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Is there still a place for vinorelbine in advanced metastatic castration resistant prostate cancer?

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Abstract

The aim of this paper was to evaluate the activity and tolerability of oral vinorelbine in patients with advanced castration resistant prostate cancer (CRPC) who progressed after a minimum of three lines including: abiraterone acetate, docetaxel, cabazitaxel, and enzalutamide.

Treatment consisted of weekly oral vinorelbine 60 mg/m^2. Chemotherapy was administered until disease progression or unacceptable toxicity.

Twenty-six patients received vinorelbine: their median age was 74 years (range 58–84 years). Twenty-four (92.3%) patients had bone metastases. A decrease in PSA levels ≥50% was observed in 2 patients (7.7%). Among the subjects who were symptomatic at baseline, pain was reduced in 3 patients (13.6%) with a significant decrease in analgesic use. Median progression-free survival was 9 weeks (95% CI: 7 to 11) and median overall survival was 17 weeks (95% CI: 12 to 22). Treatment was well tolerated, and no grade 4 toxicities were observed.

Our findings do not suggest the use of oral vinorelbine on a weekly schedule, in CRPC heavily pre-treated.

Abbreviations: CRPC = castration resistant prostate cancer, OS = overall survival, PCWG2 = Prostate Cancer Working Group 2, PFS = progression-free survival, PSA = prostate specific antigen.

Keywords: chemotherapy, prostate cancer, vinorelbine

1. Introduction

Prostate cancer is the most common cancer among occidental men.[1] Castration resistant prostate cancer (CRPC) is defines as the progression of disease after or during medical and/or surgical castration. In the setting of CRPC, several new agents with different mechanisms of action have been approved;[2] these include older or novel taxanes, novel oral anti-androgen drugs such as enzalutamide or abiraterone acetate, immunotherapy (sipuleucel-T) and bone targeted agent (radium-223).[2] All these drugs have shown to improve survival; however, most patients will progress developing resistance, underlying a medical need for this subgroup of patients. In this setting, various alternative options for heavily pre-treated patients have been proposed including: estramustine phosphate, docetaxel rechallenge and carboplatin plus etoposide, which were based on small clinical.[3–5]

Among other chemotherapeutic agents, Vinorelbine, a semi-synthetic vinca alkaloid that is a mitotic inhibitor with better therapeutic index and lower neurotoxicity with respect to other vinca alkaloids has showed certain efficacy and safety in the treatment of patients with metastatic CRPC,[6–7] in particular, the oral administration of vinorelbine that is an easy route of administration compared with intravenous, achieved results and good safety profile also in elderly patients,[8] which are ideally comparable to an heavily pre-treated population of patients.

Based on these studies, we performed a phase II study to evaluate efficacy and safety of oral vinorelbine in patients with advanced CRPC who have been heavily pre-treated.

2. Materials and methods

2.1. Inclusion criteria

Patients were enrolled if had a histologically confirmed metastatic CRPC. Patients must progress after previous lines of therapies including abiraterone acetate, docetaxel, cabazitaxel, and enzalutamide (with a minimum of 3 lines of therapies for patient), as defined by Prostate Cancer Working Group 2 (PCWG2) criteria.[9,10]

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All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all individual participants included in the study.

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All patients continued luteinizing hormone–releasing hormone agonists during CRPC status of disease. All patients had Eastern Cooperative Oncology Group performance status of ≤2, hepatic, renal adequate and hematological function. The exclusion criteria were other previous malignant disease and other clinically significant disease with a special attention with cardiovascular. All patients gave their informed consent and the protocol was approved by local Ethics Committee.

