

A rapid PSA half-life following docetaxel chemotherapy is associated with improved survival in hormone refractory prostate cancer

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Abstract

Introduction: Docetaxel chemotherapy prolongs survival in metastatic hormone-refractory prostate cancer (mHRPC), but many patients fail to respond to this therapy and there is potential for serious toxicity. Patients differ in their percent prostate-specific antigen (PSA) decline and rate of PSA decline following treatment. We propose that patients who achieve a rapid rate of PSA decline, measured as a shorter PSA half-life (PSAHL), may experience a longer overall survival (OS) than those who achieve a slower rate of PSA decline.

Methods: A chart review of patients treated with docetaxel for mHRPC in Alberta from January 2000 to May 2006 was performed. At 42 days (after 2 cycles) and 84 days (after 4 cycles) following chemotherapy, PSA response and PSAHL were determined. PSAHL could only be determined in patients with a PSA drop from baseline. Optimal PSAHL values for OS stratification were determined using the log-rank chi-square statistic. Survival analysis was carried out using Kaplan-Meier curves and regression analysis.

Results: There were 154 patients who fulfilled the inclusion criteria. Using 42-day postdocetaxel data, no associations with OS could be demonstrated. Using 84-day postdocetaxel data, patients stratified by PSAHL demonstrated a significant difference in OS (15 months vs. 25 months) and this relationship remained following multivariate analysis (hazard ratio 0.08 [0.021-0.34]).

Conclusion: A more rapid rate of PSA decline (PSAHL <70 days) measured after 4 cycles of chemotherapy was associated with a longer OS. This result was independent of other known markers of survival and allowed for a greater survival differentiation than PSA response.

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Résumé

Introduction : La chimiothérapie par docetaxel prolonge la survie dans les cas de cancer métastatique de la prostate réfractaire aux traitements hormonaux, mais de nombreux patients ne répondent pas à cette chimiothérapie qui, par ailleurs, est associée à un risque de toxicité grave. Après ce traitement, le pourcentage de baisse du taux d'antigène prostatique spécifique (APS) et la vitesse de réduction des taux d'APS diffèrent d'un patient à l'autre. Nous avançons l'hypothèse que les patients qui présentent une baisse rapide des taux d'APS, se manifestant par une réduction de la demi-

vie de l'APS, peuvent présenter une survie globale (SG) plus longue que les patients présentant une baisse plus lente des taux d'APS.

Méthodologie : Nous avons procédé à un examen des dossiers de patients traités par le docetaxel en raison d'un cancer métastatique de la prostate réfractaire aux traitements hormonaux en Alberta entre janvier 2000 et mai 2006. Aux 42^e (après 2 cycles) et 84^e jours (après 4 cycles) de chimiothérapie, on a vérifié la réponse en fonction des taux d'APS et de la demi-vie de l'APS. La demi-vie de l'APS ne pouvait être mesurée que chez les patients ayant affiché une baisse des taux d'APS par rapport aux taux initiaux. Les valeurs optimales de la demi-vie de l'APS utilisées pour la stratification des patients en vue de l'évaluation de la SG ont été cernées à l'aide d'une méthode statistique reposant sur le test de Mantel-Haenzel. L'analyse des taux de survie a été effectuée à l'aide de courbes de Kaplan-Meier et d'une analyse de régression.

Résultats : Cent cinquante-quatre (154) patients satisfaisaient aux critères d'inclusion. Selon les données recueillies après 42 jours de traitement par docetaxel, aucune corrélation avec la SG n'a pu être démontrée. Selon les données recueillies après 84 jours de traitement par docetaxel, les patients stratifiés en fonction de leur demi-vie de l'APS ont montré une différence significative quant à la survie globale (15 mois vs 25 mois), et cette corrélation a aussi été observée lors de l'analyse multivariée (RR 0,08 [0,021 à 0,34]).

Conclusion : Une chute plus rapide des taux d'APS (demi-vie de l'APS < 70 jours) mesurée après 4 cycles de chimiothérapie a été associée à une survie globale plus longue. Ce résultat s'est révélé indépendant des autres marqueurs connus de la survie et permettait une meilleure différenciation que la réponse de l'APS sur le plan de la survie.

