Granulocyte Colony-stimulating Factor as Bridging Therapy for Pediatric Decompensated Liver Cirrhosis Prior to Liver Transplantation: an Open-label Randomised Controlled Trial

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Abstract

Decompensated cirrhosis in children is a leading indication of liver transplantation (LT). Granulocyte-colony stimulating factor (G-CSF) therapy has shown promising results in adult decompensated cirrhosis. Our study aimed to investigate the effect of G-CSF on liver function, Pediatric End-stage liver disease (PELD) score, CD34+ cells mobilization, nutritional status, short-term side effects, and survival in children indicated for liver transplantation (LT).

We performed an open-label, randomized controlled trial with decompensated liver cirrhosis between 3 months to 12 years old. The intervention group received a subcutaneous injection of G-CSF (5 µg/kg/day) for twelve courses in addition to standard medical treatment (SMT) for liver cirrhosis. We measured liver function, PELD scores, CD34+ cell mobilization, the change of leucocyte and neutrophil count, nutritional status, side effects, and survival within three months.

Thirty-five pediatric patients were randomized into 17 interventional groups and 18 control groups. During the trial, 14 (82%) of the interventional group completed the intervention course. The median age was 18 months in the interventional group and 14.5 months in the control group. The alanine aminotransferase (ALT) level showed significant improvement in the intervention group, while other liver parameters, PELD score, nutritional status, and survival, did not. CD34+ cells mobilization rose in the interventional group but was statistically insignificant. Minor side effects of G-CSF were found in the intervention group.

Multiple doses of G-CSF significantly improve ALT but did not improve PELD score, nutritional status, and survival in three months.

Introduction

Liver cirrhosis is one of the leading indications of pediatric liver transplantation.¹ In Indonesia, deceased-donor liver transplantation has not been conducted, hindered by religious, cultural, and legal issues. Limited access to liver transplantation and donor scarcity contributes to the declining survival of patients in need of the procedure.²

Malnutrition is a prevalent clinical concern that must be managed prior to liver transplantation. Malnutrition increases morbidity and mortality in pretransplant patients.³ A bridging therapy is essential in prolonging the survival of these patients.⁴

Granulocyte colony-stimulating factor (G-CSF) is a myeloid progenitor from the cytokine family. The regenerative role of G-CSF in damaged tissues has been extensively studied.^{5,6} The use of G-CSF for acute-on-chronic liver failure has shown promising results in adult patients.^{4,6,7} The administration of G-CSF elicits the mobilization of CD34+, a marker of the hematopoietic stem cell, from the bone marrow to the peripheral blood.⁵ The clinical use of G-CSF in the pediatric population has been applied in treating congenital, febrile, and post-chemotherapy neutropenia.⁸⁻¹¹ The use of G-CSF in pediatric

decompensated liver cirrhosis has not yet been reported. This study is a pilot study of G-CSF treatment as an optimizing therapy prior to pediatric liver transplantation.¹² We investigated the effect of G-CSF on liver function, PELD, CD34 + cell mobilization, the change of leucocyte and neutrophil count, nutritional status, side effects, and survival within three months in pediatric patients with decompensated liver cirrhosis.

Patients And Methods

We conducted a prospective, single-center, open-label paralleled-group, equally randomized study of individuals enrolled between September 2019 and May 2021. Subjects were recruited from inpatients and outpatients clinics at dr. Cipto Mangunkusumo General Hospital (RSCM), Jakarta, Indonesia. Data were obtained by performing history taking from parents, physical examination of patients, clinical data, and electronic medical records. The overall procedure, including the protocol of G-CSF administration and standard therapy, was outlined to the parents and guardians of the participants and, if applicable, to the participants themselves. The known and probable side effects of G-CSF injection were disclosed in detail.

Patients

A total of 53 pediatric patients with cirrhosis and malnutrition were recruited. Eleven patients refused to join the study, and seven patients were excluded because of active infections. A total of 35 patients were enrolled. We calculated the sample size of approximately 17 in each group by estimating an AST interval of 75 after G-CSF administration, an α error of 0.05, and β error of 0.1, with 80% power, assuming 20% dropout.

