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A randomized, double-blind, placebo-controlled trial to evaluate the role of curcumin in prostate cancer patients with intermittent androgen deprivation

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Background: The anti-cancer activities of curcumin are well-documented from preclinical studies using prostate cancer models. Our objective was to evaluate the anti-cancer activity of oral curcumin in patients with prostate cancer.

Methods: This randomized, double-blind, placebo-controlled trial was performed on patients with prostate cancer who received intermittent androgen deprivation (IAD). Participants who finished the first on-treatment period of IAD were randomized into a curcumin or placebo group. The patients took oral curcumin (1440 mg/day) or placebo for six months and were followed up until the beginning of the second on-treatment. The primary end-point was duration of the first off-treatment. The secondary end-points were change in PSA and testosterone levels during 6 months, PSA progression rate, and health-related quality of life (HRQOL) scores at 6 months. Safety assessments included adverse event, adverse drug reaction, and serious adverse event.

Results: A total of 97 participants were randomized 1:1 to curcumin ($n = 49$) and placebo ($n = 48$) groups. Among them, 82 patients (84.5%) were evaluable for the analysis (39 and 43 patients in the curcumin and placebo groups, respectively). The median off-treatment duration was 16.3 months (95% confidence interval [CI] 12.3-20.3 months) and 18.5 months (95% CI 12.5-23.0 months) in the curcumin and placebo groups, respectively. There was no significant difference in the curve of off-treatment duration between the two groups ($P = 0.4816$). The proportion of patients with PSA progression during the active curcumin treatment period (6 months) was significantly lower in the curcumin group than the placebo group (10.3% vs 30.2%, $P = 0.0259$). The change of PSA, testosterone levels during 6 months, and HRQOL scores at 6 months were not different between curcumin and placebo groups. Adverse events were higher in the placebo group (16 of 46 vs 7 of 45 patients,

YH Choi and DH Han contributed equally to this study

$P = 0.0349$). No significant differences in the adverse drug reaction were found between the two groups.

Conclusions: Six months' intake of oral curcumin did not significantly affect the overall off-treatment duration of IAD. However, PSA elevation was suppressed with curcumin intake during the curcumin administration period. Curcumin at this dose was well tolerated and safe.

KEYWORDS

curcumin, intermittent androgen deprivation, prostate cancer

1 | INTRODUCTION

Curcumin is a major yellow pigment component of turmeric (*Curcuma longa*), a spice often found in curry powder. It works by blocking cell signaling and inhibiting cell division through specific types of enzymes and growth factors that are directly involved in cancer development.[1] Several studies have shown anti-cancer potential of curcumin against colorectal, pancreatic, breast, prostate, lung, and oral cancers; multiple myeloma; and head and neck squamous cell carcinoma.[2]

The anti-cancer activities of curcumin are well-documented from preclinical studies using prostate cancer models, including its effects on androgen receptor (AR) signaling and numerous downstream targets (eg, VEGF, PTEN, NF-kB).[3–6] Curcumin was shown to down-regulate AR expression, limit AR binding to the androgen response element of the prostate-specific antigen (PSA) gene, and reduce the expression of PSA in LNCaP cells.[7] In our previous study, curcumin (500 mg/kg through oral gavage three times weekly for 4 weeks) was also effective at delaying tumor growth and suppressing AR expression in an LNCaP xenograft model.[8]

The United States Food and Drug Administration has approved curcumin as being generally recognized as safe, and it is now being used as a supplement in several countries.[9] A phase I clinical study demonstrated that oral curcumin is not toxic to humans at doses up to 8000 mg/day for 3 months.[10] In the study by Cruz-Correa et al,[11] patients with Familial Adenomatous Polyposis (FAP) received 1440 mg of curcumin per day for 6 months. The curcumin appeared to reduce the number and size of adenomas, without appreciable toxicity. A randomized, double-blind, controlled study[12] has been performed with patients who underwent prostate biopsies because of elevated PSA level but who had negative findings for prostate cancer. They were randomly assigned to take a supplement containing isoflavones and curcumin (0.1 g/day for 6 months) or placebo daily. This study showed that PSA level decreased in the treatment group with PSA ≥10 ng/mL ($P = 0.01$). These observations provide a rationale for clinical trials with curcumin in patients with prostate cancer. Thus, our study aimed to determine if oral curcumin could inhibit cancer progression in patients with prostate cancer receiving intermittent androgen deprivation therapy (IAD). The primary hypothesis of this study is that the off-treatment interval can be prolonged when the curcumin is administered during the first androgen deprivation therapy (ADT) withdrawal period. We evaluated the anti-cancer activity of curcumin by comparing the duration of off-treatment periods in a treated group versus a placebo group.

