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Original Article

Chemotherapy in frail elderly patients with hormone-refractory prostate cancer: A “real world” experience

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ABSTRACT

Background: In elderly patients affected by metastatic castration-resistant prostate cancer (mCRPC) chemotherapic treatment may be the choice if one considers not only the chronological age, but also the clinical status, the functional reserve, and the vulnerability of patients. Several studies have confirmed the survival benefit of docetaxel and vinorelbine among every class of age. Most CRP elderly patients are defined as frail, maybe due to comorbidities: these patients, who are unable to be candidates for a standard treatment, should be candidates for a more tolerable treatment.

Methods: Twenty-six elderly, frail patients were evaluated. The patients were affected by mCRPC and were receiving chemotherapy with intravenous weekly docetaxel (12 patients) or oral metronomic vinorelbine (14 patients). Safety and efficacy were investigated evaluating clinical and objective response and tolerability. The level of patient satisfaction with treatment was assessed through a questionnaire.

Results: No significant difference was found between groups in terms of 6-month progression-free survival: 57.1% for patients treated with oral metronomic vinorelbine versus 58.3% for patients treated with docetaxel. Median progression free survival was 8.6 months (95% confidence interval: 7.1–9.4 months), and 8.2 months (95% confidence interval: 6.9–9.3 months) for patients treated with oral metronomic vinorelbine and socetaxel, respectively. Oral metronomic vinorelbine was associated with increased patient satisfaction with respect to docetaxel administration. The most frequent side effect associated with oral metronomic vinorelbine was anemia and vomiting, with similar frequency compared to patients treated with docetaxel.

Conclusion: Weekly docetaxel and oral metronomic vinorelbine are equally effective and well tolerated in elderly unfit and frail patients affected by mCRPC. Metronomic vinorelbine treatment is associated with higher patient compliance and satisfaction.

1. Introduction

Prostate cancer represents the most common cancer among American[1] and European men, and it is associated with an age-adjusted mortality rate of 10.5/100,000 patients, which is still growing all across Europe.[2] Metastatic castration-resistant prostate cancer (mCRPC) is characterized by disease progression after medical and/or surgical castration.

Nowadays, aging population is a critical issue due to the increased number of people aged ≥ 80 years. More than 69 million men in 2000 were aged ≥ 80 years, whereas in 1950 the population counted only 13.8 million men aged ≥ 80 years; furthermore, it is expected to reach 379 million in 2050.[3] In addition, scientific progress warrants increased life expectancy, so an increase in prostate cancer in elderly or older patients is expected.[4]

Chemotherapy is a standard treatment for most of patients affected by mCRPC. In elderly patients chemotherapy treatment should be tailored not only to the chronological age, but also to the clinical status, functional reserve, and vulnerability.[5]

Age-stratified analysis of patients (< 65 years, ≥ 65 years, and ≥ 75 years) has confirmed the survival benefit of docetaxel among every class of age[6]; therefore, administration of docetaxel 75 mg/m^2 every 3 weeks when indicated should be considered as the standard chemotherapy treatment of prostate cancer, independent from age.

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Several data have shown the safety and efficacy of vinorelbine in the treatment of elderly patients with mCRPC.[7,8] Most of these studies have been implemented when the oral formulation of vinorelbine has been available in order to exploit the easiest route of administration compared with intravenous drugs and evaluated the patients preferences of administration.[9]

Most of the CRP elderly patients are defined as frail, maybe due to comorbidities. These patients, who are unable to be candidates for a standard treatment, should be candidates for a more tolerable treatment.

The weekly docetaxel regimen seems to be associated with less side effects compared with the 3-week regimens.[10,11] At the same time, several studies have demonstrated the efficacy of vinorelbine in the treatment of advanced cancer,[12] especially in elderly patients with poor performance status where improved safety and compliance has been shown.[13] The intravenous administration of both vinorelbine and docetaxel as a first-line strategy in the treatment of hormone-refractory prostate cancer (HRPC) has been compared in previous publications demonstrating the equal efficacy of these two drugs.[13] To date, oral versus intravenous chemotherapy for the treatment of CRPC evaluating quality of life among elderly, unfit patients has not been investigated to date.

