Chemotherapy for older patients with prostate cancer

John Anderson, Hein Van Poppel*, Joaquim Bellmunt†, Kurt Miller‡, Jean-Pierre Droz§ and John M. Fitzpatrick¶

Department of Urology, Royal Hallamshire Hospital, Sheffield, UK, *Department of Urology, University Hospital KU Leuven, Belgium, †Department of Medical Oncology, University Hospital del Mar, Barcelona, Spain, ‡Department of Medical Oncology, Centre Léon-Bérard, Lyon, France and ¶Department of Urology, Mater Misericordiae Hospital and University College Dublin, Ireland

Accepted for publication 7 August 2006

KEYWORDS
prostate carcinoma, hormone refractory, chemotherapy, docetaxel, age

INTRODUCTION

The image of chemotherapy in prostate cancer has changed in recent years. Chemotherapy was previously thought to be limited to having a palliative role, as a range of chemotherapeutic agents relieved symptoms but failed to prolong life in metastatic hormone-refractory prostate cancer (HRPC) [1]. Attitudes have gradually been changing, with a recent survey of 232 physicians in the USA (including medical oncologists, urologists and radiation oncologists) showing that most would recommend chemotherapy for metastatic HRPC [1] (Fig. 1) [2]. This trend has now been further supported by results of two phase III trials showing a survival benefit in metastatic HRPC with docetaxel-based therapy [3,4]. Developing a successful partnership between urologists, radiation therapists and medical oncologists as part of a multidisciplinary team will be crucial to optimizing the management of those patients [5]. Other clinical trials using docetaxel, alone or combined, at earlier stages in the disease are under development, as are studies with other anticancer agents [6,7]. It is likely that the role of chemotherapy in the management of prostate cancer will expand in the next few years, making the urologist–oncologist partnership pivotal in adopting any changes in clinical practice.

There is still reluctance to use chemotherapy in the elderly because of concerns about increased toxicity and tolerability. Considering that most patients with prostate cancer are elderly, it is conceivable that this reluctance might lead to less satisfactory treatment because of patients’ age. The purpose of this review is to examine the changing population of patients with prostate cancer, the relationship between age and chemotherapy, and the lessons learned using chemotherapy to treat other types of cancer in elderly patients.

PROSTATE CANCER IN AN AGEING POPULATION

The population of the world is ageing; in the next 25 years, the global population aged ≥65 years is likely to grow by nearly 90% (by ≈1 million every month). The WHO estimated that 40% of people dying in 2025 will be aged ≥75 years [8]. In the European Union it is expected that by 2050 the number of people aged 65–79 years will increase by nearly half, while those aged >80 years will virtually double [9].

The implications for the incidence of prostate cancer are likely to be substantial. Prostate cancer is a disease that requires numerous carcinogenic steps and consequently affects older people, compared with tumours with relatively few intermediate steps, such as melanoma [10]. Although PSA screening in some countries has meant that many men are being diagnosed with prostate cancer at an earlier age, most would still be classed as elderly at the time of diagnosis. For example, in the USA, >70% of men are aged ≥65 years at diagnosis [11]. In the UK, even though the greatest percentage increase in recent years has been in younger groups, the absolute numbers are much higher for elderly men (≥50 per 100 000 population for men aged <55 years, compared with nearly 1000 per 100 000 population for those aged ≥85 years [Fig. 2]) [12]. Moreover, given the relatively long time course associated with prostate cancer, if patients are not classed as elderly at diagnosis it becomes increasingly likely they will be as the disease progresses. One study estimated that an average of 13 years passes between initial failure of radical prostatectomy and subsequent death, with ≈8 years elapsing before metastases become evident and 5 years between metastasis and death [13]. Taking all these factors into consideration, there is clearly a need to better define how to treat elderly patients with prostate cancer, as they comprise such a large proportion of the patient population.

IS THERE AGE BIAS IN USING CHEMOTHERAPY?

Despite studies supporting the benefits of chemotherapy specifically in the elderly, its use has not been universally adopted, even when recommended. For example, in breast cancer, where adjuvant therapy is an accepted part of treatment, older women (aged ≥65 years) are seven times less likely to receive adjuvant chemotherapy than women aged <50 years [14]. Another study showed an age-related decrease in the number of physicians recommending patients for adjuvant chemotherapy, despite similar acceptance rates by patients for adjuvant therapy and no age-related differences in the drug regimens recommended [15]. It is likely to be related to attitudes to age itself, rather than concerns about the suitability of chemotherapy.

The findings were similar for colon cancer; following the National Institutes of Health Consensus Conference in 1990, it was recommended that patients with stage III colon cancer receive adjuvant chemotherapy, because survival was better in clinical trials of this treatment. A recent analysis of prospective data gathered between 1990
and 2002 from hospital cancer registries in >85,000 patients found that the use of adjuvant chemotherapy in patients with stage III colon cancer had indeed increased (from 39% in 1991 to 64% in 2002) [16]. However, it remained lower in elderly patients, even though adjuvant chemotherapy increases survival in elderly patients to the same extent as in younger patients.