2 | PATIENTS AND METHODS

2.1 | Study participants

This randomized, double-blind, placebo-controlled trial included prostate cancer patients who were managed with IAD for the treatment of (i) biochemical recurrence (BCR) after localized treatments (eg, radical prostatectomy, radiation therapy, and high intensity focused ultrasound) or (ii) metastatic prostate cancer at initial diagnosis. In this study, all participants were treated with an LHRH agonist and anti-androgens for at least 6 months, and entered the ADT withdrawal (off-treatment) period after a minimum of 3 months of maintenance at the stable PSA nadir level. The exclusion criteria were previous IAD for prostate cancer, hypersensitivity to curcumin, previous treatment with dietary supplements containing curcumin or turmeric to treat or prevent prostate cancer in the 6 months prior to participating in the study, and serious medical or psychological conditions (including impaired liver, kidney, cardiac, and hematopoietic functions) aside from prostate cancer.

2.2 | Study design

Patients were randomized 1:1 to placebo or curcumin (240 mg of curcuminoid powder in capsule form), which was administered as two capsules, three times a day (1440 mg/day), for 6 months from the beginning of ADT withdrawal. The dose was determined from a published study that evaluated the efficacy of curcumin (1440 mg/day for 6 months) to reduce adenomas in patients with FAP.[11] After a pilot study in ten patients, we finally determined the dose of curcumin in this study. Randomization was stratified by type of ADT (BCR or metastasis) and performed through a random permuted block design. All patients visited once a month and had their blood testosterone and PSA levels measured for 6 months. After that, patients participated in follow-up regularly every 3 months until ADT was required again or up to 36 months.

The Institutional Review Board of Samsung Medical Center (IRB no. 2007-06-068) had previously approved the protocol, and all patients provided written informed consent before study enrollment. This study was conducted in accordance with the Declaration of Helsinki and registered with ClinicalTrials.gov (no. NCT03211104).

2.3 | Efficacy and safety evaluations

The primary end-point was duration of off-treatment, defined as the period from the start of ADT withdrawal until the restart of ADT. ADT was resumed when the patient progressed clinically or had a PSA above a predetermined threshold (BCR: PSA > 4.0 ng/mL; metastatic prostate cancer: PSA > 20 ng/mL or 50% increase over the nadir).

The secondary end-points were change from baseline in the PSA and testosterone levels during the 6 months of the curcumin treatment period. Additional end-points included the PSA progression rate and health-related quality of life (HRQOL) scores at 6 months. PSA progression was defined as a 25% increase from the baseline value along with an increase of 2 ng/mL or more in the absolute value during the off-treatment period.[13] The HRQOL was assessed using the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire, the International Prostate Symptom Score (IPSS) questionnaire, and the International Index of Erectile Function (IIEF-15) questionnaire. HRQOL assessments were performed at baseline and 6-month. The FACT-P is scored as a total summary score of five domain scores (Physical well-being, Social/Family well-being, Emotional well-being, Functional well-being, and Additional concerns), with lower scores indicating better HRQOL.[14] The IPSS consists of seven questions concerning urinary symptoms and one question concerning quality of life; lower scores reflect better HRQOL. The IIEF consists of 15 questions that examine the four main domains of male sexual function: erectile function, orgasmic function, sexual desire, and intercourse satisfaction; higher scores reflect better HRQOL.

Safety measurements included adverse events (AE), adverse drug reactions (ADR), and serious adverse events (SAE). All AEs and SAEs were classified in accordance with the Common Terminology Criteria for Adverse Events, Version 3.0. Safety measurements were assessed every month until the 6-month time point and then every 3 months until the final follow-up. Vital signs and laboratory test data were recorded every 3 months.

