Advances in Traditional Medicine
https://doi.org/10.1007/s13596-023-00737-8

RESEARCH ARTICLE

Improving cognitive function with intermittent dose escalation of curcumin extract in chemotherapy-induced cognitive impairment patients: a randomized controlled trial

Anak Agung Ayu Putri Laksmidewi[1] · I. Nyoman Bayu Mahendra[2] · Andreas Soejitno[1] · Aurelia Vania[1]

Received: 26 February 2023 / Accepted: 26 December 2023

Abstract
Chemotherapy-induced cognitive impairment (CICI) is an impairment of memory, learning power, concentration, reasoning, executive function, attention, and visuospatial during and after chemotherapy exposures. No proven safe and effective therapeutic regimen are available to improve cognitive function in CICI patients. To evaluate the safety and effectiveness of curcumin extract to improve cognitive function in CICI patients. This study was a double-blind randomized controlled trial clinical trial in patients with cervical carcinoma who underwent a carboplatin-paclitaxel chemotherapy regimen from March to October 2021 at single center hospital. Subjects divided into two groups that received curcumin and placebo caplets by dose escalation method from 240 to 400 mg intermittently (14 days on and 7 days off) between chemotherapy cycles. Cognitive function was evaluated pre- and post-therapy using the AFI questionnaire, Stroop test, and MoCA-Ina. A total of 78 subjects were equally divided into the treatment and control groups. The percentage of drop-out, mortality, and adverse drug response were relatively comparable between each treatment arm. The group of subjects receiving curcumin extract experienced clinically and statistically significant improvements in cognitive function based on the Stroop test (Δ median 8.57 vs. 2.46; Z −4.503 vs. −1.762; p <0.0001 vs. 0.078) and MoCA- Ina (Δ mean 1.53 vs. 0.72; Z −2.99 vs. −2.05; p <0.003 vs. 0.04) versus placebo in between-group and between-subject analyses, respectively. Administration of curcumin extract with intermittent dose escalation regimen proved to be safe and able to improve cognitive function of CICI patients clinically and statistically significant.

Keywords CICI · Curcumin extract · Intermittent dose escalation · Chemotherapy · Neuroprotective

Introduction

Chemotherapy-induced cognitive impairment (CICI) is neurocognitive disorder in the aspect of memory, learning, concentration, reasoning, executive function, attention, and visuospatial during and after chemotherapy administration (Ren et al. 2019; Cardoso et al. 2020). Several chemotherapeutic agents administered either as monotherapy or in combination may induce long term adverse effects against cognitive function, thus reducing their overall quality of life (Mounier et al. 2020). CICI has a relatively high prevalence among cancer patients who receive chemotherapy. Despite its magnitude, there are several reasons why CICI cannot be properly diagnosed and receive an appropriate treatment, mainly due to (1) reversible nature, despite in several studies, it was reported that cognitive function deficit can persist in the long term, (2) CICI symptoms are often minimal, thus the use of standard screening test for cognitive impairment such as MMSE may not be able to detect CICI accurately, (3) unstandardized CICI evaluation and diagnosis confirmation, (4) variations in the process of diagnostic approach, (5) there has not been any treatment to prevent CICI or to maintain cognitive function among cancer patients who receive chemotherapy.

Curcumin (C21H20O6) is an active substance of natural herbs Curcuma xanthorriza roxb. Curcumin has been widely used as a staining agent and taste compliment in

✉ Anak Agung Ayu Putri Laksmidewi
putri_laksmidewi@unud.ac.id

[1] Department of Neurology, Faculty of Medicine, Udayana University/Prof. Dr. I.G.N.G. Ngoerah Hospital, Denpasar, Bali, Indonesia

[2] Department of Obstetrics and Gynecology, Faculty of Medicine Udayana University/Prof. Dr. I.G.N.G. Ngoerah Hospital, Denpasar, Bali, Indonesia

Published online: 17 January 2024

food industry, as well as being used as a herbal medicine in Asian countries for centuries. It is used to treat vomiting, headache, diarrhea, and other diseases (Panahi et al. 2021). Recently, there has been multiple pharmacological studies done to investigate the antioxidant, antiinflamation, anticarcinogenic, and anti-bacterial effects of curcumin. Curcumin is a safe natural product to be consumed by humans (Abd El-Hack et al. 2021). Curcumin is also known to increase the effectiveness of chemotherapeutic agents via increasing cancer cells sensitization against chemotherapy and protecting normal cells from chemotherapy damage (Tan and Norhaizan 2019). Protective effect and safety profiles of curcumin against central nervous system, particularly among subjects receiving chemotherapy, has never been studied before. Therefore, in this study, we would like to evaluate the safety profile of curcumin and if curcumin administration can maintain cognitive function and prevent CICI administration among cancer patients receiving chemotherapy.

Materials and methods

This was a randomized, double-blind, placebo-controlled trial involving cervical cancer patients who underwent chemotherapy regimen of carboplatin-paclitaxel. We used a study code name of Curcumin PotentiaLApplicability and Rationale for Chemotherapy-Induced Cognitive Impariment Treatment EfficacY (abbreviated as CLARITY trial). The format of study report adhered to CONSORT statement. Study was conducted between March until November 2021. The main outcome in this study was the effectiveness of curcumin to prevent CICI among cervical cancer patients who underwent carboplatin-paclitaxel chemotherapy as measured using Attentional Functional Index (AFI), Stroop test, and Montreal Cognitive Assessment Indonesian Version (MoCA-Ina) prior to and after chemotherapy session. Moreover, we also assessed the safety profile of curcumin according to drop out rate, frequency, and severity of adverse event among patients receiving curcumin. All subjects were recruited from Obstetrics and Gynecology clinic of Prof. Dr. I.G.N.G. Ngoerah Hospital, Denpasar between March to November 2021. Inclusion criteria for this study were patients with cervical cancer, currently or about to commence carboplatin-paclitaxel treatment, patient was cooperative, able to understand instruction and communicate well, and willing to participate in this study by signing informed consent after receiving full explanation with respect to the purpose of the study, potential benefits, and adverse effects resulting from the administration of curcumin. The exclusion criteria for this study were, patients with severe depression (as measured using Hamilton Depression Rating Scale ≥ 25), mental status decline due to various causes, history of receiving chemotherapy before this study, or history of receiving hormonal chemotherapy including tamoxifen, aromatase inhibitors, or androgen treatment, patients with central nervous system infection and/or systemic infection, patients with pre-morbid cognitive impairment due to neurodegenerative diseases (including Alzheimer dementia, vascular dementia, frontotemporal dementia, Parkinson's disease with dementia), patient with pre-morbid cognitive impairment due to other intracranial disorders (e.g. metastatic brain tumors, history of traumatic brain injury with sequlae, history of intracranial infection with sequlae, history of autoimmune diseases), patients with contraindication for curcumin or prior allergic history to curcumin or gluten capsule. The protocol of this study had been approved by the Ethical Commission of Faculty of Medicine Udayana University with protocol no. LB.02.01/XIV.2.1/7933/2021. This study as conducted by adhering to WMA Helsinki Declaration regarding ethical principal in medical research involving humans as research subjects.

