eISSN (Online): 2598-0580

Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

Efficacy of Alpha Lipoic Acid Supplementation in Chemotherapy-Induced Peripheral Neuropathy

Mediarty Syahrir[1*], Yenny Dian Andayani[1], Norman Djamaluddin[1], Putri Farissa Muharramah[1], Kgs. M. Rosyidi[1], Erty Sundarita[1], Hasnawi Haddani[2], Erial Bahar[3]

[1]Department of Internal Medicine, Faculty of Medicine, Universitas Sriwijaya
[2]Department Neurology, Faculty of Medicine, Universitas Sriwijaya
[3]Department of Anatomy, Faculty of Medicine, Universitas Sriwijaya

ARTICLE INFO

Keywords:
Alpha-lipoic acid
Chemotherapy
Peripheral Neuropathy
Chronic Pain.

Corresponding author:
Mediarty Syahrir

E-mail address:
medi_sy@yahoo.com

All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.32539/bsm.v5i1.162

ABSTRACT

Background. Chemotherapy-induced peripheral neuropathy is a side effect of several chemotherapy drugs and a significant cause of chronic pain in cancer patients, which affects patients' long-term quality of life. The neurotoxic chemotherapy agents most reported to cause neuropathic pains are platinum and taxane. This study aimed to determine the efficacy of alpha-lipoic acid supplementation in chemotherapy patients. **Methods.** This study used a randomized, double-blind clinical trial in the oncology haematology clinic in the Department of Internal Medicine at Mohammad Hoesin General Hospital Palembang from November 2018 to July 2019. Samples were taken from patients who met the inclusion criteria and signed informed consent forms to join the study. This study used SPSS version 22.0 for Windows to analyze the data.**Results.** This research studied 30 subjects who were divided into alpha lipoic acid groups and placebo groups with 15 samples each. The alpha-lipoic acid group showed a significant decline in the Toronto Clinical Scoring System (TCSS) after treatment (p = 0.000) compared to the placebo group (p = 0.164). **Conclusions.** Treatment with a 600 mg single dose each day of alpha-lipoic acid for 12 weeks effectively improved patients condition significantly.

1. Introduction

Cancer is a public health problem that can affect anyone. According to WHO, the number of cancer patients in the world increases by 6.25 million people every year. In Indonesia, the prevalence of cancer is relatively high. The 2018 Indonesian Health Research data showed that the majority of cancer in Indonesia reached 1.79 per 1000 people, an increase from 1.4 per 1000 people in 2013.1–3

Chemotherapy is still one of the most effective ways to treat the malignancy and reduce mortality. Even, the substances used in chemotherapy can cause side effects and complications that hinder the administration of chemotherapy itself.4 Chemotherapy-induced peripheral neuropathy (CIPN) is a side effect of several types of chemotherapy drugs and a significant cause of chronic pain in cancer patients, which can negatively affect the patient's long-term quality of life. Some of the most widely reported neurotoxic agents are platinum, taxane, vinca alkaloid, bortezomib, thalidomide, and analogues.5,6 Around 68% of patients undergoing chemotherapy develop CIPN within the first month. CIPN results from direct injury to the peripheral nervous system by chemotherapy agents. With this high prevalence, a

better understanding of the pathophysiology and early symptoms of patients at risk, as well as better potential management plans, are essential for the prevention and treatment of CIPN.7,8

Alpha-lipoic acid (ALA), or pentanoic acid 1,2-dithiolane-3, is a natural dithiol that is synthesized enzymatically in the mitochondria of octanoic acid. ALA can also improve nerve function and conduction in peripheral neuropathy patients. In vivo research has shown that supplementation with ALA can reduce oxidative stress. Experimental evidence indicates that ALA improves glutathione levels, preventing lipid peroxidase, increasing the activity of antioxidant enzymes (such as superoxide dismutase and catalase in the peripheral nerves), and increasing nerve conduction velocity and blood flow, glucose uptake, and metabolism in the peripheral nerve.9,10

