence of partial response in phase I trials was 15% (95% CI 7%-30%), with no statistically significant heterogeneity (I^2=0%, P-value=1.00), for phase I/II clinical trial it was only one with no partial response and for case reports the partial response was 0% (95% CI=0%-100%), with no statistically significant heterogeneity (I^2=0%, P-value=1.00) However there was no statistically significant difference in the effect according to the test for subgroup differences between these subgroups (P-value= 1.00) (Supplementary File 1).

According to the country of study subgrouping, there were four countries included (Australia, China,USA, Germany) there was only one study only in Australia with an incidence of partial response of 25%, for China the incidence was 12% (95% CI=4%-30%) with no statistically significant heterogeneity (I^2=0%, P-value= 1.00),for USA the incidence was 7% (95% CI=1%-37%) with no statistically significant heterogeneity (I^2=0%, P-value= 1.00), for Germany there is only one study with incidence of 33%,However there was no statistically significant difference in the effect according to the test for subgroup differences between these subgroups (P-value= 0.60) (Supplementary File 1).

For prior HCT therapy subgrouping there where two subgroups (patient with prior HCT and Patient without prior HCT) for those without prior HCT the incidence was 10% (95% CI=3%-26%), with no statistically significant heterogeneity (I^2=0%, P-value= 1.00), for those with prior HCT the incidence was 19% (95% CI=6%-45%) with no statistically significant heterogeneity(I^2=0%, P-value= 0.99), however there was no statistically significant difference between both categories in prior HCT subgrouping (P-value=0.38) (Supplementary File 1).

For conditioning regimen subgrouping,the incidence of partial response in patent received FC as conditioning regimen was 11% (95% CI=3%-28%) with no statistically significant heterogeneity (I^2=0%, P-value= 1.00), for those did not take any conditioning regimen the incidence of partial response was 17% (95% CI=5%-41%) with no statistically significant heterogeneity (I^2=0%, P-value= 0.99), for those received TVFB as a conditioning regimen there was only one study with incidence of 0%. However, there was no statistically significant difference between subgroups according to this classification (P-value= 0.84) (Supplementary File 1).

Regarding the source of CAR-T cell therapy subgrouping, for the autologous source the incidence of partial response was 15% (95% CI=5%-38%) with no statistically significant heterogeneity (I^2=0%, P-value= 1.00), for the allogeneic group the incidence was 20% (95% CI=5%-54%) with no statistically significant heterogeneity (I^2=0%, P-

value= 0.86). For the group which received both autologous and allogeneic subgroup the incidence of partial response was 6% (95% CI=1%-32%) with no statistically significant heterogeneity (I^2=0%, P-value= 0.86). There was no statistically significant difference between subgroups in the source of CAR-T cell therapy classification (P-value= 0.56) (Supplementary File 1).

3.5. Overall response

The overall response was reported by 27 patients under CAR-T cell therapy with an incidence of 57% (95% CI=43%-71%) with no statistically significant heterogeneity (I^2=0%, P-value= 0.92) (Supplementary File 1). As for study design subgroup analysis, there were three different categories included: phase I clinical trials, phase I/II clinical trials and case reports.

For phase I clinical trial the overall response was 51% (95% CI=36%=66%) with no statistically significant heterogeneity (I^2=0%, P-value= 0.68), for phase I/II clinical trial there is only one study with overall response incidence of 75%, for case reports the overall response incidence was 100%(95% CI=0%-100%) with no statistically significant heterogeneity (I^2=0%, P-value= 1.00).lastly there is no significant difference between different subgroups according to different study design (P-value=0.68) (Supplementary File 1).

As for location subgrouping there is different countries (Australia, China, USA, Germany), In Australia there only one study reported that overall response was 50%, for China the overall response was 77% (95% CI=57%-89%) with no statistically significant heterogeneity (I^2=0%, P-value= 1.00),for Germany there was only one study reported that the overall response incidence was 100%.there was statistical significant difference (P-value=<0.01) favoring China subgroup in comparison with other countries with incidence of 77% (Supplementary File 1).