2.2. Treatment plan and assessments

Treatment consisted of weekly oral vinorelbine 60 mg/m^2. Cycles were administered if patients had adequate renal (serum creatinine ≤2.0 mg/dL), hepatic function (serum bilirubin ≤2.0 mg/dL) and hematological (leukocytes ≥3000/mm^3; hemoglobin ≥10 g/dL, platelets ≥100,000/mm^3). Patients continued to take analgesic medications to provide optimal pain control. All patients with bone metastases received bone-targeted agent if clinically indicated. Vinorelbine was administered until disease progression or unacceptable toxicity. An antiemetic pre-medication with ondansetron 8 mg per os was administered if clinically indicated.

After the first occurrence of a grade III haematologic toxicity the treatment was delayed and administered at the same dose after complete recovery. If there was grade IV toxicity, the treatment was interrupted, and after a maximum of 3 weeks for recovery, the patients restarted subsequent administrations to 30 mg. If there was another episode of grade IV toxicity, the treatment was interrupted. Anamnestic and physical evaluation was performed at baseline in all patients. Every 3 weeks, we performed blood tests including prostate specific antigen (PSA) and every 2 months we performed radiological assessments, including computed tomography scans of the thorax, abdomen, and pelvis. Follow-up data were available for all patients.

2.3. Outcome measures

PSA response was defined by ≥50% decline from baseline, while a ≥25% PSA increase, confirmed with a second PSA reading after a minimum of 3 weeks, was used to determine PSA progression and response duration. RECIST 1.1 criteria were used to assess measurable disease.[11] Median overall survival (OS) was measured from the start of vinorelbine to death or censoring. Kaplan–Meier estimates by the *STATA/IC version 12 software were used to determine p*rogression-free survival (PFS), defined as time from start of chemotherapy to time of PSA progression, symptomatic progression and/or radiographic progression. Pain symptomatology was measured at baseline and then every 3 weeks by the McGill Melzack Pain Questionnaire.[12] National Cancer Institute Common Terminology Criteria for adverse events (version 3.0 were adopted to grade the adverse events[13]).

2.4. Statistical analysis

PSA response was the primary endpoint. In accordance with Simon minimax design a sample size of 25 patients was planned, assuming a response rate of approximately 10% for other fourth-line chemotherapies, and a target level of interest of 30%, with an α of 0.05 and a β of 0.90. Overall survival, PFS, and pain response were secondary endpoints.

3. Results

From March 2016 to December 2017, a total of 26 patients were enrolled. Table 1 reported the baseline and clinical characteristics of the included patients. Their median age was 74 years (range 58–84 years). Bone metastases were present in 24 (92.3%) men. Median PSA level at baseline was 140 ng/mL (range 0.8–9820 ng/mL). All patients were treated with almost three lines of therapies for CRPC, all patients performed prior docetaxel and abiraterone acetate while 18 and 9 patients were treated with prior enzalutamide and cabazitaxel respectively.

Table 1

Patient characteristics.

Enrolled patients	26
Median age (range): years	74 (58-84)
Previous treatment	
Prostatectomy	19
Radiotherapy	13
Number of prior lines for CRPC	
3	26
>3	14
Previous therapies for CRPC	
Docetaxel	26
Abiraterone acetate	26
Enzalutamide	18
Cabazitaxel	9
Other	13
Laboratory: median serum value, range	
PSA, ng/mL	140 (0.8–9820)
Hemoglobin, g/dL	10.6 (9.0–12.4)
LDH, U/L	225 (90–1980)
Sites of metastases	
Bone	24
Lymph nodes	14
Lung/liver	6
Pain present	22
Requiring opiates	15
ECOG performance status	
0	5
1	16
2	5
Gleason Grade	
<8	13
≥8	13

Median duration of treatment with vinorelbine was 7 weeks. A decrease in PSA levels ≥30% was observed in 5 patients (19.2%) (Table 2). Out of the 9 patients previously exposed to cabazitaxel, one (11.1%) achieved a PSA response. In the subgroup of patients who received previous enzalutamide, 4 (22.2%) out of 18 patients achieved a PSA response.

After a median follow-up of 13 weeks, the median PFS was 9 weeks (95% CI: 7 to 11) and median OS was 17 weeks (95%

Table 2

Outcomes summary.

