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The New Combination Docetaxel, Prednisone and Curcumin in Patients with Castration-Resistant Prostate Cancer: A Pilot Phase II Study

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Key Words
Curcumin · Docetaxel · Castration-resistant prostate cancer · Phase II · Neuroendocrine markers

Abstract
Objectives: Favorable phase I results justified this pilot phase II study to assess the efficacy of docetaxel/curcumin in patients with chemotherapy-naive metastatic castration-resistant prostate cancer (CRPC). ***Methods:*** Thirty patients with progressing CRPC and a rising prostate-specific antigen (PSA) received docetaxel/prednisone in standard conditions for 6 cycles in combination with per os curcumin, 6,000 mg/day (day –4 to day +2 of docetaxel). The co-primary endpoint was the overall response rate determined by PSA and target assessments. An ancillary study assessed the seric values of chromogranin A (CgA) and neuron-specific enolase (NSE). ***Results:*** Twenty-six patients received the scheduled treatment, 2 progressed and 2 died before the end of treatment. A PSA response was observed in 59% of patients (14% of PSA normalization) and achieved within the first three cycles for 88% of responders. Partial response was reached for 40% of evaluable patients. The regimen was well tolerated, and no adverse event was attributed to curcumin. Twenty patients were 100% curcumin compliant. The PSA level and objective response rate were not correlated with the serum values of CgA and NSE. ***Conclusion:*** This study produced additional data on curcumin as a treatment for cancer, with a high response rate, good tolerability and patient acceptability, justifying the interest to conduct a randomized trial.

Introduction

Docetaxel is the standard first-line chemotherapy in castration-resistant prostate cancer (CRPC). After the pivotal phase III study (TAX 327), docetaxel became the first approved systemic treatment demonstrating an im-

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proved overall survival when given every 3 weeks with prednisone [1]. However, the advantage is modest, and new therapeutic modalities are clearly required for CRPC patients. A new approach is the addition of a noncytotoxic treatment to this chemotherapy.

The dietary polyphenol, curcumin, which is the yellow pigment component of turmeric *(Curcuma longa)*, has been reported to exert a significant potential as a chemopreventive agent, with beneficial effects in all carcinogenesis stages [2–4]. Experimental studies suggested that this polyphenol could inhibit tumor metastasis, invasion and angiogenesis by modulating especially the transcription nuclear factor-κB [5, 6]. Curcumin was reported to block cell cycle progression, through the expression and active inhibition of various cell cycle regulatory proteins [7, 8]. It exerts likewise proapoptotic activity mainly by decreasing the expression of the anti-apoptotic proteins and by activating proapoptotic enzymes. Curcumin decreases angiogenesis through the inhibition of the vascular endothelial growth factor expression [9] and the inhibition of androgen receptor expression in a dose-dependent manner [10].

Thus, this polyphenol acts as a counterbalance to reverse the taxane-induced nuclear factor-κB activation [11, 12]. Moreover, Choi et al. [13] reported that curcumin could reverse mechanisms involved in the acquisition of drug resistance. Furthermore, in the study of Ide et al. [14], the results indicated that the treatment of isoflavones and curcumin decreased the production of prostate-specific antigen (PSA) in LNCaP cells in patients with PSA ≥10.

Some clinical trials have studied curcumin chemoprevention but few have focused on the therapeutic domain. In the study of Chen et al. [15], 72 patients with metastatic colorectal cancer received leucovorin, 5-fluorouracil and oxaliplatin in combination with MB-6 or placebo for 16 weeks. MB-6 is a combination of soybean, green tea, *Antrodia camphorata* mycelia, spirulina, grape seed and curcumin. Significant results have been observed in the 2 groups concerning the disease progression rate and the incidence of adverse events (AE).

The study called Pomi-T compared the effect of dietary supplementations (pomegranate, green tea, broccoli and curcumin) [16]. This study was done on 199 patients with prostate cancer; they received capsules with nutrients or a placebo for 6 months. The rise in PSA in patients who received the supplement was lower than in patients who received the placebo.

Another clinical study [17] has been done on patients with pancreatic cancer. They received gemcitabine-based chemotherapy and 8 g of curcumin daily. This study shows the feasibility of this combination.

In the study by Dhillon et al. [18], 25 patients with advanced pancreatic cancer received 8,000 mg of curcumin per day until disease progression. Oral curcumin was well tolerated, 1 patient had ongoing stable disease for more than 18 months and 1 patient had a tumor regression (73%).