Treatment protocols

All eligible subjects were randomized with a ratio of 1:1 by using random number generator. All subjects and investigators did not know subjects' treatment status (treatment vs. placebo) until the information was disclosed by the principal investigator by the end of the study period. The curcumin dose administered followed the dose-escalation protocol, i.e. in the initial phase of the study period, subjects in the treatment group received curcumin extract of 60 mg (3 caplets) 4 times a day (total daily dose equals to 240 mg), whereas control group was given placebo caplet with similar dose and frequency of administration to the treatment group (i.e. 4 times a day, 3 caplets per intake). Curcumin and placebo were administred continuously for 14 days and paused temporarily for 7 days in between chemotherapy session. Curcumin dose and the amount of placebo caplets administered were increased gradually by 80 mg for every next chemotherapy series until the dose given reached 400 mg per day (equivalent of 4×5 caplets, both on treatment and control group). The administration of both curcumin and placebo were given on maintained doses during the carboplatin-paclitaxel series until the last series. Caplets containing curcumin extract were derived from *Curcuma xanthorrhiza Roxb*., packed inside a blistered and given the label "Curcuma FCT 20 mg", whereas placebo caplet contains starch with identical dimension, color, packaging, and label as to the curcumin extract. Every blister contains six caplets and was sealed from the factory. Blister containing curcumin or placebo were marked with "B1" or "BA1", respectively. All caplets in the blister were produced and provided by Indonesia SOHO Global Health.

If during the study period, there were subjects refusing to undergo treatment protocol, did not want to consume any

medications, refused to be reevaluated, or died, then the subject would be considered as dropped out. If there were any adverse event or adverse reaction pertaining to the administered treatment, then the subject's status whether or not to be involved in the study would be determined on an individual basis. If, whenever there were any serious adverse event or serious adverse reaction with respect to the treatment given, then the subjects would be immediately dropped out from the study and immediately referred to undergo treatment at the relevant health care facilities. If the drop-out percentage due to SAE or SAR was $\geq 5\%$ between group, then the study would be considered to be prematurely terminated or halted while waiting for authority's investigation. Every measured data then processed and analyzed statistically. All subjects who were dropped out was included in the statistical analysis.

Outcome evaluation

Subjects within two groups were evaluated for Attentional Functional Index (AFI), Stroop color and word test (also known as Stroop test), Montreal Cognitive Assessment Indonesian version (MoCA-Ina) by trained general practitioners under independent neurologists' supervision and blinded to this study. AFI is a subjective measurement comprises of 16 questions. AFI was meant to evaluate individual perceptions with respect to their effectiveness in performing dailiy activities requiring attention, working memory, and executive function. Every components of AFI questions were measured using 10 mm straight line with score ranging from 0 (not at all) to 10 mm (very good or significant). Subjects were asked to fill AFI independently by giving a single vertical line that intersect the horizontal straight line scale of each question according to their subjective judgment. The higher the AFI score represents the better individual's cognitive performance and its impact toward daily activities. Moreover, Stroop test consists of (1) text describing the color and printed with the same color as the correspondiong text (word card/W), (2) printed as colored box (color card/C), and (3) printed as discongruent text and color (color-word card/CW). Subjects were, in turn, asked to mention the word or color as many and as accurate as possible within 45 s. Only the right answers were counted in this test (C, W, and CW). We then performed a CW prediction score with the following formula: $Pcw = 45/\{((45 \times W) + (45 \times C))/(W \times C)\}$. Subsequently, we subtract CW score with Pcw to obtain interference score (IG). Negative IG score reflects subject's pathological impairment in inhibiting interference or noise, and vice versa. Stroop test is reliable to assess subject's ability to inhibit cognitive intereference derived from other stimuli that comes in during the simultaneous processing of a certain stimulus (Scarpina and Tagini 2017). The Stroop test is useful in evaluating a person's selective attention and executive function. A person's ability in the Stroop test is determined by his or her level of attention to focus on the correct stimulus, while ignoring other stimuli as confounders. The ability to inhibit dominant responses also reflects good executive function. Thus, the Stroop test is often as a screening tool to detect subtle, subclinical brain damage and cognitive impairment, as well as a tool to measure a person's mental flexibility (Braga et al. 2022; Friedman and Robbins 2022). The MoCA-Ina test is a series of neurocognitive tests that can detect the spectrum of mild cognitive impairment to dementia efficiently and objectively. The MoCA-Ina test is a version that has been adapted into Indonesian and has been tested for validity and reliability. MoCA-Ina measures six cognitive domains including (1) attention, (2) memory and learning, (3) language, (4) visuospatial, and (5) executive function. The MoCA-Ina test focuses on the executive function of the frontal lobe and attention so that it can detect impaired cognitive function that is not dominant in the memory domain, including CICI. The MoCA test has been used successfully to detect the incidence of CICI in hematological malignancies in previous studies (Kotb et al. 2019). Evaluation of cognitive function in the form of AFI test, Stroop test, and MoCA-Ina was performed at the beginning of the study (baseline) and repeated for each subject in the first 60 min after the last series of chemotherapy was given.

