Oncoxin-Viusid® may improve quality of life and survival in patients with hormone-refractory prostate cancer undergoing onco-specific treatments

MERCEDES IVEET FUNDORA RAMOS[1], LOURDES BOULET MADEN[1], FERNANDO ORIOL CASANOVA[2], FRANK HERNÁNDEZ CRUZ[2], CARINA SALGADO REYES[3], ADALBERTO HERNANDEZ GATO[2], ISRAEL BENÍTEZ LYNCON[3], ETNA VEGA GONZÁLEZ[4], KATIA PALAU MORALES[5], JUAN J. LENCE[6] and EDUARDO SANZ[7]

Departments of [1]Oncology, [2]Urologic, [3]Medical Imaging, [4]Laboratory and [5]Pharmacy, Hospital Universitario 'General Calixto Garcia'; [6]Department of Biostatistics, Instituto Nacional de Oncología y Radiobiología, Havana CP10400, Cuba; [7]Pharmaceutical Laboratory, Catalysis, S.L., 28016 Madrid, Spain

Received March 26, 2020; Accepted September 7, 2020

DOI: 10.3892/mco.2020.2167

Abstract. The aim of the present study was to identify the efficacy and safety of Oncoxin-Viusid (OV) as a supportive treatment for patients with prostate cancer (PCA). A prospective, non-randomised, open-label phase II clinical trial, including 25 patients with hormone-refractory PCA (HRPC) was conducted at the Hospital Universitario General Calixto García (Havana, Cuba) between June 2017 and March 2018. Each of the patients received chemotherapy (CTX) and/or radiotherapy (RT) and OV treatment. Patients had a mean age of 73 years, clinical stage IV cancer and a high risk of relapse. Six cycles of CTX were completed by 80% of the patients, adverse reactions decreased and no weight loss was observed. Among the 25 patients, 5 were lost to follow-up and 4 died of disease progression. A total of 16 of these patients survived, of which 15 had an improved quality of life and 10 responded to treatment, with a significant reduction in pain and prostate symptoms and ≥50% reduction in baseline PSA. The progression-free survival (PFS) rate was 59% and the overall survival (OS) rate 64% at 1 year after treatment began. The OV nutritional supplement was effective, leading to a significant improvement in the patients' quality of life, good nutritional status and greater treatment tolerance. A clinical and humoral response was observed, with high survival rates and a delayed appearance of signs of disease progression. The present study was registered in ClinicalTrials.gov PRS with ID #NCT03543670.

Correspondence to: Dr Mercedes Iveet Fundora Ramos, Department of Oncology, Hospital Universitario 'General Calixto Garcia', Calle 5ta 358 entre B y C apto 2 Plaza La Habana, Havana CP10400, Cuba
E-mail: mercedesf@infomed.sld.cu

Dr Eduardo Sanz, Pharmaceutical Laboratory, Catalysis, S.L., Calle Macarena 14, 28016 Madrid, Spain
E-mail: eduardo@catalysis.e.telefonica.net

Key words: prostate cancer, hormone refractory, treatment, nutritional supplement, Oncoxin-Viusid

Introduction

The World Health Organization (WHO) has predicted that by 2020 there will be ~10,000,000 cancer-related fatalities (1). Prostate cancer (PCA) is the most common neoplasm in men worldwide, with 1/7 men suffering from the disease (2,3). In the USA in 2014, 2,819 deaths were reported at a rate of 50.6 per 100,000 inhabitants (4). Cancer has been the second cause of mortality in Cuba since 1958, with 56.9 deaths per 100,000 inhabitants recorded in 2018 (5,6).

According to data from the American Society of Medical Oncology, the 5-year survival rate for PCA in the mid-1970s was ~69%. However, in recent years, with the development of new treatment options, an improved prognosis and quality of life has been observed in these patients. The results vary according to clinical stage, reaching 30% in the metastatic stage (7).

Treatment for PCA ranges from radical prostatectomy and radiotherapy (RT) in the early stages, with a low recurrence risk, to androgen deprivation combined with RT and/or chemotherapy (CTX) in the advanced stages, with an intermediate to high recurrence risk. Treatment is correlated with clinical stage, including relapse risk, based on the new TNM scoring system of the American Joint Committee on Cancer (AJCC) (8-10).

Tumour cells develop different mechanisms that allow them to survive and replicate. The result is resistant PCA, which may still respond to secondary hormonal manoeuvres. Hormone-refractory PCA (HRPC) is a cancer in which hormonal therapy is no longer effective in any form (11-14).

At the end of 2004, two studies demonstrated that docetaxel-based CTX improved survival in HRPC patients (18.9

vs. 16.4 months for mitoxantrone and prednisone). Until then, the various treatments used only resulted in symptom palliation (15).

CTX is associated with partial multi-drug resistance and a high percentages of toxicities such as neutropenia, anaemia and thrombocytopenia. This causes a delay in treatment, and a deterioration in the quality of life and nutritional status of the patients. As a result, the number of hospitalisations increases, as does the length of the hospital stay. Current supportive treatments, such as colony-stimulating factor and human recombinant erythropoietin, while improving patient outcome, are also linked to adverse effects (16).

In vitro and *in vivo* studies have suggested that oxidative stress and antioxidants play a key role in the pathogenesis of chronic diseases, including PCA. Therefore they are important in prevention therapy (17-20). Multiple investigations carried out in specialised cancer treatment centres have revealed a synergistic effect of antioxidants with standard treatment. Antioxidants increase the concentration of various anti-neoplastic drugs in tumour cells, but not in healthy ones. In turn, antioxidants sensitise tumour cells to RT (21,22).