A phase I dose escalation trial has been done in our institution and demonstrated the feasibility, safety and tolerability of escalated doses of curcumin in combination with docetaxel and prednisone therapy in 14 patients with metastatic breast cancer. A curcumin dose of 6,000 mg/day for 7 consecutive days every 3 weeks was determined as the recommended dose in combination with a standard dose of docetaxel plus prednisone. Among 8 patients with measurable lesions, 5 presented a partial response and 3 had a stable disease [19]. These observations support the idea of clinical trials with curcumin in association with chemotherapy.

Prostate cancer is commonly associated with neuroendocrine (NE) differentiation which is correlated with aggressive disease and progression to CRPC [20]. NE cells are characterized by the synthesis and secretion of a variety of neuropeptides and hormones such as chromogranin A (CgA) and neuron-specific enolase (NSE), which are the most frequently used markers to detect NE features (either at tissue or systemic level). These peptides are considered to play a significant role in prostatic growth and differentiation. Their release by NE cells may facilitate the development of androgen independence, acting as autocrine and paracrine growth factors for malignant cells. Serum levels of NE markers might reflect the NE activity of prostate carcinoma [21]. The clinical significance of these markers has been analyzed in several studies; CgA and NSE were shown to have an independent prognostic significance in prostate cancer [22]. CgA appears to be the best sensitive marker for detecting NE differentiation [22]. Ferrero-Poüs et al. [23] found that patients resistant to androgen-suppressive treatments and with elevated PSA had an increase in CgA and NSE in 62 and 29% of cases, respectively. However, their role is still unclear and their use is not yet recommended for treatment decision in CRPC.

According to the literature, new data are necessary to understand the potential of curcumin as anti-cancer compound and the role of NE markers in prostate cancer. Therefore, a phase II trial testing docetaxel/prednisone combination with curcumin in first-line treatment of CRPC was conducted. The aim of this pilot study was to

provide additional knowledge of curcumin efficacy. Thus, our clinical team wanted to know if the supplementation of this polyphenol can improve the response rate of the standard chemotherapy, docetaxel/prednisone, without additional toxicity. The primary endpoint was the response rate assessed by clinical, biological (PSA) and paraclinical examinations. The secondary endpoints were safety assessed by NCI CTCAE v3.0, time to progression (TTP) assessed by the Response Evaluation Criteria in Solid Tumors (RECIST) criteria and PSA level, compliance with curcumin capsules and impact of geriatric test score on compliance. In parallel, our ancillary study endpoint was to assess the best neuroendocine markers between CgA and NSE.

Materials and Methods

Eligibility

This was a nonrandomized, open-label, phase II trial involving 3 French centers. Thirty patients were included. Eligible patients (≥18 years old) had a histologically confirmed adenocarcinoma of prostate cancer and documented castration resistance for their metastatic disease – defined by an objective progression with at least one measurable and/or evaluable lesion according to the RECIST criteria (which is the case in 50% of patients) and/or a rise in PSA level, named 'rising PSA' (observed in 100% of patients). Rising PSA was defined as a twice-consecutive increase in PSA values (V2 and V3) of ≥5 ng/ml compared with a reference PSA dosage (V1 assessed 3 weeks before treatment). Measurements of PSA were done at ≥7-day interval. An adequate function of major organs was required [bilirubin ≤ upper normal limit (UNL), alanine aminotransferase and aspartate aminotransferase (AST) ≤1.5 × UNL, alkaline phosphatase ≤2.5 × UNL, serum creatinine <140 μmol/l, neutrophils ≥2 × 10^9/l, platelets >100 × 10^9/l, hemoglobin ≥10 g/dl], as well as life expectancy >3 months and World Health Organization performance status ≤2. Patients had been previously treated with androgen-suppressive therapy in the form of medical castration by luteinizing hormone-releasing hormone agonist or antagonist with or without anti-androgen or treatment blocking nongonadic testosterone fraction (testosteronemia <0.5 ng/ml). No previous chemotherapy, except estramustine, had been received by the patients. Liver, kidney or heart failure linked to treatment, malabsorption syndrome or disease significantly affecting gastrointestinal function, symptomatic brain metastasis, history of psychiatric disorders and concurrent severe and/or uncontrolled comorbid medical conditions were the exclusion criteria. Patients receiving treatment with NSAIDs or COX2 inhibitors or with current regimen containing dietary phytonutrients were excluded. Prior surgery and prior radiotherapy, concerning <25% of bone marrow reserve, within >4 weeks before entry were allowed. The local ethics committee (Comité de Protection des Personnes Sud Est VI) and the national review board (Agence Française de Sécurité Sanitaire des Produits de Santé) had previously approved the protocol and each substantial modification. All patients provided written informed consent before study enrollment. This study was registered with ClinicalTrials.gov, No. NCT01012141.

