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Human umbilical cord-derived mesenchymal stem cells for the treatment of decompensated cirrhosis (MSC-DLC-1): a dose-escalation, phase I trial protocol

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ABSTRACT

Introduction There are limited therapeutic options to efficiently treat patients with decompensated liver cirrhosis. This trial aims to explore the efficacy and safety of human umbilical cord-derived mesenchymal stem cells (UC-MSCs) for the treatment of patients with decompensated liver cirrhosis.

Methods and analysis This study is an open-label, dose-escalation, one-armed phase I trial. A single injection of UC-MSCs will be administered in a predetermined dose in each cohort (5.0×10^7, 1.0×10^8, 1.5×10^8 or 2.0×10^8 cells) according to the '3+3' rule. The primary evaluation measures will include the incidence of adverse events and the change in the Model for End-stage Liver Disease (MELD) score from baseline to the 28th day. Secondary evaluation measures will be evaluated at baseline and at each follow-up point. These measures will include the change in the MELD score from baseline to each follow-up point, the incidence of each complication associated with decompensated cirrhosis, liver transplant-free survival and the incidence of liver failure, among other relevant measures. All patients will be followed up for 24 months. This study will evaluate whether the use of UC-MSCs to treat patients with decompensated liver cirrhosis is safe and tolerable.

Ethics and dissemination The study has been approved by the Chinese People's Liberation Army General Hospital (Approval#: 2018-107-D-4). Once conducted, the results from the study will be published in a peer-reviewed journal.

Trial registration number NCT05227846.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The 3+3 design will be used to explore the efficacy of the new treatment, while ensuring patient safety.
⇒ The patients in this study will be followed up for 2 years, allowing the long-term safety and effectiveness of the treatment to be evaluated.
⇒ The conditions of the patients in the study will be fully documented using relevant methods, such as Model for End-stage Liver Disease score, lab tests, imaging and quality of life assessment.
⇒ Only patients with a Child-Pugh score of 7–12 will be enrolled in the study, limiting the generalisability of the results.

INTRODUCTION

Decompensated liver cirrhosis (DLC) is characterised by severely impaired liver function and other associated complications, such as portal hypertension, ascites, spontaneous peritonitis, coagulation dysfunction, gastrointestinal bleeding, hepatic encephalopathy and hepatorenal syndrome.[1] Current available treatment strategies can help improve the patients' quality of life and partially reduce the complications of DLC, and include taking diuretics and following a low-sodium diet, but there are no efficient therapeutic regimens.[2 3] Furthermore, DLC indicates that the patient is nearing the end stage of liver failure, and liver transplantation then becomes the best option.[4] However, liver transplantation carries considerable risks, since liver failure is frequently associated with liver immune disorders that may contribute to rejection of the new organ and a decrease in the patient's quality of life.[2] In the absence of a liver transplant, an alternative therapy that can effectively relieve the symptoms and promote recovery would be very helpful for patients.

Mesenchymal stem cell (MSC) therapies have emerged as a novel alternative for the treatment of end-stage liver diseases.[5 6] MSCs have a variety of useful properties, such as the secretion of cytokines, growth factors and hepatocytes, which can help improve liver functionality and regress fibrosis. Studies have also shown that MSCs can suppress the proliferation of hepatic stellate cells and induce their apoptosis.[7–10] Multiple studies

on MSCs have demonstrated their potential for treating end-stage liver disease,[11–17] but the appropriate dose and related mechanisms are still unclear. In addition, no clinical research reports have yet explored escalating the dose of MSCs for treating DLC.

Aims

We have designed an investigator-initiated, single-arm, dose-escalation clinical trial to evaluate the safety and identify the suitable dose of frozen human umbilical cord-derived MSCs (UC-MSCs) as an infusion in patients with DLC. This trial aims to provide evidence for evaluating the safety and efficacy of the UC-MSC infusion in future studies.

