

Decreased biochemical progression in patients with castration-resistant prostate cancer using a novel mefenamic acid anti-inflammatory therapy: A randomized controlled trial

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Abstract. Prostate cancer (PCa) is the second most common non-dermatological cancer in men and is a growing public health problem. Castration-resistant disease (CRD) is the most advanced stage of the disease and is difficult to control. Patients with CRD may no longer accept conventional therapies as they are not in appropriate clinical conditions or they refuse to receive it. Given that inflammation is an essential component of CRD origin and progression, anti-inflammatory agents could be a therapeutic option with fenamates as one of the proposed choices. A prospective, randomized, double-blinded, 2-arm, parallel group, phase II-III clinical trial was performed involving 20 patients with CRD-PCa (with a prostate specific antigen level <100 ng/ml) that were undergoing androgen deprivation therapy (ADT) and did not accept any established treatment for that disease stage. In addition to ADT, 10 patients received placebo and 10 received mefenamic acid (500 mg orally every 12 h) for 6 months. The primary endpoint was the change in serum prostate-specific antigen (PSA) at 6 months. The PSA levels decreased significantly with mefenamic acid (an average 42% decrease), whereas there was an average 55%

increase in the placebo group (P=0.024). In the patients treated with the placebo, 70% had biochemical disease progression (an increase of $\geq 25\%$ in PSA levels), which did not occur in any of the patients treated with mefenamic acid (relative risk=0.12; 95% confidence interval, 0.01-0.85; P=0.033). There was a significant increase in quality of life (EQ-5D-5L score) and body mass index (BMI) with the experimental treatment. In conclusion, mefenamic acid administration decreased biochemical progression in patients with castration resistant PCa, improved their quality of life and increased their BMI. Future studies are required in order to strengthen the findings of the present clinical trial. Trial registration, Cuban Public Registry of Clinical Trials Database RPCEC00000248, August 2017.

Introduction

Cancer is one of the leading causes of mortality in a number of high-income countries (1). Prostate cancer (PCa) is the second most common non-dermatological cancer in men (2-5). Based on the 2018 GLOBOCAN estimates, the age-standardized incidence rate was 29.3 per 100,000 standard population, with 1,276,106 new cases registered worldwide (3). Prostate cancer incidence rates are highly variable, with the highest incidence rates having been reported in Oceania (79.1 per 100,000 standard population), followed by North America (73.7) and Europe (62.1) (3,4). PCa is categorized as an androgen-dependent neoplasia (3). Thus, androgen deprivation therapy (ADT) is a commonly prescribed treatment that decreases androgens, such as testosterone to castration levels in an attempt to slow tumor progression and improve overall survival time in men (6). Half of all men with PCa receive ADT at some stage

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following diagnosis (7). When PCa cells acquire the capacity to proliferate without androgens, ADT becomes ineffective and the transition is termed castration-resistant disease (CRD) (8). Bone metastases are present in 90% of patients with CRD and can produce significant morbidity, including pain, pathological fractures, spinal cord compression and bone marrow failure (9). Paraneoplastic effects due to bone metastases in patients with CRD are also common, such as anemia, weight loss, fatigue, hypercoagulability and increased susceptibility to infection (9).

Radiotherapy and/or chemotherapy are treatment options that can increase the life expectancy of patients with CRD-PCa (10-12); however, they are aggressive treatments that decrease physical independence and can increase weight loss (13-18). Mortality in patients with CRD-PCa has been reported at a median follow-up period of 41 months, generally with a poor quality of life during the last months of life (19). Certain patients with CRD possess adequate knowledge of disease prognosis and the associated consequences, and thus decline the standard treatment and adopt an approach of only taking symptomatological treatment. In these instances, patient autonomy prevails, defined as having the ability to make a rational decision based on the personal understanding of his or her future, and supported by his or her own values (20). The healthcare provider is obligated to respect patient autonomy, if the law does not dictate otherwise.