The main criteria were clinically confirmed decompensated liver cirrhosis and biopsy and/or imaging regardless of the etiology. Other inclusion criteria were age between 3 months and 12 years, PELD scores 10–25, a conscious state, and a compromised nutritional status (undernourished or severely malnourished).

The exclusion criteria were malignancy, history of any transplantation procedure, acute liver failure, organ failure other than liver failure, encephalopathy, severe infection such as spontaneous bacterial peritonitis and pneumonia, and refusal to participate in the study.

Randomization

A computer-generated block was utilized to randomly assign eligible patients into one of the two groups (2:2 ratio). The primary investigator was not involved in the randomization. Informed consent was obtained at the beginning of the study before randomization.

Treatment

The intervention group received G-CSF (Leucogen; Kalbemed Pharmaceuticals, Indonesia), at a dose of 5 microgram/kilogram body weight ($\mu\text{g}/\text{kg}$) daily for five consecutive days and continued with the same

dose every three days up to 12 doses, while the control group received standard treatment only. The standard treatment includes the administration of ursodeoxycholic acid 30–50 milligram (mg)/kg/day for three days, vitamin E 1 × 50 mg, vitamin A 1 × 5000–25000 International Unit (IU), vitamin D 1×800–5000 IU, an injection of vitamin K 0.2 mg/kg/month, and enteral nutrition based on the nutritional evaluation. If ascites was present, an additional administration of spironolactone 1–6 mg/kg or furosemide 1–6 mg/kg was given, and peritoneal fluid drainage was performed upon indication.

CD34 examination

Peripheral venous blood samples were taken using a 3-mm ethylenediamine tetra-acetic acid anticoagulated tube for stem cell enumeration at baseline and Day 30. The tube was divided into two, each containing 100 mL of whole blood. One tube was processed without staining to determine the baseline, whereas the other was stained and added with 2 mL of blocking reagent (to block non-CD34-specific antibodies), 3 mL of antibody, and 1.5 mL of propidium iodine. We applied staining of CD34 with a fluorochrome-conjugated monoclonal antibodies technique. The tubes were incubated for 30 min in the freezer and wrapped with aluminum foil to prevent the direct entry of light. It was added with 500 milliliters (mL) of phosphate buffer saline prior to processings performed one hour after collection. The enumeration was accomplished based on the International Society of Hematotherapy and Graft Engineering protocol. The calculation was performed using the following formula:

$$CD34_{stemcells}(\%) = \frac{CD34_{positiveevents}}{CD44_{positiveevents}} \times 100.$$

Data collection and follow-up

Physical examination, anthropometric data (weight, height, mid-arm circumference [MAC]), peripheral blood count, neutrophil count, liver function test, procalcitonin, and the PELD score were recorded at baseline. The PELD score was measured on Day 0, 30, and 90, using an online calculator formulated by the Organ Procurement and Transplantation Network.

The mobilization of CD34 + in the peripheral blood was performed using flow cytometry at baseline and Day 30. Patients were observed for three months and monitored on Day 30, 60, and 90 for subjective assessment and observation of anthropometric and laboratory data changes. Laboratory examination was performed prior to the study on Day 0, 6, 18, 30, 60, and 90. On Day 6 and 18, laboratory examination was for peripheral blood count and neutrophil count. Clinical and laboratory evaluations were monitored meticulously throughout the trial for potential adverse effects of G-CSF. The schedules for the outpatient visits and data collection are summarized in the appendix.

Questionnaire

A manual prospective chart review was performed to assess the short-term side effects of G-CSF injection. Patients and parents were interviewed at every visit. Previously reported side effects of G-CSF, as described in Table 3, were asked thoroughly. Other parameters, including sleep quality and overall quality of life, were obtained. Parents were asked to report any other symptoms that were not included in

Outcome

The primary outcome measures were the liver function and PELD score. The secondary outcomes were CD34 + cell mobilization, the change of leucocyte and neutrophil count, nutritional status, and survival within three months. Secondary outcomes included subjective data from the patients' parents and patients themselves, if eligible. Survival was analyzed within three months of the study.