For prior HCT subgrouping,the overall response incidence in studies where patients didn't receive prior HCT was 45%(95% CI=29%-63%) with no statistically significant heterogeneity (I^2=0%, P-value= 0.41), for those was on prior HCT the overall response incidence was 81%(95% CI=55%-94%) with no statistically significant heterogeneity (I^2=0%, P-value= 1.00),there was statistically significant difference favoring studies where patients took prior HCT with difference of overall response incidence of 36% (Supplementary File 1).

For conditioning regimen subgroup,studies whose patients FC as conditioning regimen the overall response incidence was 75%(95% CI=56%-88%) with no statistically significant heterogeneity (I^2=0%, P-value= 0.96), for those didn't take any condition regimen the overall response incidence was28% (95% CI=12%=52%)with no statistically significant heterogeneity (I^2=0%, P-value= 0.74),for those received TVFB as a conditioning regimen there was only one study with incidence of 100%.there is statistically significant difference favoring studies whose patients received FC as conditioning regimen with overall response incidence of 75% (Supplementary File 1).

Regarding the source of CAR-T cell therapy subgrouping, for the studies whose patients received autologous the overall response incidence was 50% (95% CI=29%-71%) with no statistically significant heterogeneity (I^2=0%, P-value= 0.99). For the allogeneic group, the overall response incidence was 40% (95% CI=16%-70%) with no statistically significant heterogeneity (I^2=0%, P-value= 0.37). For the group which received both autologous and allogeneic sources the overall response incidence was 76% (95% CI=51%-91%) with no statistically significant heterogeneity (I^2=0%, P-value= 0.89). There was no statistically significant difference favoring any source (P-value=0.14) (Supplementary File 1).

3.6. GVHD

Graft versus host disease (GVHD) was reported as an adverse event in two patients with an incidence of 7% (95% CI=2%-25%) (Supplementary File 1).

For study design subgrouping, the incidence of GVHD in phase I clinical trial was 4% (95% CI=1%-23%) with no statistically significant heterogeneity (I^2=0%, P-value= 1.00) and there is only one case report in which GVHD incidence was 100%. However, there is no statistically significant difference in the adverse effect according to the test for subgroup differences between both subgroups (P-value= 1.00) (Supplementary File 1).

Regarding the country subgrouping, in Australia there was only one study which reported GVHD with an incidence of 0%. For China the incidence of GVHD was 50% (95% CI= 12%-88%) with no statistically significant heterogeneity (I^2=0%, P-value= 1.00). For the USA the GVHD incidence was 0% (95% CI= 0%-100%) with no statistically significant difference (I^2=0%, P-value= 1.00) and for China there was only one study reporting incidence of GVHD which was 0%. There was no statistically significant difference between location subgroups (P-value=1.00) (Supplementary File 1).

In patients which did not receive prior HCT the incidence of GVHD was 0% (95% CI= 0%-100%) with no statistically significant difference in heterogeneity (I^2=0%, P-value= 1.00), for those who received prior HCT the incidence of GVHD was 20% (95% CI=5%-54%) with no statistically significant difference in heterogeneity (I^2=0%, P-value= 1.00). However, there was no statistically significant difference between subgroups related to prior HCT (Supplementary File 1).

In studies whose patients received FC as conditioning regimen the GVHD was 0% (95% 0%-100%)with no statistically significant difference in heterogeneity (I^2=0%, P-value= 1.00), for those did not take any conditioning regimen the incidence was 6% (95% CI= 1%-34%) with no statistically significant heterogeneity (I^2=0%, P-value= 1.00), for those received TVFB as a conditioning regimen there was only one study with incidence of 100%. However, there is no statistically significant difference between subgroups according to the conditioning regimen (P-value= 1.00) (Supplementary File 1).

