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Clinical Cancer Research

Cancer Therapy: Clinical

Platinum-Based Chemotherapy for Variant Castrate-Resistant Prostate Cancer

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Abstract

Purpose: Clinical features characteristic of small-cell prostate carcinoma (SCPC), "anaplastic," often emerge during the progression of prostate cancer. We sought to determine the efficacy of platinum-based chemotherapy in patients meeting at least one of seven prospectively defined "anaplastic" clinical criteria, including exclusive visceral or predominantly lytic bone metastases, bulky tumor masses, low prostate-specific antigen levels relative to tumor burden, or short response to androgen deprivation therapy.

Experimental Design: A 120-patient phase II trial of first-line carboplatin and docetaxel (CD) and second-line etoposide and cisplatin (EP) was designed to provide reliable clinical response estimates under a Bayesian probability model with early stopping rules in place for futility and toxicity.

Results: Seventy-four of 113 (65.4%) and 24 of 71 (33.8%) were progression free after four cycles of CD and EP, respectively. Median overall survival (OS) was 16 months [95% confidence interval (CI), 13.6–19.0 months]. Of the seven "anaplastic" criteria, bulky tumor mass was significantly associated with poor outcome. Lactic acid dehydrogenase strongly predicted for OS and rapid progression. Serum carcinoembryonic antigen (CEA) concentration strongly predicted OS but not rapid progression. Neuroendocrine markers did not predict outcome or response to therapy.

Conclusion: Our findings support the hypothesis that patients with "anaplastic" prostate cancer are a recognizable subset characterized by a high response rate of short duration to platinum-containing chemotherapies, similar to SCPC. Our results suggest that CEA is useful for selecting therapy in men with castration-resistant prostate cancer and consolidative therapies to bulky high-grade tumor masses should be considered in this patient population. *Clin Cancer Res; 19(13); 3621–30. ©2013 AACR.*

Introduction

Volume and extent of cancer dissemination remain the foundation for the classification and prognostication of patients with prostate cancer. However, this anatomy-based classification does not account for the clinical and biologic heterogeneity within the disease and limits our ability to predict individualized outcomes and to conduct efficient studies of promising agents and rational combinations. As part of a broader effort to characterize patients with advanced prostate cancer, we focused on a clinically distinct subset with recognizable features; in particular, we speculated that prostate cancers that display clinical features associated with small-cell carcinoma morphology, a syndrome initially dubbed "anaplastic", have common underlying biology that may be implicated in the lethality of a significant portion of patients with prostate cancer.

Small-cell prostate carcinoma (SCPC) is rarely detected at initial diagnosis but is more frequent upon recurrence (1–7). Autopsy series show its presence in 10%–20% of men dying of CRPC (8–10). The diagnosis of small-cell carcinoma morphology is associated with clinical features not considered typical of prostate cancer, for example, visceral involvement, lytic bone metastases, and low or undetectable prostate-specific antigen (PSA) levels (1–7). It is also associated with a characteristic response profile: it is unresponsive to androgen ablation but experiences frequent (although short-lived) chemotherapy responses (3–7).

On the basis of our prior experience and that reported by others (1–6), we empirically, but prospectively, defined 7

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Translational Relevance

The clinical application of effective androgen receptor (AR) inhibition has benefitted a large number of men with castrate-resistant prostate carcinoma (CRPC). However, the driver(s) of the disease beyond AR are poorly understood. Small-cell prostate carcinoma (SCPC) is a morphologic variant of prostate cancer that does not express AR and is linked to a short survival. SCPC is rare at initial diagnosis but present in 10% to 20% of men with lethal CRPC. Moreover, clinical features characteristic of SCPC are present in a significant proportion of morphologically heterogeneous CRPCs. We hypothesized that prostate cancers that share clinical features with SCPC ("anaplastic" prostate cancers) also share its responsiveness to chemotherapy and underlying biology. Here, we used "anaplastic" criteria to select men with CRPC (plausibly enriched for AR-independent CRPC) for treatment with platinum-based chemotherapies as part of a broader effort to contribute to the development of a clinically meaningful, biologically based classification of prostate cancer.

clinical features that were considered characteristic of SCPC to select patients for this study (C1–C7; Table 1). Men who met one or more of these criteria were treated with carboplatin and docetaxel (CD), and with etoposide and cisplatin (EP) upon progression, in a single-arm sequential phase II clinical trial. Our previous studies in patients with documented SCPC histology had shown that, similarly to small-cell lung cancer, SCPC has a high response to EP-based chemotherapy (5, 6) but we had observed that, at the time of disease progression, many patients had prostate adenocarcinoma as the only detected histologic type. This spoke to the need to address both histologic components that frequently coexist in this disease. Docetaxel is the standard first-line chemotherapy for CRPC (11, 12) and has shown modest activity in small-cell lung cancer (13, 14). However, it was felt that the combination of EP with docetaxel would result in excessive toxicity. Carboplatin is considered an acceptable alternative to cisplatin for the treatment of small-cell lung cancer (15), has modest single-agent activity in CRPC (16), and has been combined with taxanes successfully for its treatment (17). Therefore, we chose to evaluate the efficacy of the combination of CD in patients with "anaplastic" prostate cancer but included EP as salvage therapy in the event that patients failed to respond to CD. This design also allowed careful monitoring of cumulative neurotoxicity, which was a concern when using these 2 regimens sequentially.

