Drugs & Aging (2019) 36:379–385
https://doi.org/10.1007/s40266-019-00643-2

ORIGINAL RESEARCH ARTICLE

Age-Associated Hematological Toxicity in Patients with Metastatic Castration-Resistant Prostate Cancer Treated with Docetaxel in Clinical Practice

Marie-Rose B. S. Crombag[1,2] · Aurelia H. M. de Vries Schultink[1,2] · Jacobine G. C. van Doremalen[1,3] · Hans-Martin Otten[4] · Andries M. Bergman[5] · Jan H. M. Schellens[2,3] · Jos H. Beijnen[1,2,3] · Alwin D. R. Huitema[1,2,6]

Published online: 8 February 2019

Abstract

Background Older patients with metastatic castration-resistant prostate cancer (mCRPC) may be more prone to chemotherapy-induced hematological toxicity, but tailored docetaxel dosing guidelines in older patients are lacking because of conflicting data.

Objective This study aims to evaluate the impact of older age on the incidence of hematological toxicity in patients with mCRPC treated with docetaxel in daily clinical practice.

Methods This study included patients with mCRPC treated with docetaxel between January 2006 and January 2016 at the Netherlands Cancer Institute and Medical Center Slotervaart for whom dosing and hematological toxicity data were available from electronic patient records. We evaluated the impact of age on the incidence of grade 3 and 4 hematological toxicity.

Results In total, 175 patients treated with docetaxel were included in the analysis, with a median age of 67 years (range 47–86). Baseline hematological laboratory values were not age related. After the first treatment cycle, hematological toxicity occurred significantly more frequently in the oldest age quartile (25%, $p = 0.02$) than in the younger age quartiles (9%, 11%, and 7%, respectively, for age quartiles 1, 2, and 3).

Conclusion The risk of hematological toxicity was significantly higher in the oldest age quartile than in younger patients with mCRPC treated with docetaxel in daily clinical practice.

Key Points

Older patients with metastatic castration-resistant prostate cancer have a higher risk of developing hematological toxicity.

Emphasis on including older patients in clinical trials and real-life studies is warranted to optimize docetaxel treatment in patients with metastatic castration-resistant prostate cancer.

1 Introduction

Docetaxel is the cornerstone of chemotherapeutic treatment of patients with metastatic castration-resistant prostate cancer (mCRPC), a disease that occurs predominantly in older men. Docetaxel is a highly toxic chemotherapeutic agent with a small therapeutic window [1]. A dose-limiting

✉ Marie-Rose B. S. Crombag
m.crombag@nki.nl

1 Department of Pharmacy and Pharmacology, Antoni van Leeuwenhoek, The Netherlands Cancer Institute and MC Slotervaart, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands

2 Division of Pharmacology, The Netherlands Cancer Institute, Amsterdam, The Netherlands

3 Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands

4 Division of Medical Oncology, MC Slotervaart, Amsterdam, The Netherlands

5 Division of Medical Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands

6 Department of Clinical Pharmacy, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

toxicity of docetaxel is hematological toxicity, which includes neutropenia and anemia [2, 3]. The aged population was well-represented in the pivotal clinical trial of docetaxel for mCRPC. However, the trial included relatively fit older patients because of its strict exclusion criteria [4]. In the selected patient cohort of this clinical trial, drug-related infections and anemia occurred at a > 10% higher rate in patients aged ≥ 65 years with mCRPC than in younger patients with mCRPC [1, 5]. The incidence of hematological toxicities may be even higher in routine clinical practice because of the heterogeneity of the treated patient population, which also includes frail patients [6, 7].

Body composition changes with increasing age, which can be expected to influence the pharmacokinetics of lipophilic chemotherapeutic agents such as docetaxel [8, 9], and the multiple comorbidities and physiological changes that occur with increasing age may also alter the pharmacokinetics of docetaxel [10–12]. These potential differences in pharmacokinetics with increasing age mean that the tolerability of docetaxel may be altered in older patients. Furthermore, older people may be more susceptible to hematological toxicity because of a reduced bone marrow reserve or increased sensitivity of bone marrow to docetaxel treatment [13].

Neither the US FDA drug label nor the European Medicines Agency summary of product characteristics describes the need for dose adjustments in older patients [1, 5], but published results regarding the safety profile of docetaxel in older patients with mCRPC in clinical trials and observational studies in routine clinical practice have been conflicting [14–17]. Thus far, no specific guidelines are available regarding the use of docetaxel in the treatment of older patients with mCRPC because conclusive evidence to support tailored advice for this heterogeneous group of patients is lacking [18].