Treatment

Docetaxel, 75 mg/m^2, was delivered as a 1-hour intravenous infusion on day 1 every 21 days for 6 cycles. Premedication with dexamethasone was required at 8 mg given 12, 3 and 1 h before the docetaxel infusion. All patients received 5 mg of prednisone or prednisolone orally twice daily, starting on day 1. Purified oral curcumin was formulated as 500-mg capsules. Each capsule contained 450 mg of curcumin after global assessment by high-performance liquid chromatography tandem mass spectrometry. Each patient received 6,000 mg of curcumin per day (12 capsules, to divide between the morning, afternoon and evening) for 7 consecutive days in each cycle (from day –4 to day +2, knowing that day 0 was the day of chemotherapy injection), as determined in the previous phase I study [19]. We aimed to 'saturate' the body during the period preceding and following chemotherapy, but avoiding a continuous curcumin treatment.

Docetaxel was suspended until recovery in the event of neutropenia <1.5 × 10^9/l or platelet count <75 × 10^9/l. In the case of a repeated event, the docetaxel dose was reduced to 60 mg/m^2. For nonhematological toxicity, the same dose reduction was performed for grades 3 or 4 (except nausea or vomiting without appropriate premedication).

Study Endpoints

The co-primary endpoint was objective response rate (ORR) of target lesions and PSA response with a focus on the evolution of PSA response. For patients with at least one bidimensionally measurable and/or evaluable lesion(s), ORR was evaluated with the use of RECIST. ORR was assessed, as standard, every 3 cycles by bone scan and thoracic-abdominal-pelvic scan. Serum PSA was measured every 3 weeks, and the response assessment was in accordance with the consensus guidelines of the PSA Working Group [24]. A response was defined as a decrease in the serum PSA level of ≥50% from baseline that was confirmed by a second value 4 weeks later. PSA progression was an increase in the PSA level ≥25% for patients with an absolute increase ≥2 ng/ml. These values were determined in the same laboratory at baseline and at each cycle.

The secondary endpoints were safety, TTP, curcumin capsule compliance and correlation between compliance and geriatric test scores. Hematological tolerance was assessed weekly. AE and laboratory variables were graded at each 3-week interval using the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) version 3.0. Serious AE were followed for 4 weeks after the last treatment cycle to document residual toxicities. Compliance was evaluated with a compliance book, completed by patients at each treatment cycle.

NE Markers

The ancillary study was to assess two NE markers on patients' serum, CgA and NSE. They were assayed in the same laboratory at the start of the study and before each chemotherapy day (CERBA and BIOMNIS laboratories). Their normal reference values reported by the laboratories were <94 ng/ml for CgA and <16 ng/ml for NSE. An NE feature is defined for patients with an elevated serum value, at baseline, of at least one of the following markers: CgA and NSE. Marker variations were evaluated for patients with an NE feature and were divided into 3 groups: increase (>25%), decrease (>50%) and stability.

Geriatric Assessment

Prostate cancer is a pathology that occurs principally in older men, and research findings suggest that in general the older population is not optimally compliant to medication recommendations [22]. Thus in this study, patients ≥70 years old (n = 13) had a geriatric assessment. This evaluation included Mini-Mental State Examination (MMSE), Activities of Daily Living (ADL), Instrumental Activities of Daily Living (IADL), Geriatric Depression Scale (GDS-15), Mini-Nutritional Assessment (MNA) and a sociocultural questionnaire. In MMSE, impairment was increased with low score; in ADL and IADL, dependence was also increased with low score. Depression was increased with a high score on GDS-15 and undernutrition was detected with a low score in MNA.

Statistical Analysis

Descriptive statistics (median and range) were used to characterize the population. Since this phase II study was a pilot transitional study between the previous phase I and a planned randomized phase II studies, only 30 patients were enrolled for this protocol. The TTP was measured from the first day of treatment to the time of disease progression or death due to cancer. The duration of PSA response was measured from the first to the last assessment with the response criteria satisfied. Correlation of geriatric assessment and curcumin compliance was performed by the χ^2 test. The χ^2 test or Spearman's rank correlation was used for the descriptive correlation between NE and patients' characteristics. A p value ≤0.05 was considered statistically significant.