Statistical analysis

All data were tested for normality. Categorical and interval data related to the basic characteristics of research subjects were evaluated using the chi-square test and independent t-test if the data were normally distributed or the Mann Whitney test if the data were not normally distributed. Differences in the scores of each component of the AFI test, Stroop test scores, and total MoCA-Ina scores between the curcumin therapy group and the control (between group) were evaluated using an independent t test if the data were normally distributed or the Mann Whitney test if the data were not normally distributed. Meanwhile, the differences in the scores of each component of the AFI test, Stroop test scores, and the total MoCA-Ina score were evaluated using paired t-test if the data were normally distributed and the Wilcoxon signed rank test if the data were not normally distributed. Interval data used a 95% confidence interval range and p value < 0.05 was considered statistically significant. All statistical analyzes were performed using IBM SPSS Statistics series 20 software (IBM, San Francisco).

Results

Subjects' selection process

Steps of subjects's selection can be seen in Fig. 1. A total of 122 subjects were evaluated according to the eligibility

criteria in order to participate in this study. Among these, 40 people did not meet the eligibility criteria, 3 people refused to participate, and 1 person was not allowed to participate by the doctor in-charge of the patient. Thus, 78 people met the eligibility criteria and were randomized 1:1 to 39 people each allocated to each of the group (curcumin extract and placebo). Among all subjects, none refused the administered treatment. In the course of treatment, 3 and 7 subjects receiving curcumin extract and placebo respectively lost contact because they could not be contacted since the first series of chemotherapy. Furthermore, 2 and 1 person died in the curcumin extract and placebo groups, respectively, while 3 subjects in the treatment group suffered from unwanted drug responses including palpitations, paresthesias, and diarrhea (1 person each). Meanwhile, as many as 2 people on the placebo group had diarrhea. All subjects who experienced an undesirable drug response stopped participating in this study (dropped out), nevertheless, the data that had been obtained were still subjected to statistical analysis (ITT).

Subjects' baseline characteristics

The basic characteristics of the research subjects can be seen in Table 1. Subjects in the placebo group had a tendency to be older, although not significant. The level of education has a relatively homogeneous distribution between groups with most of them having a high school education background. Meanwhile, some of the subjects in both groups had a diagnosis of cervical carcinoma stages 2 and 3. Meanwhile, approximately one third of the subjects in both groups had just undergone the second series of chemotherapy. The cumulative doses of the chemotherapy regimens of carboplatin and paclitaxel between the two groups were relatively homogeneous.

The scores of each AFI component 1–5 and 7–13 were not significantly different between groups of subjects receiving curcumin compared to placebo. Meanwhile, the mean score of AFI 6 was significantly higher in the group of subjects receiving curcumin (73.28 vs. 59.26; 95% CI 4.80–23.25; $p = 0.003$). Meanwhile, the initial data for the

