Time to Castration Resistance Is an Independent Predictor of Castration-resistant Prostate Cancer Survival

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Abstract. *Background/Aim: Easily assessable clinical predictors of response to chemotherapy in advanced castration-resistant prostate cancer (CRPC) are few. The objective of this retrospective study was to search for and identify such candidate predictors of outcome. Patients and Methods: A retrospective analysis of clinical data of CRPC patients entered in the Clinical Therapeutics' departmental prostate cancer database from 1996-2009 was performed. Univariate and multivariate analyses for progression-free survival and overall survival included patients receiving both docetaxel- and non-docetaxel-containing regimens. Results: From 1996 until June 2009, 286 out of 313 patients in our database were treated with chemotherapy. Prostate-specific antigen (PSA) reduction >30% correlated with improved survival irrespective of treatment. Beyond previously reported predictors, i.e. baseline PSA >30 ng/dl, hemoglobin below 10 mg/dl, weight loss, poor performance status, elevated lactic dehydrogenase and alkaline phosphatase, and time to CRPC of less than or equal to two years was associated with a poor overall survival and shorter progression-free survival upon univariate analysis. Pain was associated with shorter survival. Multivariate analysis confirmed time to CRPC, lactate dehydrogenase and alkaline phosphatase as independent predictors of overall and progression-free survival. Conclusion: Time to castration resistance is an important predictor of outcome in CRPC. PSA reduction >30% predicts survival improvement following chemotherapy for CRPC regardless of chemotherapy applied.*

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Establishing effective chemotherapy treatment in castrate-resistant prostate cancer (CRPC) has been more challenging than in other solid tumors. Advanced age at onset of disease, along with a long natural history of the disease, have hindered efficient drug development. Eventually, in 2004, single-agent docetaxel chemotherapy in combination with prednisone was found to confer a moderate yet significant survival benefit in castration-resistant metastatic disease as compared to mitoxan-trone and was thus introduced as the gold standard in clinical practice (1, 2). More recently, cabazitaxel was approved by the FDA for use in second-line therapy based on analogous findings (3).

In contrast to the case with other solid tumors, chemo-therapeutic doublets or triplets have not proven more efficacious than single-agent activity. Currently, exciting new agents such as lenalidomide, dasatinib, targeting the tumor microenvironment are being tested in the clinic, most of them in combination with docetaxel. In the meantime, androgen signaling inhibition is being revisited and the tumor microenvironment is assuming its 'nodal' role in resistance to current treatment strategies (4, 5).

In view of these exciting new developments in prostate cancer therapeutics, we reviewed our database and studied the impact of chemotherapy in an effort to assess how to best apply this treatment modality in the future. We specifically searched for clinical predictors of improved overall survival following chemotherapy other than those already identified.

Patients and Methods

Patient selection for analysis was based on the following criteria: histologically confirmed adenocarcinoma of the prostate, evidence of progressive CRPC, presence of measurable or evaluable disease,

Table I. *Patient characteristics*.

	Docetaxel-containing regimen		Non-docetaxel-containing regimen		All patients	
	No. of patients	Median (range)	No. of patients	Median (range)	No. of patients	Median (range)
Total	134		153		287	
Patient age (years)		72 (45-97)		70 (50-90)		71 (45-97)
Performance status						
0	56 (41.8%)		28 (18.3%)		84 (29.3%)	
1	55 (41%)		55 (36.0%)		110 (38.3%)	
2	18 (13.4%)		49 (32%)		67 (23.3%)	
3	5 (3.7%)		21 (13.7%)		26 (9%)	
Pain score						
0-1	87 (64.9%)		57 (37.25%)		144 (50.2%)	
2-3	33 (24.6%)		58 (37.8%)		91 (31.7%)	
4-5	13 (9.7%)		36 (23.6%)		49 (17.1%)	
Pain score missing data	1 (0.8%)		2 (1.3%)		3 (1.04%)	
Presence of bone metastases	115 (85.8%)		133 (86.9%)		248 (86.4%)	
Missing data on bone metastases	5 (3.7%)		2 (1.3%)		7 (2.4%)	
Presence of visceral metastases	17 (12.7%)		24 (15.7%)		43 (15%)	
Liver metastases	9 (6.7%)		17 (11.1%)		26 (9%)	
Missing data	7 (5.3%)		3 (2%)		10 (3.5%)	
Lung metastases	10 (7.4%)		8 (5.2%)		18 (6.27%)	
Missing data on lung metastases	8 (6%)		2 (1.3%)		10 (3.5%)	
Anemia (hemoglobin≤10 g/dl)	16 (11.9%)		23 (15%)		39 (13.6%)	
Missing data on Hb	2 (1.5%)		2 (1.3%)		4 (1.4%)	
Elevated LDH	45 (33.6%)		65 (42.2%)		110 (38.3%)	
Missing data on LDH	29 (21.6%)		71 (46.4%)		100 (34.8%)	
Elevated ALP	51 (38%)		64 (41.8%)		115 (40%)	
Missing data on ALP	20 (14.9%)		33 (21.6%)		53 (18.5%)	
Weight loss	28 (20.9%)		44 (28.8%)		72 (25.1%)	
Missing data on weight loss	4 (3%)		14 (9.1%)		18 (6.3%)	

Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 to 3. Progression was defined as a prostate-specific antigen (PSA) rise of 25% or greater than the lower value in three consecutive measurements at least 1 week apart, or as imaging evidence of progression. Time to castration resistance was calculated from the time of diagnosis irrespective of stage until confirmation of advanced CRPC. Advanced CRPC was confirmed by rising PSA in the presence of metastatic or recurrent locally advanced disease no longer amenable to existing locoregional therapeutic modalities. Pain was assessed on a scale of 0-5, with 0-1 no to minimal pain, 2-3 moderate pain and 4-5 severe pain requiring high doses of opioids.

Statistical analysis. The Clinical Therapeutics' Prostate Cancer Database was updated February 2010. Descriptive statistics and exploratory data analysis were used to summarize the patients' characteristics. Categorical data were described using contingency tables. Continuously scaled measures were summarized with descriptive statistical measures (*i.e.*, mean (±s.d.) or median (range)). Progression-free survival (PFS) and overall survival (OS) were calculated from the date of the initiation of chemotherapy. For PFS, objective progression or death from the disease were considered as events, while patients dying from other causes or with no progression were censored at the time of the last follow-up. Kaplan-Meier OS analysis was performed to estimate the OS and PFS functions. The two-sided log-rank test was used to assess the difference of survival functions among sub-groups. Multivariate analysis was performed using the Cox proportional hazards regression model to identify the independent variables affected the duration of overall survival or time to treatment failure (TTF) after adjusting for other factors. *P*-values were derived from two-sided tests and the statistical analyses were carried out using Splus version 7.0 (Insightful Corp., Seattle, WA, USA) software.

Results

Patient characteristics. From March 1996 to June 2009, 313 caucasian patients with CRPC were registered and 287 were subsequently treated with first-line chemotherapy. Baseline characteristics are given in Table I. Patients were castration-resistant by PSA and/or imaging criteria and had metastatic or locally recurrent disease not amenable to locoregional modalities.

Most patients (248, 86.4%) had bone metastases, while 43 (15%) had visceral metastases. Nearly half of the patients (49%) had moderate to severe pain with a pain score ≥2 in a scale of 0-5, while 25% experienced weight loss prior to chemotherapy initiation. Lactate dehydrogenase (LDH) and alkaline phosphatase (ALP) were elevated above normal in 110 (38.3%) and 115 (40%) patients respectively.

Chemotherapy regimens. Docetaxel-based chemotherapy was administered to 134 (46.7%) patients. Other chemotherapeutic regimens included oral etoposide and estramustine (76, 26.5%), carboplatin in combination with estramustine and oral etoposide (32, 11.4%), carboplatin with cyclophosphamide (13, 4.5%), vinorelbine (18, 6.3%), mitoxantrone, estramustine and vinorelbine combination (11, 3.8%), and mitoxantrone (2, 0.7%).

Second-line chemotherapy was administered to 175 (61%) patients (data on 32 patients are missing). It included doxorubicin plus ketoconazole (101, 57.71%), oral etoposide and estramustine (50, 28.57%) and vinorelbine (24, 13.71%). Mitoxantrone was not commonly used.

Table I depicts patient characteristics by docetaxel- and non-docetaxel-containing treatment groups. There were no differences in age nor in presence of bone or visceral metastases. Patients who received non-docetaxel-containing treatment more often had impaired performance status, pain, weight loss and higher PSA.

Median overall PFS following first-line treatment was 6 months (95% confidence interval 5.1-7.1 months). Docetaxel-based treatment conferred 6.6 months PFS (95% confidence interval (CI) 5.1-8.1 months) as compared to 5.5 months (95% CI 4.4-7.5 months) with other regimens (Figure 1A).

Median OS was 16 months (95% CI 15.1-17.1 months). There was a two-month difference in OS between patients receiving docetaxel (17 months) (95% CI 14.8-17.0 months) and those receiving treatments (15 months) (95% CI 16-23.2 months) (p=0.066) (Figure 1B). A PSA reduction >50% was reached in 148 (51.6%) patients regardless of treatment, while in 95 (33.1%), reduction exceeded >80%. Supplemental Figures A-C depict waterfall plots of PSA modulation following treatment. There was no difference between docetaxel and non-docetaxel treatment with regard to >50% or >80% PSA reduction (p-value=0.8). Overall PSA reduction >30% predicted improved OS and PFS (supplemental figures D-E) as anticipated.

Pretreatment predictors of PFS and OS. We sought possible associations between OS and PFS and pretreatment characteristics. Given the lack of significant difference in outcome, the analysis included all patients treated with chemotherapy.

Characteristics included age >70 years, pretreatment hemoglobin <10 g/dl, pretreatment PSA >30 ng/dl, elevated ALP, elevated lactic LDH, presence of visceral metastasis, extent of bone metastatic disease, impaired ECOG performance status PS ≥2, pain score and time from diagnosis to castration resistance.