Ethics approval

Informed consent

was obtained from the parents for experimentation with human subjects. The ethics committee of our institution approved the study protocol (reference 19-07-0943), and the study confirmed the Helsinki Declaration of 1977. Indonesia's Ministry of Research and Technology was the sponsor of the trial. The trial was registered at ClinicalTrial.gov, number NCT04113317.

Statistical analysis

An intention-to-treat analysis was performed for both groups. Data were expressed as means $\pm$ standard deviation (SD) for normally distributed data and medians with a range for skewed data. Baseline data were described using descriptive statistics. The normality of distribution was evaluated using the Kolmogorov-Smirnov test. Comparisons between two groups were performed using the t-test for normally distributed data, and the Mann-Whitney U test for unpaired skewed data. Multivariate analysis was performed using the repeated-measures ANOVA test. All statistical analyses were performed two-sided, with $p < 0.05$ considered statistically significant. Analysis data was performed using SPSS version 25.

Results

A total of fifty-three pediatric patients with cirrhosis and malnutrition were screened from September 2019 and May 2021, and 35 patients were enrolled (figure 1). Seventeen patients were included in the intervention group and eighteen in the control group. During the trial, fourteen (82%) patients in the intervention group completed the 12 doses of G-CSF. One patient skipped five injections because of recurrent fever and was admitted to the emergency room because of hematemesis and melena. Another patient skipped three injections due to fever and urinary tract infection. One patient was out of town at the time of his injection schedule and skipped once. Baseline characteristics are shown in table 1.

Table 1. Baseline characteristics of the study population

	Intervention group (n=17)	Control group (n=18)	P value
Sex (males:females)*	8:9	9:9	
Diagnosis*			
Biliary atresia	9	10	
Alagille syndrome	4	5	
PFIC type III	2	0	
Caroli disease	0	2	
Choledochal cyst	1	1	
Cholestasis	1	0	
Nutritional status*			
Undernourished	4	3	
Severe undernourished	13	15	
Age (months)**	18 (7-136)	14.5 (5-120)	0.585
MAC (centimeter)**	11.5 (9.5-16)	10.75(8.5-12)	0.047
PELD score***	17.35 + 4.12	18.56 + 3.88	0.381
Hb (g/dL)***	9.14 ± 1.26	8.9 ± 1.30	0.582
Leukocyte count (×10 ³ /μL)**	8.67 (3.08-22.15)	9.2 (3.19–25.35)	0.552
Neutrophil (%)***	50.16 ± 12.11	55.24 ± 10.87	0.200
Platelet count (×10 ³ /μL)***	170.59 ± 77.90	221.5 ± 111.65	0.129
Prothrombin time (second)***	12.92 ± 1.72	13.38 ± 1.77	0.442
INR	1.12 (0.97-1.71)	1.22 (1.05-1.63)	0.203
Procalcitonine (ng/mL)**	0.48 (0.07-17.34)	0.25 (0.09-1.6)	0.208
CD34+ cells**	10.7 + 10.9	7.95 + 7.54	0.700
AST (U/L)**	239 (68-644)	160 (56-948)	0.338
ALT (U/L)**	141 (18-419)	95 (24-567)	0.192
Albumin (g/dL)***	2.89 ± 0.49	2.97 ± 0.40	0.616
Total bilirubin (mg/dL)***	21.14 + 7.04	22.06 + 7.68	0.712
GGT (U/L)**	108 (37-844)	138 (25-1624)	0.987

* =n; ** = normally distributed data; ***: skewed data; PFIC=Progressive Familial Intrahepatic Cholestasis; MAC= mid-arm circumference; PELD=Pediatric end-stage liver disease; INR= International normalized ratio; AST=aspartate aminotransferase; ALT=alanine aminotransferase; GGT=Gamma-glutamyl transferase.

Primary outcome

Time to death or liver transplantation, or death due to liver disease, or death due to infection test and PELD score.