Oncoxin-Viusid (OV) is a nutritional supplement formulated with more effective antioxidants (Table I), produced by Laboratorios Catalysis. The antioxidants are treated by means of a molecular activation process, increasing their biological activity. Epigallocatechin gallate, a polyphenol present in green tea extract with anticancer properties, is particularly noteworthy. Its effects include the inhibition of the tissue necrosis factor and the potentiating of nuclear factor κ-light-chain-enhancer of activated B cells, which regulates anti-apoptotic genes and inhibits the expression of cyclooxygenase 2. Epigallocatechin gallate blocks growth factor signal transduction and inhibits the urokinase-type plasminogen activator enzyme, which stimulates tumour proliferation, decreases matrix metalloproteinase, and favours tumour invasion, angiogenesis and metastasis. In addition, the OV supplement restores cellular apoptosis by inducing P53, caspase-3 and B-cell lymphoma 2 (Bcl-2)-associated X protein expression and inhibiting anti-apoptotic protein Bcl-2. It is also an immunomodulator that stimulates the production of interferons and interleukin 12, and increases the phagocyte action of macrophages and T-helper cells. Multiple clinical and pre-clinical studies have focused on OV, demonstrating its antitumour effect (23,24).

In Argentina, a clinical trial on OV in hormone-responsive PCA was carried out. The results when hormone-therapy is associated with OV showed a greater tolerance and a good response to treatment. However, the effects and safety of OV in patients with HRPC are unknown. This proof-of-concept, phase II, prospective, non-randomised and open-label clinical trial was aimed to identify the effect of the OV nutritional supplement on quality of life, onco-specific treatment tolerance and progression-free survival (PFS), as well as annual overall survival (OS) in patients with advanced clinical stage PCA (25).

Materials and methods

Study design. A proof-of-concept, phase II, descriptive, prospective, non-randomised and open-label clinical trial was conducted on 25 male patients with a histological diagnosis of HRPC at the General Calixto Garcia University Hospital in Havana, Cuba, between June 2017 and March 2018.

Inclusion and exclusion criteria of patients. The trial was comprised by 25 men over 18 years old with compensated intercurrent diseases, Karnofsky index >70 and parameter laboratory according to undergoing CTX. All patients authorized the inclusion via informed consent. The Patients couldn't with another oncospecific product in investigation or have hipersensibility of Taxol. They neither have brain metastasis or carrier of human immunodeficiency virus (HIV).

HRPC. Patients with testosterone production suppression by orchiectomy or hormonal suppression, whose testosterone values were <0.3 ng/ml and were still undergoing disease progression, were considered hormone-resistant, according to the 2008 progression criteria published by The Prostate Cancer Clinical Trials Working Group (1). The present study included hormone-resistant patients; hormone resistance was defined as an absence of therapeutic response after 6 months of hormone therapy.

The initial study was planned to be conducted in a different center and for technical reasons was transferred to General Calixto Garcia University Hospital, for this reason was not possible to include the placebo, in order to prevent nutritional product lapse. Then it was considered a preliminary study to another more stretching study.

All 25 participating patients were treated with a 75 mg/m^2 IV dose of docetaxel in 500 ml 0.9% NaCl every 3 weeks, and 5 mg prednisone twice daily (orally). Patients received a minimum of 6 cycles of CTX; if there was a good response, it was continued for 8 cycles. RT was administered to the abdominal lymph nodes in 2 patients (total dose of 74 g cobalt 60), following 6 cycles of CTX.

Supportive treatment with OV. The 25 participants underwent treatment with a 75 mg/m^2 IV dose of docetaxel in 500 ml NaCl 0.9% every 3 weeks, and prednisone 5 mg twice daily (orally). They received a minimum of 6 cycles of CTX and, if there was a good response, continued for 8 cycles. A daily 50-75 ml (25 ml in 2 or 3 doses) OV oral solution was administered as supportive treatment following meals. It was prescribed on an ongoing basis during the onco-specific treatment, including CTX suspension periods, and was administered ≥1 month after the end of the treatment.

Objectives of clinical trial. The objectives of the clinical trial were as follows: i) To identify the quality of life of the enrolled patients; ii) to analyse clinical, humoral and imaging variables; iii) to determine CTX interruptions, as well as the number and severity of adverse reactions; iv) to estimate the annual OS rate in patients with advanced stage clinical PCA.

Data collection and processing. Data from the case report file were entered into the database created for this purpose and processed using SPSS software version 21.0 IBM.

Statistical analysis. A descriptive analysis of the data was carried out. In the case of continuous quantitative variables, such as body mass index (BMI), laboratory tests and QLQ-30

Table I. Chemical composition of Oncoxin-Viusid.

Chemical	Value, mg[a]
Glycine	2,000
Glucosamine	2,000
Arginine	640
Cystine	204
Malic acid	1,200
Monoammonium glycyrrhizinate	200
Ascorbic acid	120
Sodium methylparaben	100
Zinc sulfate	80
Grean tea extract	25
Calcium penthotenate	12
Pyridoxine	4
Manganese sulphate	4
Cinnamon extract	3
Folic acid	400
Cyanocobalamin	2

[a]Average values per 100 ml.

and -PR25 assessment scales, the mean, standard deviation and standard error were calculated, and the t-test was used for related samples, to compare the variables' mean value at different points in the treatment. In addition, Cohen's d was estimated to measure the clinical effects magnitude. For discrete quantitative variables, such as the pain scale or International Prostate Symptom Score (IPSS), the median, mode, minimum and maximum were estimated, and the absolute change and Wilcoxon signed-rank test were used to determine the variation of the median at different time intervals during treatment. $P<0.05$ was considered to indicate a statistically significant difference. Absolute and relative frequencies were calculated for the qualitative variables.

The initial variables included age and concurrent diseases. The general condition of patients was assessed based on the Karnofsky Scale, including patients with a score of ≥70. Clinical stage was evaluated based on the AJCC's TNM scale, updated in January 2018, which includes the risk of relapse.

Response variables included quality of life, nutritional status, pain, prostate symptoms, prostate specific antigen (PSA) and Response Evaluation Criteria in Solid Tumors (RECIST).

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaires (EORTC QLQ-C30 and -PR25) were used to assess the quality of life of patients. Efficacy was considered when ≥50% of patients on the OV treatment showed no signs of deterioration in their quality of life.