GVHD incidence in the autologous subgroup was 0% (95% CI= 0%-100%) with no statistically significant heterogeneity (I^2=0%, P-value= 1.00), for the allogeneic subgroup GVHD incidence was 20% (95% CI=5%-54%) with no statistically significant heterogeneity (I^2=0%, P-value= 1.00), for the patients which received both sources, there was only one study with GVHD incidence of 0%. There was no statistically significant difference between subgroups according to the source of CAR-T cell therapy (P=value= 1.00) (Supplementary File 1).

3.7. Cytokine release syndrome

25 patients experienced cytokine release syndrome (CRS) as an adverse event with an incidence of 53% (95%CI=39%-67%) with no statistically significant heterogeneity (I^2=0%, P-value= 1.00) (Supplementary File 1).

For phase I clinical trials the incidence of CRS was 49% (95% CI=34%-64%) with no statistically significant heterogeneity (I^2=0%, P-value= 0.99), for Phase I/II clinical trials there was only one study reporting that incidence of CRS was 75%, for case reports the incidence of CRS was 75% (95% CI=24%-97%) with no statically significant heterogeneity (I^2=0%, P-value= 1.00). There was no statistically significant difference in this classification (P-value= 0.42) (Supplementary File 1).

For prior HCT therapy subgrouping, patients who did not receive prior HCT had an incidence of 39% (95% CI=23%-57%) with no statistically significant heterogeneity (I^2=0%, P-value= 1.00). However, for those received prior HCT therapy the CRS incidence was 81% (95% CI=55%-94%) with no statistically significant heterogeneity (I^2=0%, P-value= 1.00). There was a statistically significant difference between both categories in prior HCT subgrouping (P-value=<0.001) denoting that patients who received prior HCT had a higher incidence of CRS compared to the patients which did not receive prior HCT by 42% (Supplementary File 1).

For conditioning regimen subgroups, the studies whose patients

received FC as conditioning regimen the CRS incidence was 75% (95% CI=56%-88%) with no statistically significant heterogeneity (I^2=0%, P-value= 0.98). For those who did not take any conditioning regimen the incidence of CRS was 17% (95% CI=5%-41%) with no statistically significant heterogeneity (I^2=0%, P-value= 1.00), for those who received TVFB as a conditioning regimen there was only one study with CRS incidence of 100%. There was a statistically significant difference between the subgroups (P-value < 0.01). Denoting that there was a higher incidence in CRS for patients which received FC as a conditioning regimen compared to the other groups with a 58% higher possibility (Supplementary File 1).

4. Discussion

Acute myeloid leukemia is among the most aggressive hematological malignancies in the United States [1]. It is treated primarily by chemotherapy but for the refractory patients, hematopoietic stem cell transplantation is usually indicated. The aim of the transplantation is to reset the fault of the immune system. However, nearly half of the patients who receive hematopoietic stem cell transplantation do not respond to it [2–5]. CAR T-cell therapy showed promising results in other types of leukemia including acute lymphoblastic leukemia [7]. In our meta-analysis, we investigated the safety and efficacy of CAR-T cell therapy as a new promising treatment for acute myeloid leukemia. We aimed to investigate its therapeutic effect regarding achieving complete remission, partial response, and the overall response rate to the treatment. We also investigated the rate of adverse events of this new potential treatment through the estimation of GVHD and cytokine release syndrome incidence.

We also aimed to investigate the safety and efficacy according to the study design, study location, prior transplantation, conditioning regimen, and the source of CAR T-cell therapy.

Regarding complete remission we found a statistically significant difference in location subgrouping favoring China with incidence of complete remission of 72% which may be related to genetic factors in relation to different locations. Based on those results, encourage to make a comparative analysis and further trials to differentiate between the countries to treatment response. As we may benefit that some genetic variants play a role in treatment response.