PFS analysis: Univariate analyses identified associations between shorter PFS and laboratory parameters such as PSA >30 ng/dl (Figure 2A), anemia (hemoglobin≤10 g/dl) (Figure 2B), elevated LDH (above upper normal limit) (Figure 2C). Interestingly age >70 years was indicative of a longer time to disease progression (Figure 2D).

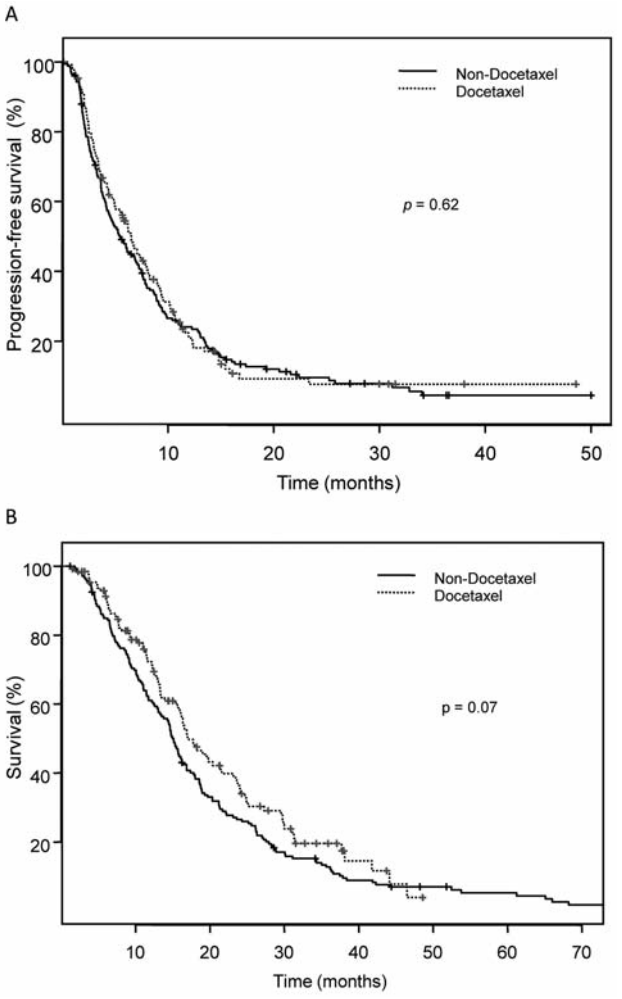

Figure 1. *A: Progression-free survival by chemotherapy type (p=0.62 in log-rank test). Median PFS is 6.6 months for docetaxel-containing regimens and 5.5 months for non-docetaxel-containing regimens. B: Overall survival (from Rx date) by chemotherapy type with median follow-up of 48 months. Median survival is 17 months for docetaxel-containing, 15 months for non-docetaxel-containing regimens, (p=0.07 in log-rank test). Supplemental Figure A-C: Waterfall plots of PSA modulation following treatment. A PSA reduction >50% was reached in 148 (51.6%) patients, while in 95 (33.1%), reduction exceeded >80% (A). There was no difference between docetaxel (B) and non-docetaxel treatment (C) with regard to >50% or >80% PSA reduction. (p-value: 0.8). D-E: PSA reduction >30% predicted improved OS (D) and PFS (E).*

Elevated ALP, weight loss (defined as >10% weight in a month) and impaired performance status (PS>1) associated with shorter PFS were marginally significant (Figure 2E-G). Importantly, time from diagnosis to castration resistance of less or equal to 2 years was strongly associated with a poor outcome (Figure 2H). A moderate or severe level of pain (pain score >2 in a 0-10 scale), presence of visceral metastases and extent of bone metastatic disease did not influence PFS.

