Neutropenia as a Potential Pharmacodynamic Marker for Docetaxel-Based Chemotherapy in Men With Metastatic Castration-Resistant Prostate Cancer

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Abstract

Docetaxel clearance appears increased with castration. Neutropenia may enable individualizing docetaxel dose in metastatic castration-resistant prostate cancer. This retrospective analysis of 221 men with metastatic castration-resistant prostate cancer who received docetaxel-based chemotherapy suggests that ≥grade 3 neutropenia on day 8 of cycle 1 was prognostic for survival. Exploration of dose escalation of docetaxel to attain ≥grade 3 neutropenia may be warranted.

Background: Docetaxel clearance appears increased in men who are castrated. Neutropenia in cycle 1 may be a pharmacodynamic marker for docetaxel, which may enable tailored dosing in metastatic castration-resistant prostate cancer (mCRPC). **Patients and Methods:** The association of cycle 1 neutropenia with overall survival (OS) was examined post hoc in a randomized phase II trial of 221 men with mCRPC who received docetaxel-prednisone combined with placebo or AT-101 (bcl-2 inhibitor); weekly blood cell counts were performed during the first cycle. Patients from both arms were combined because no outcome and toxicity differences were observed. OS was calculated from randomization by the Kaplan-Meier method, and Cox proportional hazards regression models were used to estimate the association with OS. **Results:** The difference in OS between men with day 8 ≥grade 3 neutropenia and those with ≤grade 2 neutropenia was significant after adjusting for trial stratification factors, pain, and performance status (hazard ratio [HR] 0.64; 2*P* = .048). Results were similar for logarithmic neutrophil counts adjusted for the risk group based on anemia, visceral metastasis, progression by bone scan and pain (HR 1.18; 2*P* = .07) for stratification factors (HR 1.20; 2*P* = .052) or both (HR, 1.20; 2*P* = .046). Men with ≥grade 3 neutropenia and ≥30% prostate-specific antigen level decline by day 90 had improved OS compared with men exhibiting neither (HR 0.51; 2*P* = .014). **Conclusions:** For patients with mCRPC who received docetaxel, ≥grade 3 neutropenia on day 8 was prognostic for improved OS, which suggests its utility as a pharmacodynamic marker, in this hypothesis-generating analysis. Exploration of dose escalation of docetaxel to attain ≥grade 3 neutropenia on day 8 may be warranted.

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Introduction

Docetaxel at a dose of 75 mg/m^2 intravenously every 3 weeks has improved outcomes in men with metastatic castration resistant prostate cancer (mCRPC).[1,2] However, pharmacokinetic studies demonstrate up to 10-fold differences in drug clearance despite normal hepatic function.[3] The docetaxel area under the curve (AUC) was a

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significant predictor of time to progression in non–small-cell lung cancer, and a 50% decrease in clearance was associated with a 4.3-fold increase in grade 4 neutropenia.[4] The duration of exposure >0.20 μmol/L was an independent predictor of outcomes, and reduced area under the curve was associated with shorter survival.[5]

Intriguingly, despite using similar doses of docetaxel, a lower incidence of neutropenia, its primary toxicity that results from antiproliferative biologic activity, has been observed in patients castrated with prostate cancer compared with those who are not.[6,7] Indeed, docetaxel clearance was increased by approximately 100% in men who were castrated and was associated with a 2-fold reduction in area under the curve, despite unchanged hepatic CYP3A4 activity.[8] Preclinical experiments in rats demonstrated that castration was associated with a higher uptake of docetaxel in the liver, which might be mediated by upregulation of an organic anion transporter.[8]

Given the above data, we hypothesized that grade 3 to 4 neutropenia during cycle 1 of docetaxel for mCRPC might be an excellent, readily available, and affordable pharmacodynamic marker that reflects optimal pharmacokinetics translating into enhanced long-term outcomes. Potentially, dose escalation to attain grade ≥3 neutropenia may optimize and enable tailored dosing. However, the landmark TAX327 and SWOG (Southwest Oncology Group) 9916 phase III trials performed complete blood cell counts once in an every 3 weeks cycle and did not optimally capture neutropenia, which is best captured during the second week.[1,2] Hence, we retrospectively analyzed another large randomized phase II trial (CS-205) that used docetaxel-based chemotherapy as frontline therapy for mCRPC and performed weekly complete blood cell counts during the first cycle.