Nutritional status was evaluated by BMI (BMI = weight/height^2), pain, according to an analogical numerical scale, and prostate symptoms, according to the IPSS questionnaire. A 50% decrease in the PSA baseline was considered an acceptable humoral response. RECIST criteria were used to assess measurable or quantifiable lesions by radiological means, all of which were used to assess disease progression.

Toxicity was assessed according to the WHO criteria. CTX interruptions were measured in terms of cycles, number, frequency and causes. Relative variation was defined as the change expressed in the percentage of one variable between its initial and final value.

The PFS and OS rate per year were evaluated using the Kaplan-Meier method. Mean and median time was estimated for these curves.

Results

Patient characteristics. The study included 25 male patients with HRPC. They were between the ages of 52 and 88 years, with an average age of 73 years. Concurrent diseases affected 23 patients, 92% of the analysed sample, of which 52% had >1 pathology. Cardiovascular diseases predominated, particularly high blood pressure (44%). Out of a total of 25 cases classified as high risk of relapse at stage IV, 96% presented a T category of 2b or higher with bone metastases, with only one patient presenting with a T2a extension of the primary tumour. Nevertheless, visceral and non-regional lymph node metastases appeared in few patients (n=6). There were more patients with a high histological grade. The inclusion took into account that patients had a Karnofsky index (KPS) of 70-90 to ensure treatment compliance. The PSA sample mean was 62 ng/ml (Table II).

Treatments administered, interruptions, adverse reactions to CTX and treatment response

Treatment administered. The 25 participants underwent treatment with docetaxel. Of them, 23 received 6-8 treatment cycles, according to response and toxicity (OV group). All of them had been pre-treated with hormone therapy and RT, like a high risk of relapse. Radiation was administered at the end of CTX in only 2 patients (Table III).

Interruptions. A minimum of 6 treatment cycles were received by 20 patients (80% of participants). Four transient interruptions of onco-specific + OV treatment lasting ~13 days on average were caused by urinary tract infection in 2 patients, which were resolved with antibiotic treatment, and 2 patients who travelled outside the province. There were 3 transient interruptions of OV treatment, due to viral diarrhoeal infection, acute cholecystitis and transitory anorexia, which lasted 7 days on average. A total of 9 permanent interruptions occurred, 5 due to loss of patients to follow-up and 4 due to patient mortality due to disease progression (Table II).

Adverse effects. The most frequent adverse effects associated with CTX were nausea and arthralgias, which afflicted 22 patients (88%) at the beginning of the treatment, followed by peripheral oedema present in 16, myalgia in 15 and asthenia in 13 patients. In Fig. 1, the adverse reactions were significantly decreased, when comparing the last treatment cycle with the first. The only exception was neuropathy, which remained virtually the same over time. On average, 79.1% were mild reactions, 20.7% were moderate and only 0.2% were severe. In terms of causes, 4.7% of events were not treatment-related, in 25.2% of cases it was improbable that they were, in 28.7% it

Table II. Patient characteristics (n=25).

Variables	Value
Age, years	
Mean ± SD	72.7±8.3
Range	52-88
Concurrent pathologies by system, n (%)	
HBP	11 (44)
Bronchial asthma	2 (8)
Gastritis	7 (28)
Ulcer	9 (36)
Prostatic hyperplasia	7 (28)
Renal insufficiency	1 (16)
Atrophic pyelonephritis of left kidney	1 (16)
Osteoarthritis	4 (16)
Herniated disc	2 (8)
Pathological fracture	1 (16)
Sickle cell anaemia	1 (4)
Diabetes mellitus	4 (16)
Neuropathy	3 (12)
Hemiplegia	1 (16)
Hemiparesis	1 (16)
TNM, n (%)	
T2a	1 (4)
T2b	20 (80)
T2c	3 (12)
T4	1 (4)
M_1	3 (12)
M_2	24 (96)
M_3	3 (12)
Mean PSA ± SD, ng/l	61.9±22.5
Karnofsky performance status scale, n (%)	
70 (unable to carry on normal activity or to do active work)	13 (52)
80 (normal activity with effort)	9 (36)
90 normal activity	3 (12)

SD, standard deviation; HPB, high blood pressure; PSA, prostate specific antigen; T, primary tumor; M_1, non-regional lymph node metastasis, M_2, bone metastasis; M_3, visceral metastasis.

was possible and in 46.1% probable. Of these patients, 77.4% recovered without squeal.

Response to treatment. Of the 25 patients studied, 44% showed signs of progression, 4 of which died from the disease. In the remaining worsening cases, the symptoms and number of bone lesions increased, and so did the PSA. Ten patients showed some response to treatment, 8 of which had a partial response, despite experiencing a decrease in IPSS, an increase in BMI and a new bone lesion. However, the PSA decreased without reaching normal values. The disease remained stable in 2 patients, while 4 were not assessed due to loss to follow-up (Table II).

Table III. Treatments administered, interruptions, response and status at 1 year (n=25).

Treatment	Value
Docetaxel + OV, n	23
Docetaxel + RT + OV, n	2
Interruptions	
Transient interruptions of CTX + OV, n (%)	4 (16)
Mean duration of interruptions, days	13
Transient interruptions of OV, n (%)	3 (12)
Mean duration of interruptions, days	7
Permanent interruptions of CTX + OV, n (%)	9 (36)
Response to treatment, n (%)	
Disease progression	11 (44)
Partial response	8 (32)
Stable disease	2 (8)
Not evaluable	4 (16)
Patient status at 1 year, n (%)	
Alive	16 (64)
Deceased	4 (16)
Lost to follow-up	5 (20)

Response to treatment al 6to-8vo cycle according to Response Evaluation Criteria in Solid Tumors. RT, radiotherapy; CTX, chemotherapy; OV, Oncoxin-Viusid.