Therefore, the objective of this multicenter retrospective study was to evaluate the impact of older age on the incidence of hematological toxicity in patients with mCRPC treated with docetaxel. We also assessed the influence of increasing age on the tolerability of docetaxel in patients with mCRPC by evaluating treatment discontinuation and dose intensity (DI; defined as the actual administered docetaxel dose calculated in mg/m^2/week) over multiple treatment cycles.

2 Patients and Methods

2.1 Ethical Approval

Conduct of this retrospective study was approved by the Medical Research Ethics Committee of the MC Slotervaart, Amsterdam, The Netherlands. Formal consent is not required for this type of study.

2.2 Inclusion and Exclusion Criteria

Patients with mCRPC who were treated with docetaxel between January 2006 and January 2016 at The Netherlands Cancer Institute or the Medical Center Slotervaart (Amsterdam, The Netherlands) were eligible for inclusion. Docetaxel was prescribed as monotherapy and was administered according to protocol, with fixed infusion rates, dose reduction guidelines, and anti-emetic treatment. The impact of older age was evaluated with age handled as an ordinal variable divided into quartiles and as a continuous variable.

Patients were excluded if no hematological laboratory measurements were available, only baseline measurements could be obtained, the per protocol dosage was not recorded, the patient's treatment period exceeded our study period, or if the patient was enrolled in a clinical trial that included docetaxel treatment as part of the intervention.

2.3 Data Collection

Patient characteristics and laboratory values were extracted from patients' electronic health records (EHRs). The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) equation [19]. Docetaxel administration data were collected from the EHRs and compounding protocols. Hematological toxicities were collected from EHRs and included total leukocyte counts, neutrophil counts, platelet counts, and hemoglobin measurements.

2.4 Study Design and Statistics

Hematological toxicities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 [20], which considers grade 3 toxicities as severe and grade 4 toxicities as potentially life threatening. The primary endpoint of this study was the impact of age on the incidence of grade 3 and 4 hematological toxicity developing after the first docetaxel treatment cycle. The risk of developing hematological toxicity was analyzed overall and per type of hematological toxicity in older versus younger patients. Included types of toxicity were leukocytopenia, neutropenia, thrombocytopenia, and anemia. For these analyses, age was handled both as an ordinal variable divided into quartiles and as a continuous variable.

The secondary endpoint was treatment tolerability, described as the proportion of patients per age quartile per received treatment cycle, DI, and relative DI (RDI;

defined as the administered DI divided by the per protocol DI and calculated over the median number of administered treatment cycles in our study cohort) [21].

We used descriptive statistics to depict patient characteristics and baseline laboratory values, Fisher's exact test to compare the incidence of grade 3 and 4 hematological toxicities per age quartile and to compare baseline laboratory values between age quartiles, logistic regression to evaluate the impact of age as a continuous variable on hematological toxicity, and analysis of variance to assess the impact of age on DI and RDI.

Statistical analysis was performed using R (version 3.3.1). A two-sided p value of < 0.05 for the different statistical tests was considered significant.

3 Results

3.1 Patient Population

A total of 195 patients were identified who received docetaxel between January 2006 and January 2016 at either hospital. During further data collection, 20 patients were excluded, the majority because hematological laboratory data were missing, as depicted in Fig. 1.

The median age of the 175 remaining patients was 67 years, ranging from 47 to 86 years. There was no significant difference in the distribution of baseline laboratory values between age quartiles, as shown in Table 1. Docetaxel was administered as monotherapy in a 3-weekly regimen, generally at a dose of 75 mg/m^2.

3.2 Hematological Toxicity

A trend toward more grade 3 and 4 hematological toxicity after the first treatment cycle was observed with age treated as an ordinal variable divided into age quartiles ($p = 0.08$). This difference was driven by the oldest age quartile (≥ 72 years), in which the risk of hematological toxicity was significantly higher (25%, $p = 0.02$) than in younger age quartiles (9%, 11%, and 7%, respectively, for age quartiles 1, 2, and 3). The impact of age on grade 3 and 4 hematological toxicities remained significant when age was handled as a continuous variable ($p = 0.02$, odds ratio 1.1; 95% confidence interval 1.01–1.14). For leukocytopenia, the impact of age treated either as an ordinal or as a continuous variable was significant ($p = 0.001$ and $p = 0.004$, respectively). For neutropenia, a trend toward a higher incidence of neutropenia was observed with age treated as an ordinal variable, which reached significance when age was handled as a continuous variable ($p = 0.08$ and $p = 0.02$, respectively). In these separate analyses, the risk of developing leukocytopenia and neutropenia was markedly higher for patients in the oldest age quartile than for their younger counterparts (Fig. 2).