Finally, a valid option for the treatment of this population due to lower toxicity than a maximum tolerated dose regimen is metronomic oral vinorelbine (mVNR); mVNR is administered three times per week, of a considerably lower dosage than each standard administration of standard vinorelbine in a maximum tolerated dose schedule. This schedule is now known to involve multiple mechanisms of action including an antiangiogenesis effect, modulation of the immune system, and indirect cytotoxic effect against cancer cells.[14]

2. Materials and methods

2.1. Patients

A total of 26 patients were evaluated with an age range of 70–87 years old, with performance status > 1 (Eastern Cooperative Oncology Group); all of them presented with symptomatic bone pain and were considered unfit/frail due to fatigue, slowing walking speed, and physical activity reduction.[15,16] Treatment allocation was based only on clinical evaluation.

All patients had a histological confirmed diagnosis of metastatic prostate cancer, and all had already undergone hormone therapy with luteinizing hormone-releasing hormone analogous/androgen deprivation therapy (ADT).

Of those, 12/26 (46.2%) patients were treated with intravenous weekly docetaxel 30 mg/m^2 (schedule 1, 8, 15, 22, 29, q 36); while 14/26 (53.8%) patients were treated with oral mVNR 30 mg 3 days per week for 3/4 weeks. Both cohorts also received prednisone 5 mg, twice a day (b.i.d.).

Patients were clinically evaluated at baseline and at the beginning of the course, along with prostate-specific antigen (PSA) evaluation. Computed tomography or positron emission tomography evaluation was executed every 3–4 months. All patients were followed-up for 18 months.

2.2. Evaluation of frailty

Frailty evaluation is based upon functional criteria.[15] It is positive when three out of the five of the following items are present: weight loss (4.5 kg in the past year), self-reported fatigue, handgrip reduction, physical activity reduction (evaluated by means of Physical Activity Scale for the Elderly[17]), and slowing walking speed (> 7 s/4.57 m).

2.3. Efficacy end-points

Safety and efficacy were investigated evaluating clinical response as defined by Response Evaluation Criteria in Solid Tumors (RECIST) criteria,[18] as symptom control, PSA level variations, and 6-/12-months progression-free survival (PFS).

Biochemical response was evaluated as follows: complete response = PSA < 4 ng/mL or reduction > 80% from baseline; partial response = PSA reduction > 50% from baseline; and disease progression = PSA increase > 50% from baseline; stable disease = every other condition.

Symptomatic response was evaluated as follows: complete response = performance status 0–1, absence of pain, and analgesics administration; partial response = 2 points reduction in the scale of analgesics consumption, pain, or performance status, or 1 point reduction at least in two of the previous dominium; and disease progression = 2 points reduction in the scale of analgesics consumption, pain, or performance status, or 1 point reduction at least in two of the previous dominium.

Objective response was evaluated standing on the RECIST criteria,[18] which can be summarized as follows for target lesions: complete response = disappearance of all target lesions along with pathologic lymph node(s) diameter reduction (< 10 mm); partial response = ≥ 30% reduction of the sum of the diameters of target lesions from baseline; disease progression = ≥ 20% increase of the sum of the diameters of target lesions from the lowest known value (at baseline or initial response); and stable disease = every other condition.

Response of nontarget lesions was defined (always accordingly to RECIST criteria[18] as follows: complete response = disappearance of all nontarget lesions along with pathologic lymph node(s) diameter reduction (< 10 mm), and biomarkers negativity; disease progression = increase (number or size) of nontarget lesions; borderline = one or more nontarget lesion persistent and/or biomarker positivity.

In addition, every patient was asked to fill out a questionnaire (at baseline and every 3 months afterwards) in order to ascertain their degree of satisfaction with the treatment adopted. Possible answers to the questionnaire were: satisfied, unsatisfied, and indifferent; and motivations could be enclosed.

2.4. Safety end-points

Safety of the treatment was evaluated by means of the Common Toxicity Criteria.[19]

3. Results

Among the 26 patients with metastatic prostate cancer, the mean age was 78.1 years. Every patient (26/26) had bone metastases, seven out of 26 (27%) had lymph node involvement, and three out of 26 (11.5%) had visceral metastases. In addition, nine out of 26 (35%) previously underwent radical prostatectomy, five out of 26 (20%) radiotherapy, and 26/26 previously received hormonal therapy (luteinizing hormone-releasing hormone analogous, ADT; Table 1).