Introduction

Advanced prostate cancer remains a therapeutic challenge for the clinical oncologist. Despite a constantly evolving understanding of the disease, the median overall survival (OS) for metastatic hormone refractory prostate cancer (mHRPC) is still under 2 years. Treatment of mHRPC with docetaxel in combination with prednisone has been shown to prolong survival by several months.^{1,2} Despite its adoption as a standard of care in men with mHRPC, there is still potential for serious toxicity to develop. This potential must be recognized, as only 36% to 48% of patients will experience a

prostate-specific antigen (PSA) response (defined as a reduction in serum PSA of at least 50%) with this therapy.^{1,3-6} This is particularly important when considering that men may be treated with docetaxel chemotherapy for survival improvement while being asymptomatic. Unfortunately, there is a paucity of evidence to guide clinical decisions to continue or stop docetaxel treatment in asymptomatic patients once they start treatment.

Several prognostic factors in hormone-refractory prostate cancer (HRPC) have been reported, including initial PSA, tumour Gleason grade and stage, as well as baseline hemoglobin, performance status and PSA doubling time (PSADT).^{7,8} PSA response (defined as a 50% decline in baseline PSA) has also been proposed as a predictor of survival following chemotherapy for mHRPC.⁹ However, the magnitude of this benefit has been variable between studies and there is a need for better predictors of outcome from chemotherapy in mHRPC.¹⁰⁻¹²

After receiving docetaxel chemotherapy for mHRPC, patients differ not only in their percent PSA decline, but also in the rate at which they achieve this decline. We propose that patients who achieve a more rapid rate of PSA decline, measured as a shorter PSA half-life (PSAHL), may experience a longer OS than those who achieve a slower rate of PSA decline. Furthermore, we propose that the early rate of PSA decline, measured as PSAHL at 42 days (2 cycles) postchemotherapy, may also be associated with OS and allow for earlier prognostication than traditional measures obtained 84 days postdocetaxel (4 cycles).

Methods

Study design and data collection

After obtaining approval for the study through the Alberta Cancer Board (ACB) Research Ethics Board, patients having received docetaxel chemotherapy at a standard dose and schedule¹ at the Cross Cancer Institute (Edmonton, AB, Canada) or Tom Baker Cancer Center (Calgary, AB, Canada) for prostate cancer from January 1, 2000, to November 1, 2006, were identified through the ACB Cancer Registry. Inclusion criteria for the study were: confirmation of mHRPC by 3 sequential rises in PSA with a castrate level of serum testosterone (<50 ng/dL) and metastatic disease on imaging (x-ray, computed tomography or bone scan).

A retrospective chart review was carried out on eligible patients. The data collected were: dates of initial prostate cancer diagnosis, HRPC diagnosis (defined as the date of the third consecutive PSA rise), metastatic prostate cancer diagnosis, chemotherapy failure (defined as a 50% rise from the nadir achieved on chemotherapy) and death. Laboratory

results at the time of docetaxel initiation (including hemoglobin, alkaline phosphatase and lactate dehydrogenase) and all available PSA measurements were also collected. Finally, the dates and total number of cycles of docetaxel administered were obtained.

Overall survival from the date of diagnosis of HRPC to death or last follow-up was calculated irrespective of demonstrable metastatic disease on imaging. Overall survival from the date of initiation of docetaxel chemotherapy was calculated as the time from the first day of docetaxel administration to the date of death.

The PSA doubling time (PSADT) was determined retrospectively, using PSA data available immediately after the diagnosis of HRPC (Box 1).

Percent PSA decline and PSAHL were determined after 2 cycles of chemotherapy (day 42) and after 4 cycles of chemotherapy (day 84). The baseline PSA for both of these calculations was the PSA immediately prior to docetaxel initiation. The PSAHL calculation is expanded in Box 2.

Patients who experienced a rise in PSA relative to their baseline at 42 days (29 patients) or at 84 days (33 patients) after chemotherapy onset were excluded from PSAHL determination, as the calculation would yield a negative number.

Statistical analysis

Kaplan-Meier curves were constructed to estimate OS from diagnosis of HRPC and from the first administration of docetaxel. Overall survival was also analyzed after stratifying patients by PSA response (50% decline from baseline) and by PSAHL at 42 days postdocetaxel and at 84 days postdocetaxel initiation. The log-rank chi-square statistic was applied using different PSAHL values to stratify data for OS. The optimal PSAHL stratification value was the value that provided the greatest survival differentiation. This optimal PSAHL stratification value was determined independently using the 42-day postdocetaxel data and the 84-day postdocetaxel data.