The primary objectives were to estimate the response rate and time to progression for patients with anaplastic prostate carcinoma treated with first-line CD and their response rate and time to progression to second-line EP following treatment with CD. Secondary objectives included the collection of tissues for investigating the underlying biology of this subset, because our broader goal is to contribute to the development of a biologically based, clinically meaningful prognostic and predictive classification of prostate cancer. We also sought to evaluate the toxicity of the regimens and to estimate the overall survival (OS) of patients with "anaplastic" prostate carcinoma treated with CD and salvage EP.

The results support our hypothesis that clinical features characteristic of SCPC identify a morphologically heterogeneous but clinically distinct and chemotherapy-responsive variant of prostate cancer.

Patients and Methods

Inclusion and exclusion criteria

Eligibility criteria included the presence of metastatic castrate-resistant prostate cancer with 1 or more of 7 criteria

Table 1. Clinical features of "anaplastic" prostate carcinomas (eligibility criteria)

Castrate-resistant[a] prostate carcinoma with at least 1 of the following:	*n* (%)
C1. Histologic evidence of small-cell prostate carcinoma (pure or mixed).	29 (25.4)
C2. Exclusively visceral metastases.	19 (16.7)
C3. Radiographically predominant lytic bone metastases by plain x-ray or CT scan.	16 (14.0)
C4. Bulky (≥5 cm) lymphadenopathy or bulky (≥5 cm) high-grade (Gleason ≥ 8) tumor mass in prostate/pelvis.	49 (43.0)
C5. Low PSA (≤10 ng/mL) at initial presentation (before ADT or at symptomatic progression in the castrate setting) plus high volume (≥20) bone metastases.	26 (22.8)
C6. Presence of neuroendocrine markers on histology (positive staining of chromogranin A or synaptophysin) or in serum (abnormal high serum levels for chromogranin A or GRP) at initial diagnosis or at progression. Plus any of the following in the absence of other causes: **A.** elevated serum LDH (≥2 × IULN); **B.** malignant hypercalcemia; **C.** elevated serum CEA (≥2 × IULN).	21 (18.4)
C7. Short interval (≤6 months) to androgen-independent progression following the initiation of hormonal therapy with or without the presence of neuroendocrine markers.	52 (45.6)

Abbreviation: GRP, gastrin-releasing peptide.
[a]Patients with small-cell prostate carcinoma on histologic evaluation were not required to have castrate-resistant disease.

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(Table 1). Patients with histologically confirmed SCPC were not required to have received prior androgen-deprivation therapy (ADT), but all others had to have evidence of disease progression during ADT or an unsatisfactory response to 1 or more month of castration (i.e., lack of pain control and/or <20% PSA decrease, confirmed by repeat testing on a different day) and a serum testosterone level of $\leq$1.74 nmol/L. Patients also had to have 0 to 2 Eastern Cooperative Oncology Group (ECOG) performance status and adequate organ function, including creatinine clearance $\geq$0.67 mL/s/m^2. Men with asymptomatic brain metastases not requiring corticosteroid treatment to control central nervous system symptoms could participate.

Exclusion criteria included grade 2 or greater peripheral neuropathy and treatment with: (i) 2 or more prior chemotherapy regimens; (ii) prior platinum-, etoposide-, or taxane-based therapy within 6 months of registration; and (iii) 2 or more doses of bone-seeking radioisotopes.

The study protocol was approved by the Institutional Review Boards (IRB) of both participating institutions and conducted in accordance with the precepts established by the Helsinki Declaration. Before enrollment, all patients signed IRB-approved written informed consent forms. Clinicaltrials.gov identifier was NCT00514540.

Clinical evaluations

Complete blood counts and serum creatinine, transaminase, and bilirubin concentrations were required within 14 days of enrollment. Complete history and physical examination, serum chemistries, circulating markers (Table 2), electrocardiography, bone scan, and body computed tomography (CT) or MRI scanning were required within 28 days. Contrast-enhanced MRI or CT brain scanning was required within 42 days. Optional procedures included tumor biopsy, bone marrow biopsy, and peripheral blood and urine collection for correlative studies.

Patients returned for evaluation before each cycle. Imaging and circulating markers were repeated every 2 cycles and every 6 to 8 weeks after treatment discontinuation.