3.3 Dose Intensity

After the first administered treatment cycle, 7% of patients in the oldest age quartile (≥ 72 years) but none in the youngest age quartile discontinued docetaxel treatment ($p = 0.16$). In the total cohort, a median of six cycles of docetaxel was administered. The fraction of patients that received this median number of six treatment cycles was not significantly affected by age treated as an ordinal variable ($p = 0.07$). However, the fraction of patients that received six treatment cycles was significantly smaller in the oldest age quartile

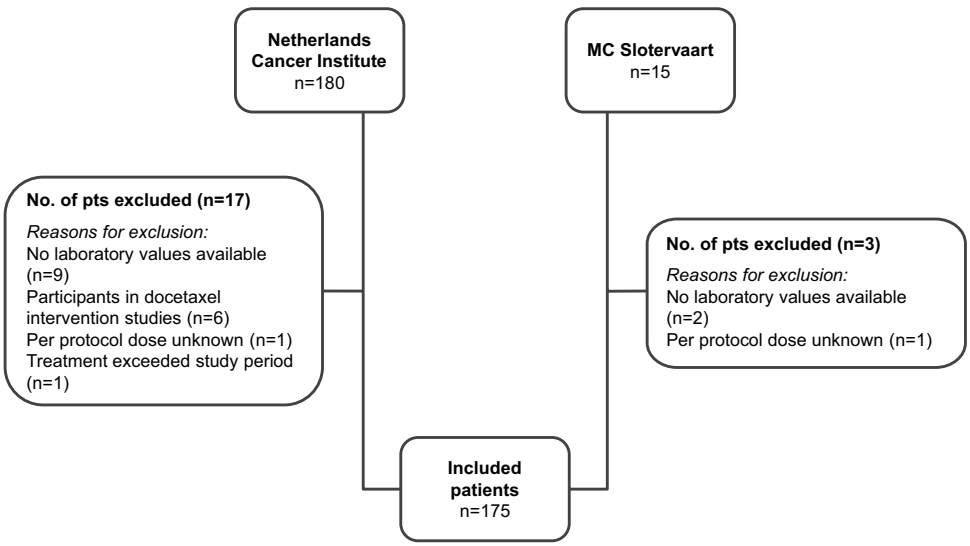

Fig. 1 Flowchart of patient inclusion in both hospitals

Table 1 Baseline patient characteristics

Parameter	Total	Age quartile				*p* value
		1	2	3	4	
Total	175	44	44	43	44	
Age, median (range)	67 (47–86)	59 (47–62)	65 (62–67)	69 (67–72)	76 (72–86)	
Hospital						
NKI	163 (93)	43 (26)	42 (26)	41 (25)	37 (23)	
MCS	12 (7)	1 (8)	2 (17)	2 (17)	7 (58)	
Baseline hematological values						
Leukocytes (10^9/L)	9 (7–12)	10 (8–12)	9 (7–14)	8 (6–11)	9 (7–12)	1
≥ 4	99	100	97	98	100	
< 4	1	0	3	2	0	
Neutrophils (10^9/L)	8 (5–11)	8 (6–11)	8 (5–13)	7 (5–10)	8 (5–11)	1
≥ 1.8	100	100	100	100	100	
< 1.8	0	0	0	0	0	
Platelets (10^9/L)	263 (222–314)	264 (219–309)	257 (232–306)	263 (222–320)	278 (208–317)	0.34
≥ 150	96	100	97	95	92	
< 150	4	0	3	5	8	
Hemoglobin (mmol/L)	8 (7–9)	8 (8–9)	8 (7–8)	8 (7–9)	8 (7–9)	0.13
≥ 8.5	34	47	23	35	31	
< 8.5	66	53	77	65	69	
Baseline organ function						
eGFR (mg/min/1.73 m^2)	92 (75–103)	95 (77–106)	95 (80–107)	97 (77–105)	82 (64–93)	0.82
> 60	88	92	87	85	87	
≤ 60	12	8	13	15	13	
Bilirubin total (μmol/L)	6 (4–8)	5 (4–7)	5 (4–7)	6 (4–8)	6 (4–11)	0.49
< 16	99	97	100	97	100	
≥ 16	1	3	0	3	0	
Alkaline phosphatase (IU/L)	149 (103–345)	149 (104–339)	176 (113–299)	161 (114–384)	127 (83–189)	0.13
< 115	35	41	28	25	47	
≥ 115	65	59	72	75	53	
Albumin (10^9/L)	45 (41–47)	46 (42–47)	43 (42–47)	45 (42–47)	43 (39–45)	0.81
≥ 35	94	97	94	91	94	
< 35	6	3	6	9	6	
ALT (IU/L)	26 (19–35)	30 (21–39)	27 (23–38)	23 (17–28)	22 (15–30)	0.07
< 45	90	81	88	97	95	
≥ 45	10	19	12	3	5	
AST (IU/L)	26 (22–36)	26 (21–33)	29 (22–54)	25 (21–34)	28 (22–36)	0.59
< 35	72	78	64	74	73	
≥ 35	28	22	36	26	27	
PSA (μg/L)	87 (31–225)	52 (17–244)	88 (33–215)	95 (52–253)	95 (34–195)	0.80
< 4	3	3	0	3	5	
≥ 4	97	97	100	97	95	

