Chemotherapy for Prostate Cancer in Senior Adults: Are We Treating the Elderly or the Frail?

Joaquim Bellmunt*

Department of Medical Oncology, University Hospital del Mar-IMIM, Passeig Marítim, 25–29, 08003 Barcelona, Spain

Chemotherapy was considered ineffective in hormone-refractory prostate cancer (HRPC) until a paradigm shift was established in 2004. Two randomised phase 3 trials were published (the TAX327 trial and the Southwest Oncology Group [SWOG] trial) [1,2] showing a statistically significant survival benefit with docetaxel in combination with estramustine1 or prednisone[2] when compared to the standard mitoxantrone prednisone (MP). Since then, docetaxel chemotherapy has become the standard first-line treatment for HRPC. However, because patients randomised in phase 3 clinical trials are highly selected, they may not represent a real-life population. Consequently, the benefit observed in both trials is only applicable to patients fulfilling specific eligibility criteria.

An updated survival analysis, including data on 310 additional deaths [3], was reported in January 2008. The analysis showed that the survival benefit of docetaxel every 3 wk persisted with extended follow-up ($p = 0.004$). In addition, subsequent data provided showed that docetaxel every 3 wk improved survival in men both older and younger than 68 yr of age. Even if the trial was not initially designed to address subgroup analysis, this and other retrospective data analysis provide some helpful information on benefit based on patients’ age and guides when to start chemotherapy. Whether there is an age limit for patients to receive chemotherapy is consequently a highly relevant question, specially taking into account that prostate cancer (PCa) affects mainly an ageing population.

In the oncologic world, there is still a general reluctance to use chemotherapy in the elderly because of concerns regarding increased toxicity and tolerability. Nowadays, the management of “senior adults” (a wider concept including the frail or nonfrail elderly) with advanced PCa is not optimal because treatment decisions are frequently based on the chronological age of the patient. Most patients with PCa may be considered unsuitable for standard docetaxel chemotherapy based on their chronological age and may receive palliative rather than a more optimal treatment. Therefore, there is a clear need to better define how to treat elderly or frail patients with PCa, as they constitute such a large proportion of the patient population. From a clinical perspective, age is highly heterogeneous and poorly reflected by chronological age. Although ageing can be associated with changes that might affect how chemotherapy acts, it is not a barrier to chemotherapy per se and is not in itself a contra-indication to standard-regimen chemotherapy. Chemotherapy decisions in patients with advanced PCa are complex and involve consideration of several factors apart from age, including the clinical disease status, life expectancy, comorbidity, and functional status. When considering chemotherapy, decisions must be based not on age but with at least one of the available screening tools of vulnerability and frailty [4].
However, clinical trials still evaluate chemotherapy in the elderly based on age, and no clinical trials have specifically addressed the strategy of geriatric assessment. Trials often have not only stringent exclusion criteria relating to age but also to comorbidities and concomitant therapies. Few studies have investigated the efficacy and safety of chemotherapy in elderly men with HRPC. Initial phase 2 trials showed there was a similar incidence of nonhaematologic adverse events in both younger and older patients. Older patients were, however, more sensitive to docetaxel-induced neutropenia, which is attributed to a declining bone marrow reserve with age [5].

Regarding the schedule and based on tolerance issues, many medical oncologists are still reluctant to use the standard 3-wk docetaxel regimen in elderly HRPC patients. Phase 3 studies show the same efficacy for chemotherapy with docetaxel (75 mg/m2 q3) plus low-dose prednisone in healthy senior adults as in younger patients (TAX327). However, the tolerance of the 3-weekly schedule has not been specifically studied in vulnerable and frail senior adults. Conversely, several clinical trials suggest that q1w dosing of docetaxel reduces the incidence of myelosuppression and may therefore be more appropriate for vulnerable and frail senior adults [6,7]; however, this has yet to be prospectively evaluated. Moreover, it is important to stress that in TAX327, weekly docetaxel did not produce a greater survival benefit than MP (even though the study was not powered to demonstrate a survival benefit).

In the present issue of *European Urology*, Italiano et al [8] report on a survey for 175 very elderly (>75 yr) patients treated for HRPC in nine tertiary cancer centres with first-line docetaxel-based chemotherapy in clinical routine. Approximately half of the patients received a “standard” 3-weekly regimen (SR) and the other half an “adapted” regimen (AR), mostly delivered on a weekly schedule. This study provides relevant information about efficacy and tolerance in elderly patients. Although retrospective, this analysis—with all its inherent biases—raises a warning sign that data coming from clinical trials are not easily applicable to the broader patient population seen in daily clinical practice. The study shows that docetaxel given on a weekly basis is less safe than generally believed, because frail patients poorly tolerated this schedule. This challenges the general belief that a weekly regimen is more suitable for frail patients.

