Title: Patient Reported Symptoms, Functioning, and Quality of Life (QoL) in Patients Treated With Chimeric Antigen Receptor T Cells for Hematologic Malignancy: A Systematic Review and Meta Analysis

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Authors- Kandhare A, Sathyanarayanan S, Kumar S

Authors Affiliation- SIRO clinpharm Pvt Ltd, Mumbai, Maharashtra, India

Supplementary Material

Search strategies:

"Hematologic Neoplasm" OR "Neoplasm, Hematologic" OR "Hematologic Malignancies" OR "Hematologic Malignancy" OR "Neoplasms, Hematologic" OR "Hematological Neoplasms" OR "Hematological Neoplasm" OR "Neoplasm, Hematological" OR "Malignancies, Hematologic" OR "Malignancy, Hematologic" OR "Blood Cancer" OR "Blood Cancers" OR "Cancer, Blood" OR "Hematological Malignancies" OR "Hematological Malignancy" OR "Malignancy, Hematological" OR "Hematopoietic Neoplasms" OR "Hematopoietic Neoplasm" OR "Neoplasm, Hematopoietic" OR "Neoplasms, Hematopoietic" OR "Hematopoietic Malignancies" OR "Hematopoietic Malignancy" OR "Malignancy, Hematopoietic" OR "acute lymphoblastic leukemia" OR "ALL" OR "splenic marginal zone lymphoma" OR "SMZL" OR " large B-cell lymphoma" OR "large B cell lymphoma" OR "LBCL" OR "DLBCL" OR "PMBCL" OR "transformed follicular lymphoma" OR "transformed FL" OR "acute myeloid leukemia" OR "AML" OR "Multiple Myeloma" OR "MM" OR "Hodgkin lymphoma" OR "HL" OR "Non Hodgkin lymphoma" OR "NHL" OR "mantle cell lymphoma" OR "MCL" OR "Chronic myeloid leukaemia" OR "Polycythaemia vera" OR "Essential thrombocythaemia" OR "Primary myelofibrosis" OR "Chronic neutrophilic leukaemia" OR "Chronic eosinophilic leukaemia" OR "Juvenile myelomonocytic leukaemia" OR "Myeloproliferative neoplasm" OR "Leukaemia" OR "Lymphoma" OR "Myeloma"

AND

"Chimeric Antigen Receptor Therapy" OR "CAR T-Cell Therapy" OR "CAR T Cell Therapy" OR "CAR T-Cell Therapies" OR "T-Cell Therapies, CAR" OR "T-Cell Therapy, CAR" OR "Therapies, CAR T-Cell" OR "Therapy, CAR T-Cell" OR "Axicabtagene ciloleucel" OR "axi-cel" OR "yescarta" OR "KTE-C19" OR "Tisagenlecleucel" OR "tisa?cel" OR "Kymriah" OR "CTL019" OR "CAR T-cell*" OR "brexucabtagene autoleucel" OR " Tecartus" OR "lisocabtagene maraleucel" OR "Breyanzi" OR "idecabtagene vicleucel" OR "Abecma" OR "ciltacabtagene autoleucel" OR "Carvykti" "Life Quality" OR "Health-Related Quality Of Life" OR "Health Related Quality Of Life" OR "HRQOL" OR "QoL" OR "Patient Reported Outcome Measures" OR "Patient?Reported Outcome Measure?" OR "Patient Reported Outcome*" OR "Patient Reported Outcome Measure*" OR "Electronic Patient?Reported Outcome Measure?" OR "ePROM" OR "e-PROM" OR "PRO" OR "PROM" OR "PROMs" OR "Self?reported outcome?" OR "Self?reported patient outcome?"

Statistical Analysis

Statistical analyses were performed using the R studio and review manager 5.3. Single-arm meta-analysis performed in R studio and direct comparisons were performed in review manager 5.3.

Single-arm meta-analysis of mean and standard deviation values was performed for five different patient reported outcomes: (1) mean change from baseline global health; (2) mean change from baseline physical health; (3) mean change from baseline cognitive health; (4) mean change from baseline fatigue and (5) mean change from baseline pain.

Whilst, a meta-analysis of proportions was performed for 5 patient reported outcomes: (1) improvement in global health; (2) improvement in physical health; (3) improvement in cognitive health; (4) improvement in fatigue and pain; (5) improvement in fatigue and pain (6) improvement in EQ-5D-5L health utility index.

For the purpose of meta-analyses, 95% confidence intervals were transformed into standard deviation values based on a method suggested by the Cochrane Handbook Chapter 6. [20]

Heterogeneity between studies was assessed with a chi-square test (Cochran's Q statistic) and quantified with the Higgins' I2 statistic. P-value < 0.1 from the chi-square test indicated statistical heterogeneity, whereas the level of heterogeneity was determined using I2 values.

I2 < 25% was considered a low heterogeneity, 25–75% a moderate heterogeneity, and I2 > 75% a high heterogeneity. If the I2 value was greater than 50%, a random-effects model was used for the meta-analysis. Otherwise, a fixed-effects model was applied.

Direct comparison were performed between Car-T cell therapy and Standard of care (SOC) for 5 patient reported outcome such as (1) mean change from baseline global health; (2) mean change from baseline physical health; (3) mean change from baseline cognitive health; (4) mean change from baseline fatigue and (5)mean change from baseline pain.

Treatment effect was expressed as a mean difference with 95% CI for continuous outcome. We used the I2 statistic to determine the pro- portion of variation in study estimates due to heterogeneity

Findings

Effect of Car-T cell on HRQoL, Physical, cognitive and fatigue pain

- Total 18 [1 to 18] included studies are used the following instrument for quality-of-life analysis, where 5 [2, 7, 14, 15, 16] studies have not mentioned the change from baseline value, hence those 5 studies are not included in analysis.
- In the 18 studies, six studies [1, 3, 4, 5, 6, 12] were found to have reported changes from baseline for global health quality of life, physical function, cognitive health fatigue, and pain assessed using the EORTC QLQ-C30 instrument. Following the treatment with CAR-T cells, the global health quality of life, physical function, cognitive fatigue, and pain have improved. Following 6 months of treatment, the mean effect of change from baseline for global health quality of life, physical and cognitive function was significantly higher, while fatigue and pain scores were significantly lower on a change from baseline basis (**Figure 1**).

Figure 1: Mean effect of change from baseline for (A) HRQoL, (B) Physical Health, (C) Congnitive health (D) Fatigue and (E) Pain



• Five of the 18 studies have also reported improvements in global health quality of life, physical function, cognitive fatigue, and pain scores [3,4,5,6,12]. There was a significant number of participants who reported improvements in their global health quality of life, physical function, cognitive fatigue, and pain as well as improvements in their health utility index score after completing the EQ-5D-5L questionnaire [3, 5, 6, 12, 17, 18](Figure 2).

Figure 2: 6 months post treatment Improvement of (A) HRQoL, (B) Physical Health, (C) Congnitive health (D) Fatigue (E) Pain and (F) EQ-5D-5L-HUL



- Moreover, there were three other randomised clinical trials in which the car-t cell therapy has been compared with the standard of care regimen,
- In a pooled analysis of those three trials [1,4,5] it was found that after 6 months, patients' quality of life, cognitive health, and physical function were remain same in car-t cell therapy and SOC, Only fatigue score was reduced significantly (p= 0.001) in car-t cell therapy as compared to SOC therapy. (**Figure 3**)

Figure 3: Standard mean diffrence of mean change from baseline value between Car-t cell therapy and SOC (A) HRQoL, (B) Physical Health, (C) Congnitive health (D) Fatigue and (E) Pain

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