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Table 1. Primary outcome

	Intervention Group (n = 17)	Control Group (n = 18)	p-value [#]	p-value [^]
AST*				
Baseline	239 (68-644)	160 (56-948)	0.338	
D-30	225 (53-658)	164 (57-948)	0.291	
D-60	202 (55-372)	178.5 (52-948)	0.961	
D-90	152 (52-336)	181 (62-948)	0.668	0.086
ALT*				
Baseline	141 (18-419)	95 (24-567)	0.192	
D-30	99 (14-317)	99.5 (23-494)	0.541	
D-60	111 (16-233)	101 (27-494)	0.729	
D-90	87.23 (±52.16)	91.62 (±41.11)	0.704	0.023
Albumin**				
Baseline	2.89 ± 0.49	2.97 ± 0.40	0.240	
D-30	3.03 ± 0.48	2.95 ± 0.49	0.833	
D-60	2.95 ± 0.43	2.90 ± 0.40	0.748	
D-90	2.98 ± 0.44	2.84 ± 0.49	0.371	0.571
Total bilirubin**				
Baseline	21.14 ± 7.03	22.06 ± 7.68	0.790	
D-30	21.69 ± 8.81	21.78 ± 8.00	0.386	
D-60	23.40 ± 9.86	21.51 ± 8.10	0.371	
D-90	22.55 ± 10.53	23.34 ± 8.30	0.525	0.168
GGT*				
Baseline	108 (37-844)	138 (25-1624)	0.987	
D-30	125 (35-797)	135 (24-1279)	0.882	
D-60	131 (29-670)	125 (26-1513)	0.869	
D-90	130 (23-729)	119.50 (11-1513)	0.754	0.629
PELD score*				
D-0	18 (10-23)	18.50 (12-25)	0.518	
D-30	18 (12-39)	19 (11-29)	0.466	
D-90	17 (10-27)	18.33 (10-29)	0.508	0.843

[#]=p-value for independent T-test (normally distributed data)/ Mann-Whitney test (skewed data); [^]=p-value for ANNOVA test; * =skewed data; ** =normally distributed data; AST=aspartate aminotransferase; ALT=alanine aminotransferase; GGT=Gamma-glutamyl transferase; PELD= Pediatric end-stage liver disease.

Alanine aminotransferase level in the intervention group showed improvement three months after G-CSF administration. In contrast, other liver function tests (AST, albumin, total bilirubin, and GGT) showed no statistical difference between the two groups. Although there was a trend of AST improvement in the

intervention group compared to the control group, it was statistically insignificant. Both groups showed no difference in PELD score.

Secondary outcome

The secondary outcomes were CD34+ cell mobilization, leucocyte and neutrophil count change, nutritional status, adverse effects, and survival within three months.

Bone marrow mobilization

Bone marrow mobilization of hematopoietic stem cells (HSC) was evaluated by CD34+ activity. Overall, both groups showed an increase of CD34+ cells levels on Day 30. In the intervention group, the CD34+ cells rise was three times higher than the control group, although it showed no statistical difference (p=0.66).

Leucocyte and neutrophil count

Leucocyte and neutrophil count significantly increased in the intervention group compared to the control group (both p=0.00). Both peaked on Day 18 and gradually decreased afterward. Leucocyte count decreased near to baseline level on Day 30, after completion of G-CSF series administration, while neutrophil count level on Day 60 decreased to the same level as Day 6 and returned to baseline level on Day 60.

Nutritional Status

A total of 75% of patients were severely malnourished at baseline in both groups. The striking result was seen the most at Day 30, in which three patients had an improved nutritional status after a month of intervention. On Day 60, an additional patient became well-nourished; however, one patient had a further decline in nutritional status. On Day 90, one well-nourished patient returned to being undernourished. Meanwhile, two severely malnourished patients showed improvement in the control group, but only after three months with standard therapy. Both groups did not show any statistical significance.

Adverse effects

There were minor adverse effects reported on the administration of G-CSF (Table 3). Ten patients had a better sleep quality in the interventional groups, and guardians of two patients reported better mood after G-CSF administration.