Chemotherapy

First-line chemotherapy was CD (carboplatin, area under the curve 5, plus docetaxel, 75 mg/m^2) on day 1 every 3 weeks. Second-line EP (etoposide, 120 mg/m^2, plus cisplatin, 25 mg/m^2) was administered daily for 3 days every 3 weeks upon tumor progression. Treating oncologists could administer the chemotherapy locally, but patients were required to return to the participating institution for evaluation after every 2 cycles.

In the absence of progressive disease (PD), patients received at least 4 cycles of CD or EP. Colony-stimulating factors were administered at the treating physician's discretion. Dose delays and reductions were within standards for these regimens.

Off-study criteria

Patients were removed from study for documented progression after EP, start of a new systemic treatment, more than 3-week delay in therapy for any reason, unacceptable toxicity that required more than 2 dosing reductions, or patient or physician decision. Data from all patients, whether or not they met eligibility criteria, were evaluated for toxicity if they received at least 1 dose of treatment.

Statistical methods

Sample size. The trial was designed to accrue up to 120 patients to provide reasonably reliable estimates of all relevant parameters based on a Bayesian probability model. This model and decision rules were used to monitor patient outcomes throughout the trial. Interim early stopping rules were applied continuously such that the trial should be stopped for futility (probability of response unacceptably low compared with a target of 30% for CD and 20% for EP following CD) or safety (risk of serious adverse event unacceptably high).

Response evaluation. After 2 and 4 cycles of chemotherapy, response was characterized by the 4-category ordinal variables taking on the values progressive disease, stable disease, partial response (PR), or complete response (CR). With these values, "response" was used in 2 ways:

1. "Tumor response" described the tumor's reaction to the chemotherapy regimens and was reported separately for (i) measurable disease [according to response evaluation criteria in solid tumors (RECIST); ref. 18]; (ii) bone disease (an increase in size or number of blastic bone lesions on bone scan, or of lytic lesions on CT, MRI, or plain x-ray, was considered progression); and (iii) serum tumor marker evaluation (PSA response was defined per PSA Working Group recommendations; ref. 19). Carcinoembryonic antigen (CEA) levels were considered evaluable if at least twice the Institutional upper limit of normal (IULN) and PSA Working Group criteria were applied to define CEA response. To be evaluable for "tumor response," eligible patients had to receive at least 2 cycles of treatment and undergo tumor marker and image evaluation.

2. "Clinical response," the primary outcome of the study, was defined as absence of progressive disease (i.e., stable disease, PR, or CR). To be evaluable for clinical response, patients had to fulfill the eligibility criteria and receive at least 1 chemotherapy cycle. Patients who did not undergo tumor marker and imaging evaluations after 2 to 4 cycles were counted as having progressive disease.

Statistical methods. Patients' characteristics were summarized using the median (range) for numeric variables and frequencies (percentages) for categorical variables. Associations between categorical variables were assessed with Fisher exact test and its generalizations. The Kaplan–Meier method was used to estimate unadjusted OS and progression-free survival (PFS). Univariate and multivariate Cox proportional hazards models were fit to assess relationships between patient covariates, including our 7 criteria, and OS and PFS. Log transformation was applied for covariates with

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Table 2. Summary of patients' characteristics ($n = 114$) and baseline serum marker values

Patient characteristics		*n* (%)[a]
Age, y; median (range)	At diagnosis	61 (36–79)
	At registration	64 (39–80)
Race	White	103 (90.4)
	Not white	11 (9.6)
Histology at diagnosis	Adenocarcinoma	
	GS 5/6	5 (4.4)
	GS 7	15 (13.2)
	GS 8	13 (11.4)
	GS 9	53 (46.5)
	GS 10	7 (6.0)
	Small-cell carcinoma	8 (7.0)
	Not available	13 (11.4)
Radiation to primary tumor	Yes	16 (14)
	No	98 (86)
Surgery to primary tumor	Yes	30 (73.7)
	No	84 (26.3)
ECOG PS at registration	0	25 (21.9)
	1	74 (64.9)
	2	15 (13.2)

Serum markers		IULN	No. (%) with values > IULN	Median (range)
ACTH	pmol/L	10.1	4/111 (3.6)	4.3 (0.88–47.3)
ADH	pmol/L	12.3	7/74 (9.5)	2.9 (0.9–270.4)
AVP	pg/mL	1.7	5/36 (13.9)	0.9 (<0.5–3.6)
Alkaline phos	IU/L	126	44/104 (42.3)	103.5 (40–1,107)
Calcitonin	pmol/L	2.5	28/88 (31.8)	1.5 (0.3–1,079.8)
Bone-sp Alkaline phos	μg/L	20	48/108 (44.4)	16.95 (1.8–404)
CEA	μg/L	3–6	28/113 (24.8)	2.5 (0–979.4)
Chromogranin A	μg/L	36.4	17/74 (23.0)	16.6 (4–615.7)
Chromogranin A,S	μg/L	225	20/35 (57.1)	251 (4–9,850)
GRP	pg/mL	500	0/57 (0)	58 (39–442)
Hemoglobin	g/L	140	78/114 (68.4)	127 (81–159)
LDH	IU/L	546	52/114 (45.6)	527 (111–1,942)
PAP	ng/mL	5	55/111 (49.5)	4.5 (0.5–2,464.8)
PSA	μg/L	4	72/114 (63.2)	8.7 (0–924.7)
Somatostatin	pmol/L	13.4	22/106 (20.8)	10.7 (3.1–33.6)

Abbreviations: GS, Gleason score; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ACTH, adrenocorticotropic hormone; ADH, antidiuretic hormone; AVP, arginine vasopressin; Alkaline phos, alkaline phosphatase; Bone-sp, bone specific; GRP, gastrin-releasing peptide.