Patients and Methods

Patient Population

The CS-205 trial compared docetaxel 75 mg/m^2 every 3 weeks plus prednisone combined with either AT-101 (bcl-2 inhibitor) or placebo in men with mCRPC. Androgen deprivation therapy was continued. This trial was conducted in centers in the Russian Federation and in the United States, and was approved by National Ethics Committees/Institutional Review Boards. Two hundred twenty-one men were stratified by baseline pain (absent vs. present) and ECOG PS (Eastern Cooperative Oncology Group Performance Status) (0-1 vs. 2), and received up to 17 cycles of treatment. All the patients had adequate hematologic function within 14 days before baseline, defined as an absolute neutrophil count ≥1.5 × 10^9/L, hemoglobin level ≥9 g/dL, and platelet count ≥100 × 10^9/L. Laboratory data were collected by protocol on days 1 (before treatment), 8, and 15 of cycle 1 and thereafter on day 1 of every cycle. Blood samples were sent to 1 of 2 central laboratories, one in the United States and one in the Russian Federation. Chemotherapy was held if the absolute neutrophil count was <1.5 × 10^9/L or the platelet count was <100 × 10^9/L on day 1. Neutropenic fever, grade 4 neutropenia that lasted ≥7 days, and grade 2 to 3 nonhematologic toxicities led to up to 2 dose reductions. Grade 4 nonhematologic toxicities led to discontinuation of therapy. Granulocyte-colony stimulating factor utilization was allowed in accordance with American Society of Clinical Oncology guidelines after the first cycle.

Statistical Analysis

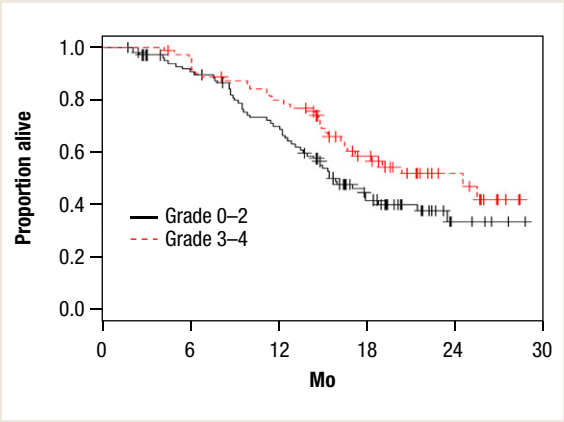
All laboratory counts are expressed as units × 10^9/L. Adverse event grading was performed according to the National Cancer Institute Common Toxicity Criteria version 3.0 for neutrophil counts as follows: <0.5 × 10^9/L (grade 4), 0.5 to <1 × 10^9/L (grade 3), 1 to <1.5 × 10^9/L (grade 2), 1.5 × 10^9/L to laboratory lower limit of normal (grade 1), >laboratory normal lower limit (grade 0). Windows were created such that any laboratory measurement on days 5 to 11 was considered within the day 8 window and, on days 12 to 18, was considered within the day 15 window, with the closest date to the target date used if a patient had multiple visits within a given window. A logarithmic transformation was performed for normalization purposes. Overall survival (OS) was calculated from the randomization date (except when specified) by using the Kaplan-Meier method. Cox proportional hazards regression models were used to estimate the effect of covariates on OS. Patient baseline risk was assessed by categorizing men into 3 risk groups (good, intermediate, poor) based on the presence of 0-1, 2, or 3-4 risk factors (pain, presence of visceral disease, anemia, and bone scan progression).[9] The likelihood reduction factor (LRF), a measure of the association between a surrogate and the true outcome of interest, was calculated.[10] The LRF quantifies the treatment effect via surrogate markers and would have a value of 1 for a perfect surrogate. All tests were 2-sided and a $2P \leq .05$ was considered statistically significant, with no multiple comparison adjustment performed. The primary statistical analysis was the univariate Cox regression, exploring whether men with docetaxel-induced grade ≥3 neutropenia was associated with improved OS. Secondary analyses were performed to demonstrate the robustness of this potential association by using supportive analyses.