3.1. Efficacy evaluation

No significant difference was found between groups in terms of PFS: 57.1% for patients treated with oral mVNR versus 58.3% for patients treated with docetaxel. Median PFS was 8.6 months (95% confidence interval: 7.1–9.4 months), and 8.2 months (95% confidence interval: 6.9–9.3 months) for patients treated with oral mVNR and docetaxel, respectively. Patients still on treatment after

Table 1
Baseline characteristics stratified for chemotherapy received.

Variables	Vinorelbine ($n = 14$)	Docetaxel ($n = 12$)
Median age (y)	77 ± 5	81 ± 6
Disease staging		
Locally advanced	0 (0)	0 (0)
Metastatic	14 (100)	12 (100)
Bone metastases only	9 (69.2)	9 (75)
Bone + lymph node involvement	4 (30.7)	3 (25)
Bone + visceral involvement	2 (14.2)	1 (8.3)
Risk evaluation		
Very low/low	5 (35.7)	3 (25)
Intermediate	6 (42.8)	7 (58.3)
High	2 (14.2)	2 (16.6)
Very high	1 (7.1)	0 (0)
Treatment of local disease		
Surgery	3 (21.4)	6 (50)
Radiotheraphy	2 (14.2)	3 (25)
Hormone therapy only	9 (64.2)	3 (25)
Prechemotherapeutic treatment		
LHRH analogous	3 (20.3)	2 (16.6)
ADT	8 (64.8)	9 (75)
Others	3 (14.9)	1 (8.3)

Data are presented as *n* (%) or mean ± standard deviation.
ADT, androgen deprivation therapy; LHRH, luteinizing hormone-releasing hormone.

12 months were four out of 14 (28.5%) among those receiving oral mVNR, and two out of 12 (16.6%) among those receiving docetaxel.

Clinical and biochemical responses were stable after the first two evaluations, with acceptable pain control and PSA levels in both groups.

Among patients experiencing disease progression, 87.5% of those receiving oral mVNR versus 100% of those receiving docetaxel also showed rising PSA values; 81.2% of those receiving oral mVNR versus 70.8% of those receiving docetaxel showed clinical progression as well.

At the 9-month analysis, six out of 14 patients receiving oral mVNR and five out of 12 patients receiving docetaxel were still on treatment. Of those, patients showing an objective positive response were four out of six (66.6%) with oral mVNR versus two out of five (40%) with docetaxel (Table 2).

3.2. Patient satisfaction

Oral mVNR was associated with increased patient satisfaction (11/14 or 78.5%) with respect to docetaxel administration (7 out of 12 or 58.3%) at the 6-month analysis, and at 18 months docetaxel was associated with reduced patient satisfaction (3 out of 12 or 25%). Furthermore, patients disclosed that satisfaction regarding oral mVNR was due to oral administration and lower perception of side effects.

3.3. Safety evaluation

The most frequent side effect associated with oral mVNR administration was anemia, with similar frequency compared with patients treated with docetaxel (8% vs. 7% Grade 3) and vomiting (5% Grade 3 vs. 2%, respectively). Grade 3 constipation was recorded in 5% of patients belonging to the oral mVNR group versus 0% of those receiving docetaxel. Severe vomiting involved only 5% of patients treated with metronomic VNB (mVNB). The incidence of other side effects are reported in Table 3.

4. Discussion

This observational study was aimed to investigate safety and efficacy of chemotherapy with oral mVNR versus intravenous docetaxel in frail elderly patients with mCRPC.

Elderly patients, are characterized by a progressive decline of physiologic systems and a consequently decreased functional reserve capacity, conferring vulnerability or frailty in the presence of environmental stressors[15,16]; frail patients, when affected by metastatic prostate cancer, are not optimally treated.[20]

Recent studies reported that early chemotherapy, especially in symptomatic patients with “high volume” disease, insures a significant survival benefit.[25] Docetaxel treatment is associated with a 10–15% response rate, with a survival prolongation of 1 year, and with an increased quality of life.[10,21]

The results of the ChemoHormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED) trial[22] have shown a benefit in overall survival of the docetaxel–ADT combination, mainly in patients with high metastatic extent, in which it had an overall survival of 17 months compared with ADT alone. The same results were recently reported in the Systemic Therapy in Advanced or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) multi-arm, multi-stage trial[23] in which the addition of docetaxel to hormonal treatment showed a survival advantage of 65 months versus 43 months, ($P = 0.002$, hazard ratio = 0.73).