Treatment would be considered effective and would support a further randomized phase II trial for ≥50% responding patients on PSA and ≥17% responding patients on measurable disease. This was based on the response rate found by Petrylak et al. [25].

Results

Patient Characteristics and Treatment

A total of 30 patients were included from October 2009 to November 2010 (table 1). This study was performed before the introduction of new hormonotherapies (abiraterone acetate, enzalutamide). The median age was 69 years (range 58–83). All tumors had a Gleason score ≥6; 11 had a score between 6 and 7, and 17 had a higher score. Prior treatments included prostatectomy or radiotherapy and hormonal therapy. All patients were treated by hormonal therapy until castration resistance for a median of 32 months (range 6–116). Indicators of disease progression before study entry were an increasing serum PSA level and an evidence of progression on bone and/or CT scans, if lesions were evaluable or measurable. The median baseline PSA was 169 ng/ml (range 18–1,005), with abnormal PSA values for all patients. The median of CgA was 103 ng/ml (range 33–1,058), and 16 patients had an elevated serum CgA. The NSE median value was 13 ng/ml (range 7–33) and 10 men had an elevated serum NSE at baseline. A total of 22 patients had at least one NE feature and 8 were devoid of any NE feature. Among patients with an NE feature, 12 had only CgA elevated, 6 only NSE and 4 had both elevated markers.

Table 1. Patient characteristics at baseline (n = 30)

Age	
Median, years	69
Range, years	58–83
>70 years	13
Gleason score	
6–7	11
8–10	17
Not available	2
Performance status	
0	12
1	12
2	6
Prior treatment	
Radical prostatectomy	4
Radiotherapy	13
Site of metastases	
Bone	13
Lymph nodes	1
Multiple	16
PSA at study entry	
Median, ng/ml	169.0
Range, ng/ml	17.9–1,005.0
Evaluable for	
PSA response	29
RECIST response	15
Toxicity	30
Curcumin compliance	30

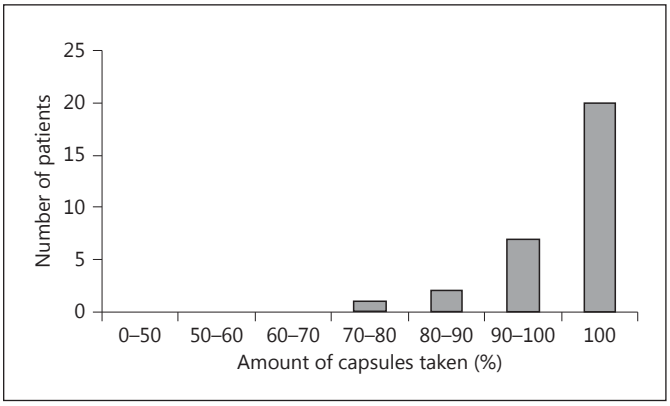

Fig. 1. Curcumin compliance. The number of patients according to the amount of capsules taken.