METHODS AND ANALYSIS

Study design

The proposed open-label, dose-escalation, one-armed phase I trial (MSC-DLC-1) aims to evaluate the safety and efficacy of human UC-MSCs for the treatment of patients with DLC. The study comprises three phases: screening+evaluation, 3+3 escalation and follow-up (figure 1). Patients with decompensated cirrhosis will be enrolled in the study. Each patient will be injected with one dose of a solution containing human UC-MSCs. After treatment, the patients will be followed up for 24 months.

This study was reviewed and approved by the ethics review board of the Chinese PLA General Hospital

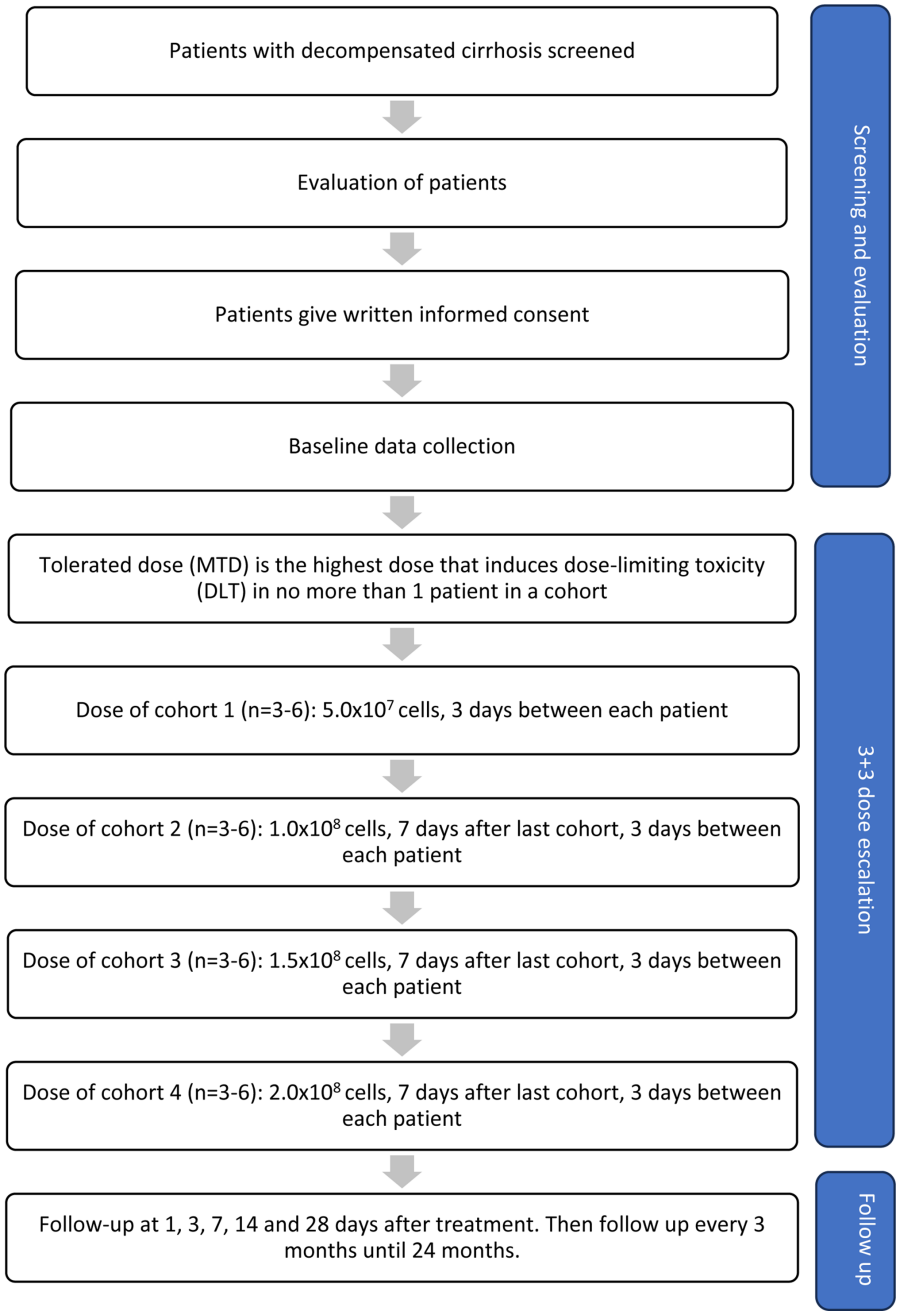

Figure 1 Study design and enrolment of patients with decompensated liver cirrhosis. MTD, maximum-tolerated dose.