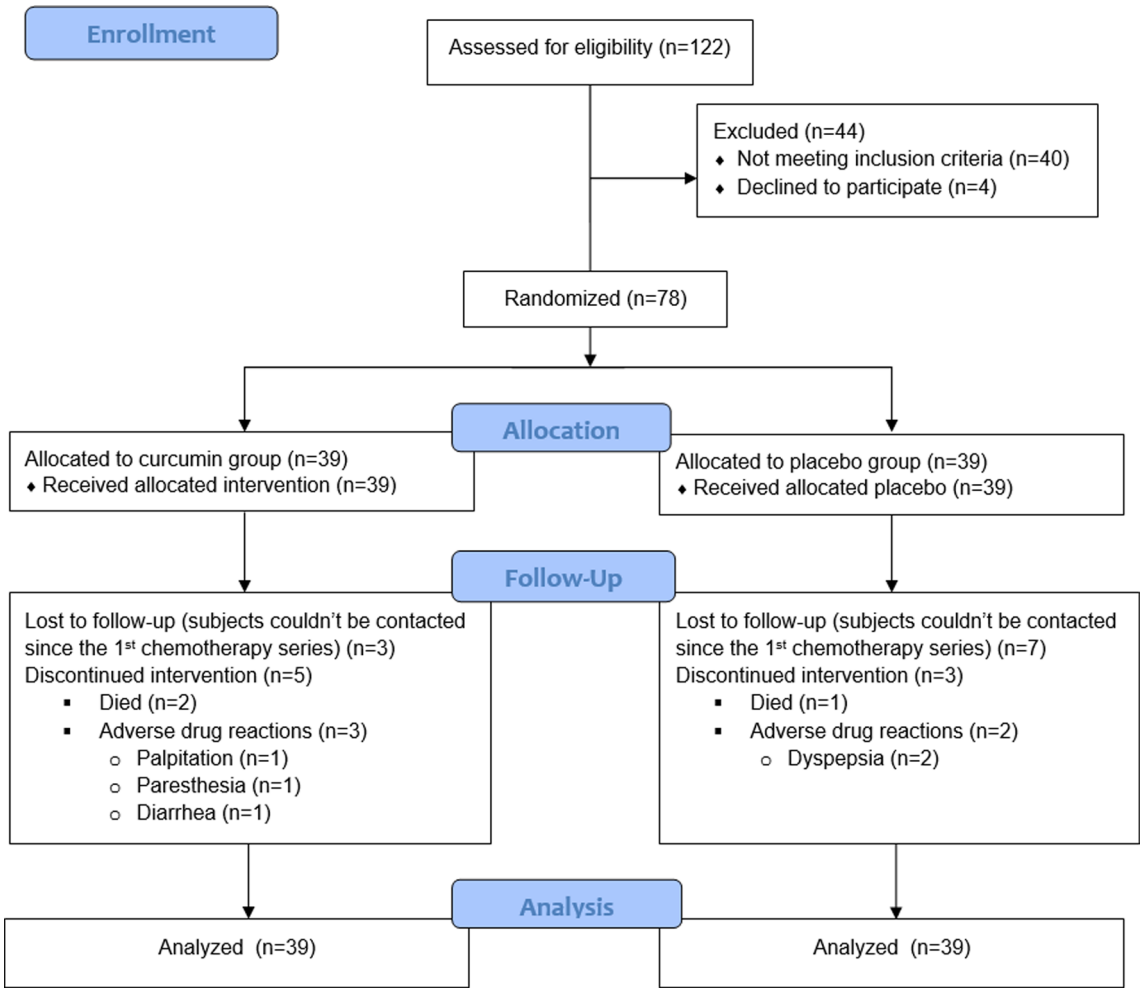

Fig. 1 A diagram of subjects' selection process

Table 1 Subjects' baseline characteristics

Parameters	Treatment group (n = 39)	Placebo group (n = 39)	*P*
Age (mean ± SD*)	46.74 ± 10.67	50.46 ± 7.02	0.074
Education level† (n, %)			
Illiterate	3 (7.7)	5 (12.8)	0.524
Elementary	7 (17.9)	12 (30.8)	
Junior high school	7 (17.9)	6 (15.4)	
Senior high school	16 (41.0)	13 (33.3)	
Scholar//Diploma	6 (15.4)	3 (7.7)	
Cervical cancer stage (n, %)			
1	6 (15.4)	4 (10.3)	0.670
2	16 (41.0)	21 (53.8)	
3	15 (38.5)	13 (33.3)	
4	2 (5.1)	1 (2.6)	
Series of chemotherapy (n, %)			
First	8 (20.6)	8 (20.5)	0.197
Second	12 (30.8)	15 (38.5)	
Third	7 (17.9)	7 (17.9)	
Fourth	8 (20.5)	4 (10.3)	
Fifth	1 (2.6)	5 (12.8)	
Sixth	3 (7.7)	0 (0)	
Paclitaxel cumulative dose (median [IQR]) mg	660.00 [585.70]	567.18 [1822.40]	0.181
Carboplatin cumulative dose (median [IQR]) mg	1456.00 [1060.40]	1096.60 [1127.70]	0.407
Curcumin cumulative dose (median [IQR]) mg	7840.00 [11.200]	N/A	

*SD standard deviation; *p* value significant at < 0.05

Stroop and MoCA-Ina tests were relatively homogeneous between groups.

Effect of curcumin extract on cognitive function and subjects' effectiveness in performing daily activities subjectively

The role of curcumin extract on cognitive function and subjects' effectiveness in performing daily activities were subjectively evaluated and compared with placebo. The patient's cognitive function and independence in performing daily activities were evaluated using the AFI questionnaire. Groups of subjects receiving both curcumin extract and placebo were evaluated for differences in median and IQR AFI scores of each component at the end of the study period (after therapy) and baseline (baseline) [within group analysis]. Then the group of subjects who received curcumin extract was compared with the group of subjects who received placebo regarding the difference in the AFI scores of each component between the two (between group analysis).

Evaluation of the AFI component in the group receiving the curcumin extract showed a significant difference between the component 11 and 13 AFI scores, namely an increase in the median [IQR] of both components at the end of the treatment period compared to the baseline (AFI 11 median = 7.00, Z=-1.188, $p = 0.235$; AFI 13 median = 51, Z=-4.983, $p < 0.001$). This indicates that subjects receiving curcumin extract felt an increased frequency of errors in daily activities and mood changes to become irritable or irritable at the end of the study period. Meanwhile, the group receiving placebo also experienced a significant increase in AFI scores of components 12 and 13 at the end of the study period compared to baseline (AFI 12 median = 4.00, $Z = -1.966$, $p = 0.049$; AFI 13 median = 9.00, $Z = -4.899$, $p < 0.0001$). This also indicates worsening memory function and changes in the subject's mood to become irritable and irritable at the end of the period compared to the beginning of the study.

The placebo group experienced an increase in AFI scores components 1, 2, 4–8 at the end of the treatment period than at the beginning of the study, but the placebo group also experienced an increase in AFI scores 10 to 13 which was inversely proportional to cognitive function and fluency in performing daily activities. This indicates an inconsistency in the subject's personal perception of cognitive function and its impact on daily activities. Meanwhile, the group of subjects receiving curcumin showed a decrease in AFI scores of components 1, 5, 6, 7, 9 at the end of the treatment period compared to the beginning of the study, while the group

also showed an increase in AFI scores of components 10, 11, and 13. This indicates that subjects receiving curcumin extract had a decreased perception of cognitive function and effectiveness in performing daily activities after receiving therapy.

According to between group analysis, there was no significant difference in median and IQR between groups receiving curcumin extract versus placebo for all components of the AFI score (Table 2). Thus, the personal perception of cognitive function in the two groups of subjects is relatively comparable and tends to worsen with increasing cycles and doses of chemotherapy.

Effects of curcumin extract on selective attention and subjects' executive function

Furthermore, an analysis was carried out regarding the role of curcumin extract on subjects' selective attention and executive function which were evaluated objectively using the Stroop test. The groups of subjects who received both curcumin extract and placebo were evaluated for differences in median and IQR of final (after treatment) and baseline (baseline) IG scores [within group analysis]. Then the group of subjects who received curcumin extract was compared with the group of subjects who received placebo regarding the difference in GI scores between the two (between group analysis). Based on Table 3, it was known that there was a statistically significant difference between the median initial and final IG scores in the group receiving curcumin extract. IG experienced a significant increase (Δ median = 8.57) indicating an improvement in selective and executive attention function in subjects who had CICI but consumed curcumin extract ($Z = -4.503$; $p < 0.0001$). Furthermore, there was also an improvement in the IG score of the placebo group at the end of the examination compared to the baseline condition, namely an increase of 2.46 points (Δ median), but not statistically significant ($Z = -1.762$; $p = 0.078$).