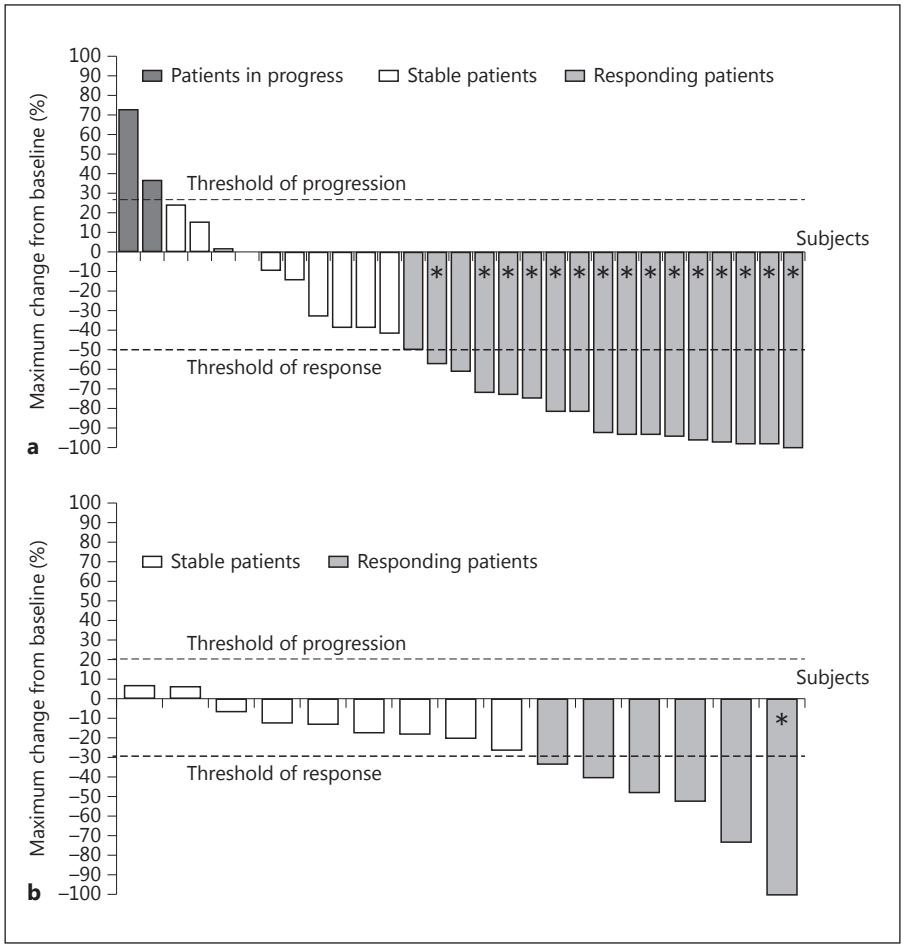

Fig. 2. Waterfall plot of maximum PSA reduction from baseline (**a**) and maximal lesion sum reduction from baseline by the RECIST criteria (**b**). **a** The threshold of progression is defined by an increase in the PSA level of ≥25% and the threshold of response by a decrease of ≥50% during the treatment period. Asterisk = Patients that responded in the first three cycles. **b** The threshold of progression is defined by an increase in the sum of lesions of ≥20% and the threshold of response by a decrease of ≥30% during the treatment period. Asterisk = A patient with a detectable lesion after treatment but not measurable and not evaluable.

One patient died with an inadequate documentation of PSA evaluation. Therefore, PSA assessment was performed in the modified intent-to-treat (ITT) population (n = 29). Fifteen patients were enrolled according to the RECIST criteria; toxicity and curcumin compliance were assessed in the ITT population. Docetaxel was given as first-line chemotherapy, 75 mg/m^2 every 3 weeks for 6 cycles. Twenty-six patients received the complete course (6 cycles) and 4 dropped out prematurely (2 progressions and 2 deaths during study). Two patients (7%) required a dose reduction of docetaxel of 16–30%, one for toxicity related to docetaxel and the other one for general state impairment. Curcumin, 6,000 mg per day, was given for 7 consecutive days in each cycle. Compliance is represented in figure 1, and data show a high compliance of curcumin in our patients with an average observance of 98%. Twenty patients were 100% compliant with treatment. Patients' misunderstanding and toxicities (probably independent of curcumin) were responsible for noncompliance. However, the reasons for noncompliance were not always available.

Treatment Response

PSA response was defined as a reduction in serum PSA level of at least 50% and has been summarized in figure 2a. Objective PSA response was obtained for 59% of patients (n = 17), 14% reached PSA normalization. Thirty-four percent had a stable PSA levels and 7% presented with a PSA progression. A rapid PSA response was mostly obtained; the median time to response was 1.38 months (range 0.53–5.50), i.e. 15 patients responding within the first three cycles and 2 after. Among the responding men, 6 had a PSA decrease between 50 and 80%, and 11 had a reduction >80%. The median PSA response duration was 4.7 months.

Among the 15 patients with measurable or evaluable lesions, 6 (40%) had a partial response and 9 (60%) a sta-

Table 2. Common treatment-related AE arranged in the order of frequency

AE	Grade			
	1	2	3	4
Asthenia	16	11	–	–
Neutropenia	1	1	5	19
Musculoskeletal pain	20	2	–	–
Diarrhea	10	2	–	–
Nausea/vomiting	11	–	–	–
Anemia	6	5	–	–
Neuropathy	6	2	–	–
Constipation	8	–	–	–
Anorexia	5	1	1	–
Edema	7	–	–	–
Ungual toxicity	2	3	1	–
Febrile neutropenia	–	–	6	–
Dysgeusia	5	–	–	–
Mucositis	4	1	–	–

Grade 1 – 4 as defined by the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) version 3.0.