Table 3. Side effects and subjective reports following G-CSF injection

Side effects

Low-grade fever	Seven patients, four of them developed a low-grade fever after 1 st dose of G-CSF
Fatigue and weakness	Difficult to evaluate
Headache	Difficult to evaluate
Bone pain	One patient
Myalgia and muscle cramp	Difficult to evaluate
Low back pain	Difficult to evaluate
Paresthesia	Difficult to evaluate
Pain at the insertion site	Difficult to evaluate
Edema	None
Periorbital edema	None
Rash	None
Nausea and vomiting	None
Flushing	None
Pruritus	None
Diarrhea	None

Subjective reports

Better sleep quality	Ten patients
Overall improved mood	Two patients

Survival

Five patients in the control group and two patients in the intervention group had mortality during the trial. Two of the patients from the intervention group who had finished their injection protocol died because of esophageal variceal rupture and hepatic encephalopathy. Five deaths were reported in the control group: one due to refractory hypovolemic shock due to esophageal variceal rupture, two due to sepsis from pneumonia, and two due to respiratory failure. Further analysis using the Kaplan-Meier test showed no statistical difference between both groups ($p=0,236$).

Discussion

Liver transplantation is the only definitive cure for liver cirrhosis, a procedure that is challenging to achieve. In many parts of the world, the acceptability of liver transplantation programs remains limited. The fourth country with the largest population globally, Indonesia currently has only one active liver transplantation center, limited to a living donor.² Generally, patients with cirrhosis do not survive due to delayed liver transplantation. Bridging therapy to improve the general condition while waiting for liver

transplantation becomes a choice to prolong patient's survival. This study aimed to find a bridging therapy for pediatric cirrhosis patients waiting for liver transplantation.

Granulocyte colony-stimulating factor (G-CSF) has been used and studied broadly for acute-on-chronic liver failure. The benefit of using G-CSF had been proven by many studies.^{7, 13, 14} However, other randomized control trials showed no significant benefit and revealed that the use of G-CSF for decompensated liver failure had been proven to lack benefit.^{15, 16} All of the studies mentioned were performed on adult patients. To our knowledge, there was only one study conducted on pediatric patients with acute-on-chronic liver failure that showed a beneficial outcome.¹⁷

There is a postulation that G-CSF can beneficially mobilize pluripotent hematopoietic stem cells from the bone marrow to the systemic circulation, which are potentially engrafted into the liver, hence may stimulate the differentiation of cells of the hepatocyte lineage.¹⁸

In our study, G-CSF only improved ALT while other liver function tests showed insignificant changes. AST showed an improvement trend, although statistically insignificant. AST and ALT are enzymes related to the transfer of amino acids to ketoglutaric acid, which become markers of hepatocellular injury. Alanine transaminase is a more sensitive marker than aspartate transaminase.¹⁹ In our study, patients who received G-CSF possibly had temporary improvement of hepatocellular injury within three months. The improvement of these markers indicates a probability of transient optimization of patients who are awaiting liver transplantation.

In our study, we did not observe any improvement in the PELD score. This parameter has been used as a guide to prioritize organ transplantation among patients on the waiting list at our center and to evaluate their 90-day mortality risk based on liver function and growth status. This result is in opposition with Sharma et al.,¹⁷ who demonstrated early survival benefits by an improvement of PELD score.

G-CSF therapy has been believed to enhance liver function and improve fibrosis by inducing the mobilization of autologous bone marrow-derived stem cells, thereby stimulating the release of hepatic progenitor cell activity and hematopoietic stem cells for cell differentiation and restoration of hepatocytes.²⁰ CD34 + is known to be one of the markers of bone marrow stem cell mobilization. Bone marrow stem cells in the peripheral blood have paracrine properties that elicit anti-inflammatory cytokine activity to initiate liver regeneration.²¹ In our study, we observed that the circulating level of CD34 + stimulated bone marrow cell mobilization in children with decompensated cirrhosis is three times higher in the intervention group. However, it is statistically insignificant ($p = 0,66$). The finding of CD34 + was similar to those of other studies that treated adult decompensated cirrhosis, and pediatric acute liver failure with G-CSF.^{17, 20, 22, 23} Other studies mentioned that effective treatment using growth factors requires a healthy baseline of bone marrow function,²⁴ which is not evident in patients with decompensated liver cirrhosis.