Between group analysis showed that the median difference in IG scores (Δ median = 5.76) was significantly higher in the group receiving curcumin extract (median [IQR] = 4.70 [9.74]) compared to placebo recipients (median [IQR]) = −1.06 [6,2]; Mann–Whitney U = 268.5; $p < 0.0001$). This indicates that the administration of curcumin extract in patients with CICI provides a protective and curative effect on selective attentional and executive functions significantly compared to placebo.

Effects of curcumin extract on overall cognitive function

Global cognitive function was evaluated based on the MoCA-Ina score. Comparison of MoCA-Ina scores was carried out before and after therapy (within group analysis) in each treatment group and the difference in the mean difference in MoCA-Ina scores between groups at the end of the study period (between group analysis). Based on Table 4, there was an improvement in the MoCA-Ina score at the end of the treatment period compared to the baseline (baseline). The difference in the mean improvement of MoCA-Ina scores in the group receiving curcumin extract was 1.53 points, which was statistically significant ($Z = -2.99$; $p < 0.003$). Meanwhile, improvements in MoCA-Ina scores were also found in the placebo group, although with a smaller difference in scores, namely 0.72 points and statistically significant ($Z = -2.05$; $p = 0.04$).

Furthermore, an intergroup analysis was conducted with respect to the difference in the mean MoCA-Ina scores

Table 2 Subgroup analysis of each AFI components between treatment and control group

Parameters	Curcumin group (median [IQR])	Placebo group (median [IQR])	Wilcoxon signed rank Z	*P*
AFI 1	−1.00 [13.00]	0 [18.00]	−0.906	0.365
AFI 2	3.00 [18.00]	3.00 [18.00]	−1.000	0.317
AFI 3	4.00 [18.00]	1.00 [16.00]	−0.150	0.881
AFI 4	1.00 [16.00]	0.00 [15.00]	−0.065	0.948
AFI 5	0 [18.00]	3.00 [12.00]	−1.115	0.265
AFI 6	0 [16.00]	2.00 [15.00]	−1.265	0.206
AFI 7	0 [14.00]	1.00 [10.00]	−0.996	0.319
AFI 8	0 [10.00]	0 [17.00]	−0.640	0.522
AFI 9	−2.00 [9.00]	0 [11.00]	−0.881	0.378
AFI 10	5.00 [16.00]	4.00 [13.00]	−0.955	0.339
AFI 11	3.00 [13.00]	5.00 [14.00]	−0.040	0.968
AFI 12	5.00 [17.00]	3.00 [13.00]	−0.540	0.589
AFI 13	0 [15.00]	4.00 [15.00]	−0.875	0.382

**P* significant at < 0.05

Table 3 IG Score Profiles at beginning and end of study period between treatment and control group

Parameters	Initial IG score (median [IQR])	Final IG score (median [IQR])	Δ median (IG_{final}-$IG_{initial}$)	Wilcoxon signed rank Z	*P*
Treatment group (n = 39)	−0.71 [13.56]	7.86 [15.22]	8.57	−4.503	< 0.0001*
Placebo group (n = 39)	3.6 [15.32]	6.06 [15.08]	2.46	−1.762	0.078

**P* significant at < 0.05

Table 4 MoCA-Ina profile scores at the beginning and end of the study period between treatment and control group

Parameters	Initial MoCA-Ina score (mean ± SD)	End MoCA-Ina score (mean ± SD)	Δ mean	Wilcoxon signed rank Z	*P*
Treatment group (n = 39)	24.23 ± 4.25	25.77 ± 3.44	1.53	− 2.99	0.003*
Placebo group (n = 39)	23.49 ± 4,89	24.21 ± 4.29	0.72	− 2.05	0.04

**P* significant at < 0.05

between the groups receiving curcumin extract and placebo. The results obtained that the difference in the mean MoCA-Ina scores was higher in the curcumin receiving group (1.54 ± 3.09) than the placebo (0.72 ± 1.99) with a mean difference between groups of 0.82 points but not statistically significant (Mann–Whitney U 615.5, $p = 0.142$).

Subgroup analysis showed a non-significant difference between the mean differences of each component of MoCA-Ina between treatment groups. Similarly, based on subgroup analysis of each component of MoCA-Ina in each treatment group (within group analysis). In general, the results were not much different between before and after the treatment period with a few exceptions. The group receiving curcumin extract experienced improvements in naming function (Δ mean ± SD = 0.18 ± 0.51; Z = - 1.072; p = 0.038) and memory delay (Δ mean ± SD = 0.56 ± 1.21; Z = − 2.654; $p = 0.008$) which was statistically significant after the treatment period. Meanwhile, in the placebo group, there was a statistically significant improvement in orientation function between before and after the treatment period (Δ mean ± SD = 0.31 ± 0.69; Z = − 2.588; $p = 0.01$).

Effect of curcumin extract on neuronal damage, inflammatory, and oxidative stress biomarkers

The administration of curcumin extract significantly decreased the median GFAP, IL-6, and Isoprostane in the treatment group, while in the control group, the median GFAP, IL-6, and Isoprostane tended to increase. In the treatment group, the median difference in the largest decreases was obtained sequentially, namely IL-6, isoprostane, and GFAP. Meanwhile, in the control group, the median difference in the largest increases was obtained sequentially, namely isoprostane, IL-6, and GFAP (Table 5).