New treatments, such as those with abiraterone or enzalutamide have shown therapeutic success in metastatic CRD-PCa, although this remains limited (21). Therefore, complementary treatments can still be researched, which can increase the anti-tumor effect of the implemented therapies or can provide an alternative for patients that are not candidates for conventional therapies (22,23). Anti-inflammatory agents are currently being investigated as a treatment option in different types of neoplasia, such as lung, cervix, ovarian, colon and gastric cancer (24). Inflammation is observed in numerous pathologies, and the current available data demonstrate that it is a critical component in the origin, proliferation and dissemination of different types of cancer, including PCa (25). In PCa, there is evidence of inflammation in the processes of DNA damage, tumor progression and tumor expansion. Hence, sustained use of nonsteroidal anti-inflammatory drugs (NSAIDs) have been proposed as a mechanism that may retard PCa disease progression by decreasing the inflammatory response in PCa cells (25). Observational studies have revealed that NSAIDs are associated with a lower risk of developing PCa (25) and a lower risk of progression to high-grade PCa (26,27), resulting in different NSAIDs being postulated for the treatment of PCa. Clinical trials have been performed with certain NSAIDs (celecoxib, ibuprofen and indomethacin) (5,28), with unsatisfactory results, upon analyzing endpoints such as PSA levels, tumor size or overall survival time (29,30).

Preclinical *in vitro* and *in vivo* (xenograft nude mouse model) studies in PCa have demonstrated that the fenamate NSAIDs have a more notable antineoplastic effect compared with previously examined NSAIDs in PCa (31). Mefenamic acid and meclofenamate demonstrate this type of antitumor effect (31). Notably, in a preclinical study, mefenamic acid, a freely sold NSAID whose everyday use is for dysmenorrhea, had a cytotoxic effect on PCa cells at concentrations that can be feasibly achieved in human plasma (31). To the best of our

knowledge, the antineoplastic use of a fenamate in humans has not yet been investigated due to advanced tumor stages of PCa, higher PSA levels and weight loss being associated with poor quality of life in patients (32,33). The aforementioned variables provide the rationale for the evaluation of the usefulness of new treatment options in PCa. In the present study the therapeutic effects of mefenamic acid on PSA levels, weight loss and quality of life were investigated in patients with CRD-PCa, who were either not candidates for standard therapy or had declined it.

Patients and methods

Study design. A prospective, double-blinded, 2-arm, controlled, randomized phase II-III clinical trial was conducted between August 2017 and March 2019. The study was performed according to the CONSORT statement guidelines for randomized controlled trials (34).

The National Commission on Scientific Research (Central Ethics Committee) of the Mexican Social Security Institute (IMSS; Colima, Mexico) approved the present study. Written informed consent was obtained from all participants. The present clinical trial was registered as MEFEPROST: RPCEC00000248 in the Cuban Public Registry of Clinical Trials (RPCEC) Database (<http://rpcec.sld.cu>). The RPCEC trial registration dataset is part of the International Clinical Trials Platform Registry database, as established by the World Health Organization and the International Committee of Medical Journal Editors.

Study subjects. A total of 46 subjects for the present clinical trial were recruited from the General Hospital Zone 1 of the IMSS and the Cancerology State Institute of the Health Department of the State of Colima (Colima, Mexico).

The following inclusion criteria were used in the present study: Male patients of any age with a histological diagnosis of prostate cancer; patients presenting with CRD according to the Prostate Cancer Clinical Trial Working Group 3 (35), who by their own decision or the clinical opinion of their treating physician, were not candidates for taxane chemotherapy or any other standard first-line treatment for that type of patient; patients whose PSA levels were at stages 1-3 of the D'Amico Risk Classification (1-100 ng/ml) (36); patients undergoing ADT prior to recruitment that was maintained under the treating physician's judgment, during the 6 months of follow-up; patients with an Eastern Cooperative Oncology Status functional status of 0-2 (37) and patients with no history of hepatic impairment (any of the Child-Pugh classification stages) (38) or renal impairment with creatinine clearance >60 ml/min.

The following exclusion criteria were used in the present study: Diagnosis of a second primary cancer; uncontrolled diabetes or high blood pressure; leukocytes <3,000 cells/ μ l, or a platelet count <10,000 cells/ μ l; leukocytes >100,000 cells/ μ l or evidence of systemic infection according to the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) (39); blood hemoglobin <9 g/dl; alcoholism and/or drug addiction; gastrointestinal ulcer; inflammatory bowel disease; diagnosis of ischemic heart disease; chronic heart failure and other pathologies at the discretion of the researcher.