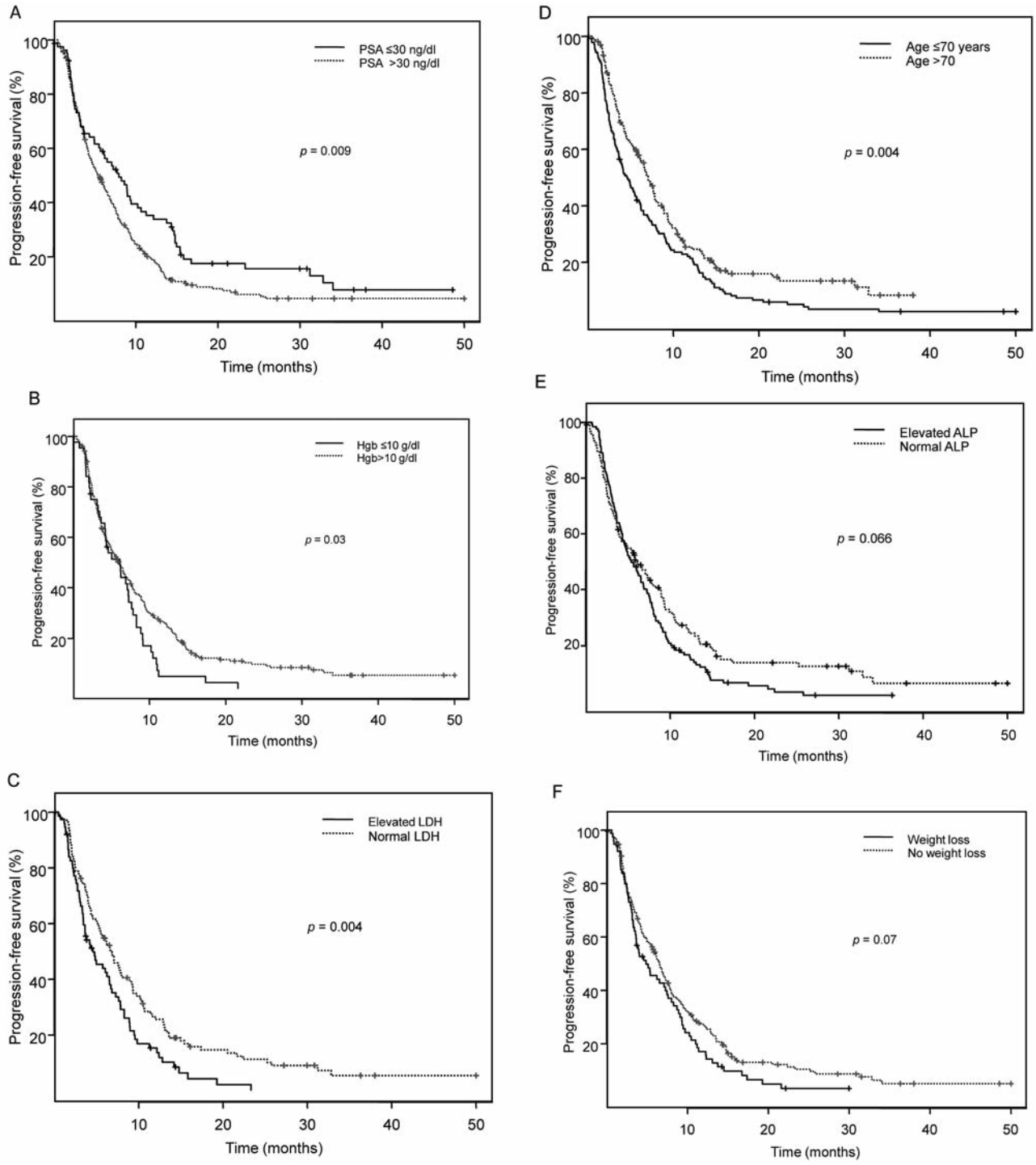

Figure 2. *continued*

Multivariate analysis for the purpose of identifying candidate prognosticators of outcome was performed. All significant, even if marginally so, univariate parameters were included, namely age >70 years, weight loss, PS ECOG >1, pretreatment elevated ALP, pretreatment PSA>30 ng/dl, anemia (hemoglobin <10 g/dl) and time to castration resistance. LDH was not included given the extent of missing data in the cohort (Table I). Finally, docetaxel-containing treatment *vs*. others was included. Baseline PSA >30 ng/dl and time to castration resistance of less than 2 years, appear

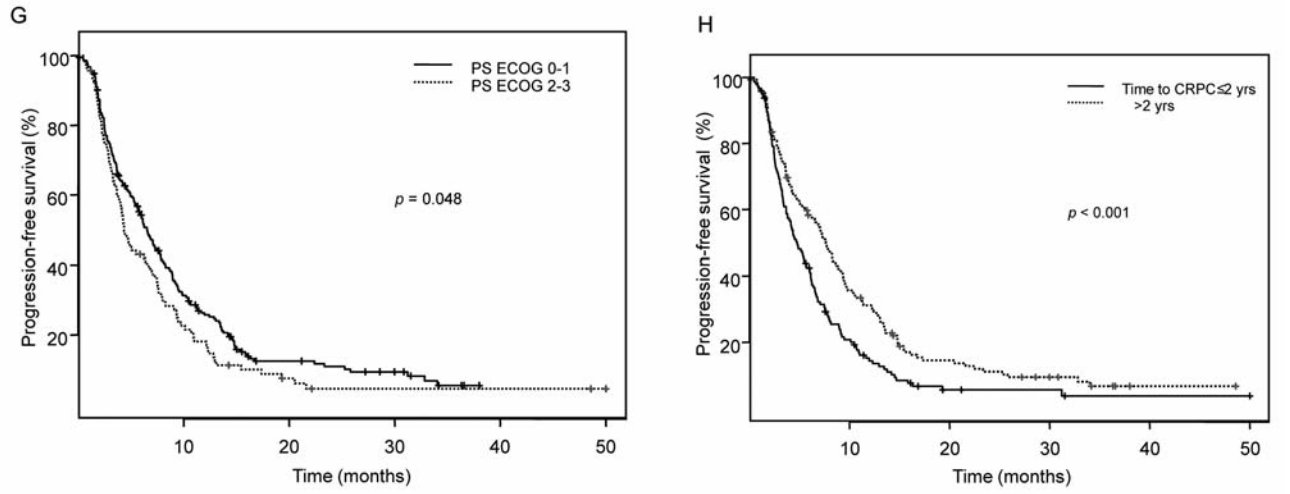

Figure 2. *Univariate analysis for PFS correlation with PSA (A), hemoglobin (B), lactic dehydrogenase (C), age (D), alkaline phosphatase (E), weight loss (F), performance status (ECOG) (G) and time to CRPC (H).*

to be independent adverse PFS predictors, with the latter marginally so (Table II).