(Approval#: 2018-107-D-4). The study will be performed at the Chinese PLA General Hospital, Beijing, China. Written informed consent (online supplemental appendix 1) will be obtained from all participating patients. This protocol was formulated in strict accordance with the Declaration of Helsinki.[8] This protocol is version 2.3, revised on 21 February 2023.

Outcomes

Primary evaluation measures

The primary outcomes are the incidence of adverse events and the change in the Model for End-stage Liver Disease (MELD) score from baseline to the 28th day after the intervention.

Secondary evaluation measures

The secondary outcomes include: (1) change in the MELD score from baseline to the score at 3 days, 7 days, 14 days, 3 months, 6 months, 9 months, 12 months, 15 months, 18 months, 21 months and 24 months after the intervention; (2) incidence of each complication associated with decompensated cirrhosis; (3) liver transplant-free survival rate; (4) incidence of liver failure; (5) plasma albumin level; (6) plasma prealbumin level; (7) total bilirubin; (8) serum cholinesterase; (9) prothrombin time; (10) Child-Turcotte-Pugh score; (11) EuroQol Group 5-Dimension Self-Report Questionnaire scale score; (12) incidence of liver cancer and (13) Chronic Liver Disease Questionnaire score.

Patients

Inclusion and exclusion criteria

The details of the inclusion and exclusion criteria can be found in table 1.

Intervention

Preparation of the UC-MSCs

The UC-MSCs (VUM02, 5×10^7 cells/10 mL/bag) will be prepared by Wuhan Optics Valley Vcanbiopharma, in China. Briefly, MSCs will be obtained according to the method described in our previous study.[18] UC tissue for sampling will be selected and collected after the mothers have signed the informed consent form. After the blood vessels are removed from the UC tissue, it will be cut into small pieces of about 1–2 mm^3, uniformly inoculated in cell culture flasks for isolation of the MSCs, and the primary cells will be digested with TrypLE digestive enzyme for 10–13 days. The primary cells will be inoculated in cell culture flasks at a density of about $2\times10^4/cm^2$ and cultured in an incubator at 37°C with a volume fraction of 5% CO_2 and saturated humidity. After being passaged for P4 generation, the cells will be cryopreserved

Table 1 Inclusion and exclusion criteria for the patients

Inclusion criteria	► Signed the informed consent form. ► Aged 18–75 years old. ► Diagnosed as having decompensated cirrhosis based on clinical presentation, laboratory tests, imaging and/or representative pathological findings. ► Child–Pugh score of 7–12.
Exclusion criteria	► Had serious complications, such as hepatic encephalopathy, refractory ascites, hepatorenal. syndrome or bleeding from oesophageal varices within the last month. ► Had at least one uncontrolled severe infection within the past 2 weeks. ► Had a hepatitis B virus DNA test result above the testing threshold. ► Has hepatitis B/C cirrhosis and has either not received antiviral treatment for more than 12 months or may stop antiviral treatment during the research period. ► Has autoimmune cirrhosis and has not been treated with glucocorticoids for more than 6 months. ► Pregnant or currently breastfeeding. ► Currently drinks alcohol and refuses to stop drinking during the research period. ► Uses illegal psychoactive substances, has a history of substance abuse or has been diagnosed with other psychological disorders. ► Has participated in other clinical studies within the last 3 months. ► Has had transjugular intrahepatic portosystemic shunt surgery less than 6 months ago. ► Has severe jaundice (total serum bilirubin level ≥170 µmol/L), has obvious deficiencies in kidney function (serum creatinine ≥1.2 times normal levels), has severe electrolyte abnormalities (serum sodium level <125 mmol/L) and/or severe leucopenia (white cell count $<1\times10^9$/L). ► Has combined biliary obstruction, hepatic, or portal, or splenic vein thrombosis, or portal vein cavernous lesions. ► Has had certain surgery, such as splenectomy or portal shunt, in the past. ► Has a confirmed or suspected malignant tumour(s). ► Has a history of any major organ transplant or any severe systemic disease involving the major organs, such as the heart, kidneys, liver or the blood. ► Has received a blood transfusion within the last month. ► Has other circumstances or complications that the researchers deem unsuitable for the study. ► Has a positive HIV antibody test result. ► Has allergies or a history of severe allergies.