[a]Data are given as numbers (and percentages) unless otherwise indicated.

skewed distributions. The proportional hazards assumption for each fitted Cox model was checked by using the method of Grambsch and Therneau (20).

All statistical analyses were carried out by using SAS 9.0, R2.9.0, or WinBUGS14 software.

Results

Patients

We enrolled 121 patients between June 2006 and October 2010. Seven were ineligible and excluded from the response analysis. Another was eligible but withdrew his consent before treatment, leaving 113 for response to CD analysis. Table 2 highlights baseline characteristics of the 114 eligible patients. Seventy-two patients (63%) had distant metastatic disease at diagnosis. The median time from diagnosis to registration was 13.9 months (range, 0.2–247.2 months). The median time from initiation of androgen deprivation therapy to registration (data available for $n = 106$) was 9.8 months [95% confidence interval (CI), 8.1–12.4 months]. Ninety patients (79%) were symptomatic at registration. Local symptoms (such as perineal pain or urinary obstructive symptoms) were reported by 39 of 96 patients (41%) for whom the information was available.

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Sixty-five of the 114 patients (57%) met more than 1 criterion (Table 1) for "anaplastic" prostate cancer. For C6, tissue specimens obtained within 6 months of enrollment and stained for chromogranin A and synaptophysin were available for 51 of the 114 patients (44.7%) and, of these, 29 (56.9%) were positive for 1 and/or the other neuroendocrine marker. However, of those 29, only 15 (51.7%) also had CEA and/or lactic acid dehydrogenase (LDH) levels twice the IULN needed to meet C6. An additional 6 patients had serum chromogranin A levels above the IULN plus elevated CEA and/or LDH levels, for a total of 21 (18.4%) patients meeting C6. Of the 63 patients (55.3%) for whom stained tissue was unavailable, 57 (90.5%) had neither elevated CEA nor LDH and thus would not have met C6 even if they had had positively staining tissues. Therefore, C6 was unknown for 6 (5.3%) of the 114 patients. As expected, C1 correlated positively with C6 ($P = 0.0001$) and negatively with C7 ($P = 0.0004$).

Table 2 shows baseline serum-marker values. The serum levels of at least 1 of the 6 neuroendocrine markers (chromogranin A, calcitonin, somatostatin, adrenocorticotropic hormone, antidiuretic hormone, and gastrin-releasing peptide) were elevated in 69 of the 114 patients (60.5%).

Response, PFS, and OS

Table 3 summarizes treatment responses. The median number of cycles of CD administered was 4 (range, 1–12 cycles). At the time of data collection, the median follow-up was 39.1 months (range, 1.07–62.47 months), and 105 patients (92.9%) had experienced progressive disease after CD, with a median time to progressive disease of 5.1 months (95%, 4.2–6.0 months).

Seventy-four of those 105 patients (70.5%) received second-line EP on study; the remainder withdrew from the study at their physician's or their own request. Of the 74 patients who received EP, 8 underwent only 1 cycle owing to rapid progressive disease or treatment complications, including 1 death from neutropenic sepsis; their data were inevaluable for "tumor response" but counted as progressive disease for "clinical response." The median number of

Table 3. Per-course responses to treatment

	First-line, *n* (%)		Second-line, *n* (%)	
	Course 1	Course 2	Course 1	Course 2
RECIST				
All evaluable	84	69	50	33
CR	1 (1)	1 (1)	0	0
PD	4 (5)	4 (6)	5 (10)	6 (18)
PR	19 (23)	23 (33)	13 (26)	10 (30)
SD	60 (71)	41 (59)	32 (64)	17 (52)
Bone				
All evaluable	85	71	49	25
CR	0	0	0	0
PD	7 (8)	3 (4)	10 (20)	5 (20)
PR	0	0	0	0
SD	78 (92)	68 (96)	39 (80)	20 (80)
PSA				
All evaluable	67	54	43	19
CR	0	2 (4)	2 (5)	1 (5)
PD	7 (10)	8 (15)	18 (42)	6 (32)
PR	19 (28)	23 (43)	5 (12)	5 (26)
SD	41 (61)	21 (39)	18 (42)	7 (37)
CEA				
All evaluable	26	20	20	14
CR	0	0	0	0
PD	3 (12)	4 (20)	2 (10)	3 (21)
PR	1 (4)	5 (25)	4 (20)	5 (36)
SD	22 (85)	11 (55)	14 (70)	6 (43)
Overall				
All evaluable	113	93	74	41
PD	19 (17)	19 (20)	31 (42)	17 (41)
No PD	94 (83)	74 (80)	43 (58)	24 (59)

Abbreviations: RECIST, response evaluation criteria in solid tumors; CR, complete response; SD, stable disease; PSA, prostate-specific antigen; CEA, carcinoembryonic antigen.

