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Original article

First-line treatment in senior adults with metastatic castration-resistant prostate cancer: A prospective international registry

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Abstract

Aims: To compare the efficacy and tolerability of taxane and nontaxane therapy in senior adults with chemonaïve metastatic castration-resistant prostate cancer (mCRPC), and examine the effect of patient health status on outcomes.

Patients and methods: Between 2009 and 2011, 333 patients aged ≥70 years with mCRPC were enrolled in a prospective international registry. Patients were categorized as having received taxane-based or nontaxane therapy, and classified as fit, vulnerable, frail, or terminal, according to investigator judgement or International Society of Geriatric Oncology guidelines. Efficacy measures included overall survival (OS) and progression-free survival. Grade 3/4 toxicities were recorded. Predictors of OS were identified using multivariate Cox regression.

Results: The proportions of fit/vulnerable/frail patients were 65%/14%/17% (International Society of Geriatric Oncology), and 39%/43%/17% (investigator). In single-factor analyses, taxane therapy improved OS (hazard ratio [95%CI] = 0.53 [0.30–0.93]; $P = 0.027$) and progression-free survival (hazard ratio [95% CI] = 0.55 [0.40–0.76]; $P < 0.001$) vs. nontaxane therapy. Patients with frailty also benefited from taxane therapy (adapted regimen in 52%). In multivariate analysis, taxanes improved OS even with poor prognostic factors present ($P = 0.017$); age was unrelated to prognosis. Taxane therapy was well tolerated; most common grade 3/4 toxicities (taxane vs. nontaxane) were fatigue (17% vs. 4%), nausea/vomiting (14% vs. 5%) and neutropenia (10% vs. 1%).

Conclusions: The results of this nonrandomized, observational study suggest that first-line taxane therapy may benefit senior adults with mCRPC more than alternative therapies. Treatment decisions should not be based on chronological age.

Keywords: Comorbidity; Docetaxel; Geriatric assessment; Taxoids

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1. Introduction

Older men with prostate cancer more often have larger, higher-grade tumors than younger men, but only a minority with high-risk localized disease receive treatment with curative intent [1–5]. Furthermore, older patients with advanced disease may be denied survival-extending treatments such as chemotherapy because of toxicity concerns [6,7].

Androgen deprivation therapy (ADT) is the mainstay treatment for newly diagnosed, hormone-naïve, metastatic prostate cancer, although this may change, following recent results showing a significant overall survival (OS) benefit from ADT combined with docetaxel in patients with high disease burden [8]. When chemonaive prostate cancer becomes castration-resistant (mCRPC), first-line treatment options include docetaxel, cabazitaxel (in patients progressing on docetaxel), sipuleucel-T, new androgen-receptor (AR)-targeted agents, and radium-223 [9–11].

Docetaxel became standard treatment for mCRPC based on the TAX327 study in which docetaxel plus prednisone significantly improved OS, pain relief, and quality of life, irrespective of patient age, vs. mitoxantrone plus prednisone [12,13]. A contemporaneous study also reported improved OS with docetaxel (plus estramustine) vs. mitoxantrone/corticosteroid [14]. The median age (range) of patients in these trials was 68 (36–92) and 70 (43–88), respectively, and it is likely that mainly fit elderly patients were enrolled because of strict inclusion/exclusion criteria.

International Society of Geriatric Oncology (SIOG) guidelines recommend treatment decisions should be based on health status, comorbidities, and physical impairments, rather than chronological age [15,16]. The standard 3-weekly (q3w) docetaxel regimen is recommended for fit and vulnerable senior patients, whereas adapted regimens (once-weekly [qw] or bi-weekly schedule [q2w] [17]) should be considered for frail patients if impairments are irreversible. New AR-targeted agents and sipuleucel-T are further options for asymptomatic or mildly symptomatic patients, but the optimal treatment protocols are not established.

Little information exists regarding the effectiveness and tolerability of taxanes and other therapies in senior men with chemonaive mCRPC in real-life practice. We therefore established an international registry to evaluate the first-line management of mCRPC in older patients in a real-world setting and the influence of health status on such management.

2. Methods

2.1. Study design

This was a prospective, international, multicentre disease registry of senior men with mCRPC. Patients were categorized as having received taxane-based or nontaxane therapy. The protocol specified 2 patient visits, at inclusion and at 6-month follow-up. At the inclusion visit, investigators collected information regarding demographic and disease characteristics, health status evaluation, and planned primary therapy. Treatments were classified according to their therapeutic class only, as per disease registry rules. This study was conducted before the introduction of the new AR-targeted agents, abiraterone acetate and enzalutamide. At the single, 6-month follow-up visit, data regarding primary therapy received, and treatment effectiveness and safety were collected. The registry was completed after this visit and no additional data were collected. All patients provided written informed consent. The protocol was approved by the institutional review board or ethics committee at each center.

2.2. Patients

Consecutive men aged ≥ 70 years with mCRPC, castrate levels of testosterone (<50 ng/dl) and evidence of disease progression (investigator judgement) were eligible. Progression was defined as prostate-specific antigen (PSA) progression or radiographical evidence of new metastases, according to physician judgement. Patients were excluded if they had previously received chemotherapy for prostate cancer.

2.3. Evaluation of health status

Health status evaluation was based on comorbidities, dependence, and nutritional status, using SIOG recommendations (Supplementary Fig. S1) [15]. Comorbidity was assessed using the Cumulative Illness Scoring Rate-Geriatrics scale [18]. For each organ system, the proportion of patients with ≥ 1 comorbidity at grade 3/4 was calculated. Dependence was assessed using the activity daily living (ADL) scale, which rates the patient's ability to accomplish basic activities of daily living [18], and the 4-item Instrumental ADL scale, which rates activities requiring higher levels of cognition and judgement [18]. For both scales, the proportion of patients exhibiting ≥ 1 abnormality was calculated. Nutritional status was evaluated by determining weight loss over the previous 3 months ($<5\%$ or $\geq 5\%$ of body weight). Concomitant medications and patient's mental health were also recorded. Investigators assessed patients using the above criteria and, using their judgement, classified them as fit, vulnerable, frail, or terminal. Patients were also classified using the SIOG health status algorithm [15].

2.4. Evaluation of treatment outcomes

At the unique follow-up visit planned in the protocol, the following information was collected: is prostate cancer progressing (yes or no), type of disease progression; is the