2.4 | Statistical analysis

The full analysis set (patients with drug compliance greater than 70% at each visit and whose primary end-point was available) was used for the efficacy analyses, and the safety population (patients who ingested the test food more than once after randomization) was used for the safety analyses. Assuming the median duration of off-treatment in placebo group of 5.8 months[15] and expecting of 11.6 months in curcumin group, 48 patients in each group were required to detect the statistical significance under the 80% power and the 5% significance level in the study with 18 months accrual duration, 36 months additional follow up period and 15% drop out rate. The distribution of the time to retreatment was assumed to follow exponential distribution. The off-treatment free curve and median time of retreatment were estimated using Kaplan-Meier method. Off-treatment free curves between the two groups were compared using log-rank test. Continuous variables were described with mean ± standard deviation or median (interquartile range: IQR) and compared between the two groups with a *t*-test or a Mann-Whitney test according to normality. Categorical variables were summarized as frequency (percentage) and compared between the two groups with a chi-squared test or a Fisher's exact test. For the ordinal variable, median (IQR) was presented and Mann-Whitney test was used for comparison between the two groups. When necessary, Bonferroni's correction was applied to the results. For all adverse events, the number and proportion of patients that developed the adverse event, and the number of cases were provided in a table. They were also organized according to severity and the causal relationship with the curcumin.

3 | RESULTS

3.1 | Demographic and baseline characteristics

The intention to treat population consisted of 97 patients, of whom 49 were randomized to the curcumin group and 48 to the placebo group. Of these patients, 82 (84.5%) were evaluable for the analysis (39 and 43 patients were evaluable in the curcumin and placebo groups (full analysis set), respectively) and 17 (17.5%) did not complete this study protocol (Figure 1). No patients were discontinued due to AEs. The baseline characteristics were balanced between the treatment groups, with a slightly higher PSA at diagnosis in the curcumin group. There were no differences in age, body mass index, PSA, testosterone, or duration for ADT between the groups (Table 1).

3.2 | Off-treatment duration

There was no significant difference in the curve of off-treatment duration between the two groups ($P = 0.4816$, log-rank test, Figure 2). The median off-treatment duration was 16.3 months (95% confidence interval [CI] 12.3 months—20.3 months) and 18.5 months (95% CI 12.5 months—23.0 months) in the curcumin and placebo groups, respectively. No significant differences in curves of off-treatment duration were found in subgroup analysis by reason for ADT (metastatic prostate cancer group [18.6 months vs 19.3 months; $P = 0.824$, log-rank test with Bonferroni's correction] and BCR group [12.8 months vs 14.2 months; $P = 1.0000$, log-rank test with Bonferroni's correction]).

3.3 | Change from baseline in PSA and testosterone levels

The changes of PSA and testosterone levels were not significantly different between the curcumin and placebo groups during the 6 months of the active study drug administration period (Table 2). The proportion of patients with PSA progression during the active curcumin treatment period was significantly lower in the curcumin

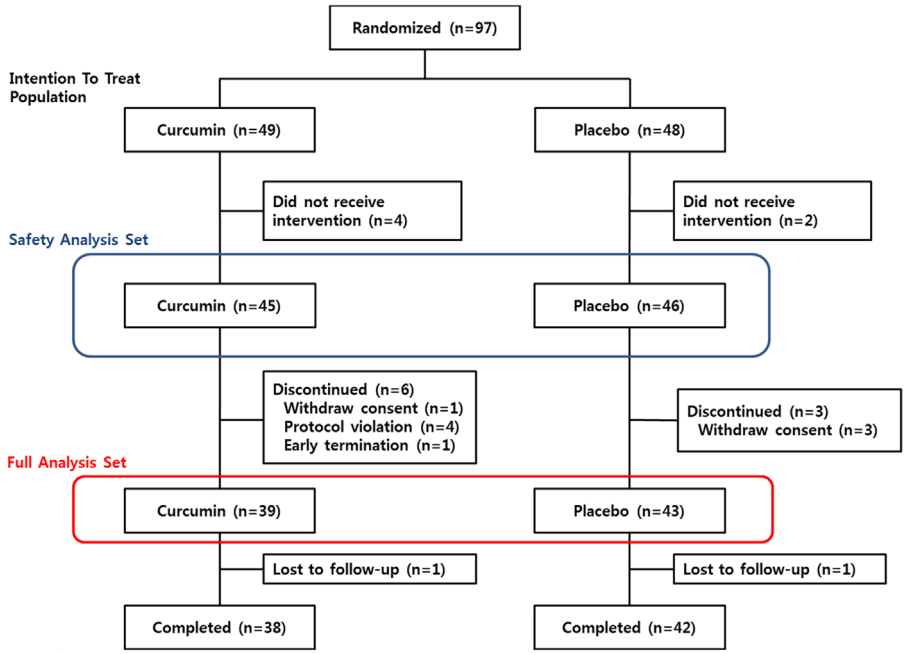

FIGURE 1 Flow diagram of study. [Color figure can be viewed at wileyonlinelibrary.com]

group than in the placebo group (10.3% vs 30.2%, chi-squared test, $P = 0.0259$, Figure 3). However, there was no statistically significant difference in the subgroup analysis (metastatic prostate cancer group, 10.5% vs 42.1%, $P = 0.0542$; BCR group, 10.0% vs 20.8%, $P = 0.8560$, with Bonferroni's correction).