The following elimination criteria were used in the present study: Patients that voluntarily abandoned the study; patients that, at some point during the study, presented with severe toxicity (grade ≥ 3) (40), according to the common terminology criteria for adverse events (CTCAE v4.0; U.S. Department of Health and Human Services) attributable to the administration of the experimental medication (mefenamic acid); and patients in whom the treating physician suspended the experimental medication for >2 weeks, regardless of the origin of the adverse event.

Following the application of all the inclusion, exclusion and elimination criteria, 20 patients (57-81 years) were randomized for the present clinical trial. The 6-month intervention consisted of two delivery arms, one with patients receiving mefenamic acid ($n=10$) and the other with patients receiving placebo ($n=10$). All patients continued to receive ADT, through the administration of gonadotropin-releasing hormone agonists (leuprolide and goserelin), oral antiandrogens (flutamide and bicalutamide) or through bilateral orchiectomy. The two study groups consisted of one group that took a 500 mg pill of mefenamic acid every 12 h for 6 months, and another group that took a sugar placebo pill every 12 h for the same length of time. The pills were recommended to be taken with meals or milk in order to decrease the risk of adverse gastrointestinal events. All patients took one tablet of 20 mg omeprazole daily during the study period to prevent severe acute NSAID-associated gastroduodenal damage.

The treating physician was blinded to the study group the patient belonged to and could prescribe additional treatment if necessary (usual medical care), including radiotherapy for symptom palliation (41).

Outcome measures and patient follow-up. Outcome measures of the present clinical trial were determined, and the primary endpoint was a clinically significant variation in PSA levels in patient blood samples at 6 months. The variation percentage was calculated and the number of patients that had biochemical disease progression was determined through an increase in PSA levels of $\geq 25\%$, in accordance with the criteria of the Prostate Cancer Clinical Trials Working Group 3. The same was done with respect to the number of patients that had a biochemical therapeutic response defined as a $\geq 50\%$ decrease in PSA levels (34). Other endpoints of the present trial were the variations in the quality of life score (through the EQ-5D-5L questionnaire) and body mass index (BMI) (42). The previously validated Spanish version of the EQ-5D-5L questionnaire was used in the present study, which evaluates 5 general domains, each one with a score ranging from 0-4 (with a lower score indicating better quality of life) (43). Complete blood count (red and white blood cells), hemoglobin, hematocrit, platelets, kidney (serum creatinine, blood urea nitrogen-BUN-, uric acid) and liver function (albumin, bilirubin, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, alkaline phosphatase and lactate dehydrogenase) serum test were monitored in all patients.

Blinding. The researchers who evaluated treatment effectiveness and performed the statistical analyses were blinded to the treatment that the patients received, as were the patients.

Sample size. The sample size calculation was based on the number of treated patients that had biochemical disease progression (a 25% increase in PSA levels), which was stipulated at 39% and was performed using ClinCalc online software (version 1; <https://clincalc.com/stats/samplesize.aspx>). This was based on a previous study on patients with CRD-PCa treated with docetaxel (44). As a comparison figure, it was stipulated that 95% of the patients with no treatment would present with biochemical disease progression. A total of 10 patients were needed in each arm of the clinical trial to reach the required power (0.8) when the sample size was calculated, using the one-tailed α (0.05). At the end of the study, the statistical power for detecting a difference between the 2 arms of the study was calculated ($\alpha=0.05$) using the number of patients with disease progression at 6 months in the mefenamic acid group and the placebo group, and the result was 100%.

Statistical analysis. The data are presented as percentages or mean \pm standard error or standard deviation. For inferential statistics, normal data distribution was first determined using the Kolmogorov-Smirnov test and the equality of variances was confirmed using the Levene's test. A paired Student's t-test was employed to compare the numerical variables (with normal distribution) between the 2 groups (mefenamic acid and placebo). The categorical values were compared using the Fisher's exact test or χ^2 test. The relative risk (RR), number needed to treat (NNT) and 95% confidence interval (CI) were calculated to determine the probability of not having disease progression (an increase in serum PSA levels $\geq 25\%$), comparing the mefenamic acid group vs. the placebo group. As the sample size was small, the Laplace/De Morgan correction was employed for the risk analysis, in which 1 was added to each cell of the 2x2 contingency table (45). The statistical analysis was performed using SPSS 20.0 (IBM Corp), with the exception of the RR and NNT, which were calculated using MedCalc v17.7.2 (MedCalc Software bvba). Sample size and the post-hoc power analysis were calculated using ClinCalc online software. One-tailed $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Clinical trial flow-process. Of the 46 CRD-PCa patients screened, 20 were randomized into two different study groups, with 10 patients in each group: 10 patients in the mefenamic acid group and 10 patients in the placebo control group. All 20 patients completed the trial (Fig. 1). The clinical characteristics and treatment procedures of the patients are presented in Table I. The results demonstrate that there is no significant difference between the groups, which is the starting point for treatment.