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EP cycles administered was 4 (range, 1–6 cycles). During the follow-up period, 72 of the 74 patients (97.3%) had experienced progressive disease in a median time of 3.0 months (95% CI, 1.6–3.5 months) after receiving EP.

Among the 113 patients treated on study, 91 (80.5%) have died. The median OS was 16 months (95% CI, 13.6–19.0 months).

We examined the interaction between the chemotherapy regimens delivered sequentially as per protocol. To determine this, we assumed that patients with stable or regressing cancers for 2 cycles of an individual regimen had derived benefit. Of the 74 patients receiving both lines of therapy, 37 (50.0%) benefited from both (median OS 19.33 months, 95%CI, 10.4–23.2) and 5 (6.8%) did not benefit from either (median OS 6.7 months, 95%CI, 19.2–38.2). Twenty-five (33.8%) had a response to CD but not to EP (median OS 14.4 months, 95%CI, 7.5–20.8) and 7 (9.4%) had a response to EP but not to CD (median OS 8.9 months, 95%CI, 13.6–32.2). The 40 patients that only received CD had median OS of 17.4 months (95%CI, 9.7–15.42).

Nine of the 113 patients (7.96%) were found to have brain metastases within the follow-up period. Three of those 9 had primary SCPC at initial diagnosis, and 3 had "secondary" SCPC at rebiopsy; the remaining 3 had no evidence of SCPC on histologic analysis.

Links of baseline characteristics with progression-free and OS

Table 4 summarizes the effects of baseline clinical and serologic characteristics, including our defined clinical criteria, C1–C7, on PFS and OS. Interpretation of P values should be tempered by the fact that multiple tests were conducted for each outcome. A conservative Bonferroni correction for multiple testing would require an individual P value to be less than 0.0015 for each test to control overall type I error at 0.05.

It is noteworthy that of the neuroendocrine markers, only levels of calcitonin seemed significantly associated with PFS and OS and that levels of LDH and CEA seemed to have greater prognostic value than did the levels of circulating chromogranin A and immunohistochemical positivity for either chromogranin A or synaptophysin. Of interest, abnormal CEA levels predicted poor OS ($P < 0.0001$) but not faster progression ($P = 0.150$) suggesting a benefit from chemotherapy despite portending a poor prognosis.

Among the 7 clinical criteria, only C4 was significantly associated with both OS ($P = 0.017$) and PFS ($P = 0.010$), and it predicted faster progression and death, whereas C6 was associated with poor OS ($P = 0.007$) but not with rapid progression ($P = 0.651$; Figs. 1 and 2). Also, the number of the 7 criteria met by a tumor was significantly associated with worse OS (HR = 1.41; $P = 0.003$).

The frequency of bulky primary tumor versus bulky lymphadenopathy was determined in 47 of 49 study patients that satisfied C4 to explore associations with outcome. Thirty-six of 47 (76.6%) had bulky primary tumors, 3 (6.4%) had both bulky primary tumors and bulky lymphadenopathy and 8 (17.0%) had bulky lymph nodes only. No differences were apparent but the numbers are too small to draw any definitive conclusions (data not shown). We also asked whether, within C6, neuroendocrine differentiation by serum or tissue criteria might be distinct in a predictive/prognostic sense from LDH and CEA. As stated above, immunohistochemistry for chromogranin A and synaptophysin on tumor tissues were only available for 51 (44.7%) of the 114 patients. To explore possible associations, we dichotomized variables based on the presence or absence of marker staining or serum levels above/below IULN. In this analysis, no obvious differences were observed (data not shown) although given the number of missing values, significance cannot be reported.

Several of the eligibility criteria were linked as reflected by the correlation analyses. To investigate these connections further, we clustered the data by clinical variables (Supplementary Fig. S1) and this pointed to the following associations:

1. C4 with metastasis at diagnosis (which would have made treatment of the primary tumor less likely), with measurable disease, and also with elevated serum neuroendocrine markers.
2. C7 with elevated levels of prostatic acid phosphatase (PAP) and/or PSA.
3. C3 with elevated levels of LDH, alkaline phosphatase, and bone-specific alkaline phosphatase.
4. A remaining group that includes C1, C2, C5, and C6 and is associated with liver metastases and high levels of CEA.