for use as the working cell bank. Subsequently, safety and biological performance tests will be conducted on the working cell bank. Following successful testing, the cells will undergo a resuscitation culture for 48–72 hour to prepare P5 generation cell formulations. The cells must meet strict criteria to be used in our study. Specifically, the expression of cell immunophenotypes CD90, CD105, CD73 must be greater than 95%; the expression of CD45, CD34, CD14, CD19 and HLA-DR must be lower than 2%; the cells must test negative for sterility and mycoplasma; and the intracellular toxins must be less than 1 EU/mL. Only UC-MSCs that pass these tests will be used for the clinical trials.

Dose escalation and dose-limiting toxicity

The single dose-escalation scheme, denoted as S-1, will be as follows 3+3: cohort 1 (5.0×10^7 cells), cohort 2 (1.0×10^8 cells), cohort 3 (1.5×10^8 cells) and cohort 4 (2.0×10^8 cells). Each patient will be observed for 3 days for signs of dose-limiting toxicity (DLT) before another patient in the same cohort can receive treatment. The last patient of each cohort will be observed for 7 days before the next cohort with a higher dose can start to receive treatment. The first three patients in a cohort will be observed to determine the next action. If one of the three patients shows signs of DLT, the next three patients in the cohort will be treated with the same dose. If two or more patients in any cohort show signs of DLT, then the study will be concluded. The study will only proceed to the next cohort if none of the first three patients shows signs of DLT after the outlined observation periods have elapsed or if only one out of the six patients in a cohort shows signs of DLT. The specific rules for dose escalation can be found in figure 2.[19]

The first dose of UC-MSCs in cohort 1 (three patients initially) will be 5.0×10^7 cells. The maximum-tolerated dose (MTD) is determined as the highest dose that induces DLT in no more than one patient among the extended cohort of six patients. Patients will be recruited into four cohorts and will begin dosing at successively higher doses until the MTD is established or up to a dosage of 2.0×10^8 cells.

Assessment of adverse events and initial efficacy

Data will be collected on the eligible patients over a period of 3 weeks, including the patients' demographics, family history, history of allergies, medical history, history of present illness, vital signs; anthropometrics, lab analysis of blood, faeces and urine, ECG, imaging of the chest and abdomen using CT, MRI, ultrasound; MELD score, Child-Pugh score and assessment of the quality of life. Follow-up will last for 24 months after the patient has received treatment and will be performed at 3 days, 7 days, 14 days, 28 days, 3 months, 6 months, 9 months, 12 months, 15 months, 18 months, 21 months and 24 months after the intervention, respectively. The study schedule can be found in online supplemental table 1.

Assessment of DLT and MTD

DLT will be evaluated according to the National Cancer Institute Common Toxicity Criteria 5.0 (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm). DLT is defined as any grade 4 haematological toxicity; grade 3 thrombocytopaenia with haemorrhage; grade 3 or greater nausea, vomiting or diarrhoea or any grade 3 or greater treatment-related non-haematological toxicity (excluding alopecia and fatigue). Groups of three patients will be recruited at a time and allocated to their respective cohorts, starting with the lowest dose. For each cohort, one patient will be given the treatment at first and then observed for 3 days for signs of DLT. The next patient's treatment will only begin after the first patient has undergone 3 days of observation. The treatment of another cohort can only