Comparison of the PSA levels in patients treated with mefenamic acid compared with those treated with placebo. Table II presents a comparison between groups for the following variables, PSA, BMI and quality of life. Before and after comparisons between baseline and after 6 months for the same group, for each variable, were evaluated, in order to determine the effects of each treatment. While comparing the percentage change per patient, there was a significant decrease

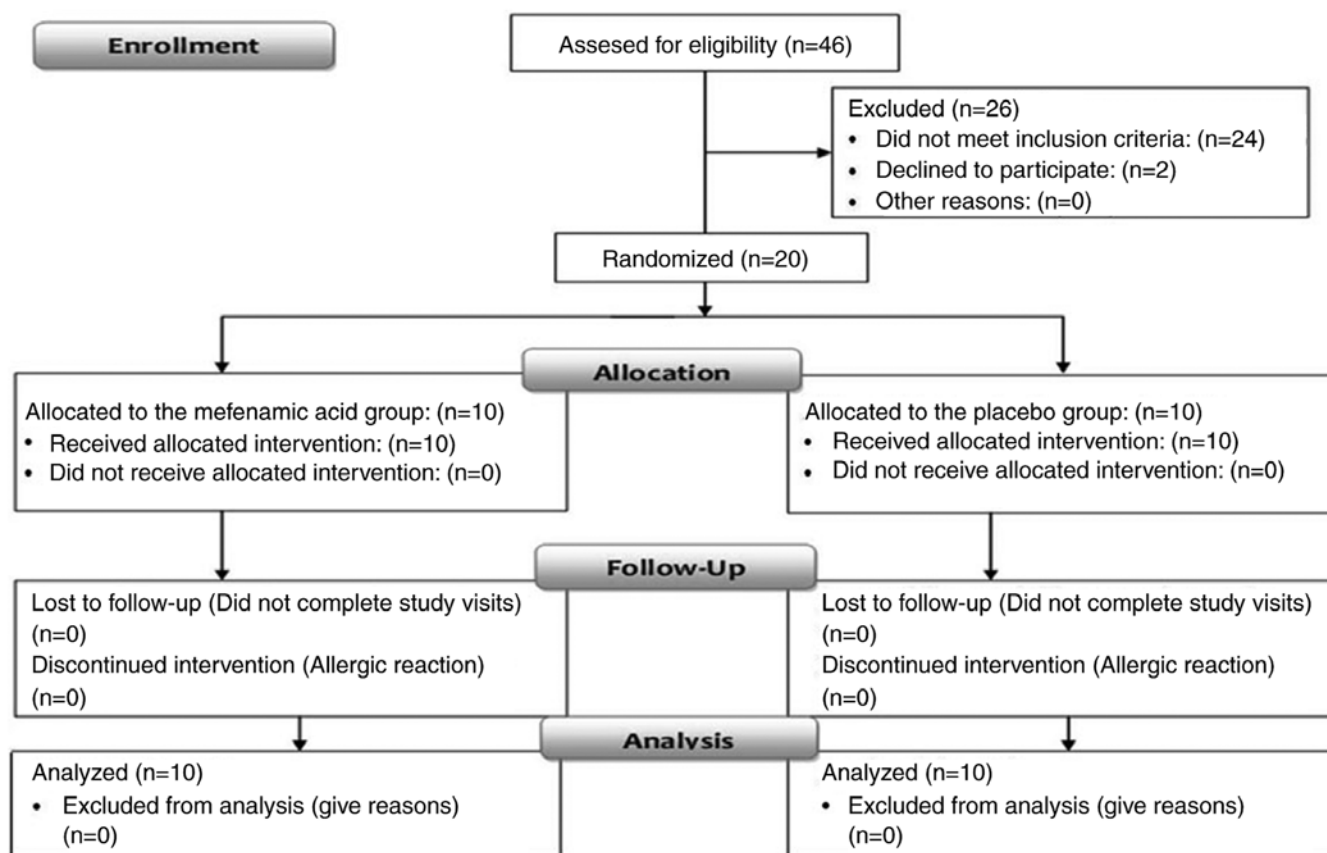


Figure 1. Consort 2010 flow diagram with the number of patients screened, included, eliminated and analyzed in the present study.