3.4 | Health-related quality of life

Patients experienced poor HRQOL at baseline, as was reflected by the high FACT-P and low IIEF-15 total summary scores (Table 3). Compared with the placebo group, there were no significant differences in the FACT-P and IIEF-15 total summary scores in the curcumin group at 6 months (Table 3). The IPSS total and QOL scores were also not significantly different between the two groups at 6 months.

3.5 | Safety

There were seven (15.6%) of 45 patients who had AEs in the curcumin group and 16 (34.8%) of 46 patients in the placebo group. The difference was statistically significant ($P = 0.0349$). There were no grade ≥3 AEs in the curcumin group, but one male patient in the placebo group had grade 3, pleural effusion. There was no probable or definite relationship with curcumin intake. The most common symptom was urinary frequency (4 cases), and all cases were mild. In the curcumin group, one case of incontinence, an SAE, was reported.

TABLE 1 Baseline demographics and characteristics of the study participants

Characteristics	Curcumin ($n = 39$)	Placebo ($n = 43$)	*P*-value
Age, years, Mean ± Standard deviation	71.5 ± 9.0	72.9 ± 6.0	0.3990[a]
BMI, kg/m^2, Mean ± Standard Deviation	24.3 ± 3.3	24.5 ± 2.9	0.8260[a]
PSA at diagnosis, ng/mL, Median (IQR)	22.4 (11.2-44.0)	17.5 (9.0-55.5)	0.8560[b]
Duration of ADT, month, Median (IQR)	9.8 (8.2-16.1)	9.8 (8.8-14.6)	0.8060[b]
Reason for ADT, *n* (%)			
MetastaticPCa	19 (48.7)	19 (32.6)	0.8620[c]
BCR	20 (51.3)	24 (67.4)	
PSA at study entry, ng/mL, Median (IQR)	0.0 (0.0-0.1)	0.0 (0.0-0.1)	0.6980[b]
Testosterone at study entry, ng/mL, Median (IQR)	0.1 (0.1 -0.1)	0.1 (0.1-0.1)	0.0860[b]

ADT, androgen deprivation therapy; BCR, biochemically recurrence; BMI, body mass index; IQR, interquartile range; PSA, prostate specific antigen.
[a]*P*-values based on *T*-test.
[b]Wilcoxon rank sum test.
[c]Chi-square test.

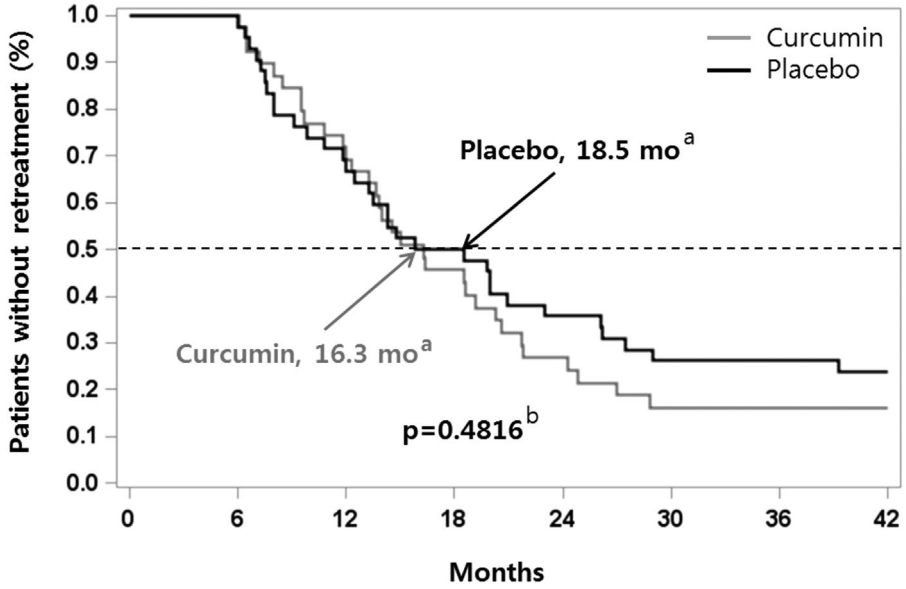

FIGURE 2 Event-free curves (event = retreatment) and median off-treatment duration. Event-free curves were estimated using Kaplan-Meier method[a] and compared using log-rank test[b]

This patient had the chest tube inserted due to dyspnea symptoms. Details about AEs, ADRs, and SAEs are summarized in Table 4. No significant differences in the frequencies of ADRs and SAEs were found between the two groups. In addition, no clinically significant differences in the vital signs or the clinical test parameters at 3 and 6 months after initiation of curcumin administration were found between the two groups. There was no discontinuation due to AEs.