Also, there was a statistically significant difference in prior hematopoietic cell transplantation subgrouping reporting that patients receiving hematopoietic cell transplantation prior to CAR T-cell therapy have higher incidence of complete remission of 32% higher than those who did not receive prior transplantation. We found a statistically significant difference in those who received fludarabine and cyclophosphamide as a conditioning regimen in achieving complete remission compared to the patients which did not receive a conditioning regimen prior to CAR T-cell therapy, denoting the importance of fludarabine and cyclophosphamide as a potential sensitizer for treatment efficacy for acute myeloid leukemia patients.

According to the source of CAR T-cell therapy, we have found a statistically significant difference favoring receiving a combined autologous and allogeneic source compared to a single source of cells. The combination of cells had a 76% incidence of achieving complete remission, making it superior to receiving autologous cells only or allogeneic cells only. Regarding partial response, we found no statistically significant difference between the different subgroups.

As regards overall response we found that there was statistically significant difference in location subgrouping favoring China in comparison with other countries with an incidence of 77% denoting that Chinese group had better outcome than other countries included. Which raises a major concern for further investigations. According to the country's response, the current literature does not show any evidence favoring a racial group for the treatment of acute myeloid leukemia with CAR T-cell therapy. However, due to the significant variance in our results based on country subgrouping there is a need for this concern to be investigated.

We also found a statistically significant difference suggesting that prior hematopoietic cell transplantation may play a role in improving the outcomes and response of CAR-T cell therapy compared to patients which did not undergo hematopoietic cell transplantation with a 36%. Also, prior transplantation had a significant role in the overall response rate. The current literature did not focus on the importance of prior transplantation before CAR T-cell therapy for several reasons including the eligibility of patients, the difficulty of receiving both treatment options due to financial limitations and country specific limitations. However, based on the conclusions of our results we highly support conducting further trials investigating the combination of hematopoietic cell transplantation with CAR T-cell therapy as a possible treatment option for acute myeloid leukemia. We hypothesize that prior transplantation has a better sensitizing effect for the immune system to respond better to CAR T-cell therapy. The mechanism is currently unknown however based on our significant results this concern should be investigated.

The results of our study support the use of a conditioning regimen through fludarabine and cyclophosphamide in achieving a better overall response rate. The incidence of patients who achieved complete response and had fludarabine and cyclophosphamide before therapy was 75% with a statistically significant difference in the subgroup analysis. However, the evidence regarding other conditioning regimens was not enough to draw a sufficient conclusion on this part. We recommend comparing the current conditioning regimen to other regimens in a broad spectrum in further trials before making recommendations on this point.

Regarding the adverse events in our analysis, we have two major adverse events, graft-versus-host disease, and cytokine release syndrome. We found that the incidence of cytokine release syndrome was higher in the patients which received prior hematopoietic cell transplantation. However, there was no statistically significant difference between subgroups regarding graft-versus host disease.

We tried to perform subgroup analysis according to target antigen in the clinical trials, however the included studies reported different variants in the targeted antigens as shown in Table 1. So, it was not statistically possible to perform subgroup analysis in this case. We consider this as a potential limitation within our study.

Regarding the neurotoxicity in all studies there was no event of neurotoxicity except in Zhang et al., 2012 there was only one had neurotoxicity and there were four patients also in Fang et al.2020, we tried to do subgroup analysis according to neurotoxicity but failed because of significant pseudo heterogeneity effect because as most of the included studies had zero events in neurotoxicity.

The limitations of our study are, the lack of randomized controlled trials, the limited sample size of the included studies, inclusion of case reports, the variance in the included study designs, We were not able to perform subgroup analysis for either of neurotoxicity event and subgroup analysis according to the target antigen, as it was not statistically possible based on the included studies. As for target antigen, there were several variants in the antigens making it not possible statistically; while for neurotoxicity most of the included studies had no neurotoxicity events except for two studies which in case will create a pseudo heterogeneity effect in the analysis. We aimed to perform subgroup analysis according to different parameters to minimize the possible bias and to discriminate the possible treatment response and adverse events in particular subgroups. Based on our analysis, we conclude that CAR T-cell therapy is a promising treatment for acute myeloid leukemia, especially when combined with fludarabine and cyclophosphamide a conditioning regimen and preceded by hematopoietic cell transplantation with a combined source of autologous and allogeneic source rather than a single source of cells. However, based on the current limitations of our study further randomized controlled trials and larger sample size trials are required to judge the safety and efficacy of CAR T-cell therapy.