Enrolled patients	26
Median duration of treatment (weeks)	7
PSA decline (%)	
≥30%	5 (19.2)
≥50%	2 (7.7)
Survival	
PFS, median (weeks; 95% CI)	9 (7–11)
OS, median (weeks; 95% CI)	17 (12–22)
Palliative response (%)	3 (13.6)
Median duration of palliative response (weeks; 95% CI)	7 (3–10)

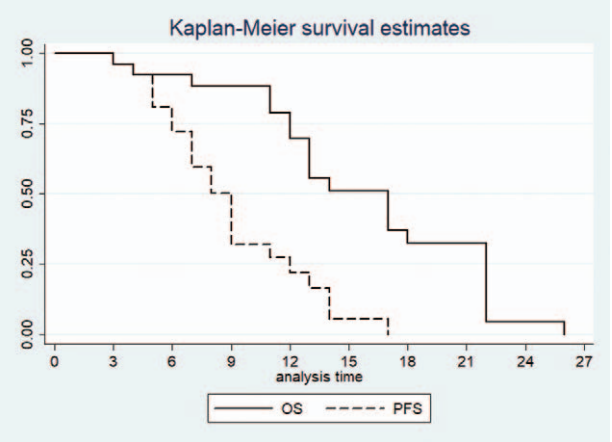

Figure 1. PFS and OS of the 26 enrolled patients.

CI: 12 to 22) (Fig. 1). Among prognostic factor, we investigated the role of basal values of PSA, we found that men with values of PSA higher than median (140 ng/mL) had a shorter PFS if compared with men with lower PSA values (6 vs 9 weeks; $P = .1$), additionally OS was further shorter in men with higher values of PSA (13 vs 15 weeks, $P = .4$), however although a trend has been observed suggesting that basal values of PSA is prognostic and predictive of efficacy, the absence of a statistical significance does not allow definitive conclusions. Among symptomatic patients, pain was reduced in 3 (13.6%) with a decrease in analgesic use. The median duration of palliative response was 7 weeks.

The regimen was generally well tolerated, and no unexpected toxic effect was observed (Table 3). No grade 4 toxicity was observed.

The most frequent side effects were neutropenia in 7 (26.9%) patients and nausea/vomiting in 3 (11.5%) which were grade 1 or 2 in most cases. Grade 3 neutropenia and thrombocytopenia occurred in 1 patient respectively. A dose reduction of vinorelbine (30 mg) was needed for these 2 patients. At the time of the analysis, 4 patients (15.4%) were still alive.

4. Discussion

The results of this study suggest that low weekly vinorelbine has a poor efficacy in heavily pre-treated CRPC suggesting no further role for this agent in this setting of disease.

The semisynthetic vinca alkaloid with cytotoxic effect "vinorelbine", a microtubule-binding agent, is currently available as an oral formulation has produce interesting results, both as a monotherapy or in combination for several solid tumors including breast cancer and small cell lung cancer.[14–16] In regard of prostate cancer, the use of vinorelbine as a monotherapy has been shown to be effective demonstrating a clinical response rate and pain control.[6,7,17,18] Specifically, clinical response was reported to range between 20% and 40% with 20% reduction of PSA levels.[6,7,17,18] In addition, the oral route of administration has suggested as a valid option the use of a metronomic oral vinorelbine.[19]