OS analysis: Univariate analyses identified associations between OS and PSA >30 ng/dl (Figure 3A), anemia (hemoglobin<10 g/dl) (Figure 3B), elevated LDH (above upper normal limit) (Figure 3C), elevated ALP (Figure 3D) and weight loss (defined as >10% weight loss in a month), time from metastatic disease diagnosis to castration resistance of less than or equal to 2 years, were again found to be strongly associated with OS. Finally pain and a poor performance status were also associated with shorter OS (Figures 3E-H). Age, presence of visceral metastases and number of bone lesions were not associated with outcome.

Multivariate analysis was performed using the same parameters as those included for PFS analysis. Time to castration resistance <2 years, elevated ALP and impaired ECOG PS >1 were identified as independently significant predictors of a poorer overall survival (Table II) and weight loss of borderline significance.

Table II. *Progression-free survival and overall survival.*

	Estimate	Hazard ratio	95% CI		*P*-value
			Lower	Upper	
Proression-free survival					
Hgb <10 g/dl	–0.25	0.78	0.54	1.13	0.18
Elevated ALP	0.08	1.08	0.80	1.46	0.62
Weight loss	0.25	1.28	0.91	1.79	0.15
Non-docetaxel treatment	–0.04	0.96	0.73	1.27	0.77
Time to CRPC <2 years	–0.27	0.76	0.58	1.00	0.050
PSA >30 ng/ml at baseline	0.34	1.40	1.01	1.94	0.044
PS=2 or 3	–0.03	0.97	0.70	1.34	0.83
Overall survival					
Hgb <10 g/dl	–0.29	0.75	0.52	1.10	0.14
Elevated ALP	0.48	1.62	1.18	2.24	0.0032
Weight loss	0.28	1.33	0.95	1.84	0.093
Non-docetaxel treatment	0.09	1.09	0.82	1.46	0.54
Time to CRPC <2 years	–0.41	0.66	0.50	0.87	0.003
PSA >30 ng/ml at baseline	0.20	1.22	0.87	1.72	0.24
PS=2 or 3	0.33	1.39	1.01	1.92	0.042

Discussion

Establishing chemotherapeutic standards of care in prostate cancer has proved a difficult task as compared to other solid tumors. It took years and many patients to establish docetaxel in treatment of metastatic CRPC (1, 2). Docetaxel has improved the quality of CRPC patients' lives and offered a longer PFS and OS.

We wished to learn from our experience of chemotherapy treatment in CRPC and identify associations of outcome with easily assessable clinical and laboratory parameters and thus propose candidate predictors of response (6-8).

We elected the agnostic route and assessed the difference in PFS and OS between docetaxel-based chemotherapy and other regimens. Interestingly, comparators were not all mitoxantrone-based but included carboplatin, etoposide and the vinca alkaloid vinorelbine.

In this retrospective analysis, we did not identify a statistically significant difference in PFS or OS between docetaxel- and non-docetaxel-containing regimens. Several factors may have contributed to this result.

Given that a two-month OS difference was indeed observed, this may be related to the smaller number of patients or the retrospective nature of the analysis. Furthermore, the docetaxel

