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Original article

Effect of combination of a polyamine-free oral nutritional supplement and docetaxel in symptomatic, metastatic castration-resistant prostate cancer patients

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ABSTRACT

Introduction: Polyamines are essential for cancer cell growth. Both reducing exogenous polyamines and blocking polyamine synthesis reduce tumor growth and potentiate chemotherapy in tumor models.

Purpose: We assessed the tolerance of a polyamine-free oral nutritional supplement alone and in combination with docetaxel in symptomatic castration-resistant prostate cancer patients.

Methods: A total of 30 patients (mean age: 71 ± 7 years) were enrolled in a prospective trial. For the first 14 days, the patients were given polyamine-free supplement only as the sole diet, the quantity of which was then progressively reduced and supplemented with low polyamine-containing foods. Combined docetaxel chemotherapy began on Day 21, which included six 75-mg/m^2 prednisone injections every 3 weeks. Clinical and biological tolerance, quality of life (QOL), performance status (PS), pain, and objective prostate-specific antigen (PSA) response were assessed.

Results: Toxicity was minimal in the polyamine-free supplement-alone phase. In addition, QOL ($p = 0.03$) and pain ($p = 0.03$) scores were improved. When the polyamine-free supplement was combined with docetaxel, Grade 1 or 2 nausea, vomiting, or diarrhea was reported in <35% of patients with no onycholysis or neuropathy. In addition, biological parameters were preserved. Nutritional parameters, PS, pain score, and anorexia were significantly improved. Sixty-three percent of patients reduced their analgesic consumption by at least 30%. Seventy percent of patients who completed the trial had an objective PSA response.

Conclusion: Observance of the polyamine-free supplement was good and it was well tolerated when given alone with significant improvements in QOL and pain scores. The tolerance of the combination of docetaxel and polyamine-free supplement is also very good with improved PS, pain score, and analgesic consumption.

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1. Introduction

Polyamines are naturally occurring, positively charged molecules found in all living organisms. The three main polyamines in animal eukaryotes are putrescine, spermidine, and spermine. The activity of polyamine depends on their electrostatic interactions with negatively charged macromolecules such as nucleic acids (RNA and DNA), nucleotides (adenosine triphosphate), proteins, and membrane phospholipids [1,2].

Polyamines are essential for cell growth, neoplastic cell transformation [3], proliferation, and differentiation [1,4,5]. Tumor cells contain higher levels of polyamines than normal cells [5]. The association between intracellular accumulation of polyamines and cell growth has been suggested by numerous studies in various cancers [5–7]. Cancer cells require higher levels of polyamines to sustain proliferation by increasing *de novo* synthesis [7] and extracellular absorption [8,9]. Therefore, inhibiting polyamine metabolism is a potential target for anticancer therapy [10].

In previously conducted experimental studies on animal models, the combination of polyamine synthesis inhibitors, neomycin (to reduce gut bacterial production), and polyamine-free foods was significantly found to reduce tumor growth [10–12] and improve chemotherapeutic outcomes [13].

In a previous clinical study, a low polyamine diet was suggested for a period of 6 months in 13 patients with metastatic castration-resistant prostate cancer (CRPC) [14], and another study suggested a similar diet for a longer period in 30 patients [15]. This diet was shown to reduce dietary polyamines to an estimated amount of 20-fold compared with a normal diet.

The dietary program was well observed and well tolerated. Performance status (PS) was either maintained or improved, and significant pain reduction was reported. In a nonrandomized prospective study, a low polyamine diet appeared to improve quality of life (QOL) and survival of metastatic CRPC patients [16].

To obtain maximal polyamine dietary depletion, foods designed for special medical purposes (FDSMPs) and containing very low amounts of polyamines, labeled NTL, have been developed. An estimated 2000-fold reduction in dietary polyamines can be obtained with exclusive NTL feeding.

In a Phase I trial for patients with symptomatic metastatic CRPC in a palliative setting treated exclusively with NTL diet for a period of 2 weeks and quasi-exclusive depletion for 3 additional weeks, observance and tolerance levels were very good. Improvements in PS and pain scores were also observed [17].

Docetaxel became the reference first-line chemotherapeutic drug for patients with CRPC following two studies showing a 3-month survival increase in patients receiving docetaxel compared with mitoxantrone [18,19].

In this study, we present the results of a trial evaluating the tolerance of NTL, a very low polyamine-containing oral nutritional supplement (ONS), combined with docetaxel in metastatic, symptomatic, CRPC patients. Patients treated in the TAX-237 trial [18] served as historical controls.