in the PSA levels at 6 months of treatment with mefenamic acid (mean decrease of $41.9 \pm 35.8\%$), whereas there was a mean increase in PSA levels in the placebo group of $55.4 \pm 43.1\%$ (Fig. 2A). Notably, 70% of the patients in the placebo group exhibited biochemical disease progression (an increase of $\geq 25\%$ in PSA levels), but this did not occur in any patients treated with mefenamic acid (Fig. 2B).

BMI and quality of life changes in the patients treated with mefenamic acid compared with those treated with placebo. Patients receiving placebo exhibited no changes in their BMI when the baseline and end of trial values were compared ($P=0.898$; Table II). In contrast, patients in the mefenamic acid arm of the trial had an increased BMI; however, this result was not significant ($P=0.064$; Table II). A statistically significant difference was observed between the BMI of the patients in the mefenamic acid and placebo groups on completion of the trial ($P=0.038$; Table II). Quality of life was evaluated using the EQ-5D-5L score, in which a lower score denotes better quality of life. The patients treated with mefenamic acid had a significantly improved quality of life at the end of the study ($P=0.015$; Table II). The patients treated with placebo had no significant changes in their quality of life at the end of the study ($P=0.108$; Table II).

Effects of mefenamic acid on disease progression and therapeutic response in patients with CRD-PCa. The NNT with mefenamic acid to prevent a patient with CRD-PCa and no chemotherapy from presenting with disease progression was

1.71 (Table III). In addition, mefenamic acid administration significantly decreased the probability of biochemical disease progression at 6 months by 88% compared with the placebo group (RR=0.1250; 95% CI, 0.0183-0.8515; $P=0.0337$; Table III). Even though there was a therapeutic response (a decrease in PSA levels of $\geq 50\%$) in four patients (40%) with the administration of mefenamic acid, the result was not statistically significant when compared with the placebo group, which had a 0% therapeutic response ($P=0.081$; Table III).

Tolerance of clinical trial. Regarding the adverse effects that were potentially associated with the experimental medication, three (30.0%) patients presented with abdominal pain/discomfort (gastritis) corresponding to grades 1 and 2 from the CTCAE (40), which is a clinical scale used in cancer trials by clinicians from the National Cancer Institute's based upon symptomatic adverse events at some point during the follow-up, but temporary suspension of the drug (2 weeks) was required in only one of the patients. Gastric symptoms ceased on insistence of patients taking the medication with meals. No pathological alterations were observed in the complete blood count or in the kidney and liver function tests of the patients. Experimental treatment was not definitely suspended due to adverse effects in any of the patients.

Discussion

The present study analyzed the effects of mefenamic acid administration for 6 months in patients with CRD-PCa by

Table I. Distribution of the main clinical characteristics and treatment procedures of study subjects.

Clinical characteristics	Mefenamic acid group	Placebo group	P-value
Number of patients	10	10	
Age, years (Mean ± standard deviation)	71.88±9.42	67.44±5.50	0.240
Clinical stage			0.370
III A	40%	30%	
III B	20%	0%	
III C	10%	20%	
IV B	30%	50%	
Diabetes mellitus	20%	40%	0.437
High blood pressure	70%	50%	0.335
Statins	30%	20%	0.563
Hyperlipidemia	20%	30%	0.437
Cardiovascular diseases	50%	40%	0.581
Antidiabetics	20%	40%	0.437
Antiplatelets	0%	20%	0.206
Anticoagulants	10%	20%	0.735
Antihypertensives	70%	50%	0.335
Depression	10%	10%	0.735
Treatments			
Radical prostatectomy	30%	10%	0.335
Radiotherapy	10%	10%	0.735
Other NSAIDs	0%	30%	0.082
Surgical castration	10%	0%	0.563
During the study			
Radical prostatectomy	0%	0%	NA
Radiotherapy	10%	10%	0.735
Chemotherapy	0%	0%	NA
Other NSAIDs	30%	0%	0.175
Gastritis	30%	10%	0.400