Table 3. Neuroendocrine response of CgA and NSE

CgA	
Decrease ≤50%	7
Stability	40
Increase ≥25%	53
NSE	
Decrease ≤50%	30
Stability	60
Increase ≥25%	10

Data indicate percentages of patients. Only patients with elevated baseline values of these markers were evaluated.

ble disease (fig. 2b). All patients had a clinical benefit (partial response or stable disease) of the combination docetaxel/prednisone and curcumin.

For the majority of patients, changes in PSA reflected radiographic changes well. Among the 6 men with partial response on RECIST, 5 had a PSA response including 2 patients with PSA normalization, and the other one had a stable PSA level. For the 9 patients with stable disease on RECIST, 6 had a stable PSA and 3 a response. The median TTP was 7.85 months (range 2.7–12.1). The median TTP of PSA was 5.8 months (range 0.7–12.5).

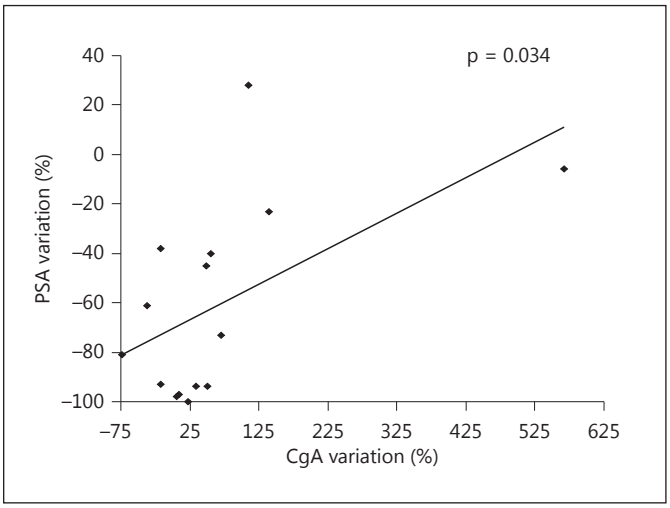

Fig. 3. PSA variation vs. CgA variation in patients with CRPC. n = 16, corresponding to the number of patients with an elevated CgA serum value at baseline.

Adverse Events

No patient withdrew due to toxicity. Concerning the two deaths occurring during treatment, one was due to cerebral hemorrhage, without platelet marker decrease during the weekly surveillance, and the other one was due to respiratory desaturation. These events were not related to study treatment by our investigation. Three cycles were delayed by 1 week following thrombopenia, diarrhea and flu symptoms, respectively.

The incidence of treatment-related grade 3 or 4 AE was low (table 2). The most frequent nonhematological toxicities were asthenia, musculoskeletal pain, diarrhea and nausea. Only 2 severe grade 3 nonhematological AE occurred. Among hematological AE, neutropenia was the most common grade 4, found in 63% of patients. As 6 patients (20%) experienced at least one episode of febrile neutropenia, a well-known docetaxel adverse event, it was not related to curcumin, as judged by the study investigators. In parallel, 8 patients received granulocyte colony-stimulating factor to limit neutropenia. No toxic effect was attributed to curcumin.

NE Markers

CgA decrease was observed in 7% of patients with an elevated CgA at baseline. For men with an elevated NSE at baseline, NSE decrease was obtained for 30% of them. CgA and NSE increase occurred in 53 and 10% of cases, respectively (table 3). Furthermore, there was a positive correlation between CgA and PSA response. CgA varia-

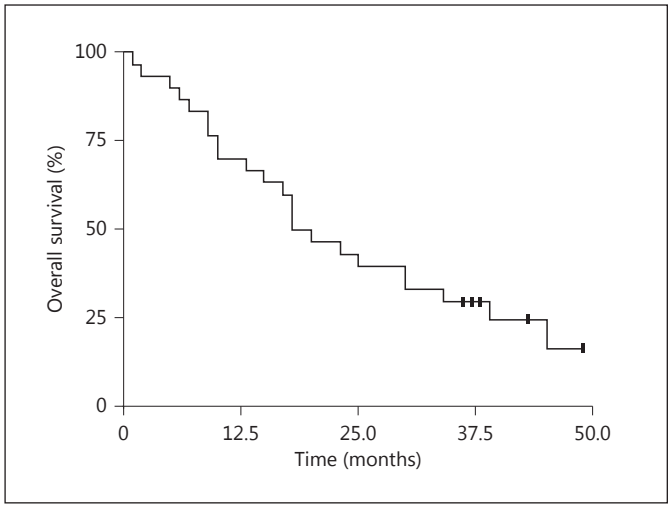

Fig. 4. Overall survival after the first treatment dose (n = 30).