2. Methods

2.1. Patients

Thirty patients with symptomatic metastatic CRPC and World Health Organization (WHO) PS $\leq$ 3 were enrolled in this prospective bicentric trial. A total of 28 patients had painful bone metastases, which were assessed by either bone scan or computed tomography. Two patients had extensive pelvic lymph node metastases with inferior limb lymphedema.

Resistance to castration was defined by serum testosterone levels $<$ 1000 pg/mL, a rise in prostate-specific antigen (PSA) on two successive assays after obtaining nadir levels, and failure of at least two hormonal manipulations. Four patients had previous first-line chemotherapy.

2.2. Procedure

(1) WHO PS, weight, and body mass index (BMI) were recorded.
(2) Treatment tolerance and adverse effects (AEs) were graded according to the WHO index.
(3) QOL was evaluated by the European Organization for Research and Treatment for Cancer (EORTC) self-questionnaire (QLQ-C30; version 3) [20]. This questionnaire incorporates nine multi-item scales: five functional scales (physical, role, cognitive, emotional, and social) and four symptom scales (fatigue, pain, nausea, and vomiting). This format results in a total of 28 items with answers graded as follows: 1, not at all; 2, a little; 3, a bit more; and 4, very much. In addition, a global health (Q29) and QOL scale (Q30) graded 1 (very poor) to 7 (excellent) were used. We calculated the QLQ-28 score by adding the grading to each item, with a minimum score of 28 (excellent QOL) and a maximum of 112 (very poor).
(4) Pain was assessed according to the EORTC pain score (0, no analgesic; 1, occasional analgesics other than morphine; 2, continuous use of analgesics other than morphine; 3, occasional morphinics; 4, continuous use of morphinics) and a numerical pain score (NPS) from 0 (no pain) to 10 (maximal pain).
(5) An analgesic score (AS) was assessed as follows: points were given for each analgesic depending on its class and dose. The score was then calculated by adding all of the points; for example, 8 points for 10-mg morphine or equivalent, 6 points for 100-mg tramadol, 4 points for 500-mg paracetamol + codeine, 1 point for 500-mg paracetamol or 50-mg ketoprofen or 200-mg ibuprofen.
(6) Blood cell counts, serum electrolytes, creatinine, glucose, albumin, C-reactive protein (CRP), bilirubin, PSA, and alkaline phosphatases levels were also analyzed.
(7) All of these items were evaluated on Day 0 (Visit, V0), Day 8 (V1), Day 14 (V2), Week 3 (V3), and then every 3 weeks (V4–V8).

Observance to the study protocol was assessed using a daily self-questionnaire completed by the patient.

2.3. Protocol

NTL ONS and low polyamine dietary program

The NTL ONS is an FDSMP characterized by its low polyamine content, developed and provided by Nutrialys Medical Nutrition (Saint-Grégoire, France). Eighty percent of the patient's caloric (1600 Kcal) and nutritional daily needs were provided by six 250-mL NTL cans. The remaining 20% was provided by a light standard continental breakfast.

During the first 14 days, the NTL ONS was the sole nutrition other than breakfast. For the next 14 days, the NTL ONS was given two times a day (four cans) with a meal containing low polyamine-containing foods [17]. Then, two cans/day with two meals were proposed for the remaining 13 weeks. In case of disease progression, the health authorities required patient withdrawal.

2.4. Chemotherapy

Docetaxel (75 mg/m^2) was administered intravenously every 3 weeks with 24 mg of dexamethasone prior to injection and 10 mg of oral prednisolone (5 mg two times/day) for six cycles beginning after the initial 3-week phase of maximal dietary polyamine depletion.

2.5. Statistics

Student *t* or nonparametric Wilcoxon tests were performed with JMP 6.0 software (SAS Institute Inc., Cary, NC, USA). A p value < 0.05 was considered to be significant.

2.6. Response criteria

Responses considered to be clinically relevant were declines (improvement) $\geq$20% in the QLQ-28 and $\geq$30% in the AS scores. For PSA, an objective response was defined as $\geq$50% PSA decline for at least 3 weeks [20,21].

The protocol was accepted by the French Health Authority (Agence Française de Sécurité Sanitaire des Produits de Santé; AFSSAPS; Reference No. A 70387-45) and the local ethics committee and was registered with the European Medicines Agency under European Union Drug Regulating Authorities Clinical Trials number 2007-002 541-21. Patients gave their informed consent prior to their participation in this study.