Results

Patient Characteristics

Patients enrolled in CS-205 were typical of mCRPC, and both arms of the trial were combined because no significant outcome differences were observed for the AT-101 and placebo arms (median OS, 18.1 vs. 17.8 months; hazard ratio [HR] 1.07, 95% confidence interval [CI], 0.72-1.55; $2P = .63$).[11] Patient characteristics have been reported elsewhere; briefly, the median prostate-specific antigen (PSA) level was approximately 80 to 90 ng/mL, sites of metastases in bone were 85% to 90% and visceral in 20% to 25%, pain was present in 57% to 61%, and the vast majority (93%-96%) had an ECOG PS 0-1. Of 221 registered patients, one was excluded because he never received study treatment, and 3 were excluded because their duration in the study was <7 days. All 217 remaining patients remained on study treatment beyond day 30 and are included. At the time of analysis, 106 (48.8%) men had died. The median neutrophil count on day 1 was 5.3 × 10^9/L (range, 1.2-17.7 × 10^9/L). At day 8, the incidence of grade 3 to 4 neutropenia (47.0% vs. 36.0%; $2P = .16$), median absolute neutrophil count (1.13 vs. 1.62 × 10^9/L; $2P = .17$), and the median absolute (3.70 vs. 3.81 × 10^9/L; $2P = .67$), and percentage (80.8% vs. 75.6%; $2P = .74$) decline in neutrophil count from baseline were similar in both arms of the trial. By day 15, only 21 (11.4%) of 185 evaluable men had grade 3 to 4 neutropenia; however, 7 of these patients also had grade 3 to 4 neutropenia on day 8. On day 1 of cycle 2, only 1 patient had grade 3 to 4 neutropenia and delayed starting cycle 2 as a result. Granulocyte growth factors

Figure 1 Overall Survival by National Cancer Institute Common Toxicity Criteria Grade of Neutropenia at Day 8



were administered after cycle 1 in similar proportions of patients in the AT-101 and placebo arms (filgrastim, 9.1% both arms; peg filgrastim 14.5%, 16.4%; sargramostim 0, <1%).

Association of Day 8 Neutrophil Count and Survival

Thirty-four men on day 1 and 31 men on day 8 did not have an available neutrophil count, and 14 had neutrophil counts measured outside the day 8 window. Of the evaluable 217 patients, 172 had neutrophil counts available in the day 8 window, of whom 71 (41.3%) had grade 3 to 4 neutropenia with a 12-month OS of 79.9% (95% CI, 68.4%-87.6%) and a median of 24.5 months (95% CI, 16.6-not reached months). Conversely, 101 men had grade 0 to 2 neutropenia, with a 12-month OS of 69.9% (95% CI, 59.5%-78.2%) and a median of 15.8 months (95% CI, 13.9-21.4 months) (Figure 1). The difference in OS between men with grade 3 to 4 neutropenia and grade 0 to 2 neutropenia approached significance (HR 0.66 [95% CI, 0.43-1.02]; $2P = .062$; LRF 0.041) (Table 1) and attained significance after adjusting for the stratification factors, pain and PS (HR 0.64 [95% CI, 0.41-1.00]; $2P = .048$). A logarithmic transformation of neutrophil count as a continuous variable approached significance as a predictor of OS (HR 1.18 [95% CI, 0.99-1.41]; $2P = .073$; LRF 0.037).

Supportive Analyses for Association of the Neutrophil Count and Survival

It was hypothesized that patients with a delay of cycle 2 due to toxicities might confound an association of neutropenia with outcomes due to reduction in dose intensity. A supportive analysis, therefore, was performed, excluding men who had cycle 2 initiated on day 28 or later (Table 2), which resulted in excluding 9 men, including 6 with no neutropenia and 3 with grade 3 to 4 neutropenia on day 8, and yielded a more significant association of grade 3 to 4 neutropenia with survival (HR 0.61 [95% CI, 0.39-0.95]; $2P = .030$, when adjusting for risk groups and stratum). Another supportive analysis was performed, that excluded men who experienced dose delays or reductions at any time during the trial, which resulted in excluding 68 men, including 37 with grade 0 to 2 neutropenia and 31 with grade 3 to 4 neutropenia on day 8, with a stronger association of grade 3 to 4 neutropenia with survival, although less statistically significant, probably due to the reduced sample size (HR 0.57 [95% CI, 0.31-1.06]; $2P = .073$, after adjusting for risk groups and stratum; or $2P = .053$, by grade after adjusting for risk groups and stratum).