We also examined the association between time on ADT before registration response to therapy (PD/noPD), time to progression (TTP), and OS. Wilcoxon rank test showed a marginally significant difference ($P = 0.05$) in the mean time on ADT before registration between patients who progressed after 2 cycles of CD ($n = 18$, 9.5 months) and those who did not ($n = 88$, 20.5 months). No difference was noted ($P = 0.775$) for response to 2 cycles of EP ($n = 28$, 12.3 months vs. $n = 38$, 21.7 months respectively). On the basis of univariate Cox regression on OS, time on ADT (as a continuous variable) was marginally significant on OS ($P = 0.09$; HR, 0.99— longer time on ADT had better OS); but not significant on TTP-CD ($P = 0.51$; HR, 0.997) nor TTP-EP ($P = 0.14$; HR, 0.99).

Toxicity

In all, 544 cycles of CD were administered to 113 patients on study and 226 cycles of EP were administered to 74. Four men died during treatment: 1 from neutropenic sepsis after EP and 3 from rapid progressive disease after 2 cycles of CD ($n = 1$) and after 1 cycle of EP ($n = 2$). We observed no grade 3 or 4 sensory neuropathy. Grade 4 adverse events included thrombosis ($n = 2$) and thrombocytopenia ($n = 1$); the most common grade 3 events were infection with normal absolute neutrophil count or grade 1 or 2 neutropenia ($n = 8$), febrile neutropenia ($n = 3$), fatigue ($n = 2$), and vomiting ($n = 2$).

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Table 4. Summary of fitted univariate Cox proportional hazards models for OS and progression-free survival (PFS)

		OS				PFS			
	n	HR	Low 95%	High 95%	*P*	HR	Low 95%	High 95%	*P*
Race (w vs. not-w)	114	1.066	0.514	2.211	0.863	0.973	0.490	1.935	0.939
Mets.at.diagnosis	114	1.686	1.075	2.643	0.023	1.524	1.012	2.296	0.044
log.T.diag	114	0.842	0.734	0.965	0.014	0.832	0.729	0.950	0.007
No. of criteria = C1+. . ..+C7	114	1.410	1.126	1.766	0.003	1.211	0.970	1.511	0.092
C1	114	1.564	0.981	2.493	0.060	1.354	0.860	2.131	0.191
C2	114	1.088	0.641	1.846	0.755	1.096	0.651	1.846	0.730
C3	114	1·230	0.693	2.182	0.479	1.362	0.786	2.362	0.271
C4	113	1.682	1.098	2.575	0.017	1.677	1.132	2.485	0.010
C5	114	1.013	0.616	1.666	0.960	0.710	0.438	1.148	0.163
C6	108	2.150	1.235	3.741	0.007	1.126	0.673	1.882	0.651
LDH > 546	114	2.834	1.837	4.375	<0.0001	2.472	1.645	3.714	<0.0001
CEA > 6	114	3.241	1.973	5.325	<0.0001	1.400	0.889	2.205	0.150
IHC (+ vs. –)	52	1.229	0.675	2.238	0.500	0.919	0.515	1.641	0.780
C7	114	0.796	0.525	1.206	0.281	0.859	0.581	1.270	0.446
GS ≥ 8	101	1.203	0.730	1.984	0.470	1.393	0.864	2.244	0.170
PS = 0	25				Ref.				Ref.
PS = 1	74	2.396	1.316	4.363	0.004	1.904	1.149	3.154	0.012
PS = 2	15	3.985	1.818	8.733	0.001	3.003	1.513	5.961	0.002
Age	114	1.003	0.977	1.029	0.822	0.994	0.973	1.016	0.618
log.ACTH	101	1.134	0.774	1.662	0.517	1.121	0.775	1.621	0.545
log.ADH	74	1.159	0.930	1.444	0.190	1.094	0.872	1.372	0.436
log.Alk	104	1.249	0.953	1.636	0.107	0.896	0.681	1.178	0.431
log.BS.Alk	108	1.292	1.040	1.605	0.021	1.002	0.815	1.233	0.983
log.Calcitonin	88	1.581	1.202	2.079	0.001	1.566	1.196	2.050	0.001
Calcium	113	0.683	0.439	1.064	0.092	1.039	0.694	1.557	0.851
log.CEA	113	1.523	1.325	1.752	<0.0001	1.263	1.083	1.474	0.003
log.ChrA-1	74	0.871	0.702	1.079	0.206	0.941	0.769	1.151	0.553
log.ChrA-2[a]	35	1.630	1.010	2.610	0.045	1.200	0.803	1.789	0.375
log.GRP	57	0.791	0.501	1.247	0.313	0.794	0.537	1.173	0.247
Hb	114	0.804	0.709	0.912	0.001	0.915	0.817	1.025	0.127
log.LDH	114	2.714	1.698	4.340	<0.0001	2.570	1.693	3.901	0.0001
log.PAP	111	1.080	0.952	1.226	0.231	1.084	0.956	1.229	0.211
log.PSA	114	1.029	0.913	1.161	0.639	1.031	0.921	1.155	0.591
PSA DT	52	1.066	0.935	1.216	0.340	1.012	0.916	1.118	0.810
log.Somat	106	2.253	1.320	3.845	0.003	1.763	1.072	2.899	0.025
log.uNTX	61	1.404	0.970	2.031	0.072	0.986	0.699	1.392	0.936