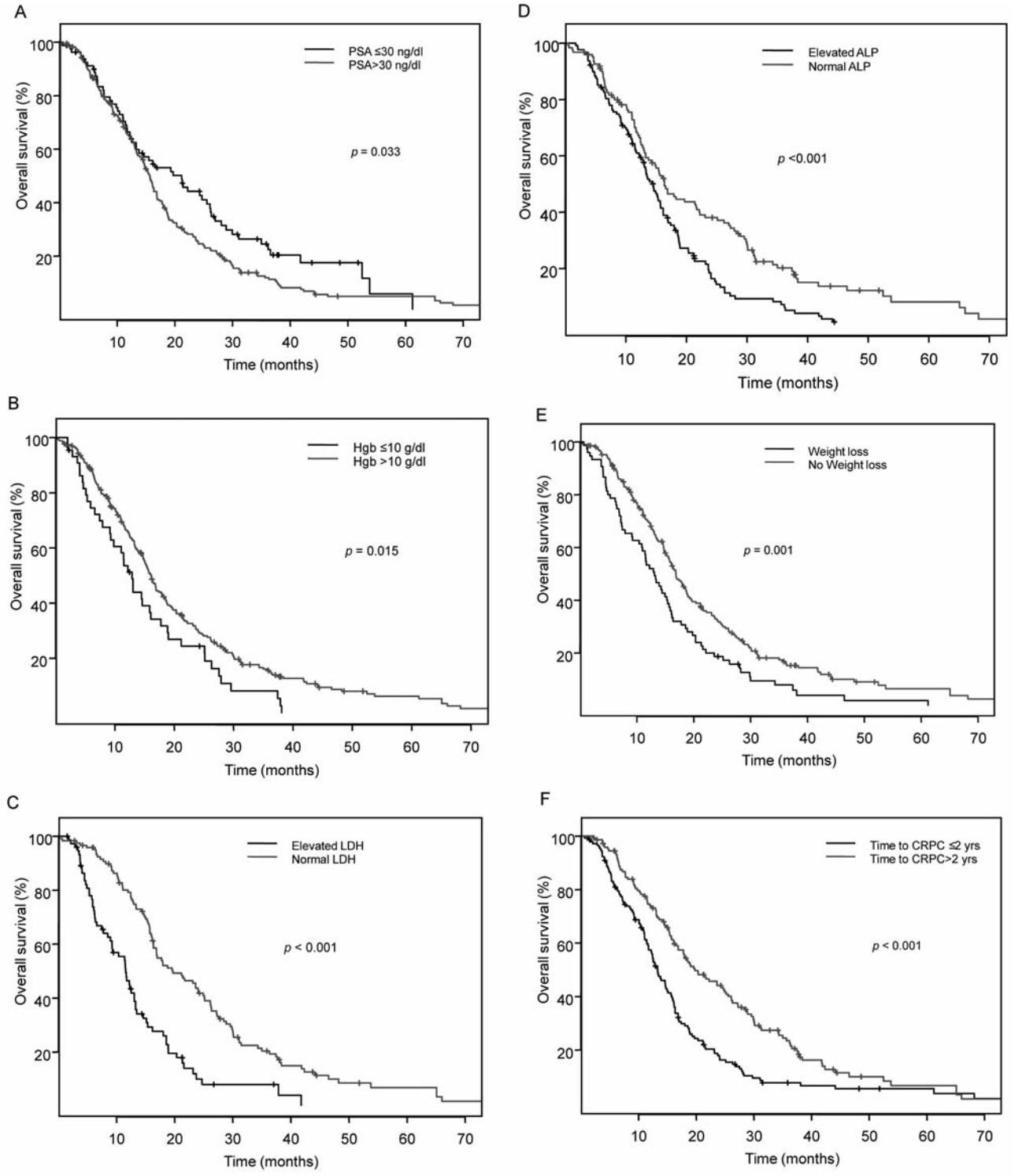

Figure 3. *continued*

regimen used was mainly that of an every two-week administration, which may be inferior to standard treatment. More importantly, in our opinion, the comparator arm did not consist of single therapy mitoxantrone but included mainly combination therapy that may very well be of analogous efficacy (9). Given the lack of difference between the regimens, we opted to assess candidate pretreatment prognosticators of PFS and OS in the entire chemotherapy cohort.

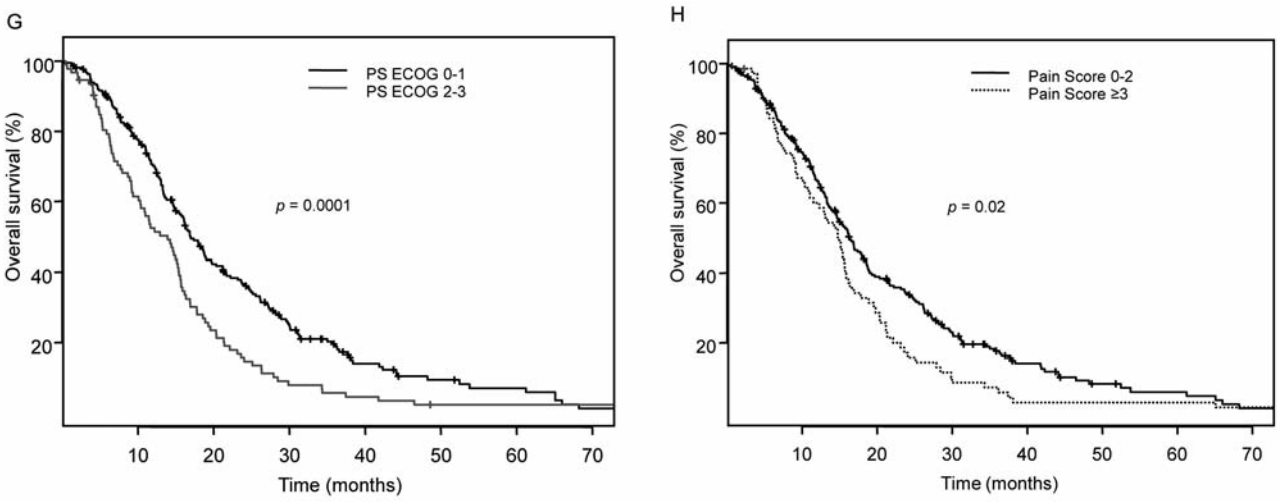

Figure 3. *Univariate analysis for OS correlation with PSA (A), hemoglobin (B), lactic dehydrogenase (C), alkaline phosphatase (D), weight loss (E), time to CRPC (F), perfomance status (ECOG) (G) and pain score (H).*