4 | DISCUSSION

This study is one of the largest randomized, placebo-controlled studies performed to date in patients with prostate cancer who were managed with curcumin. And it is the first clinical trial to evaluate the anti-cancer effect of curcumin alone in prostate cancer. The results demonstrate that treatment with oral curcumin (1440 mg/day for 6 months) was well tolerated and safe. However, curcumin administration does not significantly affect overall off-treatment duration of IAD. Although this study failed to show the difference of the off-treatment duration in the curcumin group, it seems to be valuable because it is the first clinical trial to evaluate the anti-cancer effect of a curcumin alone in prostate cancer.

During the initial 6 months of the current study in which curcumin was administered, PSA progression rate was significantly lower than in the control group without any other significant changes (10.3% vs 30.2%, $P = 0.0259$). Although oral curcumin lowered PSA levels, it did not contribute to changes in clinical outcomes. Two additional trials have evaluated the effect of curcumin on PSA progression in men with prostate cancer. In the first of these studies, reported by Thomas et al, 199 patients under active surveillance or watchful waiting for localized prostate cancer were randomized to receive a polyphenol-rich food supplement that contained a blend of pomegranate, green tea, broccoli, and turmeric (Curcuma longa), or placebo for 6 months.[16] The increase in PSA was significantly lower in the food supplement group than in the placebo group (14.7% vs 78.5%, $P = 0.0008$). However, the results of this study make it difficult to contribute to our understanding of the efficacy of curcumin in patients with prostate cancer. They reported changes in PSA levels rather than changes in PSA doubling times used by other studies.[17–19] In addition, the food supplement mainly consisted of polyphenol-rich compounds other than curcumin. Another phase II trial also reported results similar to those of our study. In that study, docetaxel and curcumin combination therapy showed a high PSA response rate (59%) in patients with castration-resistant prostate cancer (CRPC) even though there was no control group.[20]

There might be several reasons why this study failed to show the difference of the off-treatment duration in the curcumin group. In this study, the duration of curcumin administration was determined by referring to two previous studies performed under different clinical

TABLE 2 Change from baseline in PSA and testosterone level between curcumin versus placebo

	PSA (ng/mL)			Testosterone (ng/mL)		
	Curcumin ($n = 39$)	Placebo ($n = 43$)	*P*-value	Curcumin ($n = 39$)	Placebo ($n = 43$)	*P*-value
Baseline	0.0 (0.0-0.1)	0.0 (0.0-0.1)		0.1 (0.1-0.1)	0.1 (0.1-0.1)	
Month 6	0.54 (0.13-1.26)	0.34 (0.1-2.91)		2.88 (1.16-3.94)	2.98 (1.98-4.82)	
Change	0.52 (0.07-1.06)	0.32 (0.08-2.85)	0.7592	2.7 (1.11-3.7)	2.85 (1.87-4.75)	0.1599

PSA, prostate specific antigen. Data for continuous variables are presented as median (interquartile range). *P*-values based on Mann-Whitney test.

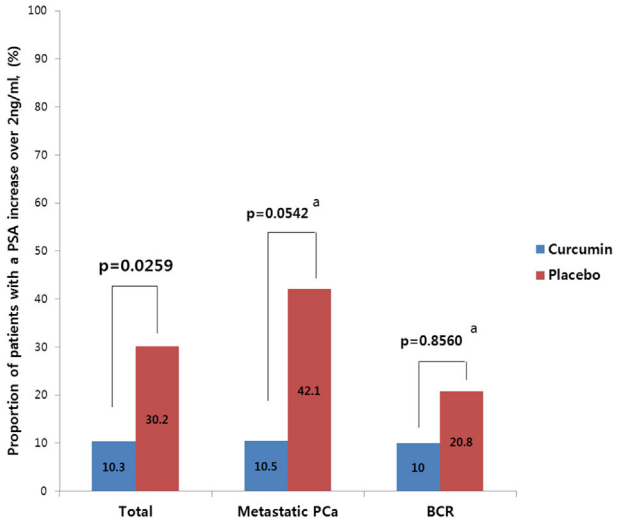

FIGURE 3 The proportion of patients with PSA increased by more than 2 ng/mL during the 6 months of the curcumin treatment period. BCR, biochemical recurrence; PCa, prostate cancer. *P*-values based on Chi-square test (total, metastatic PCa) and Fisher's exact test (BCR)[a] with Bonferroni's correction due to subgroup analysis. [Color figure can be viewed at wileyonlinelibrary.com]