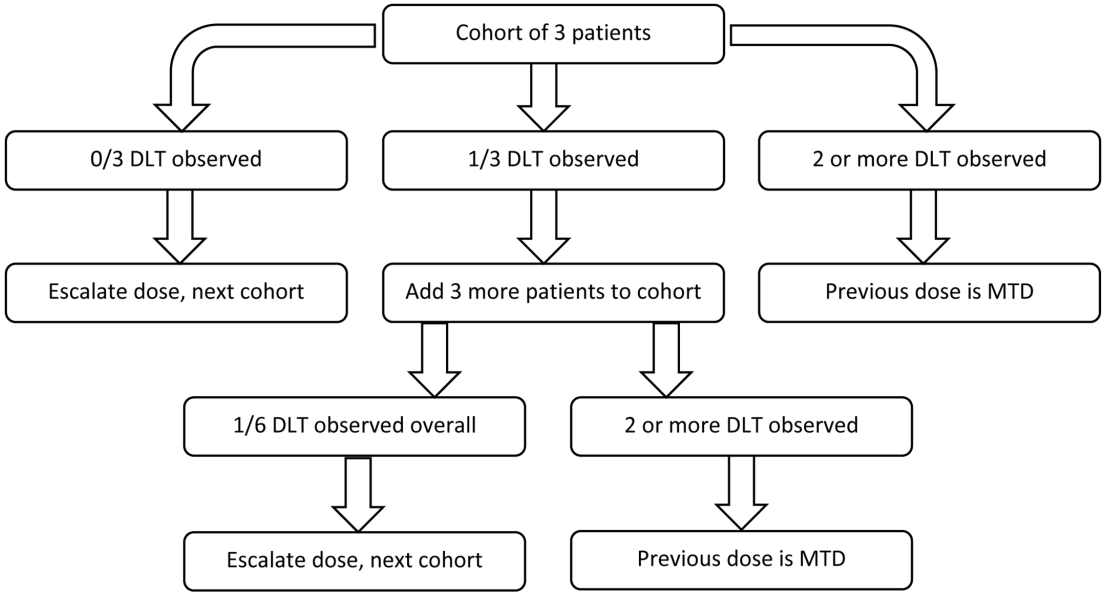

Figure 2 Dose-escalation flow chart. DLT, dose-limiting toxicity; MTD, maximum-tolerated dose.

start after the previous cohort has experienced at least 7 days of observation.

The trial will proceed as follows to ensure safe dose escalation and determine the MTD: (1) If there is no DLT observed in all three patients of a cohort, the trial will proceed to the next dose cohort; (2) If one of the three patients of a cohort experiences DLT, then three more patients will be included and tested in this dose cohort. If still only one of the six patients experiences DLT, the trial will proceed to the next dose cohort. However, if two or more of the six patients experience DLT, the previous dose will be considered as the MTD; (3) If two or all three of the three initial patients experience DLT in a cohort, the MTD will remain undetermined.

Statistical considerations

Sample size

This is a proof-of-concept study. A total of 3–6 patients will be recruited for each dose cohort, comprising low, medium, high and super high-dose groups, denoted as cohorts 1, 2, 3 and 4, with three patients in each cohort initially. The additional patients will be added to the cohort if DLT is presented. A total of 12–24 patients will be recruited for the study.[19]

Statistical analysis

Efficacy will be assessed according to the intention-to-treat analysis principle, while safety will be assessed by analysing adverse events within the cohorts and noting their category and severity. Continuous variables will be expressed as the mean with the SD. Categorical variables will be expressed as a number count together with the rate or composition ratio. The χ^2 test or Fisher's exact test will be used to compare categorical variables between different doses used by the cohorts for evaluating efficacy. They will also be used to compare the rate of adverse events occurrence between cohorts to assess safety. The change in the patients' lab values in each cohort after treatment will also be described to explore any potential correlations between these changes and the occurrence of adverse events. Continuous variables will be compared using the t-test. However, comparisons will be made using the Wilcoxon signed-rank test when analysing changes in continuous quantitative variables before and after treatment. The 95% CI will be calculated for the outcomes of the continuous variables. A more detailed plan for the statistical analysis will be formulated and finalised before the data gathering is finished for the study. This final plan will dictate the method and content of the study's statistical analysis. A $p<0.05$ will be considered as showing statistical significance. All the statistical analyses will be performed using SAS V.9.4 (Statistics Analysis System).

Patient and public involvement

The patients and the public were not involved in any stage of the project's design or planning. There are also no plans to involve the patients or the public when conducting the study or gathering data.