Table 4. ORR and PSA response according to NE features

	Patients with NE feature	Patients without NE feature	p value
ORR			
Partial response	5	1	0.91
Stability	6	3	
Progression	0	0	
PSA response			
Complete response	3	1	0.84
Partial response	10	3	
Stability	7	3	
Progression	2	0	

Patients with an NE feature are defined by an elevated baseline serum value of CgA and/or NSE.

Table 5. Baseline values of PSA correlated with soluble NE markers before treatment

	PSA ≤300 ng/ml	PSA >300 ng/ml	p value
Mean of initial CgA, ng/ml	178.9	355.8	0.029
Mean of initial NSE, ng/ml	18.9	12.0	0.036

tion was significantly associated with PSA response, i.e. patients with the highest PSA decrease also had the highest CgA decrease (p = 0.034; fig. 3).

Treatment response according to NE features was assessed. Patients with NE features had the same ORR and PSA response rate than patients without these characteristics (table 4). Moreover, these markers were not predictive of TTP. These NE markers were correlated with PSA before treatment (table 5). The mean value of serum PSA was 300 ng/ml, and patients with an inferior concentration had a significantly lower CgA value than those with higher PSA (178.9 vs. 355.8 ng/ml, respectively, p = 0.029). Baseline NSE was also correlated with PSA values before treatment. Patients with lower PSA (<300 ng/ml) had a significantly higher initial NSE value than men with PSA >300 ng/ml (18.9 vs. 12.0 ng/ml, respectively, p = 0.036).

Overall Survival

Patients had a follow-up for survival of 50 months after the first treatment dose. No patient was lost to follow-up. Twenty-three patients died and 7 are still alive with a median time of 18 months (range 1–45; fig. 4). Overall survival was correlated with NE markers. The survival of patients with an abnormal serum value of CgA was not significantly different than the survival of patients with a normal CgA value (p = 0.13). However, patients with an abnormal value of NSE had a higher overall survival than patients with a normal value (32.10 vs. 20.11 months, respectively; p = 0.027).

Correlation of Geriatric Assessment and Compliance

Geriatric assessments were performed for patients ≥70 years old. The median MMSE score was 26/30 (range 21–30), which corresponds to a normal score. The median scores for ADL and IADL were 6/6 (range 4.5–6) and 7/8 (range 1–8), respectively; these high scores were correlated with patient's autonomy. The median GDS-15 score was 4/15 (range 1–11), which meant a high probability of depression in our oldest patients. The MNA median score was 23.8/30 (range 14.0–27.5), which corresponds to no malnutrition risk. The geriatric assessment and sociocultural evaluation did not appear to influence compliance with curcumin intake.

Discussion

This was the first phase II trial to evaluate the combination of curcumin and docetaxel/prednisone in first-line treatment in patients with CRPC. The previous phase I trial studied the feasibility, safety and tolerability, and

allowed to define the daily recommended dose of curcuminoids in association with docetaxel/prednisone (6,000 mg/day) [19].

This nonrandomized phase II has demonstrated encouraging results of the docetaxel/prednisone and curcumin combination in CRPC patients, with a tumor objective response in 40% and a PSA response in 59% of men. Therefore, these results supported the expected statistical results that a PSA response would be achieved for >50% of patients and an ORR for ≥17% of men with measurable disease. These objectives were constructed from the pivotal studies of Petrylak et al. [25] and Tannock et al. [1]. However, the highlights of the present study were the percentage of PSA decrease and the rapidity of response. In fact, in the majority of cases (65%), the PSA decrease was >80%, and 36% of these responders reached PSA normalization. Moreover, these responses occurred in the first three cycles for 88% of responders.

No other clinical trials have investigated this association between docetaxel and curcumin in CRPC. However, several clinical trials have studied the association of docetaxel with other anticancer agents like tyrosine kinase inhibitors, antiangiogenic agents, inhibitors of antiapoptotic proteins or cytotoxic agents [26]. They obtained a modest increase in the response rate compared to docetaxel monotherapy but increased toxicity. Some studies have investigated the combination of docetaxel plus estramustine, and the first data support a possible advantage for this combination [27, 28]. Eymard et al. [27], in phase II, have obtained a PSA response in 68% of patients. The large randomized phase II study of docetaxel plus estramustine for the Southwest Oncology Group protocol 9916 (SWOG 9916) achieved a PSA response rate of 50%. However, this combination was associated with thromboembolic complications and gynecomastia.