Nutritional status. Body mass index was the indicator used for patient follow-up. No significant body weight loss occurred during treatment. The t-test for correlated samples was used to contrast the presence of mean differences between the initial BMI and the third, sixth and final cycle. The P-values obtained were 0.34, 0.53 and 0.32, respectively, all >0.05. This supports the argument that the differences observed between the BMI mean throughout the study were due to chance and not to significant nutritional changes in the patients during treatment (data non shown).

Pain assessment at the different cycles (Table IV). A visual numerical pain scale was used, which at the start of treatment had a median of 7, positioning the patients' pain level at severe. At this point, 20 patients (80%) reported having pain of >6, the most frequent score being recorded in 46.2% of participants. A marked and sustained decrease in pain was observed as treatment cycles progressed, with the pain between the first and second cycles being moderate, and that in the third cycle being mild. The pain continued to decrease until the eighth cycle, where no patient scored >4 in their assessment, meaning that 100% of patients experienced mild pain at the end of the treatment. The Wilcoxon signed-rank test results showed statistically significant differences between the mean pain scores between the treatment onset, and the third, sixth and eighth cycles. For each of these three comparisons, the result was P<0.001 (see Table II).

Prostate symptoms. At the beginning of treatment, the IPSS score that assesses prostate symptom severity was a median

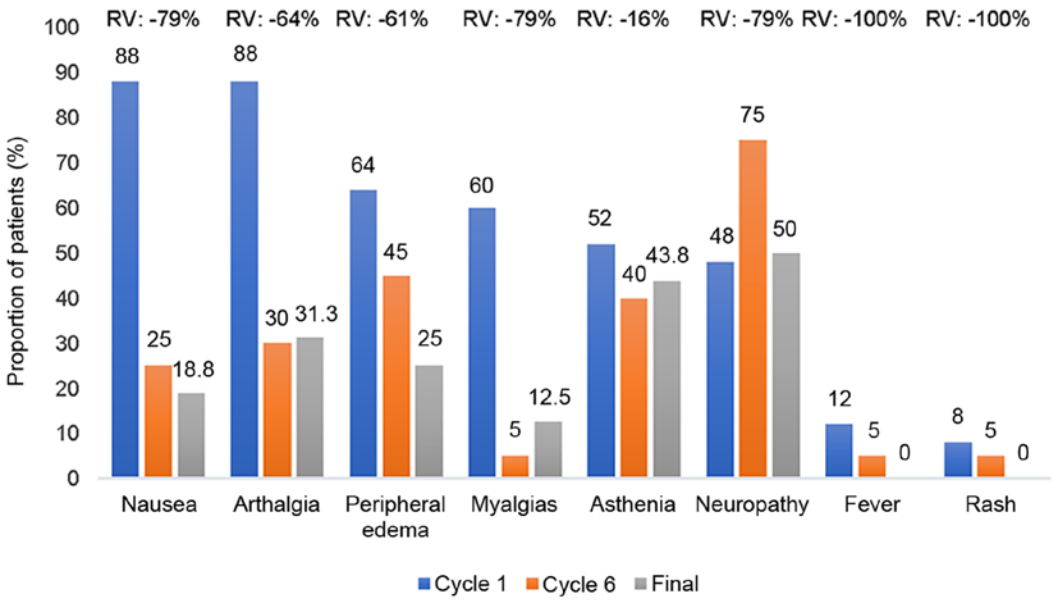

Figure 1. Adverse events. The RV between cycle 1 and the final cycle appears in parentheses. RV=V_1-V_2/V_1 x100, with V_1 being the initial value and V_2 the end value. Blue corresponds to the first, orange to the sixth and gray to the final cycle. RV, relative variation.

of 25, ranking patients at the severe symptom level. This indicator began to decrease after the first cycle, with the symptom level being moderate in the second cycle and mild in the seventh cycle. Wilcoxon signed-rank test results showed that the differences in the mean ISSP scores between the start of the treatment, and the third, sixth and eighth cycles were statistically significant (P<0.001; Table III).

Other clinical symptoms. Other dominant symptoms included oedema and functional impairment of the lower limbs, affecting 72 and 52% of patients, respectively. Symptomatic remission was observed in 78% of patients suffering from oedema. The 13 patients who exhibited functional impairment at the beginning of the study recovered their functional capacity. It was related with the KPS, as shown in Table I, however it was preferred to be included in the QLQs to evaluate all those symptoms in context.

Evolution of PSA levels. PSA levels only normalised in the 2 patients who received a combined CTX and RT treatment. However, prostate antigen levels were reduced by analysing their numbers between the first, and the third, sixth and final treatment cycles. The t-test results for mean differences of related samples were significant for all 3 cases (P<0.05), and the mean PSA of the treatment group at the end of the study had dropped by 50% from the baseline (Table V).

Evolution of other laboratory parameters. A significant decrease in the mean enzyme lactate dehydrogenise (LDH) value of patients between the beginning and end of treatment (P=0.028), which is indicative of the decrease in chronic inflammation and oxidative stress. The heamogram values, as well as leukocyte and platelet counts, remained stable. In addition, no evidence of CTX-related haematological toxicity was identified. In terms of liver function tests, alanine aminotransferase and aspartate aminotransferase mean levels were slightly higher than baseline values, but without statistical significance (P=0.498 and P=0.059). Creatinine was slightly increased, although not significantly different from the baseline levels. No significant changes were observed in total protein, albumin, calcium and glycaemia, which remained within the normal ranges, confirming the absence of a nutritional or metabolic impact on patients.

Quality of life. The EORTC QLQ-C 30 (version 3) and QLQ-PR 25 questionnaires were used for patients at the beginning of, and 1 year after, their inclusion in the study, to measure their quality of life. Of the 16 patients who reached 1 year of treatment, 15 cases (representing 60% of the initial sample) showed an improved quality of life, and 1 suffered no deterioration of this indicator from the beginning of the study. As shown in Table V, the mean total quality of life rose by 83.5% at the end of treatment, as compared with its initial values. This increase was not only statistically significant (P<0.001), but also showed an effect size of 1.9 (>0.8), which on the Cohen scale represents a large-scale, clinically perceptible effect. Similar behaviour, although more modest, was observed in the scales corresponding to physical, cognitive, social and emotional functions, where a significant increase was observed in the mean value of the dimensions from a statistical point of view (P<0.05), with a Cohen d index of 0.5-0.9. In other words, a medium-to-high and clinically perceptible effect size was observed in all cases. Similarly, there was a significant reduction in parameters associated with symptoms such as fatigue, pain, insomnia, anorexia and constipation (P<0.05).