Data are presented as %, *n* (%), or median (interquartile range, 25–75%) unless otherwise indicated

Age quartiles 1–4: patients divided by age into four equally sized age groups

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *eGFR* estimated glomerular filtration rate calculated using the MDRD equation, *MCS* Medical Center Slotervaart, *MDRD* modification of diet in renal disease, *NKI* Netherlands Cancer Institute, *PSA* prostate-specific antigen

(45%, $p < 0.001$) than in the three younger age quartiles (64%, 66%, and 72% for age quartiles 1–3, respectively). The mean DI over the first treatment cycle was not age related ($p = 0.56$ and $p = 0.88$ for age treated as an ordinal or continuous variable, respectively). Likewise, no age-related difference in RDI over the first treatment cycle was observed

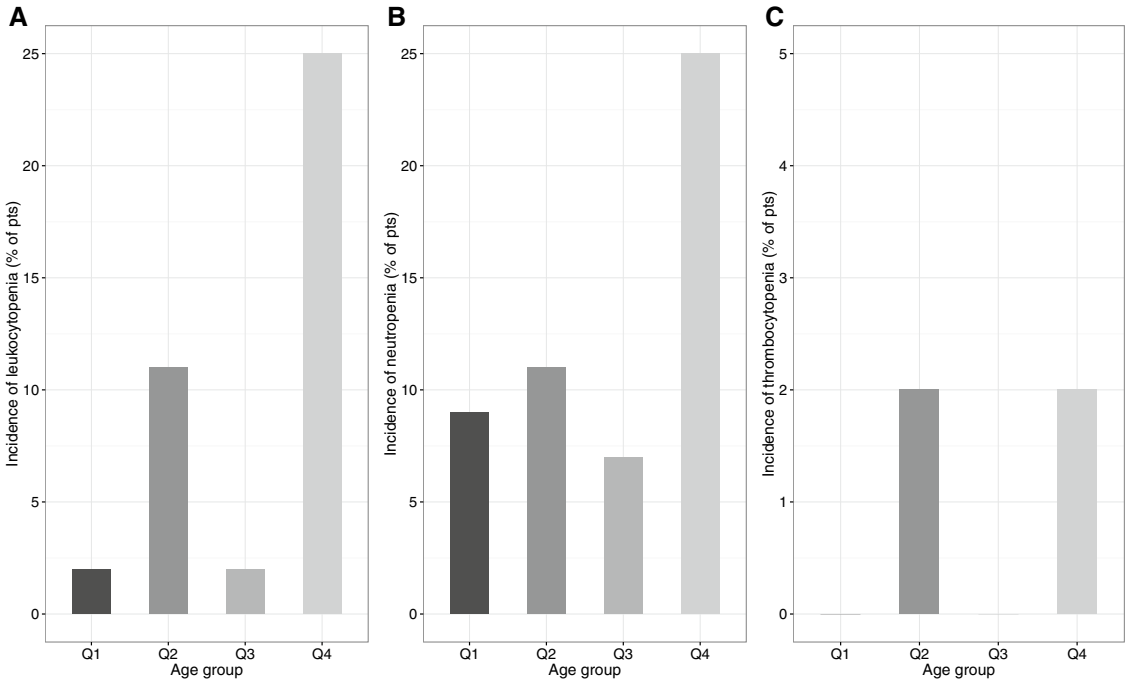

Fig. 2 Incidence of grade 3/4 hematological toxicity in patients with metastatic castration-resistant prostate cancer (mCRPC). Incidence of **a** leukocytopenia, **b** neutropenia, and **c** thrombocytopenia after the first treatment cycle in patients with mCRPC. *Q1–Q4* age quartiles 1–4, with patients divided by age into four equally sized groups. No patients with mCRPC developed anemia after cycle 1