There was no significant association between day 15 neutropenia and OS (HR 0.97 [95% CI, 0.52-1.82]; $2P = .93$). Similarly, the neutrophil count at day 15 was not statistically prognostic for OS when using other definitions or after adjusting for day 8 neutrophil counts (Table 2). Lymphopenia and thrombocytopenia during cycle 1 displayed no association with OS (data not shown). Also, the percentage and absolute change in the neutrophil count from baseline to day 8 and day 15 exhibited no significant association (data not shown).

Day 8 Neutropenia Complements Clinical Risk Groups and PSA Decline ≥30% By Day 90 as a Prognostic Factor

Results were similar if the effect of logarithmic neutrophil counts was adjusted for baseline risk group status (HR 1.18; $2P = .07$), stratification factors (HR 1.20; $2P = .052$), or both (HR 1.20; $2P = .046$).[9] The OS for patients by grade of neutropenia (0-2 or 3-4) and the risk groups are shown in Figure 2A. The LRF for the multivariate model, including grade 3 to 4 neutropenia and risk groups was 0.131.

The PSA level declines of ≥30% by day 90 was examined for association with neutropenia, given its moderate surrogacy for OS.[12,13] Of the overall evaluable population for day 8 neutropenia (n = 172), there were 17 men with no survival information beyond day 90 (14 of whom had grade 0 to 2 neutropenia) and 2 men with no postbaseline PSA level measurements (both having grade 0 to 2 neutropenia). Therefore, 153 men had measurable day 8 neutrophil counts, survived beyond day 90, and were assessable for PSA level decline. Sixty-eight percent of men with grade ≥3 neutropenia and 57% of men with grade 0 to 2 neutropenia on day 8 exhibited confirmed PSA level declines ≥30% by day 90 ($2P = .20$). In this population, day 8 neutropenia did not attain significance as a prognostic factor for OS when used as a continuous outcome (HR 1.16 [95% CI, 0.96-1.40]; $2P = .13$) or as a categorical outcome (HR 0.75 [95% CI, 0.47-1.19]; $2P = .22$) after adjusting for the PSA level decline ≥30% by day 90 or both ≥30% PSA level decline by day 90 and baseline risk group (HR 0.77 [95% CI, 0.48-1.24]; $2P = .29$). Although not statistically significant, the magnitude of the HR remained relatively constant. Men who had both grade 3 to 4 neutropenia on day 8 and ≥30% PSA level decline by day 90 had improved OS compared with men who did not have both conditions (HR 0.51 [95% CI, 0.29-0.87]; $2P = .014$) (Figure 2B). The 48 men with both grade 3 to 4 neutropenia on day 8 and ≥30% PSA level decline by day 90 had a 12-month OS beyond day 90 of 71.3% (95% CI, 55.6%-82.3%), whereas 12-month OS beyond day 90 for the remaining 105 men was 44.0% (95% CI, 33.7%-53.9%). Twenty-nine men had a PSA level decline <30% by day 90 and grade 0 to 2 neutropenia on day 8, and demonstrated similar outcomes compared with patients who demonstrated only one of these factors.

Table 1 Day 8 Neutrophil Counts and Survival

Factor Definition	n	1-Year OS (95% CI)	HR (95% CI)	*P* Value
Grade 0-2	101	69.9 (59.5-78.2)		
Grade 3 or 4	71	79.9 (68.4-87.6)	0.66 (0.43-1.02)	.062
Adjusted for strata			0.64 (0.41-1.00)	.048
Adjusted for risk groups			0.68 (0.44-1.06)	.088
Adjusted for strata and RG			0.65 (0.42-1.02)	.060
Not assessed	45	75.5 (58.1-86.5)		
Grade 0	67	70.5 (57.3-80.3)		
Grade 1	11	55.6 (20.4-80.5)		
Grade 2	23	73.9 (50.9-87.3)		
Grade 3	23	86.4 (63.4-95.4)		
Grade 4	48	76.9 (62.1-86.5)	0.91 (0.81-1.04)	.16
Adjusted for strata			0.90 (0.80-1.03)	.12
Adjusted for risk groups			0.93 (0.81-1.05)	.24
Adjusted for strata and RG			0.91 (0.80-1.04)	.15
Grade 0 and $\geq 2.5 \times 10^3/\mu L$	50	68.0 (52.0-79.7)		
Grade 0 and $< 2.5 \times 10^3/\mu L$	17	76.5 (48.8-90.4)	0.50 (0.20-1.22)	.13
Univariate log (continuous)	172		1.18 (0.99-1.41)	.073
Adjusted for strata	172		1.20 (1.00-1.43)	.052
Adjusted for risk groups	166		1.18 (0.99-1.41)	.070
Adjusted for strata and risk groups	166		1.20 (1.00-1.44)	.046

Abbreviations: HR = hazard ratio; OS = overall survival.