2.7. Patient characteristics

The main characteristics of patients are listed in Table 1 and include the following: (1) age, nine patients (33%) were <70 years, 18 patients (66%) were $\geq$70 years, and 11 patients (40%) were >75 years; (2) PS, three patients (11%) had PS = 0, 14 patients (51%) had PS = 1, and 10 patients (37%) had PS = 2; (3) pain, 23 patients (85%) reported pain even when using prescription analgesics. Approximately 48% took Class 3 morphinics, 26% took Class 2 opiates, and 11% took Class 1 analgesics; and (4) nutritional status, only one patient had a BMI $<$ 21 kg/m^2. None of the patients aged $<$ 70 years were malnourished (defined by an albumin level $<$ 30 g/L). For patients aged $>$ 70 years, 28% were moderately malnourished (albumin $<$ 35 g/L) and 11% were severely malnourished (albumin $<$ 30 g/L).

Table 1 – Patient characteristics.

	Mean ± SD	Median	Spread
Age (y)	71 ± 7	73	58–81
Weight (kg)	75 ± 14	73.7	55–110
BMI kg/m^2	27 ± 4	26	20–38
VAS	4.4 ± 3	5	0–10
EORTC score	2.8 ± 1.4	4	0–4
Analgesic score	61 ± 83	21	0–276
QLQ-28 sum	56 ± 14	54	34–93
QLQ-29	3.7 ± 1.3	4	1–6
QLQ-30	3.9 ± 1.6	4	1–7
PSA (ng/mL)	305 ± 532	95	1–2082
Alkaline phosphatases (IU)	420 ± 403	236	62 ± 1552
Hemoglobin (g/dL)	11.2 ± 1.4	11.3	7.4–14.7
Leukocytes (n/mL)	7873 ± 3426	6920	3230–23,600
Neutrophils (n/mL)	5976 ± 2990	4956	1918–15,000
Lymphocytes (n/mL)	1285 ± 1543	985	180–13,216
Platelets (n/mL)	236,338 ± 70,100	236,000	19,000–443,000
Albumin levels (g/L)	39 ± 5	39	28–49
CRP	33 ± 55	10	0.13–368

BMI = body mass index; CRP = C-reactive protein; EORTC = European Organization for Research and Treatment for Cancer; PSA = prostate-specific antigen; SD = standard deviation; VAS = visual analog scale; y = years.

3. Results

Two patients withdrew their consent a few days after initiating the trial. Self-reported and estimated NTL observance was good (85%). One patient withdrew from the study at Day 6 because of intestinal intolerance (bloating).

Twenty-seven patients were evaluated for the NTL-alone phase from V0 to V3.

Nine patients did not complete the trial due to the following reasons: (1) one patient presented with a transient Grade 4 neutropenia, requiring no Granulocyte-Colony Stimulating Factor (G-CSF) prescription. Even though the patient had a PSA response with >50% decline, the investigator withdrew the patient from the trial; (2) seven patients had disease progression; and (3) one patient died after V5 due to bilateral interstitial pneumonia.

Eighteen (66%) patients completed all six docetaxel cycles at scheduled dates with no dose reduction, 7/9 patients (77%) aged $<$ 70 years, 11/18 patients (61%) aged $>$ 70 years, and 6/11 patients (54%) aged $>$ 75 years.

3.1. Tolerance

During the NTL ONS-alone phase, one patient withdrew because of gastrointestinal intolerance (bloating). Side effects observed while receiving NTL alone or in combination with docetaxel are reported in Table 2. No alopecia, nail changes, or onychonychia were reported.

Table 2 – Adverse effects at D0 (due to prior medication), during the neoadjuvant NTL ONS-only phase (D0–D21), and during the combination of NTL + docetaxel (V4–V8).

Adverse effects (WHO grades)	D0	D0 to D21 (V3) NTL alone	Combination of docetaxel and NTL	Docetaxel alone[a]
Diarrhea (1 or 2)	14	22	25	32
Nausea (1 or 2)	28	30	33	72
Vomiting (1 or 2)	24	8	23	42
Constipation (1 or 2)	47	15	20	—
Neuropathy	4[b]	4[b]	12[b]	32
Skin toxicity	0	0	0	30
Onychonychia				
Edema	4	4	4	24
Neutropenia (Grade 3–4)	0	0	11	32
Total	113	75	103	264

Data are presented as %.
[a] Published adverse effects for docetaxel use alone.
[b] Grade 1 neuropathies.