Physicians are also reluctant to prescribe chemotherapy in men with HRPC, especially if the men are of advanced age. A survey published in 2003 showed that the main barriers to physicians prescribing chemotherapy for HRPC were concerns about toxicity and lack of efficacy [2]. This attitude might have changed with the recent publication of the results of the phase III docetaxel trials [3,4].

Lastly, there is evidence that older patients are significantly under-represented in clinical trials using chemotherapy, despite the bulk of patients with cancer in the general population being elderly [17,18]. A recent systematic review stated that only 25–33% of potentially eligible older patients were enrolled into clinical trials [19]. The reasons for this are unclear, but trials often have stringent exclusion criteria relating to age, comorbidities and concomitant therapies. Nevertheless, it is likely that clinicians are reluctant to put elderly patients forward for inclusion into trials [18,19]. Physicians’ concerns often relate to comorbid conditions and the toxicity of the treatment under investigation, yet in some cases the greatest barrier to accrual of older patients was actually the physicians’ perception [19].

Collectively, these data show that there is a tendency for older patients to be denied the best available treatment to fight cancer. Considering that most men with prostate cancer, especially with late-stage disease, are elderly, this gives cause for concern.

DEFINING THE TREATMENT NEEDS OF ELDERLY PATIENTS

PHYSIOLOGICAL EFFECTS OF AGEING

It is known that the ageing process is not uniform and that patients show variable declines in organ function. Some people at 75 years old might be as fit, if not more so, than others at age 60 years [20]. This leads to the question of who is an ‘elderly’ patient.

Many trials and regulatory authorities classify this as ≥65 years, although some stipulate >70 or >75 years [21]. However, a threshold age of 65 years is ‘young’ for those with prostate cancer.

Age-related physiological changes in function can affect most pharmacokinetic variables, including first-pass metabolism, volume of distribution, plasma protein binding and renal excretion [22]. Few studies have specifically examined age as a factor influencing the pharmacokinetics and pharmacodynamics of chemotherapy. Although changes in some physiological variables are predictable, it is well recognized that there is more heterogeneity in the elderly than in younger individuals [21].

Thus, age is highly heterogeneous from a clinical perspective and poorly reflected by chronological age. Consequently, it is important to distinguish between fit and frail elderly patients, and not to judge solely on chronological age when considering suitability for chemotherapy.

AGE IS NOT A BARRIER TO CHEMOTHERAPY

It is important that age is not of itself a contraindication to standard-regimen chemotherapy, but to acknowledge that comorbidities and poor performance status can often be limiting factors [21]. Thus, ‘fit elderly’ patients might tolerate the standard dose and schedule of chemotherapy with no significant side-effects, and obtain the same
FIG. 3. Willingness to accept the chemotherapy in American and French patients with or without cancer [26].

![Bar chart showing willingness to accept chemotherapy in American and French patients with or without cancer.](image)

The type of cancer and the type of chemotherapy used can also influence how chemotherapy is tolerated in elderly patients.

Nevertheless, as chemotherapy shows a relatively narrow therapeutic index compared with most other drugs, the physiological changes and consequent effects of ageing on pharmacokinetics can potentially affect toxicity. Thus, some ‘fit elderly’ patients might still have age-related pharmacokinetic/pharmacodynamic changes that might result in increased toxicity. In some cases, supportive or protective agents can be particularly helpful in limiting haematological toxicity in elderly patients who are known to be at increased risk. For example, growth factors such as granulocyte macrophage colony stimulating factor or granulocyte colony stimulating factor might be used as prophylaxis to prevent febrile neutropenia when receiving moderately toxic chemotherapy [24].

In summary, although ageing can be associated with changes that might affect how chemotherapy acts, age is not a barrier to chemotherapy per se. Other factors such as comorbidities assume far greater importance when making treatment decisions.

THE ATTITUDE OF PHYSICIANS TO CHEMOTHERAPY IN THE ELDERLY

Many physicians assume that older patients might not wish to face the toxic effects of chemotherapy to prolong survival. Indeed, there is evidence that elderly patients are as motivated as younger ones to accept chemotherapy for a potential survival benefit [25]. A survey of 195 French and USA patients aged 70–95 years, with or without cancer, found that most would consider chemotherapy [Fig. 3] [26]. At least two-thirds of these patients would be willing to undergo mild (i.e. lower toxicity) chemotherapy, irrespective of whether they had cancer at the time of questioning. When asked whether they would try strong (i.e. higher toxicity) chemotherapy, more than two-thirds of French and USA patients with cancer said they would; however, while patients with cancer reported similar high levels (70.5–77.8%) of acceptance in both countries, the value decreased considerably in those French patients who did not have cancer, to about a third. The occurrence of cancer can thus dramatically influence the acceptance of chemotherapy, with a vast majority of elderly patients willing to accept strong chemotherapy in such situations. In conclusion, it is essential that patients are viewed by urologists and oncologists not just according to their chronological age.