Results of the supplementary QLQ-25 questionnaire for patients with PCA showed a statistically significant decrease in mean values achieved between the start of and 1-year of treatment for urinary symptoms, incontinence, intestinal symptoms and hormone treatment-related symptomatology; the effect size was large from a clinical point of view. Dimensions associated with sexual activity and function did not change significantly (P>0.05; Table VI).

Table IV. Clinical evolution (pain and IPSS scale) during treatment cycles.

A, IPSS

Treatment cycles	N	Median	Mode	Minimum	Maximum	Absolute change (median)	Clinical evaluation
Initial	25	26	19	9	35	-	Severe pain
Cycle 1	25	23	19	10	31	-3	
Cycle 2	25	16	15	9	30	-7[a]	Moderate pain
Cycle 3	25	16	19	4	28	0	
Cycle 4	23	12	6	6	33	-4[a]	
Cycle 5	22	10	6	2	25	-2	
Cycle 6	20	9	6	2	20	-1	
Cycle 7	16	7	6	4	19	-2	Mild pain
Cycle 8	16	6	6	4	20	-1	

B, Pain scale

Treatment cycles	N	Median	Mode	Minimum	Maximum	Absolute change (median)	Clinical evaluation
Initial	25	7	7	3	10	-	Severe symptoms
Cycle 1	25	6	5	4	8	-1	Moderate symptoms
Cycle 2	25	4	5	2	7	-2	
Cycle 3	25	3	4	1	6	-1	Mild symptoms
Cycle 4	23	3	2	1	6	0	
Cycle 5	22	2.5	2	1	6	-0.5	
Cycle 6	20	2	3	1	5	-0.5	
Cycle 7	16	2	2	1	5	0	
Cycle 8	16	2	2	1	4	0	

[a]Statistically significant. IPSS, International Prostate Symptoms Score.

Table V. Comparison of PSA between treatment initiation and cycles 3, 6 and final cycle.

	Mean					
PSA at the beginning and end of treatment	Estimate, ng/l	n	Standard deviation	Standard error	Mean difference	P-value (mean difference)
Initial PSA	61.9	25	22.5	4.5	20.42	<0.001[a]
PSA in cycle 3	41.5	25	27.7	5.5		
Initial PSA	59.7	20	24.3	5.4	31.18	0.017[a]
PSA in cycle 6	41.4	20	29.9	6.7		
Initial PSA	61.4	16	23.1	5.8	31.31	0.001[a]
PSA final cycle	30.5	16	24.0	6.0		

[a]Statistically significant. t-test for related samples. PSA, prostate-specific antigen.

OS and PFS

PFS. The estimated probability that an individual would remain disease- or relapse-free from the date of entry into the study to t1=26 weeks (6 months) and t2=52 weeks (1 year) was 0.69 and 0.50, respectively. At the end of the study 14 patients had not yet developed signs of progression, exhibiting a PFS rate of 59%. The mean PFS time was 39 weeks [95% confidence interval (CI), 33-45 weeks] with a mean standard error of 3 weeks (Fig. 2).

OS. The estimated probability that an individual would survive from the date of entry into the study to t1=26 weeks (6 months) and t2=52 weeks (1 year) was 0.90 and 0.81, respectively. At the end of the study, 16 patients were still

Table VI. Comparison of the mean values on the quality life questionnaires scales (QLQ-C30 and PR25).

QLQ C30	Initial evaluation at start	Evaluation after one year	Mean relative variation, %	P-value (mean difference)	Effect size (Cohen's d)
Overall	40.6	74.5	83.5	<0.001	1.9
Physical function	77.5	86.7	11.9	0.018	0.7
Emotional wellbeing	77.6	87.0	12.1	0.04	0.5
Cognitive function	87.5	99.0	13.1	0.022	0.9
Social function	82.3	92.7	12.6	0.036	0.7
Fatigue	36.1	14.6	-59.6	0.001	-1.3
Pain	45.8	21.9	-52.2	<0.001	-1.5
Insomnia	47.9	14.6	-69.5	<0.001	-1.4
Anorexia	37.5	8.3	-77.9	<0.001	-1.6
Constipation	19.7	4.2	-78.7	0.029	-0.9
PR25					
Urinary symptoms	40.1	9.6	-76.0	<0.001	-2.6
Incontinence	14.6	0.0	-100.0	0.030	-0.9
Intestinal symptoms	5.2	1.0	-80.1	0.015	-0.8
Hormonal treatment-symptoms	18.8	9.7	-48.1	0.001	-1.4
Sexual activity	64.6	53.1	-17.8	0.060	-0.7

C30 is for all type of cancer, and PR25 is more specific to prostate cancer. The statistical methods used for comparison were t-test for related samples and Cohen's d for clinical repercussion. QLQ, Quality of Life Questionnaire.

