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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