NA, not applicable; NSAIDs, non-steroidal anti-inflammatory drugs.

monitoring tumor progression and quality of life markers. There was a statistically significant 42% decrease in serum PSA level in the group treated with mefenamic acid compared with the placebo group. In addition, there was an adequate therapeutic response (PSA level decrease of ≥50%) in 40% of the patients treated with mefenamic acid. Mefenamic acid also prevented biochemical disease progression.

The percentage of patients treated with mefenamic acid that had a therapeutic biochemical response (40%) was similar to that of treatment with abiraterone (46,47) or docetaxel (48). Patients in the present study received abiraterone and docetaxel as part of their normal medical care. The effect of mefenamic acid on biochemical response in the present study was not statistically significant, which maybe attributable to the small sample size of the present study. On the other hand, in the present study, treatment with mefenamic acid significantly prevented biochemical disease progression in patients with CRD-PCa. Mefenamic acid was well-tolerated and no serious adverse effects were reported in the current study, unlike chemotherapy and radiotherapy that can result in considerable

adverse effects (49). The abandonment or temporary suspension of treatment with abiraterone and/or chemotherapy is often caused by the presence of adverse effects (50,51). Patients with CRD-PCa do not adequately tolerate conventional treatment regimens due to their clinical condition (52,53). Therefore, the results of the present study pose a benefit and potential alternative therapeutic option for patients with CRD-PCa.

Preclinical and clinical trials have demonstrated that the administration of certain NSAIDs, such as celecoxib does not produce a therapeutic effect (54,55). However, there are reports stating that chronic aspirin consumption lowered PSA levels in patients by 5-10% at the time of PCa diagnosis, compared with patients that did not take aspirin (25,27,29). To the best of our knowledge, the mechanism by which aspirin decreases PSA levels at the time of diagnosis has not yet been determined, nor has whether that effect is associated with disease progression (56-58). Notably, in the present clinical trial, mefenamic acid was demonstrated to decrease PSA levels when administered to patients with CRD-PCa. Fenamate NSAIDs have been reported to decrease tumor

Table II. Comparison of body mass index, prostate specific antigen and quality of life (EQ-5D-5L) scores within and between patients in the placebo and mefenamic acid groups.

Parameters per group	Time		^b P-value
	Baseline (Mean ± standard deviation)	6 months (Mean ± standard deviation)	
Prostate-specific antigen, ng/ml			
Placebo	10.15±7.17 ng/ml	17.18±13.04 ng/ml	0.012
Mefenamic acid	7.00±7.80 ng/ml	5.38±7.80 ng/ml	0.018
^a P-value	0.383	0.024	
Body Mass Index			
Placebo	27.70±1.87	27.70±3.63	0.898
Mefenamic acid	30.33±4.79	32.50±5.75	0.064
^a P-value	0.112	0.038	
EQ-5D-5L score			
Placebo	6.66±2.05	5.38±0.75	0.108
Mefenamic acid	7.33±2.00	5.66±0.66	0.015
^a P-value	0.513	0.422	

^aMefenamic acid groups vs. balanced placebo. ^bBaseline vs. 6 months.