In addition, docetaxel administration is also correlated to better pain control, reduced levels of PSA, and an improvement of quality of life.

In elderly patients, even if chemotherapy showed a clear benefit in terms of survival and post-treatment quality of life, it is still

Table 2
Responses to chemotherapy stratified for type and treatment.

Follow-up	Parameter	Vinorelbine ($n = 14$)	Docetaxel ($n = 12$)
3 mo	PSA	SD: 4 PR: 8 DP:2	SD: 6 PR: 4 DP:2
	Clinical	SD: 4 PR: 9 DP:1	SD: 7 PR: 3 DP:2
	Imaging	SD: 4 PR: 8 DP:2	SD: 6 PR: 4 DP:2
6 mo	PSA	SD: 2 PR: 6 DP:4	SD: 4 PR: 3 DP:3
	Clinical	SD: 3 PR: 6 DP:3	SD: 5 PR: 3 DP:2
	Imaging	SD: 3 PR: 5 DP:4	SD: 4 PR: 3 DP:3
9 mo	PSA	SD: 3 PR: 3 DP:2	SD: 3 PR: 2 DP:2
	Clinical	SD: 4 PR: 2 DP:2	SD: 4 PR: 2 DP:1
	Imaging	SD: 3 PR: 3 DP:2	SD: 3 PR: 2 DP:2
12 mo	PSA	SD: 3 PR: 2 DP:1	SD: 1 PR: 1 DP:3
	Clinical	SD: 2 PR: 2 DP:2	SD: 2 PR: 1 DP:2
	Imaging	SD: 3 PR: 1 DP:2	SD: 2 PR: 0 DP:3

DP, disease progression; PR, partial response; PSA, prostatic-specific antigen; SD, stable disease.

Table 3
Side effects and adverse events stratified for treatment group.

Events	Vinorelbine (% of patients)				Docetaxel (% of patients)			
WHO grade	1	2	3	4	1	2	3	4
Neutropenia	18	18	12	11	27	24	25	3
Thrombocytopenia	18	12	3	0	26	15	3	1
Anemia	21	12	8	1	22	10	7	2
Nausea	19	26	3	0	11	15	2	0
Vomiting	2	1	5	0	2	1	2	1
Mucositis	12	8	0	0	15	12	2	0
Alopecia	8	10	3	0	15	28	20	0
Constipation	18	24	5	1	7	10	0	0
Neurotoxicity	5	3	0	1	13	18	9	1
Pain	13	5	0	1	11	7	4	1
Fever	8	5	0	1	14	19	4	1
Fatigue	11	9	0	1	28	30	11	3

WHO, World Health Organization.

questioned due the toxicity.[5] A recent study from the UK showed that most prostate cancer patients with advanced age were not considered suitable for chemotherapy.[24]

Conversely, most elderly patients wish to be treated as younger patients seeking the potential survival benefit of chemotherapy despite the risk of toxicity.[25]

Indeed, considering the toxicity reported with docetaxel,[6,10] a previous study by Tannock et al[10] described a change with different schedules of administration: every 3 weeks recorded more frequent G3-4 neutropenia (32% vs. 2%) and alopecia (65% vs. 50%), while the weekly schedule had registered increased tearing (21% vs. 10%) and epistaxis (17% vs. 6%). Weekly[27] or twice per week[13,26] administration may represent a choice for elderly unfit patients.

The study of Fosså et al[27] involved 109 patients randomly assigned to weekly docetaxel associated with prednisone b.i.d or to the latter alone, biochemical response was significantly better among the first group of patients (54% vs. 26%). In addition, PFS was 11 months versus 4 months, respectively. Overall median survival was 27 months for patients administered with docetaxel versus 18 months for patients administered with prednisone alone. In conclusion, pain relief and quality of life evaluation definitely demonstrated superiority of the treatment regimen including docetaxel. Most common adverse effects associated with the latter medication were neutropenia and thrombocytopenia; with treatment delay for no more than 2 weeks. Grade-2 stomatitis and Grade-3 peripheral neuropathy warranted a dose reduction of weekly Docetaxel (25 mg/m^2).

Oral vinorelbine demonstrated to be an attractive alternative also due to its pharmacokinetic characteristics: rapid absorption (1.5–3 hours), 40-hour half-life with 40% bioavailability not influenced by meals, even though nausea and vomiting are less frequent when medication is taken postprandial; specifically all those characteristics are not influenced by patients' age.