3.2. QOL

Significant mean global QLQ-C28 score improvement was observed between V0 and V2 ($p = 0.035$; Fig. 1). Some degree of degradation was observed with chemotherapy, but not statistically worse than at V0. Fourteen patients (52%) presented a ≥20% QLQ-C28 score improvement, eight patients at V1, 10 patients at V2, and 44% between V0 and V3. During chemotherapy, 28% of patients showed a ≥20% improvement. For the measure of global health (QLQ-C29), a significant improvement was observed between V0 and V2, V5, V6, V7, and V8 ($p < 0.05$). In the QOL evaluation (QLQ-C30), there was a significant improvement between V0 and V2, V8 ($p < 0.05$). More specifically, important clinical factors such as asthenia, anorexia, nausea, and vomiting were improved during the trial (Tables 3–6).

3.3. PS

The WHO PS improvement was observed ($p = 0.056$) at V4 and this became significant at V6 ($p < 0.03$; Fig. 2).

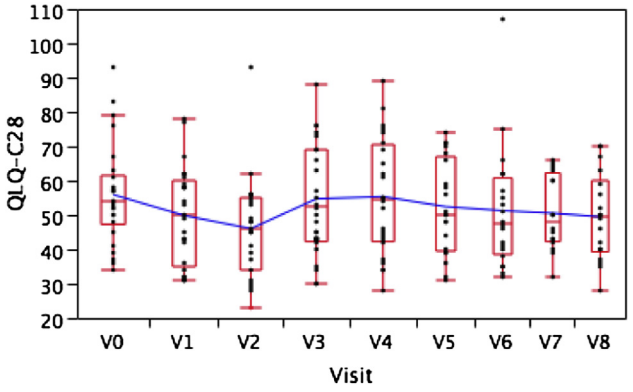

Fig. 1 – QLQ-C28 global QOL scores with a significant improvement at V2 ($p = 0.035$) after 15 days of NTL alone. QOL = quality of life; V = visit.

Table 3 – Asthenia (QLQ-C30 questionnaire) expressed as % of patients.

Asthenia	Not at all	A little	Quite a bit	Very much
V0	22	39	20	13
V1	22	61	4	13
V2	36	54	0	10
V3	30	35	26	7
V4	26	22	26	26
V5	16	55	22	16
V6	25	56	19	0
V7	25	56	13	6
V8	18	53	29	0

3.4. Pain

For NPS, a significant improvement was observed starting from V2 (Fig. 3). No significant difference was noted in the EORTC score. For AS, no significant difference was noted when comparing means, but the AS score dropped by at least 30% in 17 patients (63%). More specifically, the scores dropped by 30% as follows: V2 (8/27 patients: 30%), V3 and V4 (9/27: 33%), V5 (13/27: 48%), V6, V7, and V8 (11/27: 41%). Fifteen patients (55%) showed both a drop of at least 30% in the AS and a stable NPS or decreased NPS.

3.5. Biochemical analysis

3.5.1. Blood counts

No significant differences in mean hemoglobin levels, white blood cells, or platelets were observed (Table 7). Two patients

Table 4 – Anorexia (QLQ-C30 questionnaire) expressed as % of patients.

Anorexia	Not at all	A little	Quite a bit	Very much
V0	39	17	13	30
V1	52	26	17	4
V2	63	23	5	9
V3	43	26	26	5
V4	56	17	18	9
V5	50	33	17	0
V6	50	31	19	0
V7	56	38	6	0
V8	59	35	6	0

Table 5 – Nausea (QLQ-C30 questionnaire) expressed as % of patients.

Nausea	Not at all	A little	Quite a bit	Very much
V0	65	19	12	4
V1	73	15	4	8
V2	75	8	12	0
V3	68	24	8	0
V4	66	17	13	4
V5	75	10	10	5
V6	76	18	6	0
V7	70	30	0	0
V8	71	29	0	0

Table 6 – Vomiting (QLQ-C30 questionnaire) expressed as % of patients.

Vomiting	Not at all	A little	Quite a bit	Very much
V0	80	16	0	4
V1	96	0	4	0
V2	83	9	4	0
V3	86	12	0	4
V4	79	13	8	0
V5	90	5	5	0
V6	82	1 8	0	0
V7	94	6	0	0
V8	100	0	0	0

exhibited transient Grade 3–4 febrile neutropenia after the fourth docetaxel cycle, which resolved without specific treatment.