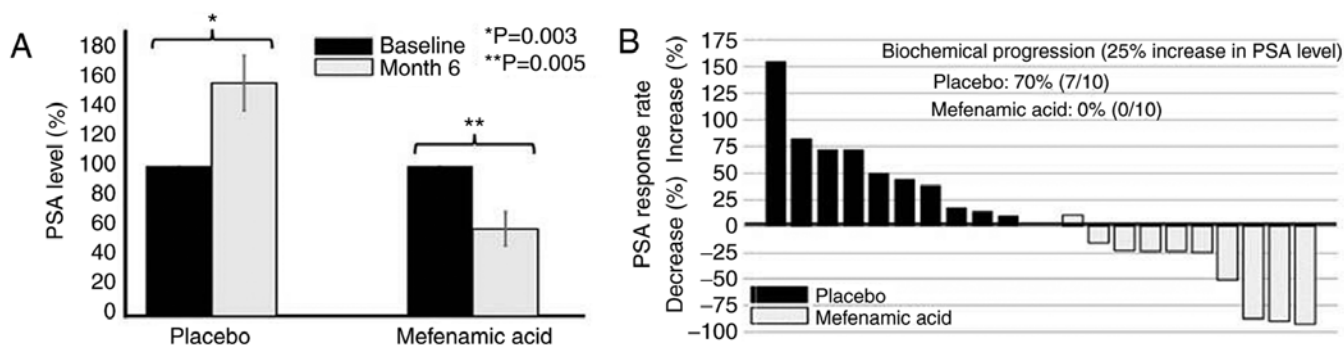


Figure 2. PSA level percentage variations in patients with castration-resistant prostate cancer treated with mefenamic acid and placebo. (A) Comparison of baseline and month 6 PSA levels (%) within the placebo and mefenamic acid groups. (B) Response rates of patients in the placebo group and mefenamic acid group at follow-up (6 months). PSA, prostate specific antigen.

size and favor apoptosis of PCa cells in *in vitro* and *in vivo* models with Foxn1nu mouse strain (31). Different regulatory mechanisms for cell proliferation and their role in cancer have been proposed for mefenamic acid. Previous studies have demonstrated that mefenamic acid is an inhibitor of cyclooxygenase 1(COX-1) and cyclooxygenase 2 (COX-2) isoforms; COX-2 inhibition leads to matriptase inhibition. Matriptase is an enzyme that is responsible for the extent of extracellular matrix degradation. According to a report by Ko *et al* (59), Cox-2 inhibition hinders PCa cell migration in culture by inhibiting the action of matriptase. In addition, the aforementioned study reported that Cox-2 inhibition produces androgen receptor (AR) inhibition. The AR is vital in the production of prostaglandins, such as prostaglandin e2 (PGE2). At the same time, PGE2 is an autocrine and paracrine lipid signal inducer that functions by binding to the rhodopsin family of G-protein coupled receptors. PGE2 can

contribute to tumor development by promoting cell survival, angiogenesis and motility (51).

In addition, mefenamic acid has been demonstrated to induce apoptosis in human cancer cell lines through the caspase-3 pathway (60). Mefenamic acid is also a very potent aldo-keto reductase (AKR) inhibitor (61). AKR enzymes may contribute to the growth of certain types of cancer and their inhibition, particularly of AKR family 1 member C3 (AKR1C3), which potentially exhibits antineoplastic effects (62). Relatively high AKR1C3 mRNA expression was observed in human prostate and mammary glands, where it was involved in regulating ligand access to the androgen and estrogen receptors. AKR1C3 is an interesting target for the development of therapeutic agents for hormone-dependent forms of cancer, such as prostate cancer, breast cancer and endometrial cancer. NSAIDs, specifically indomethacin, celecoxib and fenamates, have been reported as potent inhibitors (63,64). Thus, the

Table III. Association between mefenamic acid treatment and therapeutic effect.

Parameters of therapeutic effect	Mefenamic acid group (%)	Placebo group (%)	RR (95% CI)	NNT	P-value
Response	40	0	0.63 (0.38-1.05)	3.00	0.081
Progression	0	70	0.12 (0.01-0.85)	1.71	0.033

Response is defined $\geq 50\%$ decrease in PSA levels and progression is defined as $\geq 25\%$ increase in PSA levels. CI, confidence interval; NNT, number needed to treat; PSA, prostate specific antigen; RR, relative risk.

inhibitory effect of mefenamic acid on AKR1C3 is proposed to be one of its main antineoplastic mechanisms (31). To the best of our knowledge, no previous studies have yet evaluated the antineoplastic effect of mefenamic acid in humans.

Furthermore, patients treated with mefenamic acid had an increased BMI based on the results of the present study and a significant difference was observed between the mefenamic acid and placebo groups. To the best of our knowledge, there are no previous reports that demonstrate that NSAIDs modify body weight. However, this is the first time the drug has been administered for a prolonged period of time. Mefenamic acid has been postulated to significantly increase both carbohydrate absorption and postprandial metabolism in the intestine, through an increase in intestinal blood flow and oxygen consumption (65), which could have been the cause of the weight gain observed in patients in the treatment arm of the present study. Future studies are required in order to confirm the aforementioned results.