Table 5 Median changes of GFAP, IL-6, and Isoprostane at the beginning and end of the study period between treatment and control group

Parameters	Treatment group (n = 39)	Placebo group (n = 39)
Δ *GFAP*		
Median (IQR)	− 0.29 (0.60)	0.01 (0.80)
*P**	0.004	
Δ *IL-6*		
Median (IQR)	− 16.26 (47.85)	4.09 (47.70)
*P**	0.003	
Δ *Isoprostane*		
Median (IQR)	− 9.65 (66.83)	19.83 (76.52)
*P**	0.009	

**P* significant at < 0.05

Discussion

CICI is a relatively common problem in cancer patients who are currently undergoing or have completed chemotherapy regimens. The incidence of CICI varies but tends to be high, between 17 and 70% (Lv et al. 2020). Carcinomas suffered by women tend to have a high prevalence of CICI. For example, in breast carcinoma, CICI may account for 75% of all subjects undergoing chemotherapy (Wefel et al. 2015). Meanwhile, in ovarian cancer, the prevalence of CICI reaches 70% of the total patients (Pearre and Bota 2018). Whereas in cervical carcinoma, 64.5% of subjects reported subjective cognitive impairment after undergoing chemotherapy (Zeng et al. 2017). Thus, the high prevalence of CICI to date has not been matched by adequate diagnosis and treatment efforts. For example, until now there is no universal and uniform CICI diagnostic criteria. Cognitive function examination methods also differ in each health facility, both for research and therapeutic purposes. Furthermore, until now there is no clinical and scientifically proven therapeutic regimen that can prevent the occurrence of CICI, or improve impaired cognitive function after suffering from CICI.

Curcumin extract from the natural plant *Curcuma xanthorrhiza Roxb.* has been widely studied its benefits as a medical and adjuvant therapy (Panahi et al. 2021). Curcumin extract has several advantages, including having a pleiotropic effect as anti-inflammatory, antioxidant, and antiapoptotic (Panahi et al. 2021; Abd El-Hack et al. 2021). Furthermore, curcumin extract also has anti-carcinogenic effects. Thus, the combination of various mechanisms of action makes curcumin extract a comprehensive therapeutic modality to prevent or treat cellular damage, especially due to exposure to neurotoxic and oxidative stress chemotherapeutic agents (Liu et al. 2019; Akbari et al. 2020). In addition, curcumin extract also has a low toxicity index, so it has a broad and safe therapeutic window profile (Aggarwal et al. 2016). Clinically, curcumin extract has been widely tested

and is known to have neuroprotective effects. For example, curcumin extract can inhibit cognitive function impairment caused by the oxidative stress of cigarette smoke (Muthuraman et al. 2019). In the context of chemotherapy, curcumin has been shown to improve neurogenesis and synaptogenesis that play a role in brain plasticity, as well as increase hippocampal autophagy so that it can suppress the process of apoptosis in the central nervous system, after exposure to cisplatin-based chemotherapy (Yi et al. 2020). Thus, administration of curcumin extract in carcinoma patients undergoing chemotherapy regimens can help prevent, even improve, the symptoms of CICI. A case report documented the administration of one form of the active substance curcumin (theracurmin) proved to be able to completely treat impaired cognitive function in patients with previously diagnosed CICI (Erken et al. 2020).

In this study, a comparison was made between groups of subjects who received curcumin extract derived from *Curcuma xanthorrhiza Roxb*. The dosage formulation and therapeutic regimen of curcumin extract were determined by the researchers themselves after going through an extensive study, considering that there was no standard regimen related to this. The dosing method was carried out in an escalating manner and at the time of this study, drug holidays were still given at intervals of 1 week for every 2 weeks of therapy, to ensure safety and prevent unwanted drug reactions. In this study, the drop-out rates were 20.5% and 25.6% in the treatment arm and placebo respectively, which were still within reasonable limits for the experimental clinical research category (Bell et al. 2013). The drop-out rate was not significantly different between the treatment and control groups, including the number of subjects who died (2 and 1 person, respectively). Furthermore, there was 1 subject in each arm who experienced a response to the unwanted effects of treatment, namely diarrhea and dyspepsia. Both complaints are mild and resolve on their own after discontinuation of therapy (self-limited upon treatment discontinuation). Meanwhile, two undesirable response effects in the treatment group, namely palpitations and paresthesias were considered unrelated to the administration of curcumin extract and potentially caused by the chemotherapy regimen, based on the assessment by the PI and the pharmacovigilance team.

Administration of curcumin extract did not improve the subject's perception of cognitive function and effectiveness in carrying out daily activities subjectively. Subjects who underwent chemotherapy regimens actually felt a worsening of cognitive function and independence as the series and dose of chemotherapy increased. Similar findings also occurred in the control group. This was actually predicted by the research team, considering that based on the natural course of subjects with CICI, more than half (65%) of worsening perception of cognitive function occurred at the end of the chemotherapy regimen (Li and Caeyenberghs 2018). This is thought to be related to the accumulation of chemotherapy doses because the incidence of CICI is dose-dependent (Malacrida et al. 2019; Schagen et al. 2022), coupled with the possible side effects of other chemofetherapy such as pain, tingling, and anemia that can reduce quality of life and affect mood or affective subjects in general (Lewandowska et al. 2020; Burgess et al. 2021). This is important to clarify, considering that the AFI questionnaire measures cognitive function subjectively, only based on the subject's personal perception.

Furthermore, administration of curcumin extract was shown to improve selective attentional and executive functions as assessed by the Stroop test. Stroop test is an efficient, accurate, and objective method of evaluating cognitive function. The group of subjects who received curcumin extract was shown to have significantly improved attention and executive function, both clinically and statistically, compared to the control group. This is evidenced by the pathological condition in the group of subjects receiving curcumin extract at the beginning of the study (baseline) compared to normal conditions in the control group, as indicated by a negative interference score (IG) in the first group. However, administration of curcumin extract could improve cognitive function dramatically at the time of this interim study. The Stroop test is a dynamic and time-dependent evaluation of cognitive function and covers many cognitive areas, including specific attention, executive, working memory, conflict monitoring, and visuospatial (Periáñez et al. 2021). Thus, the improvement in cognitive function evaluated based on the Stroop test is valid evidence that curcumin extract can objectively improve the cognitive function of CICI patients, even though the patient's personal perception does feel that cognitive function is worsening.