Vinorelbine is a semisynthetic vinca alkaloid with cytotoxic effect against some different neoplasms. It is a mitotic inhibitor with better therapeutic index and lower neurotoxicity with respect to other vinca alkaloids, due to the lower axonal degradation associated with its use. Use of vinorelbine in the treatment of prostate cancer, although limited, has been shown to be effective: several studies[7,8,28,29] previously showed clinical response rate and pain control. Specifically, clinical response was reported to range between 20–40% with 20% reduction of PSA levels.[7,8,28,29]

Furthermore, an Italian study[30] investigated the association of oral vinorelbine (60 mg/m^2) plus prednisone (5 mg b.i.d.) among 33 elderly and unfit patients affected by mCRPC. That paper clearly showed acceptable safety and efficacy of this treatment with positive clinical and biochemical responses in about one third of patients, a median PFS of 13.4 weeks, and an overall median survival of 45 weeks. Most frequent adverse events involved hematopoiesis.

Aiming to enhance tolerability preserving effectiveness, a metronomic schedule of oral administration has been previously validated. It consists of low-doses administered at close intervals, in order to avoid extended outages from therapy.[31] This strategy not only represents an easy-to-use protocol for the patients, but also demonstrated satisfactory safety profile and effective results. Standing on its pharmacokinetic characteristics, vinorelbine results optimal for oral administration every other day (3 times per week) even for long periods (3–4 weeks); thus limiting treatment-related toxicity.[32]

A recent Greek study[12] evaluated different dosages (30 mg, 40 mg, and 50 mg) of oral mVNR in the treatment of some metastatic solid cancers (breast, prostate, nonsmall cell lung cancer); the final conclusion was that 50 mg dosage (3 times per week) was associated with best responses and acceptable toxicity. The absence of clinically-relevant toxicity correlated to prolonged and effective doses of oral mVNR was impressive, indeed blood counts suppression was rare, nonhematological toxicity was negligible, and peripheral neuropathy was minimal; even in those patients who were on treatment for some months or years.[12]

Safety and efficacy of oral mVNR has been studied also in 34 elderly patients with metastatic breast cancer, and complete responses were seen in 6% of patients, while 32% of patients showed partial responses; with a median PFS was 7.7 months, and overall median survival was 15.9 months.[32] The protocol was well tolerated in all patients whom received at least three cycles of therapy. Hence, oral mVNR may represent a robust alternative also for patients with HRPC.

Taking into account that patients included in this experience were all elderly and frail, reported results appears to be satisfactory, as shown by 6-month PFS of 58.3% (7 out of 12 patients), and 12-month PFS of 16.6% (2 out of 6 patients still on treatment after 1 year). Biochemical response (58.3% at 6 months) and pain control (66.6%) of docetaxel-allocated patients were as well impressive. Grade-3 neutropenia was the most frequent adverse event associated with the administration of docetaxel (31%), which anyway did not prompt a dose reduction.

The intravenous administration was well tolerated by patients, even though percentage of patient satisfaction was lower in comparison with oral vinorelbine (58.3% vs. 78.5%). This result was mainly correlated to the route of administration.

Most common side effects associated with oral mVNR administration were nausea, and constipation; of note the incidence of high grade toxicity was very limited.

All six patients treated with oral mVNR who reached final evaluation gave satisfactory responses to the questionnaires, much more than what seen among docetaxel patients. Patient opinion was driven mainly by oral administration, and the low incidence of side effects.

Our study, despite its small sample size (26 patients), demonstrated the noninferiority of oral mVNR with respect to docetaxel, as confirmed by similar 6-month PFS. Clinical and biochemical responses confirmed effectiveness of treatment both at 6-month and 9-month evaluations. After 1 year the percentage of patients continuing treatment was higher among those receiving oral mVNR.

In conclusion, elderly unfit and frail patients affected by HRPC, whom are frequently ruled out from chemotherapy treatment, can be treated with traditional drugs by means of an alternative scheduling: weekly docetaxel and oral mVNR are equally effective and well tolerated; mVNR treatment is associated with higher patient compliance and satisfaction.

Obviously, further and larger studies are needed to confirm these findings. Meanwhile, given the absence of any other experiences in frail patients, oral mVNR or weekly docetaxel should be considered for the treatment of those patients affected by CRPC suitable for chemotherapy.

Conflicts of interest

No potential conflict of interest

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