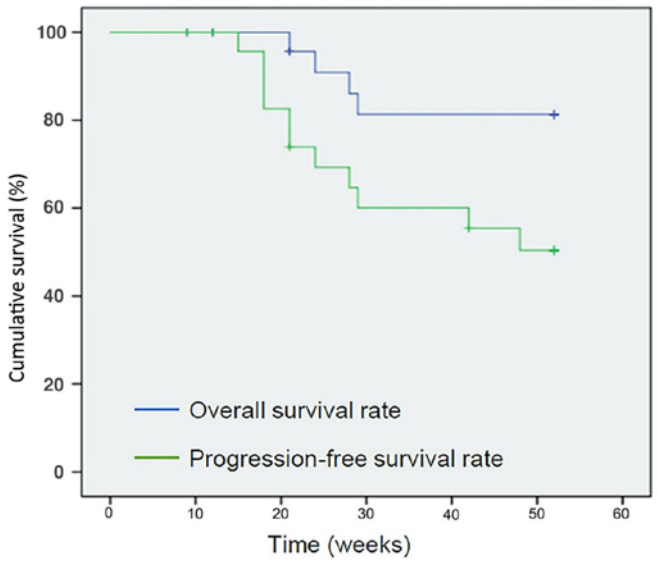

Figure 2. Progression-free and overall survival rates using Kaplan-Meier analysis.

alive, exhibiting an OS rate of 64%. The mean survival time was 47 weeks (95% CI, 43-51 weeks), with a mean standard error of 2 weeks (Fig. 2).

Discussion

In this proof-of-concept, phase II, prospective, non-randomised and open-label clinical trial, we explored the efficacy and safety of OV in 25 male patients with a histological diagnosis of HRPC.

PCA patients are generally diagnosed in locally advanced stages (III-IV) at the age of >50 years old and with associated chronic co-morbidities. HRPC exhibits significant heterogeneity. Cases only showing an elevated PSA are markedly different from cases with metastatic disease. The expression of the PSA in these cases is lower than that of hormone-sensitive tumours and may not correlate with cell proliferation. When hormone therapy has failed, the course of the disease is aggressive, with a variable progression rate of 18-24 months and survival rate of 24-36 months. The prognostic change according molecular subtypes through a genetic variability: 17 Genes assay to predict PCA aggressiveness in the context of Gleeson grade heterogeneity, multifocality and biopsy under sample (26-29).

It is important to emphasise that the patients in the present study displayed unfavourable prognostic factors: Advanced age, high PSA and Gleason score, metastatic disease stage and affected performance status. (Table II). Patient ages was 52-88 years old, which approaches the range recorded in national statistics (60 and 80 years old). In Cuba, cancer continues to be the second leading cause of mortality, exceeded only by cardiovascular diseases, which explains the prevalence of cardiovascular pathologies (56%) in the sample. The ages and clinical stages found in the present study coincide with those found in studies focusing on the primary and secondary medical assistance of Cuba (30-32). The clinical symptoms exhibited by patients and the mean PSA value of 65.9 ng/ml were due to advanced disease. Studies have shown that patients with a PSA of a >49 are 6 times more likely to have a positive scan (33,34).

The KPS scale was first used in 1949 on patients receiving CTX (35). Since then it has been used to predict cancer patient

evolution. Performance status was affected in 52% of patients, who were unable to carry out their daily tasks or work (KPS of 70). A significantly worse prognosis has been reported in HRPC patients with a <80% Karnofsky score. In a study of gastric tumours, a statistical correlation was observed between KPS and patient survival (36,37).

In the 90s, several studies reported an amplification of the Bcl-2 gene in HRPC. Docetaxel is a second-generation taxane that acts at the micro-tubule level and promotes apoptosis through the induction of Bcl phosphorylation. Two phase III clinical trials, one American (Southwest Oncology Group) and a second Canadian and European (TAX 327), demonstrated the superiority of docetaxel over mitoxantrone. The significant improvement in pain control and quality of life was relevant (22%). The PSA response rate was 45-48% (P<0.001). The mean survival of patients treated with docetaxel every 3 weeks was 18.9 months. The most common non-haematological adverse effects included alopecia (50-65%), fatigue (49-53%), nausea (36-41%), diarrhoea (32-34%) and neuropathy (24-30%). Subsequently, treatment was considered to achieve symptom control, improved survival and low toxicity (38-41).

The patients of the study were at an intermediate and high risk, and they were treated following the protocol. Only 2 patients received radiation at the end of treatment. In a retrospective study, 1,024 patients with intermediate-risk PCA were treated with radiation with or without neoadjuvant and concurrent Androgen-Deprivation therapy (ADT). Multivariate analysis revealed that a primary Gleason pattern 4, percentage of positive biopsy scores of ≥50, and presence of >1 intermediate-risk factor (Tic, T2b-c, PSA 10-20 ng/ml, Gleason score 7) were significant predictors of increased incidence of distant metastasis. The authors then used these factors to separate the patients into unfavourable and favourable intermediate-risk groups, and determined that the unfavourable intermediate-risk group had a worse PSA recurrence-free survival, distant metastasis, and PCA-specific mortality than the favourable intermediate-risk group. Thus, the study concluded that external beam radiation therapy + ADT + docetaxel was a reasonable treatment option in appropriate men with high- and very-high-risk disease (42).

The 2015 version of the guidelines added systemic therapeutic options for men with progressive castration-naïve PCA. Docetaxel combined with ADT was an option for men with high-volume metastatic disease, based on results from the phase III ECOG 3805 trial, also known as the Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED), where a total of 790 randomly allocated men with metastatic, androgen-stimulated PCA were treated with docetaxel plus ADT or ADT alone. The patients in the combination arm experienced a longer OS than those in the ADT arm [57.6 vs. 44.0 months; hazard ratio (HR), 0.61; 95% CI, 0.47-0.80; P<0.001]. Subgroup analysis showed that the survival benefit was more pronounced in the 65% of participants with high-volume disease (HR, 0.60; 95% CI, 0.45-0.81; P<0.001). Men with low-volume disease in CHAARTED may have benefited from the inclusion of docetaxel in terms of survival (HR, 0.60; 95% CI, 0.32-1.13; P=0.11), although the median OS was not reached in either arm of the study, and the number of patients was low. The Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) trial, a multi-arm, multistage phase III trial, included patients with both M0 and M1 castration-naïve PCA starting ADT. The extent of metastatic disease was not evaluated in the 1,087 men with M1 disease, but the median OS for all patients with M1 disease was 5.4 years in the ADT/docetaxel arm vs. 3.6 years in the ADT arm (a difference of 1.8 years between groups, as compared with a 1.1-year difference in CHAARTED). The strong statistical power of STAMPEDE (n=2,962) had a clear survival advantage to the upfront CTX approach (43).