2. Methods

This research study was a randomized, double-blind clinical trial that used a pilot study technique. This research was carried out in the Department of Internal Medicine and Department of Neurology, Mohammad Hoesin General Hospital Palembang from November 2018 to July 2019. The study population was cancer patients undergoing chemotherapy in the haematology oncology clinic in the internal medicine department. The study sample comprised cancer patients who met the inclusion criteria, namely, having no neuropathic abnormalities in their electroneuromyography (ENMG). The other exclusion criteria were a history of diabetes mellitus, stroke, leprosy, chronic kidney failure, physical trauma to head, and taking medications such as isoniazid, statins, and phenytoin.The sample size was calculated using a paired numerical, analytical test formula, and the result should include 15 patients who received ALA treatment and 15 patients who received placebo treatment. The sampling technique used was non-probability consecutive sampling.

The study began with all cancer patients undergoing chemotherapy using platinum and taxane, followed by ENMG examination and calculation of TCSS scores. Patients who met the criteria were randomized into two groups: those in the ALA group were given ALA capsules with a dose of 600 mg per day, and those in the placebo group were given one placebo capsule per day for 12 weeks. At the 4th, 8th, and 12nd weeks, all patients were reevaluated for clinical signs, adherence, and side effects.

3. Results

Baseline characteristics

Baseline characteristic of the patients was described in **Table 1,** and most of the subject is male (60%).

Comparison of CIPN severity based on TCSS before and after treatment

The severity of CIPN in both groups was assessed before and after treatment using TCSS. The majority of patients in the ALA group (40%) had moderate polyneuropathy, and the majority of patients in the placebo group (46.7%) had mild polyneuropathy. The results of the analysis using the chi-square test showed a p-value of 0.202, which means there was no significant difference in the TCSS score before and after treatment between the two groups (p-value 0.202 vs 0.238). Comparison of both groups was described in **Table 2.**

Effect of ALA on CIPN

The TCSS scores before and after treatment for both groups are shown in Figure 1. Statistically, there was a significant difference in the change in TCSS scores between the ALA group and the placebo group (2.73 ± 2.15 vs -0.8 ± 2.11). The Mann Whitney test showed a p-value of 0.000, which means there is a very significant difference between the two groups in terms of the change in TCSS scores before and after treatment.

Table 1. Baseline characteristics.

Characteristic	Group		p-value
	ALA	**Placebo**	
Gender, n (%)			0.264***
▪ Male	11 (73.3)	7 (46.7)	
▪ Female	4 (26.7)	8 (53.3)	
Age (years)			0.496**
▪ Mean ± SD	50 ± 15.25	46.4 ± 13.25	
▪ Median (Minimum-Maximum)	49 (19–79)	5 (25–63)	
Body Mass Index (kg/m^2)			0.005**
▪ Mean ± SD	22,38 ± 3.64	18.88 ± 2.46	
▪ Median (Minimum-Maximum)	21.4 (16.4–29.6)	18.80 (14.5–23.2)	
Body Mass Index (kg/m^2), n (%)			0.054***
▪ < 18.5	2 (13.3)	7 (46.7)	
▪ 18.5–22.9	6 (40)	7 (46.7)	
▪ 23–24.9	4 (26.7)	1 (6.7)	
▪ > 25	3 (20)	0 (0)	
Body Surface Area (sqm)			0.062*
▪ Mean ± SD	1.55 ± 0.16	1.47 ± 0.13	
▪ Median (Minimum-Maximum)	1.54 (1.37–1.99)	1.44 (1.35–1.87)	

* Mann Whitney test, p = 0.05
**Independent t-test, p = 0.05
*** Chi-square 0.05

Table 2. Comparison of CIPN severity based on TCSS scores before and after treatment

Characteristic	Group		p-value
	ALA	Placebo	
TCSS before treatment, n (%)			0.202*
▪ Without polyneuropathy	2 (13.3)	5 (33.3)	
▪ Mild polyneuropathy	5 (33.3)	7 (46.7)	
▪ Moderate polyneuropathy	6 (40)	3 (20)	
▪ Severe polyneuropathy	2 (13.3)	0 (0)	
TCSS after treatment, n (%)			0.238*
▪ Without polyneuropathy	7 (46.7)	4 (26.7)	
▪ Mild polyneuropathy	7 (46.7)	6 (40)	
▪ Moderate polyneuropathy	1 (6.7)	2 (13.3)	
▪ Severe polyneuropathy	0 (0)	3 (20)	