Box 1. Calculation of PSA doubling time

$$\text{PSADT} = (0.693 \times t) / [\ln(\text{PSA2}) - \ln(\text{PSA1})]$$

Where: "t" is the time (in days) between PSA measurements, "PSA2" is the PSA defining HRPC (third rising PSA), "PSA1" is the next available PSA level

PSA = prostate-specific antigen; PSADT = prostate-specific antigen doubling time; HRPC = hormone-refractory prostate cancer

Box 2. Calculation of percent PSA decline and PSAHL

$$\text{PSAHL} = (0.693 \times t) / [\ln(\text{PSA2}) - \ln(\text{PSA1})]$$

Where: "t" is the time (in days) between PSA measurements, "PSA2" is the PSA 42 days or 84 days after docetaxel initiation, "PSA1" is the PSA immediately prior to docetaxel initiation

PSA = prostate-specific antigen; PSAHL = prostate-specific antigen half-life

Univariate and multivariate Cox-regression analyses were then performed using known prognostic factors in HRPC (initial PSA, Gleason score, stage, age, hemoglobin, alkaline phosphatase and lactate dehydrogenase), in addition to PSA decline and PSAHL 42 days (2 cycles) and 84 days (4 cycles) postdocetaxel initiation.

Results

Patient characteristics

A total of 154 patients fulfilled the criteria for mHRPC. The mean number of cycles of docetaxel administered was 6 (range 1 to 26). The clinical and pathological characteristics, biochemistry, PSA and treatment variables are summarized in Table 1.

PSA response and PSA half-life

The mean PSA decline 42 days after docetaxel initiation was 17% (range, -951% to 99%). Seventy-one percent of patients (84/119) with available PSA measurements at this time point, achieved a PSA decline. PSAHL was determined in these patients and ranged from 6 days (very rapid rate of PSA decline) to 12 734 days (very slow rate of PSA decline),

with a mean PSAHL of 404 days. By applying the log-rank chi-square statistic using different PSAHL values to stratify data, the optimal PSAHL stratification for OS at this time point (42 days postdocetaxel) was 71 days. Using this cutoff, 55 patients achieved a rapid rate of PSA decline (PSAHL \leq 71 days) and 35 patients achieved a slow rate of PSA decline (PSAHL >71 days) after 42 days of docetaxel.

The mean PSA decline 84 days after docetaxel initiation was 10% (range, -1841% to 100%), with 92/126 patients (73%) with available PSA measurements achieving a PSA decline at this time point. PSAHL was determined in these patients and ranged from 13 days (very rapid rate of PSA decline) to 3151 days (very slow rate of PSA decline), with a mean of 136 days. By applying the log-rank chi-square statistic using different PSAHL values to stratify data, the optimal PSAHL stratification for OS at this time point (84 days postdocetaxel) was 70 days. Using this cutoff, 47 patients achieved a rapid rate of PSA decline (PSAHL \leq 70 days) and 45 patients achieved a slow rate of PSA decline (PSAHL >70 days) after 84 days of docetaxel.

Kaplan-Meier survival analysis

During the follow-up period, 54% of patients died and disease progression was documented in 74% of all patients. The median OS from diagnosis of HRPC was 49 months and the median OS from initiation of docetaxel was 16 months for the entire group. For those patients with a PSA rise at 42 days, the median OS was 12.1 months; for those patients with a PSA rise at 84 days, the median OS was 11.5 months.

Stratifying patients by those having no or any PSA decline (\geq 0%) at 84 days after docetaxel initiation did not predict OS ($p = 0.84$). However, stratifying patients by PSA response, as defined as a \geq 50% PSA decline, correlated with OS, with a median survival of 22 months in patients with a PSA response compared with 16 months in those without a PSA response ($p = 0.0028$) (Fig. 1). After excluding patients with a PSA rise following docetaxel, PSA response was no longer associated with OS.

Using early PSAHL data (determined 42 days postdocetaxel initiation), it was not possible to demonstrate an association with survival, even with the optimal PSAHL stratification of 71 days ($p = 0.20$). Using PSAHL data determined at 84 days postdocetaxel initiation, we found a strong association with OS was demonstrated, with a median survival of 25 months in patients with a rapid rate of PSA decline (PSAHL <70 days) compared with a median survival of 15 months in patients with a slow rate of PSA decline (PSAHL \geq 70 days) ($p = 0.00051$) (Fig. 2).