conditions.[11,12] In those studies, 6-month administration of oral curcumin had clinically significant effects on the patients. In the current study, although PSA progression was significantly lower in the curcumin group during the initial 6 months, it showed no difference in the overall off-treatment time between two groups. It might be related with the much longer off-treatment time after relatively short curcumin administration period. If curcumin had been administered for a longer time, significant changes could have been observed in the off-treatment time.

Another possible reason to fail to show the difference of primary endpoint is the relatively low dose of oral curcumin to affect clinical outcomes. In the current study, the dose of curcumin was determined from a published study in which curcumin was administered for 6 months.[11] Sharma et al performed a phase II dose escalation study in 15 patients with advanced colorectal cancer.[21] In that study, the highest daily dose (3.6 g) changed biologic markers dramatically and was recommended because there was no dose-limiting toxicity. In another clinical trial, 6000 mg/day of curcumin was used for 7 days every cycle with docetaxel in CRPC patients.[20] During the six cycles, the regimen was well tolerated, and there was no adverse event related with curcumin. However, a higher dose of curcumin should be considered more carefully for clinical use. A phase II trial evaluated the efficacy of curcumin in combination with gemcitabine against advanced pancreatic cancer.[22] Seventeen patients received 8000 mg/day of curcumin orally for 4 weeks. However, 29% of patients discontinued curcumin due to intractable abdominal fullness or pain, and 12% of patients reduced the dose of curcumin to 4000 mg/day because of abdominal complaints.

In this study, treatment with curcumin (1440 mg/day for 6 months) was well tolerated and safe. The curcumin group had fewer overall AEs (15.6% vs 34.8%, $P = 0.0349$). And none of the patients had AEs with grade 3 or higher. In one patient, there was an SAE in the curcumin group that was not related to curcumin ingestion. That patient underwent artificial urinary sphincter placement for post-prostatectomy incontinence. Based on several human studies,[2,21,23–26] the nontoxicity, safety, and tolerability of curcumin at doses up to 8 g/day are well established. However, there are some AEs including diarrhea, nausea, and skin rashes and an increase in serum lactate dehydrogenase and alkaline phosphatase. These are believed to occur in response to high doses.[27] Curcumin is also an active iron chelator causing iron deficiency anemia in mice. This makes it ineffective in

TABLE 3 FACT-P, IPSS total, IPSS QoL, and IIEF-15 total scores between curcumin versus placebo in baseline and 6-month

	Curcumin (*n* = 39)	Placebo (*n* = 43)	*P*-value
FACT-P (Total)			
Baseline	121.0 (99.0-138.1)	113.7 (102.0-129.3)	0.9590
Month 6	113.3 (98.0-138.6)	115.2 (103.5-135.0)	0.7401
IPSS (Total)			
Baseline	11.0 (7.0-18.5)	12.0 (11.0-15.0)	0.6600
Month 6	12.0 (7.0-18.0)	12.5 (11.0-17.0)	0.8125
IPSS (QoL)			
Baseline	2.0 (2.0-3.0)	2.0 (2.0-3.0)	0.6890
Month 6	2.0 (2.0-3.0)	2.0 (2.0-3.0)	0.3857
IIEF-15 (Total)			
Baseline	5.0 (5.0-7.0)	5.0 (5.0-7.0)	0.9795
Month 6	5.0 (5.0-7.0)	5.0 (5.0-7.0)	0.8035

FACT-P, functional assessment of cancer therapy-prostate; IPSS, International Prostate Symptom Score; QoL, quality of life; IIEF-15, international index of erectile function-15. Data for continuous variables are presented as median (interquartile range). *P*-values based on Mann-Whitney test.