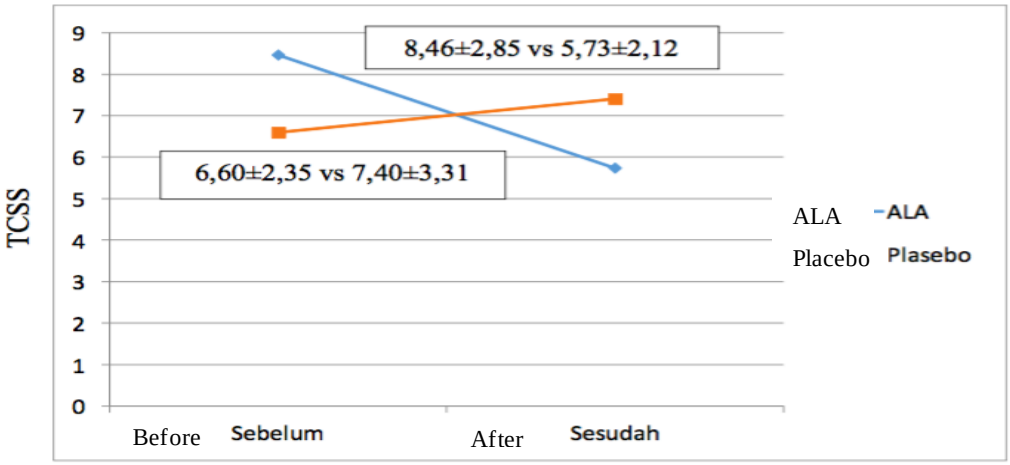

Figure 1. Comparison of TCSS scores before and after treatment in both groups.

4. Discussion

This research study consisted of 30 patients who were divided into two groups: ALA and placebo. Most of the subjects were male (60%); even several studies have found that gender is not one of the risk factors for CIPN. The clinical features of CIPN differ depending on the chemotherapy agent, dosage, and duration of administration. In the platinum group, CIPN is strongly influenced by the total dose and intensity of the amount given. Various classes of chemotherapy drugs cause neuropathy and affect the structure of specific peripheral nervous systems by different mechanisms, such as neuronopathy, axonopathy, and myelinopathy.[11,12]

Gedlicka et al. (2003) reported CIPN in 8 of 14 cancer patients who received docetaxel 400 mg/m^2 for eight sessions, and they reported significant clinical improvement of CIPN after giving 600 mg of ALA intravenously each day for three to five weeks followed by 1800 mg of ALA orally for two months. Zheng et al. (2015) conducted a multicenter study involving 126 CIPN patients divided into two groups: the ALA group (600 mg IV/day) and the control group (mecobalamin 500 µg IV each day). This research study concluded that CIPN improvement was better in the ALA group than in the control group after two weeks of treatment [80.95% (51/63) vs 47.62% (30/62)]. Zheng et al. further concluded that the combination of ALA and mecobalamin is a safe and effective agent for managing CIPN.[17]

TCSS is a tool for measuring the sensory symptoms of diabetic polyneuropathy and is widely used in various extensive studies. This tool has never been used to measure peripheral neuropathy in chemotherapy. Still, it works well to detect the disorders that occur in neuropathy in diabetes which has the same clinical picture as CIPN, namely symmetrical distal polyneuropathy. In addition to being able to see peripheral neuropathy with a high diagnostic value, the TCSS score scale can also be used to assess the severity of symptoms and changes that occur.[15,16]

The results of multivariate linear regression analysis in the placebo group found that the severity of neuropathy was significantly positively correlated with BMI. This finding means that patients with a higher BMI have higher degrees of neuropathy. Based on lesions in the peripheral nerves, the proinflammatory cytokines increased axonal damage and nerve demyelination. Therefore, systemic inflammation induced by obesity can aggravate neuropathic pain.[18,19]

5. Conclusion

TCSS scores significantly decreased with the administration of ALA 600 mg in a single dose for 12 weeks in patients with CIPN at Mohammad Hoesin General Hospital Palembang.