Table 1. Baseline demographics, biochemistry and cancer characteristics

	No.	%	Range
Demographics			
No. of patients	154		
Age at docetaxel initiation, yrs	69		(44-87)
Cancer characteristics at original diagnosis			
Tx N0 M0	69	45	
N1-2 or M1	71	46	
Unknown TNM stage	14	9	
Gleason \leq 6	68	44	
Gleason 7	23	15	
Gleason 8-10	63	41	
PSA (μ g/L)	238		(2-3672)
Pre-chemotherapy biochemistry			
Hemoglobin (mmol/L)	127		(73-178)
Alkaline phosphatase (U/L) (normal <350 U/L)	309		(57-2975)
LDH (U/L) (normal <150 U/L)	127		(108-9353)
PSA (μ g/L)	298		(1-3212)

Empty cells do not have any applicable data associated with them. Tx = tumour; N0 = no regional lymph node metastasis; M0 = no distant metastasis; N1 = metastasis with a single lymph node mass 2 cm or less in greatest dimension, or multiple lymph nodes 2 cm or less in greatest dimension; N2 = metastasis with a single lymph node mass larger than 2 cm, but no more than 5 cm in greatest dimension, or multiple lymph nodes no more than 5 cm in greatest dimension; M1 = distant metastasis; TNM = tumour, node, metastasis; PSA = prostate-specific antigen; LDH = lactate dehydrogenase.

Univariate and multivariate Cox-regression analysis

Hemoglobin, alkaline phosphatase, PSA response and PSAHL (determined 84 days after docetaxel initiation) correlated with OS in the univariate analysis. After correcting for these factors in multivariate analysis, only PSA response and PSAHL determined 84 days after docetaxel initiation correlated to OS (hazard ratio 0.08 [0.021-0.34]) (Table 2).

Discussion

Prostate-specific antigen half-life is a simple tool to determine the rate of decline of PSA following chemotherapy. The only parameters required to calculate it are the baseline PSA (before chemotherapy), the PSA after chemotherapy and the number of days between the 2 PSA determinations (i.e., 42 or 84 days). Prostate-specific antigen half-life assumes that tumour killing after docetaxel is logarithmic

Table 2. Univariate and multivariate Cox-regression analysis for survival using known prognostic factors in hormone refractory prostate cancer, prostate-specific antigen and prostate-specific antigen half-life

Variable	No.	Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	<i>p</i> value	Hazard ratio (95% CI)	<i>p</i> value
Gleason at initial diagnosis					
≤6	68	1.0	-	1.0	-
7	23	1.20 (0.62-2.33)	0.58	3.85 (0.71-20.77)	0.12
8-10	63	0.99 (0.62-1.58)	0.96	0.77 (0.20-2.75)	0.68
PSA at initial diagnosis					
<20	40	1.0	-	1.0	-
≥20	75	0.79 (0.48-1.30)	0.35	1.02 (0.33-3.10)	0.97
Stage at initial diagnosis					
Tx	69	1.0	-	1.0	-
N1-2 or M1 (5-7)	71	0.71 (0.45-1.11)	0.13	0.41 (0.10-1.62)	0.21
Age at start of docetaxel					
<70	70	1.0	-	1.0	-
≥70	84	1.29 (0.83-2.00)	0.26	0.35 (0.09-1.27)	0.11
Hb at start of docetaxel					
Normal	105	1.0	-	1.0	-
Low (<120)	47	2.61 (1.67-4.10)	<0.0001	0.67 (0.20-2.31)	0.53
Alk phos at start of docetaxel					
Normal	69	1.0	-	1.0	-
High (>150)	78	2.59 (1.60-4.20)	0.0001	2.43 (0.79-7.47)	0.12
LDH at start of docetaxel					
Normal	54	1.0	-	1.0	-
High (>350)	89	1.18 (0.74-1.88)	0.49	1.92 (0.57-6.46)	0.29
Early pre-chemotherapy PSADT					
>70 days	55	1.0	-	1.0	-
≤70 days	93	0.69 (0.44-1.09)	0.12	0.76 (0.29-1.98)	0.58
PSA response 84 days after docetaxel					
<50% decline	70	1.0	-	1.0	-
≥50% decline	55	0.38 (0.22-0.67)	0.0007	0.16 (0.05-0.48)	0.001
PSAHL 42 days after docetaxel					
>71 days	56	1.0	-	1.0	-
≤71 days	33	0.66 (0.36-1.23)	0.2	0.86 (0.23-1.67)	0.34
PSAHL 84 days after docetaxel					
>70 days	47	1.0	-	1.0	-
≤70 days	45	0.34 (0.18-0.64)	0.009	0.08 (0.021-0.34)	0.0005