3.5.2. *Albumin levels and CRP*

There was no change in mean albumin levels. A gradual and significant improvement of CRP levels (inflammation) was noted at V4 (3 weeks after the first docetaxel injection) (Table 8). Ten patients had albumin levels ≤ 35 g/L, defined as malnourishment, at V0. Among these patients, only three

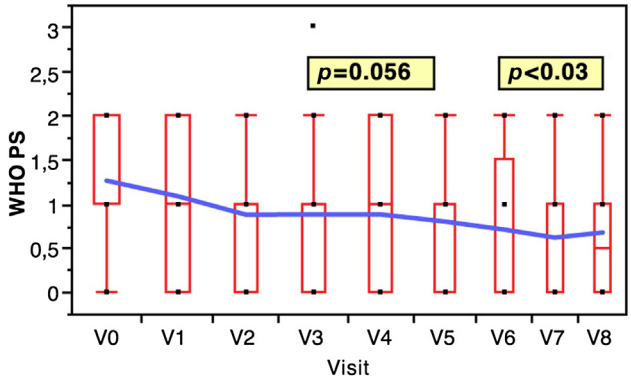

Fig. 2 – WHO PS scores with significant improvement between V1 and V6, V7, V8. PS = performance status; V = visit; WHO = World Health Organization.

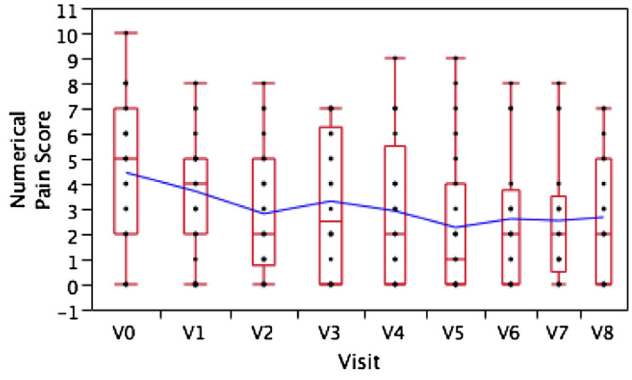

Fig. 3 – Numerical pain scores. Significant improvement between V0 and V2, V4, V5, V6, V7, and V8 ($p < 0.05$). V = visit.

Table 7 – Blood counts levels, expressed as mean ± standard deviation.

	V0	V1	V2	V3	V4	V5	V6	V7	V8
Hemoglobin (g/dL)	11.7 ± 1.6	11.4 ± 1.9	11.3 ± 1.7	11.1 ± 1.7	10.9 ± 1.3	10.9 ± 1.1	11.1 ± 0.9	11.2 ± 0.8	11.1 ± 0.8
Leukocytes (n/mL)	6820 ± 2394	7596 ± 2513	7124 ± 2378	7808 ± 4202	8450 ± 4063	8983 ± 3450	7704 ± 3500	8414 ± 4100	8250 ± 3894
Neutrophils (n/mL)	4864 ± 1873	5300 ± 2100	4986 ± 2035	5846 ± 2560	6522 ± 3404	7034 ± 3097	5965 ± 3352	6832 ± 3963	6785 ± 3890
Lymphocytes (n/mL)	1284 ± 1491	1422 ± 1494	1453 ± 1606	1486 ± 2452	1347 ± 1816	1336 ± 1695	1102 ± 582	970 ± 551	941 ± 550
Platelets (n/mL)	221,890 ± 71,970	225,120 ± 88,720	234,480 ± 77,312	230,154 ± 64,903	223,040 ± 70,900	235,750 ± 64,750	248,000 ± 63,520	256,222 ± 52,090	273,471 ± 58,748

Table 8 – Mean ± standard deviation for body weight, albumin levels, and C-reactive protein (CRP).

	V0	V1	V2	V3	V4	V5	V6	V7	V8
Weight (kg)	75 ± 14	75 ± 14	75 ± 14	75 ± 15	76 ± 15	77 ± 14	79 ± 14	78 ± 13	77 ± 13
Albumin (g/L)	38 ± 6	39 ± 5	39 ± 4	39 ± 6	39 ± 5	40 ± 4	39 ± 4	39 ± 3	39 ± 4
CRP	42 ± 57	69 ± 94	32 ± 34	53 ± 72	23 ± 42	18 ± 34	7 ± 7	18 ± 28	22 ± 35 *

* $p < 0.05$.

were able to complete the six chemotherapy sessions, whereas 15 of the 17 patients with albumin levels > 35 g/L did complete all 6 sessions (Chi square test = 9.63, $p < 0.01$). Among the 10 patients with albumin level ≤ 35 g/L at V0, six patients had a normalized level (>35 g/L) with the low polyamine nutritional program, and two of these patients were able to complete chemotherapy. The other four patients did not complete chemotherapy due to disease progression rather than treatment complications.