($p = 0.97$ and $p = 0.37$ for age as an ordinal or continuous variable, respectively). Over the median number of six treatment cycles, mean DI and RDI were not significantly affected by age handled as an ordinal variable divided into quartiles ($p = 0.16$ and $p = 0.22$, respectively). However, the oldest age quartile (≥ 72 years) had a significantly lower mean DI than did the three younger age quartiles ($p = 0.02$): 23 versus 24 mg/m^2/week in the oldest and all three younger age quartiles, respectively. This difference remained significant when age was handled as a continuous variable ($p = 0.03$). Correspondingly, the mean RDI over six treatment cycles was significantly lower in patients in the oldest age quartile (73%, $p = 0.002$) than in their younger counterparts (82%, 80%, and 86% for age quartiles 1–3, respectively), as shown in Fig. 3. The impact of age as a continuous variable on RDI nearly reached significance ($p = 0.05$).

4 Discussion

The oldest fraction of patients with mCRPC (≥ 72 years) in our cohort developed significantly more hematological toxicity than their younger counterparts when treated with docetaxel in daily clinical practice. The impact of age on hematological toxicity remained significant when age was handled as a continuous variable. No age-related difference in the first administered dose was noted, but significantly lower absolute DI and RDI values were observed in the oldest patient group after the median of six treatment cycles. Furthermore, the oldest patient group had a significantly higher discontinuation rate. More than half of patients in the oldest age group versus approximately one-third of patients in the younger age quartiles did not receive the median number of six treatment cycles.

Although various previous studies showed that docetaxel could be safely administered to older patients with mCRPC [17, 22], this was balanced by multiple other studies showing an increased risk of docetaxel-related hematological toxicity in older patients with mCRPC [14–16, 23], which is also accordingly reported in the FDA drug label [5]. Our results support that hematological toxicity is increased in the oldest group of patients with mCRPC treated in daily clinical practice. On the other hand, the relatively low incidence of hematological toxicity observed in younger patients with mCRPC in this cohort may be caused by potentially higher clearance and thus lower docetaxel exposure in patients with mCRPC compared with those with other solid tumors, as has previously been suggested for patients with castrated prostate cancer [24]. Consequently, one may argue that instead of treating the oldest patients more vigilantly, younger patients with mCRPC may benefit from higher doses of docetaxel.

Baseline hematological values were not age related, suggesting that the increased hematological toxicity observed in the elderly is related to increased sensitivity of bone marrow