CI = confidence interval; PSA = prostate-specific antigen; Tx = tumour; N0 = no regional lymph node metastasis; M0 = no distant metastasis; N1 = metastasis with a single lymph node mass 2 cm or less in greatest dimension, or multiple lymph nodes, 2 cm or less in greatest dimension; N2 = metastasis with a single lymph node mass larger than 2 cm, but no more than 5 cm in greatest dimension, or multiple lymph nodes, no more than 5 cm in greatest dimension; M1 = distant metastasis; LDH = lactate dehydrogenase; Hb = hemoglobin; Alk phos = alkaline phosphatase; PSADT = prostate-specific antigen doubling time; PSAHL = prostate-specific antigen half-life.

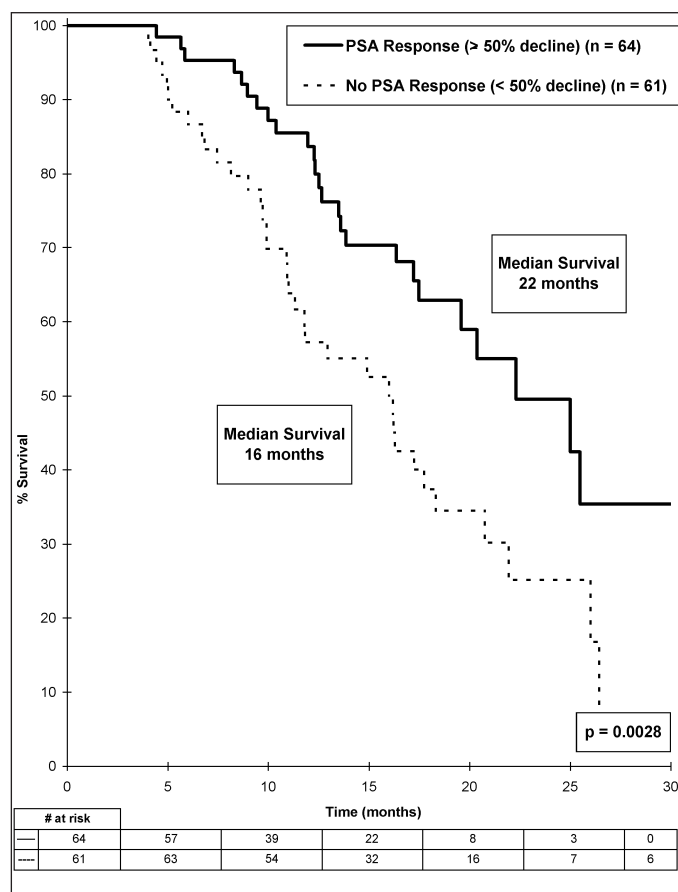


Fig 1. Overall survival stratified by prostate-specific antigen (PSA) response (PSA decline $\geq 50\%$) 84 days after starting docetaxel.

(as opposed to PSA response, which assumes it to be linear). This idea is somewhat analogous to PSADT, which assumes that tumour growth is logarithmic. In this multi-centre, retrospective analysis of mHRPC, we have demonstrated that when applied to patients having received 4 cycles of chemotherapy, the survival differentiation between a low PSAHL (< 70 days) and a high PSAHL (≥ 70 days) is greater than the survival differentiation between a PSA response and no PSA response. This result was independent of other known markers of survival and was a better predictor of survival than PSA response. Interestingly, we did not find an association between PSADT and survival following docetaxel chemotherapy in our study, even if previous investigators have noted such an association.⁸ This finding may be explained by the fact that our PSADT data was determined retrospectively, and included PSA measurements determined at different time points following treatment.

The relatively large survival difference (10 months) seen in patients with a rapid rate of PSA decline is particularly compelling given that patients who experienced a rise in PSA 84 days after starting docetaxel were excluded from PSAHL analysis. Exclusion of these nonresponders was