A plausible explanation for this finding is that the study population was not balanced because patients treated with an AR (docetaxel not administered every 3 wk) were older, in poorer general status, and more symptomatic than patients treated with the SR. Another limitation of the study is that the selection of a standard or an adapted regimen was based on the clinician’s decision, and oncologists generally believe that a weekly regimen is more adapted to the frail. However, a standard way to define frail in the elderly population was not applied, and no objective geriatric assessment was used.

This is the first study assessing the use of docetaxel in daily routine practice among very elderly patients (>75 yr) with HRPC. This study provides two important messages: (1) It confirms the prior assumption that patients >75 yr of age considered fit for the SR by their medical oncologist had a similar safety and efficacy profile to younger patients; (2) a weekly docetaxel regimen in elderly cancer patients is less safe than generally believed and was found in the TAX327 study [2].

The use of the AR—specifically, the weekly docetaxel regimen—in this poor performance status (PS) population might not necessarily be the “better” regimen to give, because the major side-effect of the weekly regimen is fatigue, which is already most prominent in patients with poor PS. Conversely, one could consider that even in the elderly, the side-effect profile of myelosuppression most frequently seen in the q3 weeks of docetaxel can be reversed with the use of myeloid growth factors, making this treatment more acceptable.

An extremely important lesson learned is that the study reinforces the need to systematically apply better ways to measure comorbidities. It clearly highlights the need to integrate a comprehensive geriatric assessment in the clinical decision-making process in frail patients. There is an urgent need to define the appropriateness of docetaxel dose and schedule for frail patients. Several aspects of docetaxel administration, such as dosage, timing of rest periods, and impact on quality of life (QoL) remain to be elucidated in the subset of frail patients. For example, it is not known whether decreasing the dose further in a weekly schedule might produce a benefit through a different mechanism of action, because weekly taxanes have been shown to have an antiangiogenic mechanism in addition to the well-known cytostatic effect [9]. For that, we need specific and carefully designed clinical trials. Meanwhile, the optimal chemotherapy schedule remains to be established in this setting.

To summarise, in elderly and frail senior adults, two crucial concepts must be clearly established when determining treatment. The first is to define what constitutes frail; the second is to define what constitutes optimal treatment.
When defining who is frail, we must consider that treatment decisions should be made based on the overall health status of the patient, comorbidity being a key driver of life expectancy. Effective assessment provides a detailed insight into the function of the patient, allows risk classification of the patient, and ultimately aids in the treatment decision-making process [10]. The use of life expectancy tables, such as those produced by the US National Center for Health Statistics [11], allows physicians to make reasonable predictions about how long a patient is likely to live. In addition, as stated in the Italiano paper [8], several lines of evidence indicate that a comprehensive geriatric assessment can predict tolerance to chemotherapy, morbidity, and mortality in older cancer patients more accurately than PS or a simple numeric evaluation of comorbidities [4].

When defining the optimal treatment, there are no comprehensive recommendations for elderly patients with HRPC, and the International Society of Geriatric Oncology is currently developing guidelines to use in this setting. The SIOG proposes to assign patients to four different categories according to a simple geriatric assessment: good health, vulnerable, frail, and palliation. Good health patients are fit and healthy seniors who should receive standard chemotherapy. Vulnerable patients have some form of reversible comorbidity and can be treated like their younger counterparts after this comorbidity has been treated. Frail patients have irreversible comorbidities, and modified regimens such as q1w docetaxel chemotherapy may be appropriate [10]. However, to date, these guidelines are not based on validated assumptions and should be prospectively tested. Further trials in the elderly and frail senior population showing proven efficacy in specific settings and using validated instruments are required.

Nowadays, good news is coming for senior adults with PCa. Less toxic oral compounds, such as new targeted strategies like irreversible inhibitors of CYP17 (P450c17), inhibitors of 17α-hydroxylase and c17, 20-lyase (abiraterone) [12], and highly potent inhibitors of the androgen receptor (AR) MDV3100, which inhibits AR function by blocking nuclear translocation, DNA binding [13], have now shown signs of promising efficacy with a good tolerability profile. Activity of these compounds has been demonstrated even in patients failing docetaxel. Those compounds might have a suitable place either combined with or instead of chemotherapy.

Conflicts of interest: The author has nothing to disclose.

References


doi:10.1016/j.eururo.2008.08.065