TABLE 4 Summary of the adverse events, adverse drug reactions, and serious adverse events in the safety population

	Curcumin (% of 45)	Placebo (% of 46)	*P*-value	Severity	Relationship
Adverse events	7 (15.6%)	16 (34.8%)	0.0349		
Gastrointestinal					
Diarrhea	0	1		Mild	Unrelated
Gastrointestinal ulcer	0	1		Mild	Unrelated
Melena	1	0		Mild	
Others					
Incontinence	1[a]	1[b]		Moderate[a]/ Mild[b]	Unrelated
Urinary discomfort	0	1		Mild	Unrelated
Urinary frequency	2	2		Mild	Unrelated
Urinary hesitancy	1	0		Mild	Unrelated
Chest discomfort	1	0		Mild	Unrelated
Cold sweat	0	1		Moderate	Unrelated
Dyspnea	0	1		Mild	Unrelated
Diplopia	0	1		Mild	Unrelated
Eye discomfort	0	1		Mild	Unrelated
Flushing	0	1		Mild	Unrelated
Hand numbness	0	1		Mild	Unrelated
Hypertension	0	1		Mild	Unrelated
Mild cognitive impairment	0	1		Mild	Unrelated
Palpitation	1	0		Mild	Unrelated
Pleural effusion	0	1		Severe	Unrelated
Triglyceride level elevation	0	1		Mild	Unrelated
Adverse drug reactions	1 (2.2%)	1 (2.2%)	1.0000		
Constipation	1	0		Mild	Possible
Diarrhea	0	1		Mild	Possible
Serious adverse events	1 (2.6%)	3 (7.0%)	0.6174		
Abdomen pain	0	1		Severe	Unrelated
Appendicitis	0	1		Severe	Unrelated
Incontinence	1	0		Severe	Unrelated
Right ICA stenosis	0	1		Severe	Unrelated

ICA, internal carotid artery. Severity: mild, moderate, severe, life threatening or disabling, death. Relationship defined as definite, probable, possible, unrelated, or unknown. One patient had moderate urinary incontinence[a] in the curcumin group, and one had a mild urinary incontinence[b] in the placebo group.

people with suboptimal iron levels.[28] In our study, there was no discontinuation or administration delay due to study drug. Therefore, toxicities of curcumin did not appear to be a limitation of this clinical trial.

One limitation of this study is that the subjects included two groups of patients with different clinical situation of prostate cancer; one is BCR after localized treatments, and the other is metastatic disease. However, all the patients were receiving ADT and well controlled. The inclusion criteria were designed based on a stable PSA nadir over 3 months under ADT. The groups had similar baseline characteristics including baseline PSA.

5 | CONCLUSIONS

A 6-month intake of oral curcumin (1440 mg/day) did not significantly affect overall off-treatment duration of IAD. However, PSA elevation was suppressed with curcumin intake during the 6 months of active curcumin treatment period. Curcumin at this dose was well tolerated and safe. These results suggest that curcumin has potential beneficial effects in patients with prostate cancer although it has not demonstrated a clinically valid change. A larger clinical study with a longer duration of curcumin may elucidate this potential role of curcumin in patients with prostate cancer.

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CONFLICTS OF INTEREST

The authors have stated that they have no conflicts of interest, including any financial or personal relationships with other people or organizations that could inappropriately influence their work.