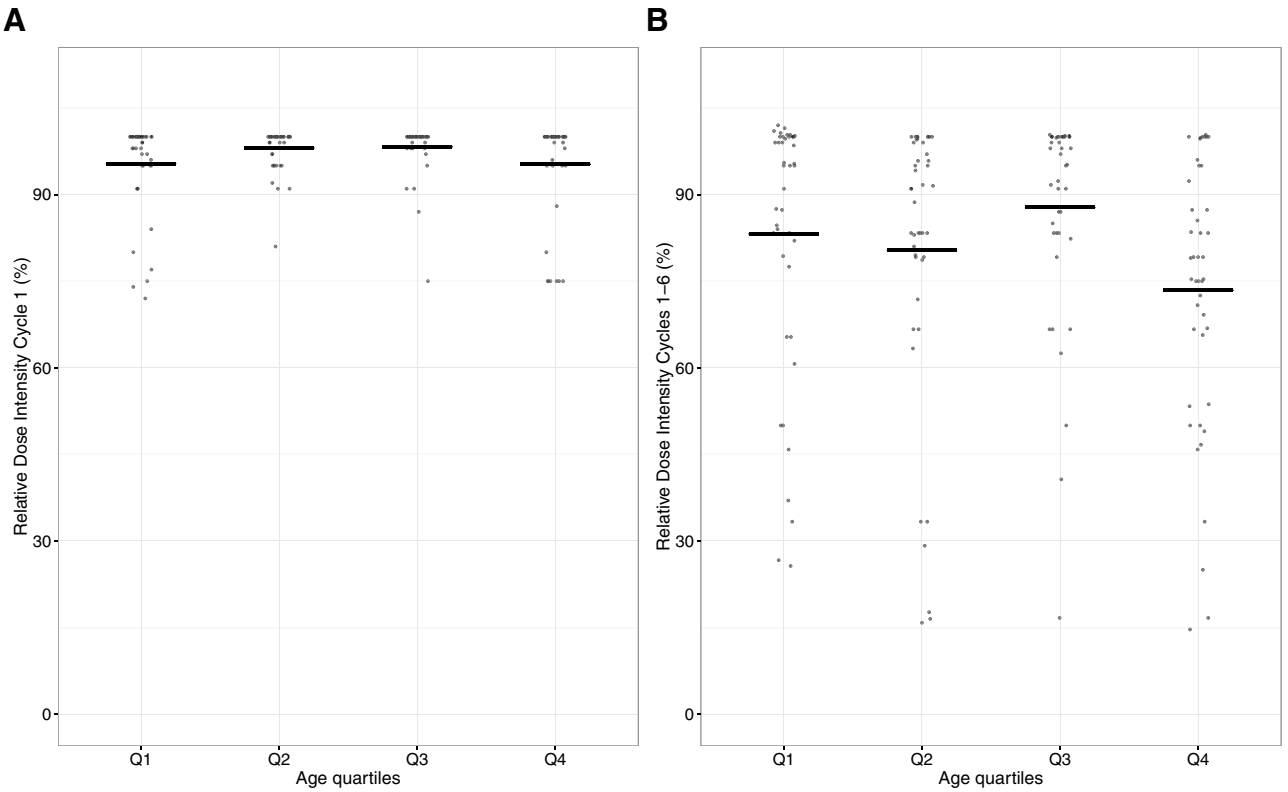

Fig. 3 Relative dose intensity. Relative dose intensity over **a** cycle 1 and **b** cycle 1–6 of docetaxel, with the crossbars representing the mean relative dose intensity per age quartile. *Q1–Q4* age quartiles 1–4, with patients divided by age into four equally sized groups

or myeloid precursors to chemotherapy [13]. Besides, potential pharmacokinetic differences may partly explain why the risk of developing hematological toxicity is higher in older than in younger patients with mCRPC. The significantly lower absolute and relative docetaxel doses administered to these oldest patients with mCRPC may also partly be ascribed to these lower nadirs, requiring physicians to treat the oldest patients with mCRPC more vigilantly. The palliative intent of this highly toxic treatment may lower the threshold for dose reductions for all treated patients. This may explain why the observed difference in dose reductions over the different age quartiles is small. However, it should be kept in mind that physicians' preference may recently have shifted toward more aggressive treatment of patients with metastatic prostate cancer following results indicating improved survival with earlier docetaxel treatment [25, 26].

In the current analysis, the impact of age was evaluated both as an ordinal variable, with patients divided into equally sized age groups, and as a continuous variable. A limitation of our study is its retrospective design. Data on performance status or geriatric assessments were not fully available. Because we had no sound information on the administration of prophylactic intravenous granulocyte-colony stimulating factor (G-CSF) during docetaxel treatment in our cohort, we included hematological toxicities after only the first treatment cycle of docetaxel. Although age ≥ 65 years is considered a risk factor for developing neutropenia during chemotherapy treatment [27], no prophylactic G-CSF administration was applied in either hospital during the first treatment cycle. To reach higher DI or continued treatment duration, and ultimately improved disease control and survival [28], prophylactic use of G-CSF may be considered in older patients treated in clinical practice [29]. Recently, this was especially advocated in the castration-naïve setting for upfront docetaxel treatment [30].

5 Conclusion

Within the limits of a retrospective study, we conclude that the risk of developing hematological toxicity is significantly higher in the oldest (≥ 72 years) patients with mCRPC than in their younger counterparts treated in clinical practice. More prospective pharmacokinetic/pharmacodynamic research is warranted to optimize docetaxel treatment in patients with mCRPC.

Compliance with Ethical Standards

Funding No sources of funding were used to assist in the conduct of this study or the preparation of this article.

Conflict of interest JHB and JHMS are part-time employees and shareholders of Modra Pharmaceuticals and hold a patent on oral taxane pharmaceutical formulations. M-RBSC, AHMdVS, JGCvD, H-MO, AMB, and ADRH have no conflicts of interest that are directly relevant to the content of this article.

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