The leukocytes and neutrophil counts in the intervention group showed a significant increase, parallel with G-CSF administration. The peak was seen on Day 18. Contrary to the concerns of G-CSF causing potentially fatal leukocytosis, our studies confirmed G-CSF use in children to be safe as no adverse events were recorded during the highest peak of the leukocyte count.

Malnutrition and infection are the main problems of pediatric cirrhosis patients who are waiting for liver transplantation. We evaluated nutritional factors between the groups regarding changes in body weight, height, and mid-arm circumference. Our study did not reveal significant improvements in these nutritional parameters, which contrasts with the previous findings of Verma et al.,²³ who demonstrated a substantial increase in MAC.

The reported death in the control group is higher than the intervention, although it is statistically insignificant. The reported deaths of patients from our study were unlikely to be related to G-CSF administration. Two patients died more than ten days following G-CSF administration in the intervention group because of esophageal variceal bleeding. G-CSF reaches its peak concentration in four hours, and the half-life is approximately eight hours.¹⁸ The clearance rate of G-CSF is reported to be 0,6 mL/min/KgBW.²⁵ The incidents of death that occurred did not chronologically match with the administration of the treatment, even though this finding needs further evaluation.

Our study revealed that parents of patients reported subjective improvement from the intervention group throughout a certain period of G-CSF administration. Parents reported enhanced quality of sleep, less irritability, and displayed significant mood improvement. The reason for this remains obscure. General improvement of the quality of life is thought to be associated with cytokine levels, which will be evaluated in future studies. This study showed the benefit of G-CSF administration as a bridging therapy. The lack of statistical significance of our results might be due to the small size of our study sample. Further studies will be carried out with more significant study samples and evaluation of cytokines as a parameter for changes in the systemic milieu that potentially stimulate liver regeneration.

Conclusion

This report was a study on the effect of G-CSF in children with decompensated liver cirrhosis awaiting LT. Multiple doses of G-CSF significantly improve ALT level, while other liver function tests, PELDS score, nutritional status, and survival after three months did not show significant improvement. Mobilization of CD34 + cells was achieved with G-CSF, although insignificant.

Declarations

Funding

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Conflicts of Interest/Competing interests

There is no conflict of interest nor competing interest reported by the authors.

Ethics Approval

The ethics committee of our institution approved the study protocol (reference 19-07-0943), and the study confirmed the Helsinki Declaration of 1977.

Clinical Trials Registration

NCT04113317 at Clinicaltrials.gov.

Consent to Participate

A written informed consent was obtained from every legal guardian of research participant.

Consent for Publication

A written informed consent of publication without disclosing personal information was obtained from every legal guardian of research participant.

Availability of Data and Material

Digital raw data and materials are available from the corresponding author upon request, should they be required to be reviewed.

Plant Reproducibility

NA

Code availability

NA

Authors' contributions

Conceptualization: Tri Hening Rahayatri, Aria Kekalih, Alida Harahap, Aryono Hendarto, Hanifah Oswari, Zakiudin Munasir, Rianto Setiabudy, Akmal Taher; Methodology: Tri Hening Rahayatri, Aria Kekalih, Alida Harahap, Hanifah Oswari, Rianto Setiabudy, Akmal Taher; Formal analysis and investigation: Tri Hening Rahayatri, Aria Kekalih; Writing - original draft preparation: Tri Hening Rahayatri; Writing - review and editing: Tri Hening Rahayatri, Aria Kekalih, Alida Harahap, Aryono Hendarto, Hanifah Oswari, Zakiudin Munasir, Rianto Setiabudy, Akmal Taher; Funding acquisition: Tri Hening Rahayatri; Supervision: Aryono Hendarto, Hanifah Oswari, Zakiudin Munasir, Rianto Setiabudy, Akmal Taher

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Appendix

The Appendix is not available with this version

Figures

Figure 1

Study design and flow diagram of patient's selection (G-CSF: granulocyte-colony stimulating factor; SMT: standard medical therapy).

Figure 2

Repeated measures ANOVA test showed improvement of ALT level

Figure 3

Repeated measures ANOVA test showed the increase of leukocyte and neutrophil counts after G-CSF administration, with the peak on Day 18