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REFERENCES

1. Shehzad A, Lee J, Lee YS. Curcumin in various cancers. *Biofactors*. 2013;39:56–68.
2. Gupta SC, Patchva S, Aggarwal BB. Therapeutic roles of curcumin: lessons learned from clinical trials. *AAPS J*. 2013;15:195–218.
3. Wei X, Du ZY, Cui XX, et al. Effects of cyclohexanone analogues of curcumin on growth, apoptosis and NF-kappaB activity in PC-3 human prostate cancer cells. *Oncol Lett*. 2012;4:279–284.
4. Du Y, Long Q, Zhang L, et al. Curcumin inhibits cancer-associated fibroblast-driven prostate cancer invasion through MAOA/mTOR/HIF-1alpha signaling. *Int J Oncol*. 2015;47:2064–2072.
5. Jordan BC, Mock CD, Thilagavathi R, Selvam C. Molecular mechanisms of curcumin and its semisynthetic analogues in prostate cancer prevention and treatment. *Life Sci*. 2016;152:135–144.
6. Zhou DY, Zhao SQ, Du ZY, Zheng XI, Zhang K. Pyridine analogues of curcumin exhibit high activity for inhibiting CWR-22Rv1 human prostate cancer cell growth and androgen receptor activation. *Oncol Lett*. 2016;11:4160–4166.
7. Teiten MH, Gaascht F, Eifes S, Dicato M, Diederich M. Chemopreventive potential of curcumin in prostate cancer. *Genes Nutr*. 2010;5:61–74.
8. Hong JH, Lee G, Choi HY. Effect of curcumin on the interaction between androgen receptor and Wnt/beta-catenin in LNCaP xenografts. *Korean J Urol*. 2015;56:656–665.
9. Goel A, Jhurani S, Aggarwal BB. Multi-targeted therapy by curcumin: how spicy is it?. *Mol Nutr Food Res*. 2008;52:1010–1030.
10. Cheng AL, Hsu CH, Lin JK, et al. Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions. *Anticancer Res*. 2001;21:2895–2900.
11. Cruz-Correa M, Shoskes DA, Sanchez P, et al. Combination treatment with curcumin and quercetin of adenomas in familial adenomatous polyposis. *Clin Gastroenterol Hepatol*. 2006;4:1035–1038.
12. Ide H, Tokiwa S, Sakamaki K, et al. Combined inhibitory effects of soy isoflavones and curcumin on the production of prostate-specific antigen. *Prostate*. 2010;70:1127–1133.
13. Scher HI, Halabi S, Tannock I, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. *J Clin Oncol*. 2008;26:1148–1159.
14. Hong JH, Jeon SS, Lee HM, Choi YH, Kim S, Choi HY. The Functional Assessment of Cancer Therapy-Prostate (FACT-P) scales in men with prostate cancer: reliability and validity of the Korean version. *J Korean Med Sci*. 2006;21:295–299.
15. Park CM, Jeon SS, Choi HY. Improved Quality of Life (QOL) During the Off-treatment Intervals of the Intermittent Androgen Deprivation (IAD) in the Prostate Cancer Patients. *Korean J Urol*. 2000;41:1063–1070.
16. Thomas R, Williams M, Sharma H, Chaudry A, Bellamy P. A double-blind, placebo-controlled randomised trial evaluating the effect of a polyphenol-rich whole food supplement on PSA progression in men with prostate cancer-the U.K. NCRN Pomi-T study. *Prostate Cancer Prostatic Dis*. 2014;17:180–186.
17. Pantuck AJ, Leppert JT, Zomorodian N, et al. Phase II study of pomegranate juice for men with rising prostate-specific antigen following surgery or radiation for prostate cancer. *Clin Cancer Res*. 2006;12:4018–4026.
18. Paller CJ, Ye X, Wozniak PJ, et al. A randomized phase II study of pomegranate extract for men with rising PSA following initial therapy for localized prostate cancer. *Prostate Cancer Prostatic Dis*. 2013;16:50–55.
19. Pantuck AJ, Pettaway CA, Dreicer R, et al. A randomized, double-blind, placebo-controlled study of the effects of pomegranate extract on rising PSA levels in men following primary therapy for prostate cancer. *Prostate Cancer Prostatic Dis*. 2015;18:242–248.
20. Mahammedi H, Planchat E, Pouget M, et al. The new combination docetaxel, prednisone and curcumin in patients with castration-resistant prostate cancer: a pilot phase II study. *Oncology*. 2016;90:69–78.
21. Sharma RA, Euden SA, Platton SL, et al. Phase I clinical trial of oral curcumin: biomarkers of systemic activity and compliance. *Clin Cancer Res*. 2004;10:6847–6854.
22. Epelbaum R, Schaffer M, Vizel B, Badmaev V, Bar-Sela G. Curcumin and gemcitabine in patients with advanced pancreatic cancer. *Nutr Cancer*. 2010;62:1137–1141.
23. Dhillon N, Aggarwal BB, Newman RA, et al. Phase II trial of curcumin in patients with advanced pancreatic cancer. *Clin Cancer Res*. 2008;14:4491–4499.
24. Bayet-Robert M, Kwiatkowski F, Leheurteur M, et al. Phase I dose escalation trial of docetaxel plus curcumin in patients with advanced and metastatic breast cancer. *Cancer Biol Ther*. 2010;9:8–14.
25. Sharma RA, McLelland HR, Hill KA, et al. Pharmacodynamic and pharmacokinetic study of oral Curcuma extract in patients with colorectal cancer. *Clin Cancer Res*. 2001;7:1894–1900.
26. Carroll RE, Benya RV, Turgeon DK, et al. Phase IIa clinical trial of curcumin for the prevention of colorectal neoplasia. *Cancer Prev Res (Phila)*. 2011;4:354–364.
27. Shehzad A, Lee J, Lee YS. Curcumin in various cancers. *Biofactors*. 2013;39:56–68.
28. Shehzad A, Qureshi M, Anwar MN, Lee YS. Multifunctional curcumin mediate multitherapeutic effects. *J Food Sci*. 2017;82:2006–2015.

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