Thus, our combination appears to yield higher results than docetaxel alone [1]; they are close to those obtained in studies with docetaxel plus estramustine. These results appear interesting, but according to the number of patients enrolled, this deserves more conclusive comparisons.

Unlike other clinical trial molecules, curcumin (6,000 mg/day) was well tolerated, without systemic toxic effects. The AE observed were consistent with those detected with docetaxel monotherapy, i.e. principally low-grade AE with asthenia, diarrhea and musculoskeletal pain, and higher-grade AE with neutropenia [1]. Moreover, only 3 patients had their treatment delayed in our study because of thrombopenia, diarrhea and flu symptoms, and these toxic effects were not due to curcumin ingestion. Two men had docetaxel dose adjustment (50 and 63 instead of 75 mg/m^2) for diarrhea and general state impairment. So, toxicity did not appear to be a limitation of this combination. Previous phase I studies of curcumin have shown that this agent can be administrated safely at oral doses of up to 8,000 mg/day and up to 12,000 mg/day with only grade I diarrhea and headache as AE [19, 29, 30]. However, in those studies, the important volume of curcumin taken daily was considered unacceptable by some patients.

In our phase II, the number of curcumin capsules (12 per day for 7 consecutive days) might be a limitation, especially considering the patients' age (median of 69 years). However, 89% of patients' cycles conformed to a perfect compliance, and no difference was observed for older men. Thus, the number of capsules did not seem to be a disadvantage of this combination.

Fifty months after the first treatment, the overall survival was 18 months. Also, the results show a longer overall survival for patients with an abnormal serum value of NSE than for patients with a normal NSE value. It is a pilot study with a low number of subjects, so it is difficult to compare and to conclude on these results.

The ancillary study analyzed the treatment impact of the NE markers CgA and NSE. NE variation was different according to the markers, with a higher decrease rate for NSE than CgA. This treatment seemed to be more active on NSE than CgA; this was in accordance with the results reported by Fléchon et al. [31] that showed an NSE decrease for 31% of cases and a CgA decrease for 7%. Moreover, docetaxel/prednisone and curcumin acted similarly on PSA and tumor response regardless of the NE features (elevated or not). Similarly to us, other authors found that NE features were not significant predictors of response [32, 33]. However, comparison seemed difficult as their treatments were different and not exclusively given as first line. Inversely, Cabrespine et al. [34] found that CgA was predictive of response for CRPC patients treated by paclitaxel/carboplatin or mitoxantrone. They found a better response in patients with elevated CgA at baseline. However, our treatment seemed to have a broader effect than that of their therapies. Curcumin seems to potentiate docetaxel/prednisone with a larger action on tumor lesions. Curcumin was reported experimentally to enhance the cytotoxicity of docetaxel/prednisone through the blocking of cell cycle progression, sensitization of prostate cancer cells to apoptosis, angiogenesis inhibition and downregulation of growth factor involved in progression [35]. In our study, the CgA value was positively associated with initial PSA. Similarly, Zissimopoulos et al.

[36] found that CgA values were significantly correlated with PSA values ($p < 0.001$) in metastatic prostate cancer patients. In fact, biologically endocrine cells characterized by CgA may simultaneously express the exocrine marker PSA via paracrine mechanisms [37]. Furthermore, we have found an association between NE change and treatment response. CgA had a similar evolution to PSA. One study has found the same correlation between CgA and PSA response [34]. CgA evolution seemed parallel to PSA response; thus, a concomitant evaluation of CgA may improve treatment response assessment. In contrast to CgA, lower NSE was associated with a high PSA value. Only 2 studies investigated this association, one in CRPC patients, although they did not find a link between these parameters.

The single-arm, nonrandomized design of the study and the low number of patients poses limitations in determining the relative benefit of the combination compared with docetaxel/prednisone alone. However, this combination is considered innovative and has never been investigated in CRPC. Likewise, these preliminary results demonstrated the feasibility of these agents with a high response rate without extra toxicity, and the treatment was well accepted by patients. However, poor absorption has been reported for curcumin [4], and in futures trials it will be necessary to extensively investigate the pharmacokinetics parameters. Thus, the data of this trial justify a randomized phase II trial comparing docetaxel/prednisone plus curcumin versus docetaxel/prednisone plus placebo, which would lead to the consideration of curcumin alone as a maintenance treatment.

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Disclosure Statement

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

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