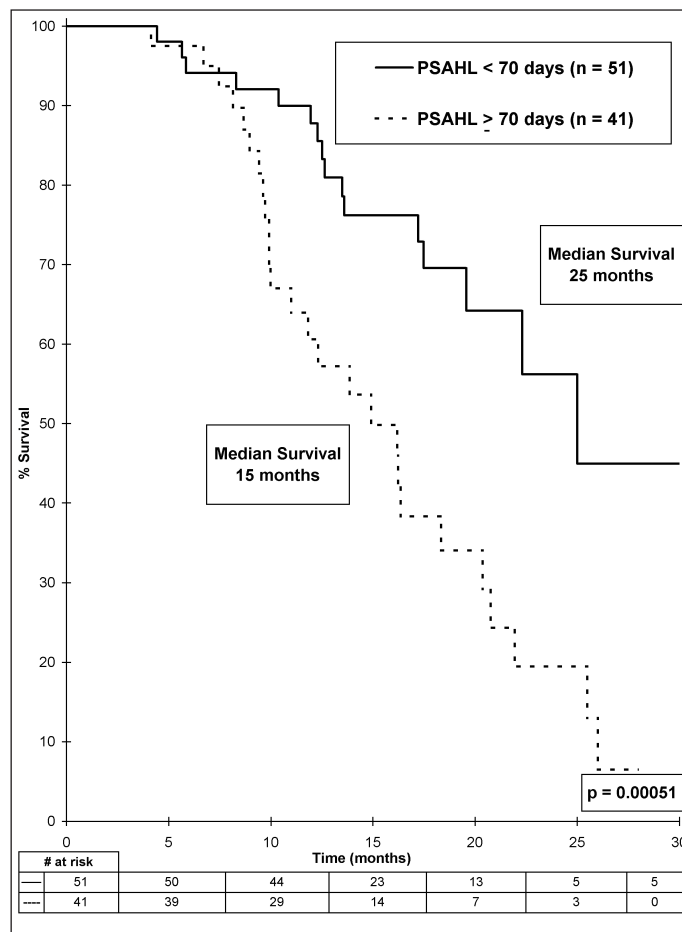


Fig 2. Overall survival stratified by prostate-specific antigen half-life, determined 84 days after starting docetaxel.

necessary because, mathematically, it is not possible to calculate a PSAHL for a patient whose PSA is rising (a negative number of days for PSAHL would result). Exclusion of this high-risk group is expected to bias the PSAHL results, resulting in a more homogeneous cohort (with a longer survival). However, we found that segregating these patients according to PSAHL (even after excluding the high-risk patients) actually yielded groups with more distinct OS compared with a PSA response-based segregation. If patients with a PSA rise on chemotherapy had been similarly excluded prior to stratifying patients based on PSA response, the survival difference between patients achieving a PSA response and those without a PSA response would no longer be significant.

A recent subgroup analysis of the TAX 327 study has suggested that the optimal PSA decline cutoff to stratify patients based on survival is a PSA decline of 30%.¹³ In this analysis, a survival difference of 8.6 months (21.6 months vs. 13.0 months) was demonstrated between groups with a PSA decline of 30% versus those without a PSA decline of 30%. In our study, stratifying patients based on PSAHL was associated with an even greater survival difference (10

months). Furthermore, PSAHL analysis requires that patients with a rising PSA be excluded from analysis, which should result in a more homogenous group, as previously discussed, yet this method still stratified patients to a greater degree than a 30% PSA decline.

We also studied the relationship between early PSAHL (determined after only 42 days or 2 cycles of docetaxel) and OS. The potential advantage of finding an association at this earlier time point would be to allow oncologists to predict survival earlier in the course of treatment and tailor the subsequent therapy accordingly. Unfortunately, neither PSAHL nor PSA response determined 42 days postdocetaxel correlated to survival in Kaplan-Meier analysis or Cox-regression analysis. This finding may be a result of a delayed PSA response to docetaxel noted in some patients such that a minimum number of cycles must be administered before a conclusion can be drawn about the effectiveness of the treatment. Thus, if patients are tolerating therapy, a minimum of 4 cycles of treatment should be given before making decisions about the effectiveness of treatment.

Conclusion

For men who are taking docetaxel therapy to palliate cancer symptoms, improvements in quality of life should supersede laboratory values in determining whether or not to continue therapy. However, due to survival improvements seen in randomized clinical trials, many men are offered chemotherapy to improve survival, even if they are asymptomatic. In these patients, early determination of who will benefit most from chemotherapy before toxicity arises would be very beneficial. We hope that PSAHL will help oncologists and their patients to decide whether to carry on with or discontinue docetaxel after 4 cycles of treatment. In particular, we feel that PSAHL may be of use in patients experiencing treatment-related side effects.

The major limitation of our study is the retrospective nature of the analysis; this limits the data collection to what is available in the charts and electronic records. Larger, prospective studies are required to further validate this new clinical tool. A larger study will also allow for a more definitive analysis of PSAHL determination at earlier time points after docetaxel initiation.

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