Discussion

Our retrospective analysis demonstrated an extension of OS in men with mCRPC who received frontline docetaxel-based chemotherapy every 3 weeks who attained ≥grade 3 neutropenia on day 8 of cycle 1. We combined both arms of the CS-205 trial, because we detected no significant difference in the effect of AT-101 or placebo on neutrophils or on OS. Men who exhibited ≥grade 3 neutropenia on day 8 of cycle 1 had statistically significantly improved OS after adjusting for the trial's stratification factors, pain, and PS (HR 0.64; $2P = .048$). Similar results were observed across risk groups, although only a trend to significance ($2P = .07$) occurred, probably due to the modest sample size (Figure 2A). In addition, the association of neutropenia and OS was strengthened after excluding patients who experienced delays during therapy, which may result in a reduced treatment effect. Men who had both day 8 ≥grade 3 neutropenia and ≥30% PSA level decline by day 90 had significantly improved OS compared with men who did not have both (HR 0.51; $2P = .014$). Hence, day 8 ≥grade 3 neutropenia may be an early pharmacodynamic marker for the biologic activity of docetaxel.

Although day 8 ≥grade 3 neutropenia was not significantly associated with OS after adjusting for PSA level decline ≥30% by day 90, with or without baseline risk group (HR 0.77; $2P = .29$), the magnitude of HR remained relatively similar, and the lack of independent significance may be attributable to the limited numbers of patients evaluable for this analysis (n = 153) (Table 2). When examining neutropenia at any time (day 8 and 15 or day 1 of cycle 2) during cycle 1, the association with OS was not statistically significant, although similar HRs were maintained (data not shown), which suggests that caution is warranted when interpreting our findings, although these data may be limited by small numbers of patients who developed neutropenia ≥grade 3 beyond day 8. However, this finding may also indicate that the timing of neutropenia as a pharmacodynamic marker may be important, eg, early neutropenia may capture the antiproliferative effect of docetaxel, whereas delayed neutropenia may suggest slower clearance due to host factors rather than an antiproliferative effect.

Other retrospective studies have identified an association between chemotherapy-induced cytopenias and improved clinical outcomes in advanced non–small-cell lung cancer, gastric cancer, glioblastoma multiforme, and in the setting of adjuvant therapy for breast cancer.[14-17] One recently reported prospective adjuvant randomized trial of 1535 patients in the setting of breast cancer compared standard doses of FEC (fluorouracil, epirubicin, cyclophosphamide) with escalated FEC dosing for grade 0 to 2 leukopenia during cycle 1.[18] Five-year distant disease-free survival (HR 0.80; $2P = .14$) and disease-free survival (HR 0.76; $2P = .04$) showed better HRs for the tailored dosing group. However, leukopenia was first measured on day 10 (and not on day 8), which may be suboptimal compared with neutropenia for capturing the biologic antiproliferative activity of docetaxel, and all patients did not demonstrate grade 3 to 4 leukopenia after dose escalation.[19]

It has been hypothesized that biologic activity in surrogate epithelial tissue (eg, buccal mucosa, hair follicle) may better translate into anti–epithelial-tumor activity than biologic activity in hematopoi-