Intermediate surrogates of response are of interest given the need for measures that will help shorten trial follow-up in a disease with such a long natural history. As previously reported, our analysis confirmed PSA reduction ≥30% from baseline as an important surrogate associated with both improved PFS and OS (10). We remain cautious with regard to the value of PSA modulation, given the shift in therapeutics such as active immunotherapy and microenvironment targeting agents (11, 12). Furthermore, when therapeutic agents directly target the androgen signaling axis, PSA modulation may only serve as a pharmacodynamic measure as it may be unlinked with treatment efficacy in the castration-resistant state. The primary goal of this analysis was to search for easily assessable pretreatment predictors of outcome. With that in mind, we included clinical and laboratory information that pertain to standard CRPC work up.

Performance status and constitutional symptoms, such as weight loss along, with cancer-related pain, have been associated with OS in CRPC. Pain interference score was proposed as an independent predictor of OS in a retrospective analysis of 590 patients following a series of smaller reports based mainly on results from univariate analyses (13, 14). Interestingly, the presence of visceral metastasis as a binary variable or extent of bone disease did not correlate with OS or PFS in our analysis, unlike other reports (15).

It is quite possible that the presence of pain is a more accurate surrogate for extent of bone metastatic disease (16, 17). In our analysis, moderate and severe pain correlated with OS, as has been recently reported, while impaired performance status had an even stronger association. We elected the performance status for the multivariate analysis as it is assessed more commonly and easily than the pain score.

Elevated LDH and ALP and high pretreatment PSA have all been associated with poor outcome. In our multivariate analysis, LDH data were not included given the lack of a significant amount of data. ALP, more accurately the bone-specific component, is a bone turnover marker that has been associated in multiple reports with outcome and skeletal events (15). Our multivariate analysis confirmed elevated ALP to be an independent prognosticator of outcome for OS but not PFS.

According to our analysis, time to castration resistance is an important prognosticator for both PFS and OS following chemotherapy. A short time to castration resistance is invariably associated with increased PSA velocity or short PSA doubling-time, parameters that have been associated with a poor outcome in multiple CRPC reports (18, 19). The advantage of time to castration resistance is that it is easily assessable as it does not require prior PSA measurements, which may not always be available. As all patients were chemotherapy-treated and no untreated control was available, we can only speculate as to whether this is a specific prognosticator of chemotherapy outcome. Given the central role of the androgen signaling axis in prostate cancer progression, it would be reasonable to consider time to castration resistance as an independent prognosticator of disease outcome *i.e.* regardless of chemotherapy given. Yet in this case, the parameter remains significant, even though not strongly so, for PFS as well, which is an outcome more likely to be treatment-specific. Alternatively, there is considerable room for speculation that a subset of prostate cancer patients inherently do better than others, despite treatment provided. Undoubtedly, patients with short time to castration resistance should be offered novel experimental therapeutic approaches, if available, given the impetus to improve their quality of life and OS.

In conclusion, we performed this analysis in an effort to identify easily applicable candidate prognosticators of outcome in CRPC. Asymptomatic or oligosymptomatic patients with normal ALP in combination with a time to castration resistance longer than two years may stand to gain from chemotherapy. Of course this approach does not preclude using other lines of hormonal therapy prior to chemotherapy, or even a combination of intermittent chemotherapy with hormonal therapy.

Given current research on maximal androgen ablation with agents such as abiraterone acetate and mdv3100 (4, 5), it will be of interest to study whether time to chemotherapy treatment will be prolonged with such agents or whether a combination of maximal androgen ablation with chemotherapy will be warranted at least following initial castration resistance.

References

1 Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, Oudard S, Théodore C, James ND, Turesson I, Rosenthal MA, Eisenberger MA; TAX 327 Investigators. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med *351(15)*: 1502-1512, 2004.

2 Petrylak DP, Tangen CM, Hussain MH, Lara PN Jr., Jones JA, Taplin ME, Burch PA, Berry D, Moinpour C, Kohli M, Benson MC, Small EJ, Raghavan D and Crawford ED: Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med *351(15)*: 1513-1520, 2004.

3 Sartor AO, Oudard S, Ozguroglu M, Hansen S, Machiels JH, Shen L, Gupta S and De Bono JS: Cabazitaxel or mitoxantrone with prednisone in patients with metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel: Final results of a multinational phase III trial (TROPIC). Abstract 9A, ASCO 2010.

4 Reid AH, Attard G, Danila DC, Oommen NB, Olmos D, Fong PC, Molife LR, Hunt J, Messiou C, Parker C, Dearnaley D, Swennenhuis JF, Terstappen LW, Lee G, Kheoh T, Molina A, Ryan CJ, Small E, Scher HI and de Bono JS: Significant and sustained antitumor activity in post-docetaxel, castration-resistant prostate cancer with the CYP17 inhibitor abiraterone acetate. J Clin Oncol *28(9)*: 1489-1495, 2010.