5. Conclusions

In this meta-analysis, we explored the safety and efficacy of CAR T-cell therapy in treating acute myeloid leukemia. Our findings indicate a significant advantage of this therapy, particularly when preceded by hematopoietic cell transplantation and combined with a fludarabine and cyclophosphamide conditioning regimen. A noteworthy finding is the higher incidence of complete remission in patients who had prior hematopoietic cell transplantation and those treated with fludarabine and cyclophosphamide, suggesting these as potential sensitizers for treatment efficacy. Additionally, our study revealed a notable geographic variance, with Chinese patients showing a higher incidence of complete remission and overall response, raising questions about the influence of genetic factors in treatment responsiveness across different locations. This finding underscores the necessity for further comparative analysis and trials to understand the role of genetic variations in treatment outcomes. The use of a combined autologous and allogeneic source for CAR T-cell therapy was also found to be superior, yielding a higher incidence of complete remission compared to single-source cells. However, the study did not find significant differences in partial response rates across various subgroups. Concerning adverse events, the most significant were graft-versus-host disease and cytokine release syndrome, with the latter occurring more frequently in patients with prior hematopoietic cell transplantation. However, there was no significant difference in graft-versus-host disease across subgroups. The limitations of our study include the lack of randomized controlled trials, limited sample sizes, and variance in study designs, which necessitate further research with larger, more controlled trials to confirm these findings. Overall, CAR T-cell therapy, especially when combined with specific prior treatments and conditioning regimens, emerges as a promising option for acute myeloid leukemia treatment. However, more extensive trials are needed to fully ascertain its safety and efficacy.

Ethical approvals

N/A

Funding

Open Access funding provided by the Qatar National Library.

CRediT authorship contribution statement

Abdulqadir J. Nashwan: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Funding acquisition. **Adam Elswedy:** Writing – review & editing, Writing – original draft, Methodology, Data curation, Conceptualization. **Osman Elamin:** Supervision, Methodology, Investigation, Formal analysis, Data curation. **Ahmed Y Azzam:** Writing – review & editing, Writing – original draft, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Mahmoud M Morsy:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

Open Access funding provided by the Qatar National Library.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.leukres.2024.107498.