The European GETUG-AFU 15 trial compared ADT and ADT + docetaxel treatment, but no survival benefit was identified (median OS, 58.9 vs. 54.2 months; HR, 1.01; 95% CI, 0.75 1.36) (41). Retrospective subset analysis from this trial showed that participants with a high-volume metastatic disease showed a non-significant 20% reduction in the risk of mortality, with no reduction observed in the low-volume subgroup (44).

Different authors have attempted to establish a model to determine prognosis of tumours. Nguyen *et al* (45) suggested that the number of unfavourable risk factors is significantly associated with PCA-specific mortality. PCA is the leading cause of mortality in men with a minimum of three risk factors. Therefore, novel agents should be considered for clinical trials designed to assess whether they can prolong survival. A previous study showed that survival remains disappointingly low in men presenting with M1 disease who receive long-term ADT alone, despite active treatment with supplement Oncoxin, even the majority of patients was M1 disease being available at first failure of ADT (45,46).

Antioxidants had been used for the prevention and treatment of cancer (47-50). They work by restoring the natural antioxidants in the body, which are often depleted following the completion of CTX, resulting in decreased side effects and increased survival time for patients undergoing CTX. The nutritional supplement OV is a composite formulation that contains antioxidants. The extract of green tea, present in the OV supplement, is an antioxidant studied for the prevention of cancer. Its antitumour effect is mainly due to catechins, and particularly the epigallocatechin-3-gallate, which is found in a high concentration in green tea. Green tea extract is the most studied and most active in the inhibition of oncogenesis and reduction of oxidative stress. OV also contains vitamin C. It is an essential nutrient acting as an antioxidant and a co-factor for various enzymes. Heaney *et al* (51) concluded that vitamin C supplementation may exert adverse effects during cancer treatment. The redox active from of vitamin C has a therapeutic effect on tumour cells and synergistic effects with CTX. This antitumour effect is based on the induction of apoptosis and cell cycle arrest (52-55).

The quality of life of patients has become a consideration in oncology, as a consequence of the development of highly aggressive treatments. It now is thought that the effect of the therapeutic strategy on the patient's quality of life should be an endpoint of clinical trials. Quality of life is important in the research of advanced PCA (56). According to QLQ-30, the overall quality of life of the patients improved significantly (P<0.001) with clear clinical evidence (Cohen's d of 1.9), which affected all aspects of the individual: Physical, emotional, cognitive and social. Anorexia, asthenia and weight loss are

common in advanced stages of the disease. In the present study, fatigue, oedema and bone pain led to functional impairment, with difficulty walking observed in the studied patients. However, a significant decrease in fatigue, pain and anorexia, as well as a lack of weight loss (BMI), occurred when the two treatments were combined. The literature supports that nutritional care should be integrated into oncology, due to its significant contribution to quality of life. Nutritional intervention increases the tolerance and response to cancer treatment (57,58).

A previous study with 640 patients provided evaluable information on protocol-defined progression that led to further treatment. An evaluation of men in a post-docetaxel setting should consider the type of progression, duration of treatment, and known pre-treatment prognostic factors. The study also provided evidence of benefits resulting from the continuation of CTX beyond progression, but only for men who exhibited isolated worsening of pain. A nomogram was constructed and internally validated with a concordance index of 0.70 (59). However, when OV was used alongside CTX, even the patients in the present study that had exhibited moderate and severe pain pre-treatment, saw benefits in their quality of life post-OV treatment. OV is a vitamin-rich nutritional supplement with carbohydrate-protein nutritional requirements, which improves asthenia, and therefore quality of life. A preclinical study on OV in Her2-positive breast cancer led to weight gain and improvement of quality of life in participants (60).

The IPSS is used to evaluate changes in the severity of symptoms and efficacy of treatment. A significant improvement in urinary symptoms was shown by QLQ 25. The same was suggested by the ISSP in lower urinary tract diseases, where a significant improvement was observed in the third and second treatment cycles. In 2006, a randomized, double blinded, placebo-controlled study was performed as a 1-year proof-of-principal trial to assess the safety and efficacy of catechins for chemoprevention in PCA. That was the first study showing that catechins have a potent *in vivo* chemopreventive effect in human PCA. A secondary observation was the significant improvement of lower urinary tract symptoms, as determined by the IPSS and Quality of Life Scale (61,62). OV contains green tea catechins, which explain the similar results obtained in both studies. Urinary obstruction is associated with the T2b tumour size of the prostate gland. The improvement in prostate symptoms suggested tumour reduction following combination treatment. In a preclinical study of colorectal cancer metastasis in the liver, it was demonstrated that Ocoxin oral solution slows down tumour growth (63). It may be used in combination with a standard therapy to potentiate antiproliferative action in acute myeloid leukaemia and lung cancer (64,65).

Although a high PSA was observed in the majority of cases, it decreased in 80% of them, with a decrease observed in 50% of the baseline. Improved survival was observed in patients with HRPC and a >50% drop in PSA levels. This correlated with a 68% response in the measurable disease (66-68). In the trial, 9,346 (INT-0162) the value following androgen deprivation was a strong independent predictor of survival in new metastatic PCA (69).

LDH is released into the blood from different tissues, mainly the liver. It is considered a prognostic and predictive biomarker for visceral metastatic disease. High values suggest a poor prognosis. Visceral metastasis only occurred in 2 patients, both of whom succumbed to the disease. In general, cancer produces chronic inflammation with high LDH levels. Treatment with CTX and RT releases free radicals and produces oxidation. However, this enzyme decreased significantly in the present study, pointing to a potential compensatory effect induced by OV in this context (70), and suggesting a better response to combination therapy. The study on metastatic renal cell carcinoma demonstrated LDH as a biomarker for survival (71).