5 Scher HI, Beer TM, Higano CS, Anand A, Taplin ME, Efstathiou E, Rathkopf D, Shelkey J, Yu EY, Alumkal J, Hung D, Hirmand M, Seely L, Morris MJ, Danila DC, Humm J, Larson S, Fleisher M, Sawyers CL; Prostate Cancer Foundation/Department of Defense Prostate Antitumour activity of MDV3100 in castration-resistant prostate cancer: a phase 1-2 study. Cancer Clinical Trials Consortium. Lancet *375(9724)*: 1437-1446, 2010.

6 Bamias A, Bozas G, Antoniou N, Poulias I, Katsifotis H, Skolarikos A, Mitropoulos D, Alamanis C, Alivizatos G, Deliveliotis H and Dimopoulos MA: Prognostic and predictive factors in patients with androgen-independent prostate cancer treated with docetaxel and estramustine: a single institution experience. Eur Urol *53(2)*: 323-331, 2008.

7 Berry WR, Laszlo J, Cox E, Walker A and Paulson D: Prognostic factors in metastatic and hormonally unresponsive carcinoma of the prostate. Cancer *44*: 763-775, 1979.

8 Emrich LJ, Priore RL, Murphy GP and Brady MF: Prognostic factors in patients with advanced stage prostate cancer. Cancer Res *45*: 5173-5179, 1985.

9 Thall PF, Logothetis C, Pagliaro LC, Wen S, Brown MA, Williams D and Millikan RE: Adaptive therapy for androgen-independent prostate cancer: a randomized selection trial of four regimens. J Natl Cancer Inst *99(21)*: 1613-1622, 2007.

10 Petrylak DP, Ankerst DP, Jiang CS, Tangen CM, Hussain MH, Lara PN Jr., Jones JA, Taplin ME, Burch PA, Kohli M, Benson MC, Small EJ, Raghavan D and Crawford ED: Evaluation of prostate-specific antigen declines for surrogacy in patients treated on SWOG 99-16. J Natl Cancer Inst *98(8)*: 516-521, 2006.

11 Drake CG and Antonarakis ES: Update: immunological strategies for prostate cancer. Curr Urol Rep *11(3)*: 202-207, 2010.

12 Kelly WK, Halabi S, Carducci MA, George DJ, Mahoney JF, Stadler WM, Morris MJ, Kantoff P, Monk III JP and Small EJ: A randomized, double-blind, placebo-controlled phase III trial comparing docetaxel, prednisone, and placebo with docetaxel, prednisone, and bevacizumab in men with metastatic castration-resistant prostate cancer (mCRPC): Survival results of CALGB 90401.J Clin Oncol *28*: 7s (suppl; abstr LBA4511), 2010.

13 Halabi S, Vogelzang NJ, Kornblith AB, Ou SS, Kantoff PW, Dawson NA and Small EJ: Pain predicts overall survival in men with metastatic castration-refractory prostate cancer. J Clin Oncol *26(15)*: 2544-2549, 2008.

14 Berthold DR, Pond G and De Wit R: Association of pain and quality of life (QOL) response with PSA response and survival of patients (pts) with metastatic hormone refractory prostate cancer (mHRPC) treated with docetaxel or mitoxantrone in the TAX-327 study. J Clin Oncol *24*: 221s (suppl, abstr 4516), 2006.

15 Armstrong AJ, Garrett-Mayer ES, Yang YC, de Wit R, Tannock IF and Eisenberger M: A contemporary prognostic nomogram for men with hormone-refractory metastatic prostate cancer: a TAX327 study analysis. Clin Cancer Res *13*: 6396-6403, 2007.

16 Sabbatini P, Larson SM, Kremer A, Zhang ZF, Sun M, Yeung H, Imbriaco M, Horak I, Conolly M, Ding C, Ouyang P, Kelly WK and Scher HI: Prognostic significance of extent of disease in bone in patients with androgen-independent prostate cancer. J Clin Oncol *17*: 948-957, 1999.

17 Soloway MS, Hardeman SW, Hickey D, Raymond J, Todd B, Soloway S and Moinuddin M: Stratification of patients with metastatic prostate cancer based on extent of disease on initial bone scan. Cancer *61*: 195-202, 1988.

18 Hussain M, Tangen CM, Higano C, Schelhammer PF, Faulkner J, Crawford ED, Wilding G, Akdas A, Small EJ, Donnelly B, MacVicar G and Raghavan D: Absolute prostate-specific antigen value after androgen deprivation is a strong independent predictor of survival in new metastatic prostate cancer: Data from the Southwest Oncology Group trial 9346 (INT-0162). J Clin Oncol *24*: 3984-3990, 2006.

19 Stewart AJ, Scher HI, Chen M-H, McLeod DG, Carroll PR, Moul JW and D'Amico AV: Prostate-specific antigen nadir and cancer-specific mortality following hormonal therapy for prostate-specific antigen failure. J Clin Oncol *23*: 6556-6560, 2005.

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