There were no changes in quality of life between the placebo and mefenamic acid groups, upon comparing the 5Q-5D-5L scores. Nevertheless, when analyzing the intragroup quality of life scores, only the mefenamic group showed improvement in relation to the baseline scores. This improvement in the mefenamic group could be explained by the treatment with NSAIDs and the consequent decrease in baseline pain levels. According to a recent study, a decrease in pain levels is associated with an improvement in quality of life (66). However, in the present study, there was no statistically significant difference between the baseline and final pain levels measured by the EQ-5D-5L, which is why the effect observed was perhaps not due to a decrease in pain level. On the other hand, there is an association between PSA levels, weight loss and quality of life in patients with prostate cancer (67-69). Therefore, quality of life improvement can be explained by the decrease in PSA levels and the increase in BMI. BMI maintenance is important in patients with cancer. Men with PCa and a BMI < 22.5 are at greater risk for cancer-specific death (70), and general mortality is twice as great with a body weight loss of more than 5% in patients with a BMI < 22.5 (19). Weight loss is the main component of cachexia due to cancer and acts as an indicator of negative energy balance and a pro-inflammatory state (71). The latter decreases the efficacy of antitumor treatment (67). Improvement in quality of life and BMI with NSAID use has been reported in a previous clinical trial (28), concurring with the results of the present study.

Notably, the dose of mefenamic acid administered in the present study (1 g oral dose/day) was lower than the maximum

daily recommended dose (1.5 g/day). This lower dose was selected for patients who consumed the drug for a prolonged period of time. There were no serious adverse events reported in the present study due to drug ingestion. Even though no kidney function alterations occurred in patients treated with mefenamic acid, prolonged NSAID use can cause kidney damage (49). This was one of the reasons the decision was made not to administer the drug longer than 6 months.

Another relevant observation is that only patients with PSA levels < 100 ng/ml were evaluated in the present study and results may be different in patients with higher PSA levels. Future studies investigating patients with PCa in early clinical stages or hormone-sensitive cancer would be of interest. In preclinical trials, mefenamic acid has been reported to increase the sensitivity of certain types of cancer to chemotherapy and radiotherapy, including colon cancer and lung adenocarcinoma (72). Therefore, future clinical trials to investigate the effect of mefenamic acid in combination with other therapies in patients with PCa are required. PSA kinetics, which is a bone metastasis and survival predictor, was not investigated in the present study (73). However, certain studies have demonstrated contradictory results in PSA kinetics secondary to antineoplastic drug mechanisms (74,75). PSA values at baseline and at 6 months of treatment were investigated for the mefenamic acid and placebo groups in the present study. According to the criteria of the Prostate Cancer Clinical Trials Working Group 3, this is a useful measurement to determine therapeutic efficacy and tumor progression in clinical trials (34,76).

The present study had limitations, such as small sample size and the length of follow-up. Future studies with a higher number of patients evaluated for a longer period of time with strict monitoring of adverse effects are required in order to confirm the results of the present study.

In conclusion, mefenamic acid administration decreased biochemical progression, increased BMI and improved quality of life in patients with CRD-PCa. Future studies with a higher number of patients investigating the effects of mefenamic acid in combination with other therapies and at different clinical stages of PCa disease, are needed to evaluate its therapeutic potential.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author upon reasonable request.

Authors' contributions

IDE, JGE, JDE and IRS designed the present study, performed the analyses and drafted the initial manuscript. DTJ, SZF, OAZ, MMH, JCP, ABA, LBR, LLZ and JPF participated in the clinical evaluation of the patients. MMF, DTJ and CMR performed the statistical analyses. JDE was the clinical trial administrative coordinator. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the National Scientific Commission of the Mexican Social Security Institute (Central Ethics Committee) (R-2018-785-058), and all patients agreed and signed an informed consent form to participate in the study. Patient anonymity was guaranteed in the study. All procedures performed in this protocol were in accordance with The Declaration of Helsinki. The present clinical trial was registered as MEFEPROST: RPCEC00000248 in the Cuban Public Registry of Clinical Trials Database.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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