The group of subjects receiving curcumin extract also experienced improvements in global cognitive function at the end of the treatment period compared to the baseline, as evaluated by MoCA-Ina. MoCa-Ina scores increased by a mean of 1.53 points at the end of the study period and were clinically and statistically significant. However, between group analysis (between group analysis) did not show a significant difference in MoCA-Ina scores between groups receiving curcumin extract compared to placebo, although the treatment group had a higher score of 0.82 points. This has also been predicted by the research team, considering that MoCA-Ina is a dementia evaluation modality that tends to be persistent and multi-domain. While CICI is acute, dynamic, and transient. So the use of MoCA-Ina is considered less sensitive to detect small but significant changes in CICI, for example to assess the therapeutic effect or intervention as carried out in this study. However, the use of the MoCA questionnaire to evaluate CICI has been carried out previously (Kotb et al. 2019) and in this study

a significant improvement in cognitive function was found between before and after treatment with curcumin extract.

Finally, we also noted objective evidence of reduction in neuronal damage, inflammatory and oxidative stress biomarkers. In this study, the administration of curcumin extract significantly reduced median GFAP concentration. GFAP levels correlate with the extent and severity of neuronal damage, thus seeing the serum levels declining post-treatment indicates neuroprotective effects of curcumin extract toward neurons (Amalia 2021; Abdelhak et al. 2022). Curcumin extract administration also dramatically reduced median serum isoprostane levels, whereas the reverse was true for placebo group. Isoprostane is known as a sensitive biomarker for neuronal oxidative stress (Signorini et al. 2018; Sidorova and Domanskyi 2020), therefore its reduction indicates anti-oxidant effect of curcumin against chemotherapy's adverse effects. The latter effect may also correlates with the dramatic reduction of median serum IL-6 levels among treatment group, whereas IL-6 serum levels were found to increase among control group. Curcumin, thus also exerts its anti-inflammatory properties and can be proven on a clinical level. The inflammation and oxidative stress interacts and modulates each other, and curcumin extract seemed to ameliorate both of this events simultaneously.

Based on the results of the analysis of this study, valid evidence was found that the administration of curcumin extract with the new regimen was proven to be safe and effective in improving cognitive function in patients with CICI due to carboplatin-paclitaxel chemotherapy regimen. Currently, there are still several research questions that require answers along with the completion of this interim study, including whether the administration of curcumin extract can maintain the integrity of the cognitive function of subjects receiving chemotherapy, whether the dosage regimen of curcumin extract without interruption of therapy is proven to be more effective in preventing and/or improving CICI, and whether the subject's personal perception of cognitive function and effectiveness in performing daily activities, as well as global evaluation of cognitive function can show significant improvement after long-term administration of curcumin extract.

Conclusion

Administration of curcumin extract with a dose escalation system of 320–400 mg once every 2 weeks during the administration of carboplatin-paclitaxel-based chemotherapy was proven to improve cognitive function of patients with clinical and statistical significance. Administration of curcumin extract with this dosage regimen has also been shown to have a good safety profile.

Acknowledgements Support from Udayana University and Indonesia SOHO Global Health, Ltd. is gratefully acknowledged.

Author contributions AAAPL designed the study, conducted the trial, analyzed the data, and wrote the manuscript. INBM designed the study, conducted the trial, and contributed in writing the final version the manuscript. AS designed the study, conducted the trial, analyzed the data, and wrote the manuscript. AV conducted the trial, analyzed the data, and contributed in writing the final version the manuscript. All authors have read and approved the final manuscript.

Funding This study received grant from Udayana University for the category of invention research (grant no. 303/UN14/HK/2021). The caplet containing curcumin extract and placebo was supported by Indonesia SOHO Global Health, Ltd. (agreement no. 260/SIP-Udayana/Penelitian/IV/2021).

Data availability The data that support the findings of this study are available from the corresponding author, AAAPL, upon reasonable request.

Code availibility Not applicable.

Declarations

Ethics approval This study was a single center, randomized, and double-blind controlled clinical trial. The protocol of this study had been approved by the Ethical Commission of Faculty of Medicine Udayana University with protocol no. LB.02.01/XIV.2.1/7933/2021. This study was conducted by adhering to WMA Helsinki Declaration regarding ethical principal in medical research involving humans as research subjects. All information collected from patients was kept confidential; only the study researchers had access to it.

Conflict of interest A. A. A. Putri Laksmidewi has no conflict of interest. I. Nyoman Bayu Mahendra has no conflict of interest. Andreas Soejitno has no conflict of interest. Aurelia Vania has no conflict of interest.

Consent to participate Written informed consent was obtained from all individual participants included in the study.

Consent for publication Not Applicable.

References

Abd El-Hack ME, El-Saadony MT, Swelum AA et al (2021) Curcumin, the active substance of turmeric: its effects on health and ways