EVIDENCE SUPPORTING THE USE OF CHEMOTHERAPY IN ELDERLY PATIENTS WITH PROSTATE CANCER

Despite younger and older men with HRPC having a similar overall survival and progression-free survival [27], relatively few studies have investigated the efficacy and safety of chemotherapy in elderly men with HRPC or assessed the relationship between these variables and ageing. It was shown recently that some form of geriatric evaluation might help to screen patients who have vulnerability criteria or who are at risk of vulnerability [28]. This allows a better evaluation of the health status of elderly patients than chronological age. Nevertheless, in clinical trials the evaluation of chemotherapy in the elderly is currently still based on age.

In a phase II study conducted by the Eastern Cooperative Oncology Group, 56 men with metastatic HRPC aged ≥70 years (median 78) received a weekly regimen of low-dose docetaxel (25 mg/m²) and estramustine (280 mg for 3 days) for six cycles. There was a decrease in PSA level by half or more in 63% of men; at 1 year, 17% of patients were estimated to be progression-free. Treatment was well tolerated, with no grade 4 treatment-related adverse events and a relatively low incidence of grade 3 treatment-related adverse events [29]. These comprised fatigue/asthenia (13%), arrhythmia, thrombocytopenia and dyspnoea (all 4%).

The influence of age on the efficacy and tolerability of weekly docetaxel (36 mg/m²) for six cycles was further analysed in a pooled analysis of two phase II studies in men with metastatic HRPC [30]. Men aged ≥70 years had lower baseline haemoglobin and higher baseline PSA levels than men aged <70 years, but the efficacy was similar in both groups. There were PSA responses in 47% of older men vs 40% of younger men (P = 0.75). Moreover, there was no significant difference in time to progression (P = 0.28) and overall survival (P = 0.52). Both groups also showed a similar incidence of severe (grade 3–4) haematological and non-haematological toxicity.

Lastly, a preliminary subgroup analysis of the phase III TAX 327 study, which compared docetaxel (75 mg/m² every 3 weeks)/prednisone with mitoxantrone (12 mg/m² every 3 weeks)/prednisone for 10 cycles confirmed that the survival benefit with docetaxel-based therapy was consistent across subgroups defined according to age (<65, ≥65, ≥75 years), presence or absence of pain at baseline, and Karnofsky performance status (KPS) score (≤70% vs ≥80%) (Fig. 4) [4,31]. The safety results of this subanalysis
have yet to be reported. However, the pharmacokinetic and toxicity profile of docetaxel in similar conditions of administration (75 mg/m² once every 3 weeks) were prospectively evaluated in elderly patients (≥65 years) with advanced prostate cancer, compared with younger patients (<65 years) [32]. Overall, there was no statistically significant difference in pharmacokinetics between elderly and younger groups. There was also a similar incidence of non-haematological adverse events in both groups. Older patients were more sensitive to docetaxel-induced neutropenia, which is attributed to declining bone marrow reserve when older [21].

At present there are no recognized factors for selecting the most appropriate patients with prostate cancer for treatment with chemotherapy. Therefore, patients must be systematically defined, e.g. by using the inclusion criteria from large clinical trials, such as the TAX 327 study, and age should not represent a limiting criterion.

CONCLUSIONS

Considering the demographics of men with prostate cancer and the predicted increase in life-expectancy, decisions about the treatment of prostate cancer should not be based on age alone, as this could prevent a large proportion of patients from receiving appropriate therapy. This was not considered to be a major issue when chemotherapy had relatively little effect. The survival benefit seen with docetaxel has meant it has been adopted for treating metastatic HRPC [33]. This has created an urgent need for an analysis of the possible relationship between age and the efficacy and safety of chemotherapy. All treatment options should be considered when treating elderly patients with prostate cancer, including chemotherapy, with decisions based on clinical findings rather than on the age of the patients. Clinical findings should be based on comprehensive geriatric assessment, or at least on one of the available screening tools of vulnerability and frailty [34]. As a consequence of the success with docetaxel in HRPC, interest in the early use of chemotherapy in high-risk localized prostate cancer has been renewed. For example, a multicentre phase III study comparing the impact of immediate and deferred adjuvant hormonal therapy, with or without docetaxel, on progression-free survival in men with high-risk localized disease treated with radical prostatectomy and no upper limit of age as inclusion criteria, is currently ongoing. The issue of chemotherapy in the elderly is therefore increasingly likely to become a topic for debate.

CONFLICT OF INTEREST

K. Miller is a paid consultant to sponsor and a study investigator funded by sponsor.

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FIG. 4. The TAX 327 study [4,31]: the better survival with docetaxel/ prednisone given every 3 weeks is consistent between age classes, symptomatic and asymptomatic patients at baseline, and levels of KPS. The data were analysed using a backward Cox proportional-hazards model. ITT, intent-to-treat population; q3w, every 3 weeks.
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Correspondence: John Anderson, Department of Urology, Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JF, UK. e-mail: johnanderson@clara.co.uk

Abbreviations: HRPC, hormone-refractory prostate cancer; KPS, Karnofsky performance status.