6. References

1. Miller KD, Siegel RL, Lin C, Mariotto AB, et al. Cancer treatment and survivorship statistics 2016. Ca Cancer J Clin. 2016;66:271-89.
2. Chan HK, Ismail S. Side effects of chemotherapy among cancer patients in a Malaysian general hospital: Experiences, perceptions and informational needs from clinical pharmacists. Asian Pac J Cancer Prev. 2014:15(13);5305-9.
3. Balitbang Kemenkes RI. Riset Kesehatan Dasar; RISKESDAS. Jakarta: Balitbang Kemenkes RI; 2018.
4. Muthalib A. Prinsip dasar terapi sistemik pada kanker: Setiati S, Alwi I, Sudoyo AW, Simadibrata M, Setiyohadi B, Syam AF. Buku Ajar Ilmu Penyakit Dalam Jilid III. Edisi VI. Jakarta: Interna Publishing; 2014. p. 2882-9.
5. Stewart BW, Kleihues P. Mechanisms of tumor development. World Cancer Report. Lyon: IARC Press; 2003:83-125.
6. Tofthagen C, McAllister D, McMillan SC. Peripheral Neuropathy in Patients with colorectal cancer receiving oxaliplatin. Clin J of Oncology. 2011;182-9.
7. Starobova H, Vetter I. Pathophysiology of Chemotherapy-Induced Peripheral Neuropathy. Front Mol Neurosci. 2017;10:174.
8. Kaley TJ, DeAngelis LM. Therapy of chemotherapy induced peripheral neuropathy. British J of Haematology. 2009;145:3-14.
9. Holzbaur E, Scherer SS. Microtubules, axonal transport and neuropathy. N Engl J Med. 2011;365:24.
10. Kucukgoneu, et al. Alpha-Lipoic Acid (ALA) as a supplementation for weight loss: Results from a meta-analysis of randomized controlled trials. Obese Rev. 2017; (18) 5: 594-601.
11. Grisold W., et al. Peripheral Neuropathies from Chemotherapeutics and Targeted Agents: Diagnosis, Treatment, and Prevention. Neuro-Oncology Journal. 2012;14:45-54.
12. Badros A, Goloubeva O, Dalal JS, Can I, Thompson J, Rapoport AP, et al. Neurotoxicity of bortezomib therapy in multiple myeloma: A single-center experience and review of the literature. Cancer. 2007 Sep 1;110(5):1042–9.
13. Lopez, et al. Fetal fibronectin (fFN) detection as a predictor of preterm birth in actual clinical practice. Am J Obstet Gynecol. 2000;182:1103-6.
14. Gedlicka C. Amelioration of docetaxel/cisplatin-induced polyneuropathy by alpha-lipoic acid. Annals of Oncology. 2003;14(2):339-340.
15. Park HJ. Chemotherapy induced peripheral neuropathic pain. Korean J Anesth. 2014;67(1):4-7.
16. Wozniak KM, Vornov JJ, Wu Y, Nomoto K, Littlefield BA, DesJardins C, et al. Sustained accumulation of microtubule-binding chemotherapy drugs in the peripheral nervous system: Correlations with time course and neurotoxic severity. Cancer Res. 2016;76:3332–9. doi: 10.1158/0008-5472.CAN-15-2525
17. Zheng ZG CY, Hong DH, Lin YB, Zheng WH. Efficacy of α-lipoic acid combined with mecobalamin for chemotherapy-induced peripheral neuropathy. Evaluation and Analysis of Drug-Use in Hospitals of China. 2015;15:729-31.
18. Hozumi J, Sumitami M, Matsubayashi Y, Abe H, Oshima Y, Chikuda H, Takeshita K, Yamada Y. Relationship between neuropathic pain and obesity. Pain Research and Management Hindawi. 2016; 22:1-6.
19. Andrade P, Visser-Vandewalle V, Philippens M, et al. Tumor necrosis factor-α levels correlate with postoperative pain severity in lumbar disc hernia patients: Opposite clinical effects between tumor necrosis factor receptor 1 and 2. Pain. 2011;152(11):2645-52.