to improve its bioavailability. J Sci Food Agric 101:5747–5762. https://doi.org/10.1002/jsfa.11372
Abdelhak A, Foschi M, Abu-Rumeileh S et al (2022) Blood GFAP as an emerging biomarker in brain and spinal cord disorders. Nat Rev Neurol 18:158–172. https://doi.org/10.1038/s41582-021-00616-3
Aggarwal ML, Chacko KM, Kuruvilla BT (2016) Systematic and comprehensive investigation of the toxicity of curcuminoid-essential oil complex: a bioavailable turmeric formulation. Mol Med Rep 13:592–604. https://doi.org/10.3892/mmr.2015.4579
Akbari S, Kariznavi E, Jannati M et al (2020) Curcumin as a preventive or therapeutic measure for chemotherapy and radiotherapy induced adverse reaction: a comprehensive review. Food Chem Toxicol 145:111699. https://doi.org/10.1016/j.fct.2020.111699
Amalia L (2021) Glial fibrillary acidic protein (GFAP): neuroinflammation biomarker in acute ischemic stroke. J Inflamm Res 14:7501–7506. https://doi.org/10.2147/JIR.S342097
Bell ML, Kenward MG, Fairclough DL, Horton NJ (2013) Differential dropout and bias in randomised controlled trials: when it matters and when it may not. BMJ 346:e8668–e8668. https://doi.org/10.1136/bmj.e8668
Braga PLG, Henrique JS, Almeida SS et al (2022) Factors affecting executive function performance of Brazilian elderly in the Stroop test. Braz J Med Biol Res Rev Bras Pesqui Med Biol 55:e11917. https://doi.org/10.1590/1414-431X2022e11917
Burgess J, Ferdousi M, Gosal D et al (2021) Chemotherapy-induced peripheral neuropathy: epidemiology, pathomechanisms and treatment. Oncol Ther 9:385–450. https://doi.org/10.1007/s40487-021-00168-y
Cardoso CV, de Barros MP, Bachi ALL et al (2020) Chemobrain in rats: behavioral, morphological, oxidative and inflammatory effects of doxorubicin administration. Behav Brain Res 378:112233. https://doi.org/10.1016/j.bbr.2019.112233
Erken N, Dost Gunay FS, Soysal P, Isik AT (2020) The effect of theracurmin on cognitive function in an older patient with chemobrain. Clin Interv Aging 15:691–693. https://doi.org/10.2147/CIA.S252229
Friedman NP, Robbins TW (2022) The role of prefrontal cortex in cognitive control and executive function. Neuropsychopharmacology 47:72–89. https://doi.org/10.1038/s41386-021-01132-0
Kotb MG, Soliman AER, Ibrahim RI et al (2019) Chemotherapy-induced cognitive impairment in hematological malignancies. Egypt J Neurol Psychiatry Neurosurg 55:56. https://doi.org/10.1186/s41983-019-0104-9
Lewandowska A, Rudzki G, Lewandowski T et al (2020) Quality of life of Cancer patients treated with chemotherapy. Int J Environ Res Public Health 17:6938. https://doi.org/10.3390/ijerph17196938
Li M, Caeyenberghs K (2018) Longitudinal assessment of chemotherapy-induced changes in brain and cognitive functioning: a systematic review. Neurosci Biobehav Rev 92:304–317. https://doi.org/10.1016/j.neubiorev.2018.05.019
Liu X, Tonello R, Ling Y et al (2019) Paclitaxel-activated astrocytes produce mechanical allodynia in mice by releasing tumor necrosis factor-α and stromal-derived cell factor 1. J Neuroinflamm 16:209. https://doi.org/10.1186/s12974-019-1619-9
Lv L, Mao S, Dong H et al (2020) Pathogenesis, assessments, and management of chemotherapy-related cognitive impairment (CRCI): an updated literature review. J Oncol 2020:1–11. https://doi.org/10.1155/2020/3942439
Malacrida A, Meregalli C, Rodriguez-Menendez V, Nicolini G (2019) Chemotherapy-induced peripheral neuropathy and changes in cytoskeleton. Int J Mol Sci 20:2287. https://doi.org/10.3390/ijms20092287
Mounier NM, Abdel-Maged AES, Wahdan SA et al (2020) Chemotherapy-induced cognitive impairment (CICI): an overview of etiology and pathogenesis. Life Sci 258:118071. https://doi.org/10.1016/j.lfs.2020.118071
Muthuraman A, Thilagavathi L, Jabeen S et al (2019) Curcumin prevents cigarette smoke extract induced cognitive impairment. Front Biosci (Elite Ed) 11:109–120. https://doi.org/10.2741/E850
Panahi Y, Vahedian-Azimi A, Saadat A et al (2021) The effects of curcumin on the side effects of anticancer drugs in chemotherapy: a randomized controlled trial. Adv Exp Med Biol 1328:255–273. https://doi.org/10.1007/978-3-030-73234-9_17
Pearre DC, Bota DA (2018) Chemotherapy-related cognitive dysfunction and effects on quality of life in gynecologic cancer patients. Expert Rev Qual Life Cancer Care 3:19–26. https://doi.org/10.1080/23809000.2018.1443811
Periáñez JA, Lubrini G, García-Gutiérrez A, Ríos-Lago M (2021) Construct validity of the stroop color-word test: influence of speed of visual search, verbal fluency, working memory, cognitive flexibility, and conflict monitoring. Arch Clin Neuropsychol 36:99–111. https://doi.org/10.1093/arclin/acaa034
Ren X, Boriero D, Chaiswing L et al (2019) Plausible biochemical mechanisms of chemotherapy-induced cognitive impairment (chemobrain), a condition that significantly impairs the quality of life of many cancer survivors. Biochim Biophys Acta Mol Basis Dis 1865:1088–1097. https://doi.org/10.1016/j.bbadis.2019.02.007
Scarpina F, Tagini S (2017) The stroop color and word test. Front Psychol. https://doi.org/10.3389/fpsyg.2017.00557
Schagen SB, Tsvetkov AS, Compter A, Wefel JS (2022) Cognitive adverse effects of chemotherapy and immunotherapy: are interventions within reach? Nat Rev Neurol 18:173–185. https://doi.org/10.1038/s41582-021-00617-2
Sidorova Y, Domanskyi A (2020) Detecting oxidative stress biomarkers in neurodegenerative disease models and patients. Methods Protoc. https://doi.org/10.3390/mps3040066
Signorini C, De Felice C, Galano J-M et al (2018) Isoprostanoids in clinical and experimental neurological disease models. Antioxidants (Basel, Switzerland). https://doi.org/10.3390/antiox7070088
Tan BL, Norhaizan ME (2019) Curcumin combination chemotherapy: the implication and efficacy in Cancer. Molecules 24:2527. https://doi.org/10.3390/molecules24142527
Wefel JS, Kesler SR, Noll KR, Schagen SB (2015) Clinical characteristics, pathophysiology, and management of noncentral nervous system cancer-related cognitive impairment in adults. CA Cancer J Clin 65:123–138. https://doi.org/10.3322/caac.21258
Yi L-T, Dong S-Q, Wang S-S et al (2020) Curcumin attenuates cognitive impairment by enhancing autophagy in chemotherapy. Neurobiol Dis 136:104715. https://doi.org/10.1016/j.nbd.2019.104715
Zeng Y, Cheng AS, Liu X, Chan CC (2017) Cervical cancer survivors' perceived cognitive complaints and supportive care needs in mainland China: a qualitative study. BMJ Open 7:e014078. https://doi.org/10.1136/bmjopen-2016-014078