ETHICS AND DISSEMINATION

The study has been approved by the Chinese People's Liberation Army General Hospital (Approval#: 2018-107-D-4). The research process will be carried out in strict accordance with the requirements of the State Food And Drug Administration (SFDA) Quality Control Practice for Drug Clinical Trials and the Helsinki Declaration. The patient or their legal representative must read and understand and sign the informed consent form before enrolling in the study.

Regarding the safety of MSCs

MSCs are naturally found within the human body. Past research has yet to find instances of MSCs developing into cancer. When MSCs have been used as treatments, adverse events that have occurred have been closely related to contaminants within the fluids used to suspend the cells and not the cells themselves. A meta-analysis was conducted by the authors on the existing literature, and the only adverse event that was found to correlate with MSCs infusion was fever.

Overall, the use of MSCs as treatment has been shown to rarely lead to adverse events. The adverse events that do occur are often those that can be easily alleviated with no known lasting consequences. Having closely examined the available evidence, the authors are confident that the infusion of MSCs is likely safe as an experimental treatment.

Plans for dissemination

Once conducted, the results from the study will be written up for publishing in a peer-reviewed journal.

DISCUSSION

MSC therapy is generally considered a potentially relevant therapeutic strategy for patients with DLC.[11–17] However, the results of the existing studies are not entirely consistent, which may be related to the heterogeneity in dosage.[20] To date, the dose of MSCs prescribed to end-stage liver disease patients is frequently based solely on experience. Our study aims to explore the optimal dose when using UC-MSC infusions to treat DLC in terms of safety and efficacy. To this end, we will evaluate the DLT and MTD of UC-MSC infusions used to treat patients with DLC, which may lay the groundwork for further study and phase II and III trials.

In this study, we plan to apply a traditional 3+3 dose-escalation design to explore the appropriate dose and safety of treating decompensated cirrhosis with UC-MSC infusions.[11 21] This dose-escalation methodology has been proven to be appropriate for use in a predetermined approach or preferably adjusted to toxicity.[11]

An appropriate cell dose should be selected according to the syndrome, treatment timing and transplantation route. Researchers from various countries have used various doses for different diseases in phase I studies and quantitative exploration.[22–28] According to those

reports, the number of peripheral intravenous stem cells is generally around 5×10^5 to 1×10^7 cells/kg, which varies depending on the different diseases. In a clinical study of acute respiratory distress syndrome (ARDS) patients, low, medium and high doses of UC-MSCs were applied as 1×10^6, 5×10^6 and 1×10^7 cells/kg, respectively. In that study, no infusion-related adverse events occurred after the highest dose infusion, which suggested that a 1×10^7 cells/kg dose was safe for ARDS patients.[29] Besides, another study treated patients with DLC using the highest dose of 2×10^8 cells/time, and found that there were no adverse events, even at this high dose.[6] Therefore, we chose escalation doses of 5.0×10^7, 1.0×10^8, 1.5×10^8 and 2×10^8 cells for this study's dose-escalation strategy, respectively.

One potential limitation of the proposed study is our inability to control the conditions under which the patients are treated. As such, changes observed over the follow-up period, such as lab value changes or adverse events, may be induced by factors other than the UC-MSC infusions. We hope to alleviate this by thoroughly reviewing any factors that may affect our results during the evaluation phase, such as the medications that patients are using, and by anticipating the impacts these may have. Furthermore, we aim to conduct a further study to analyse the related mechanism underlying the treatment of UC-MSCs for DLC patients.

We will report our findings in a peer-reviewed biomedical journal and present them at national and international conferences.

Trial status

The approved protocol version was modified on 21 February 2023. This trial is ongoing. The anticipated study started on 22 March 2022, and the trial finishing date is estimated as 30 June 2024.

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Contributors F-SW and LS conceived and designed the trial. LS, ZW, TL, ZZ, MY and MS participated in the administration of this study and drafted the present manuscript. F-SW and E-QL revised the manuscript and gave additional suggestions. All the authors approved the final version of this manuscript and consent for it to be published.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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