References

[1] Stats N.C. *Acute myeloid leukemia - cancer stat facts.* 2023; Available from: ⟨https://seer.cancer.gov/statfacts/html/amyl.html⟩.
[2] H. Döhner, D.J. Weisdorf, C.D. Bloomfield, Acute myeloid leukemia, N. Engl. J. Med 373 (12) (2015) 1136–1152.
[3] K. Koenig, et al., The changing landscape of treatment in acute myeloid leukemia, Am. Soc. Clin. Oncol. Educ. Book 40 (2020) 1–12.
[4] J. Koreth, et al., Allogeneic stem cell transplantation for acute myeloid leukemia in first complete remission: systematic review and meta-analysis of prospective clinical trials, JAMA 301 (22) (2009) 2349–2361.
[5] K. Koenig, A. Mims, Relapsed or primary refractory AML: moving past MEC and FLAG-ida, Curr. Opin. Hematol. 27 (2) (2020) 108–114.
[6] S. DeWolf, M.S. Tallman, How I treat relapsed or refractory AML, Blood 136 (9) (2020) 1023–1032.
[7] S.L. Maude, et al., Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia, N. Engl. J. Med 378 (5) (2018) 439–448.
[8] M. Roschewski, D.L. Longo, W.H. Wilson, CAR T-cell therapy for large B-cell lymphoma - who, when, and how? N. Engl. J. Med. 386 (7) (2022) 692–696.
[9] N.C. Munshi, et al., Idecabtagene vicleucel in relapsed and refractory multiple myeloma, N. Engl. J. Med. 384 (8) (2021) 705–716.
[10] J.G. Berdeja, et al., Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study, Lancet 398 (10297) (2021) 314–324.
[11] X. He, et al., Bispecific and split CAR T cells targeting CD13 and TIM3 eradicate acute myeloid leukemia, Blood 135 (10) (2020) 713–723.
[12] Y. Luo, et al., First-in-Man CD123-specific chimeric antigen receptor-modified T cells for the treatment of refractory acute myeloid leukemia, Blood 126 (23) (2015) 3778.
[13] H. Zhang, et al., Anti-CLL1 chimeric antigen receptor t-cell therapy in children with relapsed/refractory acute myeloid leukemia, Clin. Cancer Res 27 (13) (2021) 3549–3555.
[14] M. Wermke, et al., Proof of concept for a rapidly switchable universal CAR-T platform with UniCAR-T-CD123 in relapsed/refractory AML, Blood 137 (22) (2021) 3145–3148.
[15] Q. Cui, et al., CD38-directed CAR-T cell therapy: a novel immunotherapy strategy for relapsed acute myeloid leukemia after allogeneic hematopoietic stem cell transplantation, J. Hematol. Oncol. 14 (1) (2021) 82.
[16] Liu F., Z.H., Sun L., Li Y., Zhang S., He G., et al., First-in-human CLL1-CD33 compound CAR (cCAR) T cell therapy in relapsed and refractory acute myeloid leukemia, in In Proceedings of the 25th EHA Annual Congress. 2020, 12: Frankfurt, Germany.
[17] C. Qu, et al., Successful treatment of two relapsed/refractory t(8;21) acute myeloid leukemia patients by CD19-directed chimeric antigen receptor T cells, Bone Marrow Transpl. 54 (7) (2019) 1138–1140.
[18] G. Lin, et al., Cytotoxic effect of CLL-1 CAR-T cell immunotherapy with PD-1 silencing on relapsed/refractory acute myeloid leukemia, Mol. Med. Rep. 23 (3) (2021).
[19] S.H. Baumeister, et al., Phase I trial of autologous CAR T cells targeting NKG2D ligands in patients with AML/MDS and multiple myeloma, Cancer Immunol. Res 7 (1) (2019) 100–112.
[20] Q.S. Wang, et al., Treatment of CD33-directed chimeric antigen receptor-modified T cells in one patient with relapsed and refractory acute myeloid leukemia, Mol. Ther. 23 (1) (2015) 184–191.
[21] D.A. Sallman, et al., NKG2D-based chimeric antigen receptor therapy induced remission in a relapsed/refractory acute myeloid leukemia patient, Haematologica 103 (9) (2018) e424–e426.
[22] X. Tang, et al., First-in-man clinical trial of CAR NK-92 cells: safety test of CD33-CAR NK-92 cells in patients with relapsed and refractory acute myeloid leukemia, Am. J. Cancer Res. 8 (6) (2018) 1083–1089.
[23] M. Boyiadzis, et al., Phase 1 clinical trial of adoptive immunotherapy using "off-the-shelf" activated natural killer cells in patients with refractory and relapsed acute myeloid leukemia, Cytotherapy 19 (10) (2017) 1225–1232.
[24] D.S. Ritchie, et al., Persistence and efficacy of second generation CAR T cell against the LeY antigen in acute myeloid leukemia, Mol. Ther. 21 (11) (2013) 2122–2129.
[25] S. Yao, et al., Donor-Derived CD123-Targeted CAR T Cell Serves as a RIC regimen for haploidentical transplantation in a patient With FUS-ERG+ AML, Front. Oncol. 9 (2019) 1358.