Abbreviations: ACTH, adrenocorticotropic hormone; ADH, antidiuretic hormone; Alk, alkaline phosphatase; BS, bone-specific; C1–C7, eligibility criteria 1–7; ChrA-1, serum chromogranin A measured by Calbiotech chemiluminescence ELISA at Quest Diagnostics; ChrA-2, serum chromogranin A measured by homogeneous time-resolved fluorescence conducted at Mayo Medical Laboratories; DT, doubling time; GRP, gastrin-releasing peptide; GS, Gleason score; Hb, hemoglobin; IHC, immunohistochemistry; Mets, metastases; PS, performance status; Somat, somatostatin; T.diag., time from diagnosis; uNTX, urine N-telopeptides; w, white.

[a]During the study, the method for measuring serum chromogranin A was changed in the MD Anderson laboratory from Calbiotech chemiluminescence ELISA at Quest Diagnostics to homogeneous time-resolved fluorescence conducted at Mayo Medical Laboratories.

Discussion

This study is part of our broader effort to characterize patients with aggressive variant prostate cancer. It builds on the observation that prostate cancers that share clinical features with SCPCs also share their sensitivity to chemotherapy and the hypothesis that they are likely to share their underlying biology. We used 7 previously reported characteristics of SCPC (1–6) to select patients for this study. Our observations support the hypothesis that we can prospectively identify a distinct category of patients with

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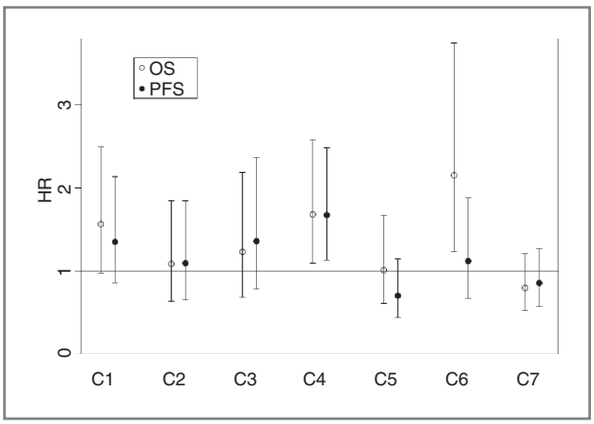

Figure 1. Effect of eligibility criteria on outcome. HR (and 95% CI) of the presence of each eligibility criterion (C1–C7, described in Table 1) for OS and PFS. HR = 1 implies no difference in OS/PFS given the presence or absence of the eligibility criterion.

castrate-resistant prostate cancer characterized by a distinctive pattern of progression, frequent but fleeting response to platinum-containing chemotherapy, and short survival.

Most of the patients treated experienced clinical benefit from the chemotherapy combinations despite having considerable tumor burden. However, this benefit was not reflected in the tumor-response rates using Prostate Cancer Clinical Trials Working Group (21) or RECIST criteria, which seem similar to response rates reported in first- and second-line clinical trials in castrate-resistant advanced prostate cancer (11, 12, 22, 23). Whether adding platinum agents to the chemotherapy regimen contributed to the high rate of benefit in our population cannot be determined from this trial but is the subject of an ongoing prospective randomized phase II study in which patients are stratified for the presence or absence of "anaplastic" criteria.

The clinical similarities between SCPC and the "anaplastic" variant suggest that they share underlying biologic mechanisms of tumor progression. Several lines of experimental evidence implicate neuroendocrine pathways in progression to androgen-independent prostate cancer (24). Neuroendocrine differentiation has primarily been defined as the presence of chromogranin A immunoreactivity and, as such, seems to confer a worse prognosis in castrate-resistant disease (25, 26). However, it has not been shown to define a distinct disease phenotype nor to predict therapy response (23, 27–29). In our patients, serum levels of calcitonin (but not chromogranin A) were associated with worse PFS and OS, suggesting that markers other than chromogranin A, or a combination of neuroendocrine markers, might show stronger associations and define a distinct phenotype. Nonetheless, neuroendocrine differentiation was present in slightly more than half of our patients. One plausible explanation is that the expression of neuroendocrine markers is simply an epiphenomenon and not mechanistically implicated in progression. Another possibility is that the "anaplastic" category contains more than one aggressive variant, which would limit the ability to identify a meaningful association between neuroendocrine marker expression and the clinical phenotype of the entire group.