Table 2 Supportive Analyses for Association of Neutropenia With Survival

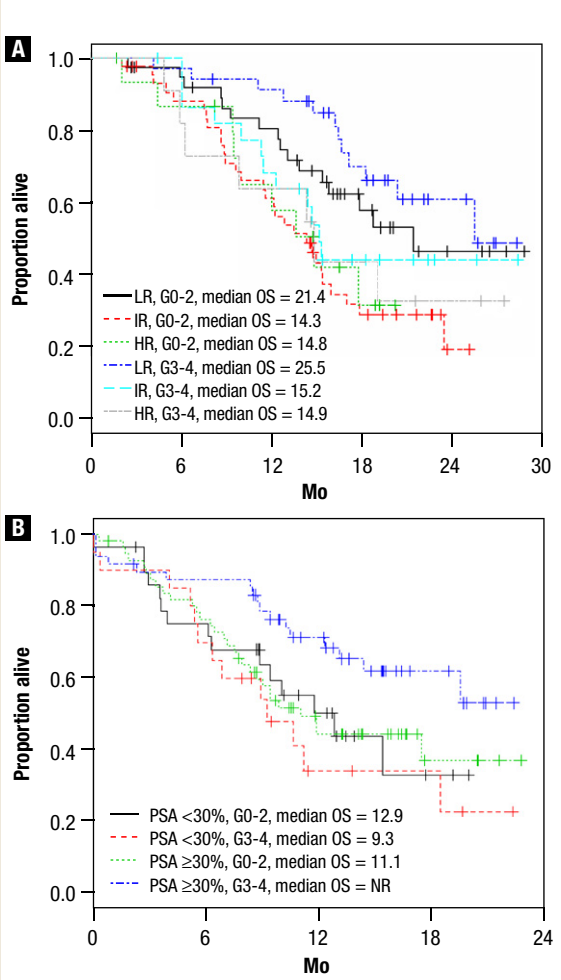
Day	Factor Definition	n	1-Year OS (95% CI)	HR (95% CI)	*P* Value
Day 8 Neutropenia Grade, Excluding Patients With Delayed Cycle 2 (day 28 or later)					
	Grade 0-2	95	68.4 (57.6-77.0)		
	Grade 3 or 4	69	80.7 (69.1-88.3)	0.61 (0.39-0.95)	.029
	Not assessed	43	76.6 (58.5-87.6)		
	Grade 0	61	68.2 (54.3-78.6)	0.89 (0.78-1.01)	.069
	Grade 1	11	55.6 (20.4-80.5)		
	Grade 2	23	73.9 (50.9-87.3)		
	Grade 3	23	86.4 (63.4-95.4)		
	Grade 4	46	78.0 (63.0-87.5)		
Day 15 neutropenia					
	Grade 0-2	164	73.0 (65.2-79.4)		
	Grade 3 or 4	21	69.1 (43.6-84.8)	0.97 (0.52-1.82)	.93
	Not assessed	38	84.9 (67.4-93.5)		
	Grade 0	130	72.6 (63.7-79.7)	0.96 (0.80-1.16)	.67
	Grade 1	11	72.7 (37.1-90.3)		
	Grade 2	17	75.0 (46.3-89.8)		
	Grade 3	16	66.7 (37.5-84.6)		
	Grade 4	5	80.0 (20.4-96.9)		
	Continuous (log)	185		0.96 (0.76-1.20)	.69
Grade 3-4 vs. 0-2 neutropenia					
	Day 8			0.67 (0.43-1.04)	.077
	Day 15			1.09 (0.54-2.18)	.81
Continuous (log) scale neutrophil count					
	Day 8			1.21 (1.00-1.46)	.050
	Day 15			0.87 (0.66-1.15)	.33
Day 8 neutrophils count (continuous)		153[a]		1.16 (0.96-1.40)	.13
Change in PSA level by day 90				0.98 (0.81-1.18)	.80
Grade 3 or 4 neutropenia at day 8		153[a]		0.75 (0.47-1.19)	.22
≥30% PSA level reduction by day 90				0.70 (0.44-1.12)	.13
Grade 3 or 4 neutropenia at day 8		148[a]		0.77 (0.48-1.24)	.29
≥30% PSA level reduction by day 90				0.76 (0.47-1.23)	.26
Risk groups				1.47 (1.09-1.98)	.013

Abbreviations: HR = hazard ratio; OS = overall survival; PSA = prostrate-specific antigen.
[a] The patients must have survived ≥90 days; OS taken from day 91.

etic cells. It is also possible that the effect of docetaxel on neutrophil proliferation may not correlate with antiproliferative activity in epithelial tumor cells, given the different proliferation kinetics or resistance mechanisms. Moreover, docetaxel delivery to myeloid precursors in the bone marrow is likely not hindered by factors operative in the tumor microenvironment, eg, high interstitial fluid pressure. In addition, neutropenia cannot be expected to capture the non-antiproliferative activity of docetaxel, eg, androgen receptor inhibition.[20] Thus, neutropenia, at best, may capture only a component of the biologic activity of docetaxel. Conversely, neutropenia has been associated with favorable docetaxel pharmacokinetics, which appears to yield better antitumor activity.[5] However, our study could not evaluate docetaxel pharmacokinetics, because these data were not measured in the CS-205 trial. Another limitation in our study was that day 8 neutrophil counts were unavailable in all evaluable patients, albeit were available in the vast majority (172 [79.3%] of 217). Finally, it is noted that this was a retrospectively planned study, and, as a result, these findings can only be interpreted as hypothesis generating and that further study is warranted.