The response to treatment with symptomatic and PSA-lowering outcomes was significant. However, according to the RECIST criteria, a partial response to treatment predominated (8 patients). This criterion assumed more value in the disease progression analysis. The typical full response, partial response, stable disease and progressive disease criteria are not very useful in HRPC. This is due to the fact that 80-90% of patients do not have bi-dimensional measurable disease, based on imaging tests. Bone metastases are difficult to quantify. The mixed responses, in which the regression of certain osseous metastases is followed by the progression of others, and interindividual variability in the interpretation of the explorations, mean that they are not systematically used to evaluate treatment response. Angulo *et al* (72) in his report on survivors of castration-resistant PCA reached the conclusion that the treatment extends survival expectations in a clinical practice setting, and that prognostic predictors can be identified in these patients. The study found that younger patients without metastasis at diagnosis had a better prognosis. Patients with higher PSA levels (>45 ng/ml; P=0.09) and a Gleason pattern 5 in the biopsy had a less favourable outcome (69). Schröder reported similar findings (73).

de Bono *et al* (74) found differences in metastatic castration-resistant PCA between favourable and unfavourable prognostic factors. Patients with unfavourable pre-treatment circulating tumour cells (CTCs; 57%) had a shorter OS (median OS, 11.5 vs. 21.7 months). The unfavourable post-treatment CTC count also predicted a shorter OS (median OS, 6.7-9.5 vs. 19.6-20.7 months). According to de Bono *et al* (74) results which were based on patients with unfavourable prognostic factors, the mean estimate of the post-treatment survival time was 47 weeks (74). Different authors have attempted to establish a model to determine the prognosis of tumours (75,76).

Overall, treatment adherence was positive: 80% of the cases completed the 6 CTX cycles with a decrease in toxicity frequency and intensity observed throughout the treatment. The most frequent toxicities were arthralgia, myalgia, asthenia, anorexia and neuropathy. The neuropathy seemed to increase during treatment; it was an effect of neuropathy caused by pathologies present in the patients, including diabetes and nervous system disease. It was described as the accumulative effect over 400 mg/m^2, which explain the increment by cycles. Although, determining the causes of the slow performance status and pain through the physical exam was challenging, and there was no physiopathology test to confirm, it was up to the patients to describe their symptoms. The neuropathy was an imprecise sign, even though it was compensated at the end of the study. Rashes disappeared during treatment. No patients exhibited neutropenia, which is the most frequent docetaxel-related haematological toxicity (77,78).

The findings in the PCA patients could be an due to the supportive treatment with OV, given its anti-inflammatory and immunomodulator properties. Several studies have shown a decrease in the CTX and RT toxicities, with an increase in the OS rate, as a result of the synergism of the treatments. In a Japanese clinical study carried out in terminal stage patients of hepatocellular carcinoma, it was observed that 21% of patients were alive at the end of the treatment in the treatment group, whereas in the control group they were dead (79). Another clinical study in Bangladesh demonstrated more tolerance to cancer treatment, which was found to improve patient survival and quality of life (80). A clinical study of pancreatic cancer proved that OV reduced the stromal-mediated chemoresistance (81). More recently, clinical studies of head and neck and cervico-uterine cancer reported a decrease in toxicity and improvement in the quality of life of patients following supportive OV treatment (82-84).

A study by Tan (84) reviewed recent abstracts and literature through Medline/Pub Med, using the following key words: Androgen-independent/HRPC, novel treatment options, Phase II, III trials, and meeting abstracts/presentations. Tan concluded that there is a need to improve on this survival benefit, since, with the standard treatment, the relapse-free survival among responders is often short (6 months) and patients often exhibit cancer progression, which leads to mortality. There is a need to develop less toxic drugs that would significantly improve survival (85,86). OV, when used as supportive therapy, decreased the toxicity of docetaxel and improved patient survival.

In conclusion, the OV nutritional supplement, when used in combination with onco-specific treatment in patients with PCA, was found to be highly efficient, as it significantly improved the overall quality of life of patients, promoted greater tolerance to CTX, and reduced the occurrence of related adverse events. Therefore, it contributed to a greater number of treatment cycles being completed per patient. The above results, combined with the fact that the prostate antigen decreased, nutritional status was preserved, and haematological and hepatic complications were avoided, resulted in high survival rates and a delayed onset of signs of progression.

Acknowledgements

The authors would like to thank Mr. David Márquez Soriano (Molecular Biologist, Catalysis S.L., C/Macarena 14, 28016 Madrid, Spain) for his general support and help for facilitating the communication between Spain and Cuba.

Funding

The present study was supported in part by a grant from Laboratorios Catalysis (Madrid, Spain), who provided the Oncoxin-Viusid for the study protocol, but played no role in the study design, collection and interpretation of data, writing of the manuscript or submission for publication.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

MIFR contributed in conducting the clinical trial, is the corresponding author and contributed to writing the paper. The author has been involved in contributions to conception and design, acquisition of data, analysis and interpretation of data, and drafting the manuscript or revising it critically for important intellectual content. LBM, FOC, FHC, CSR and AHG contributed as research participants. They were involved in acquisition of data, and discussion and interpretation of the results. CSR and IBL assisted with imaging realization and interpretation. EVG and IBL helped with lab tests and imaging realization and interpretation. KPM contributed to the pharmacy labours, and provided important support in the treatment, control of the trail and revising the manuscript. JJL contributed to conception, design, biostatistical analysis and data management. ES was involved in the study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content and statistical analysis, and corresponding author. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by Ethics and Clinical Research Committee of General Calixto Garcia University Hospital (approval no. 000181/12). At recruitment, all patients signed the informed consent form which explained the objective and design of the study and provided information regarding the product of research. It also explained that the patient could abandon the trial without any damage or deny the medical assistance. The consent referred to the confidentiality of the patient with a code number.

Patient consent for publication

All patients that participated in the present study provided written informed consent for the publication of any associated data.

Competing interests

The authors declare that they have no competing interests.

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