Over the past years, the new agents abiraterone acetate, enzalutamide, and cabazitaxel were approved for the treatment of advanced CRPC. However, the optimal sequencing of these new drugs remains unclear.[20–23] Unfortunately, there is a shortage of data on the efficacy of a further line of treatment in heavily pre-treated CRPC. In 2014, Buonerba et al investigated in a small study the combination chemotherapy with carboplatin plus etoposide in a population of patients who progressed after several therapeutic drugs for CRPC: 2 out of 7 patients with measurable disease had a partial response, median PFS was 11 weeks (range: 8–18), and median OS was 18 weeks (range: 12–26).[3] In addition, another small study suggested that low dose Estramustine phosphate with concomitant low dose acetylsalicylic acid is a safe treatment option with some activity for patients with advanced CRPC who have been heavily pretreated. Thirty-one patients were enrolled. A total of 9 patients (29.0%) gained a PSA response. Median PFS was 3.6 months and median OS 7.6 months.[4] Finally, another small study reported a decrease in PSA levels ≥50% in 7 patients (26.9%); a median PFS of 4.4 months and median OS of 10.7 months for the combination of weekly docetaxel combined with weekly epirubicin in patients with advanced CRPC previously exposed to docetaxel and abiraterone acetate.[5]

In contest, there is an advantage of an oral route of administration offered by oral vinorelbine in a group of frail CRPC patients such as those heavily pre-treated of the our study, unfortunately we have demonstrated a very poor efficacy of vinorelbine with a decrease in PSA levels ≥50% observed in 2 patients (7.7%); a median PFS of 9 weeks and median OS of 17 weeks. However, we have to report that this study has enrolled a very poor prognostic group of patients compared with the aforementioned (Table 4). One of the most interesting data is that in 9 patients previously exposed to cabazitaxel, only one (11.1%) achieved a PSA response but in the subgroup of patients who received previous enzalutamide, 4 (22.2%) out of 18 patients achieved a PSA response. Although the small number of involved patients do not allow definitive conclusions this last data may require further investigation and seems reflect the trend of successful use of chemotherapy in heavily pre-treated patients not exposed to previous cabazitaxel.[5] Finally, as expected, we observed a good safety profile with no grade 4 toxicity or discontinuation of therapy. However, it is noteworthy that there are several limitations in our study: first, the small numbers of patients precluding possible definitive conclusions. Second, the PFS is a mixed endpoint that includes PSA progression, clinical progression and disease progression and caution therefore may be taken before drawing firm conclusions and finally the absence of a comparison or placebo.

In conclusion, as we all await additional studies which may clarify the optimal sequencing of the new available agents in advanced CRPC, the present analysis seems to not suggest the use of oral vinorelbine on a weekly schedule, in CRPC heavily pre-treated.

Table 3

Number of patients experiencing the most frequent treatment-related adverse events.

	Grade 2	Grade 3
Neutropenia	7 (26.9%)	1 (3.8%)
Anemia	2 (7.7%)	0
Trombocytopenia	2 (7.7%)	1 (3.8%)
Nausea/vomiting	3 (11.5%)	0
Abdominal pain	1 (3.8%)	0
Diarrhea	1 (3.8%)	0

Table 4

Previous studies with chemotherapy in heavily pretreated CRPC.

Study	Agent	Number of patients	Previous Systemic Therapies For CRPC (%)	50% PSA Response (%)/Pain Response (%)	Median PFS (months)/ Median OS (months)
Buonerba et al [3]	Carboplatin+ etoposide	15	Docetaxel: 100 Abiraterone acetate: 86.7 Enzalutamide: 13.3 Cabazitaxel: 100 Other: 0	6.7/ 33.3	*2.75/ *4.5
Petrioli et al [4]	Estramustine posphate	31	Docetaxel:100 Abiraterone acetate: 100 Enzalutamide: 0 Cabazitaxel: 51.6 Other: 48.4	29/ 38.7	3.6/ 7.4
Petrioli et al [5]	Docetaxel+Epirubicin	26	Docetaxel: 100 Abiraterone acetate: 100 Enzalutamide: 0 Cabazitaxel: 15.4 Other: 0	26.9/ 38.1	4.4/ 10.7
Roviello et al	Vinorelbine x os	26	Docetaxel: 100 Abiraterone acetate: 100 Enzalutamide: 69.2 Cabazitaxel: 34.6 Other: 50	7.7/ 13.6	*2.25/ *4.25

* Reported as weeks.

Author contributions

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