Despite these caveats, neutrophil counts are highly affordable and easily, and objectively measurable, and may facilitate the optimization of the dose of docetaxel in mCRPC. Unlike PSA level declines,

Figure 2 OS by Grade of Neutropenia and (A) Risk Groups and (B) ≥30% Reduction in Prostate-specific Antigen Level by Day 90



(A) Abbreviations: G0-2 = grade 0-2; G3-4 = grade 3 to 4; HR = high risk; IR = intermediate risk; LR = low risk; OS = overall survival.*Risk groups (low, intermediate, high) were classified based on the presence of 0-1, 2, or 3-4 risk factors (pain, presence of visceral disease, anemia, and bone scan progression) as defined by Armstrong et al.[9] (B) G0-2 = grade 0-2; G3-4 = grade 3-4; NR = not reached; OS = overall survival.

circulating tumor cell changes, alkaline phosphatase changes, and objective tumor regressions, neutropenia appears relevant at an extremely early time point.[13,21-23] This finding may be akin to the pharmacodynamic value of rash with epidermal growth factor receptor inhibitors predicting better outcomes in advanced non–small-cell lung cancer and colorectal cancer, and for the association of hypertension with better outcomes with anti-angiogenic therapy for renal cell carcinoma.[24-27] Given that the strength of the association of day 8 ≥grade 3 neutropenia with OS was stronger after excluding patients that experienced delays, it may be reasonable to hypothesize that, to avoid underdosing due to toxicities, dosing to attain grade 3 neutropenia rather than grade 4 neutropenia may confer a more favorable therapeutic index. Indeed, in another study, women who received adjuvant chemotherapy who had major dose reductions owing to severe neutropenia experienced less benefit.[28] The caveat is that patients with delayed cycle 2 may have poorer outcomes independent of attenuation of dose intensity.

Our data do not address or justify the study of high doses of chemotherapy that require granulocyte growth factor or autologous hematopoietic stem cell support. Although dose-dense or high-dose chemotherapy are of proven value in other malignancies (eg, breast cancer and non-Hodgkin lymphoma, respectively), these strategies do not customize dose based on pharmacodynamic markers or neutropenia.[29,30] Hence, a trial with men with mCRPC to evaluate the value of dose escalation (or de-escalation if prior grade 4 neutropenia is observed) to attain grade 3 neutropenia on day 8 may be justified in comparison with a conventional dose of 75 mg/m^2 every 3 weeks. This strategy is similar to trials that demonstrated improved responses by escalating the dose of cetuximab in those with mild or no rash in colorectal cancer.[31,32]

Conclusions

In men with mCRPC who receive docetaxel-based chemotherapy, ≥grade 3 neutropenia on day 8 was prognostic for improved OS, which suggests its utility as a pharmacodynamic marker in this hypothesis-generating analysis. Exploration of dose modulation of docetaxel to attain ≥grade 3 neutropenia on day 8 may be warranted. Even in this era of biologic agents, a rational and tailored strategy for optimal dosing of chemotherapy that uses readily available biomarkers for antiproliferative activity, eg, neutropenia, may enhance patient outcomes for little additional cost. Future drug development probably should also account for differing host environments (eg, castration) and carefully develop and select the optimal dose. Neutropenia ≥grade 3 on day 8 may signify the minimal necessary dose of docetaxel that yields antiproliferative activity that translates to antitumor activity.

Clinical Practice Points

- Docetaxel clearance appears to be increased in men who are castrated, which appears to be mediated by higher uptake in the liver by upregulation of an organic anion transporter.
- This retrospective hypothesis-generating analysis of a phase II trial of 221 men with mCRPC who received docetaxel-based chemotherapy suggested that ≥grade 3 neutropenia on day 8 of cycle 1 was prognostic for survival.
- Potentially, ≥grade 3 neutropenia during cycle 1 of docetaxel for mCRPC might provide a readily available and affordable pharmacodynamic marker that reflects optimal pharmacokinetics that translate into enhanced long-term outcomes.
- These data require validation and dose modifications to attain grade 3 neutropenia rather than grade 4 neutropenia may be hypothesized to confer a more favorable therapeutic index.

Disclosure

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