No difference was observed in alkaline phosphatases and total and conjugated bilirubin levels.

3.5.3. *PSA*

Thirteen patients (60% of patients having had at least three cycles of docetaxel) had a PSA decline > 50% for 3 weeks, with an 8-week median response duration. One patient presented an 80% PSA decrease during the initial NTL-alone phase.

4. Discussion

Despite therapeutic advances, metastatic CRPC patient management remains palliative. As physicians, our objective is to offer the patients the best possible QOL throughout their various treatments.

Malnourishment is often underestimated in CRPC patients as observed in 39% of the elderly patients in this trial. This factor must be explored and managed when considering chemotherapy. A polyamine-free diet combining the NTL ONS and a light breakfast (± one low polyamine-containing meal) during 4 weeks was feasible and very well observed by patients with painful, advanced disease. The tolerance rate was very good. The QOL and pain scores were improved prior to chemotherapy. A 30% decrease in analgesic consumption for 30% of these symptomatic patients was noteworthy. Asthenia, anorexia, nausea, and vomiting were improved in patients predominantly under morphinic or opiate medication. An objective response with a PSA drop of 80% was observed in one patient.

The improvement shown here could be due to the glutamate *N*-methyl-D-aspartate (NMDA) receptor, which is widely present in the central nervous system and plays an essential role in pain control and morphinic-induced hyperalgesia [21,22].

The NMDA receptor is inhibited by anesthetics such as ketamine [23]. It is stimulated by spermine, which acts on a specific NR2b region site [24,25]. Conversely, it has been experimentally demonstrated that a very low polyamine-containing diet significantly reduces pain [26] and morphine-induced allodynia and hyperalgesia due to a specific action on the NMDA receptor [21].

In this study, pain improvement and analgesic reduction, particularly when dietary polyamine depletion is maximal, tend to clinically support these experimental data. The combination with docetaxel was of interest because of a potential synergistic action of docetaxel and polyamine depletion on microtubule polymerization, the main docetaxel target [27].

As polyamine deprivation potentiates chemotherapy in animal models, one of our main concerns was that it could enhance docetaxel's AEs. However, docetaxel was very well tolerated, with a trend of fewer side effects than reported previously [18] (Table 3).

One Grade 1 neuropathy case was observed compared with the 25% reported rate [18]. This protection could also involve the NMDA receptor [28]. A recent animal study has shown the role of dietary polyamine depletion in oxaliplatin neurotoxicity prevention [29]. Blood cells were preserved. Only two (11%) Grade 4 neutropenia cases, one of which was rapidly resolved without correction with leukocyte growth factors, were observed. The majority of patients presented Grade 1 anemia but did not require transfusion or erythropoietin.

Apart from the discontinuation of chemotherapy due to disease progression, all docetaxel cycles were given at scheduled dates and doses. In a Groupe d'Etude des Tumeurs Uro-Génitales - Association Française d'Urologie (GETUG-AFU) 15/0403 study in hormone-naïve metastatic prostate cancer patients, who were treated with a combination of castration and docetaxel, the docetaxel dose had to be reduced in 53% of cases and the cycle postponed in 20% [30]. The systematic use of leukocyte growth factors was recommended by the authors due to a 30% occurrence of Grade 3 or Grade 4 neutropenia including two fatal cases.

From a nutritional perspective, patient weight was maintained, and six of the 10 malnourished patients were nutritionally improved. Sixty percent of patients who had at least three cycles of docetaxel and 70% who had all six cycles had an objective PSA response for a median duration of 8 weeks. This finding corresponds to the response rate reported in the literature [18].

In conclusion, management with a very low polyamine-containing ONS, either alone or in combination with docetaxel, is feasible and very well observed and tolerated in symptomatic CRPC patients. The results showed improved PS, decreased pain, and reduced analgesic consumption. The nutritional status of patients was improved, contributing to a better QOL. Further studies comparing this approach to standard management should be conducted.

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