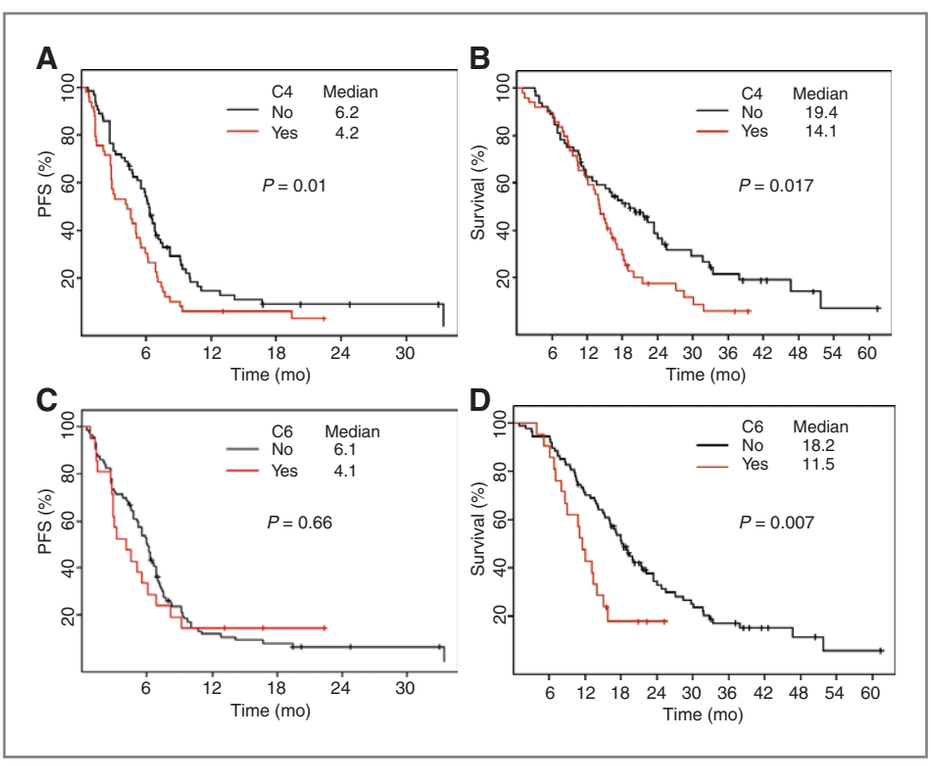

Figure 2. Kaplan–Meier estimates of OS and PFS for patients meeting eligibility criteria C4 and C6. A, PFS of patients meeting/not meeting eligibility criterion C4 (bulky ≥ 5 cm lymphadenopathy or high-grade tumor mass in prostate/pelvis). B, OS of patients meeting/not meeting eligibility criterion C4. C, PFS of patients meeting/not meeting eligibility criterion C6 (presence of neuroendocrine markers on histology or serum plus elevated serum LDH and/or malignant hypercalcemia and/or elevated serum CEA). D, OS of patients meeting/not meeting eligibility criterion C6.

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This heterogeneity has potential clinical implications. For instance, another important characteristic of SCPCs is that they are androgen-receptor (AR) negative and thus presumably driven by AR-independent mechanisms. Therefore, the "anaplastic" prostate cancers should be enriched for truly AR-independent disease. However, of the 17 patients (14.9%) who met only criterion C7, 8 (47.0%) had predominantly bony disease and elevated PSA levels without measurable disease by RECIST (data not shown). These features are closer to those of conventional AR-driven prostate carcinomas and suggest that, among men with "anaplastic" disease, at least some with short responses to ADT have early castrate-resistant AR axis—regulated disease rather than true AR-independent disease. Nonetheless, at least 1 of these patients experienced progression with biopsy-proven SCPC in the primary tumor and the liver after prolonged stable disease following treatment with CD. Detailed molecular studies of tissues collected from these patients will help elucidate this heterogeneity.

It is noteworthy that increased CEA levels in this study were significantly associated with patient outcome. Blood levels of CEA are increased in 53%–65% of men with biopsy-proven SCPC (5, 6). Additionally, older literature reported serum CEA to be elevated in 23%–80% of patients with prostate carcinoma, without a definite correlation with tumor stage (30), although the cutoffs to define an elevation varied between studies. This marker's prognostic value was investigated in a National Cancer Institute study that pooled the CEA values of 141 men with "androgen-independent metastatic" prostate cancer participating in clinical trials between 1990 and 1996. In that study, CEA levels more than 2.5 μg/L had minimal prognostic value and no usefulness as a response marker (31). However, studies that used higher cutoffs to define an abnormal value found plasma CEA to be a sensitive marker of the clinical status of prostate cancer during chemotherapy (32, 33). Our data showing that high CEA levels are associated with worse OS but not PFS suggest that this marker identifies a population with aggressive disease that nevertheless benefits from chemotherapy.

Another observation in this population is that many patients suffered substantial morbidity from progression at an untreated or radiorecurrent primary site. Some 24% to 44% of men treated for prostate cancer with noncurative intent will develop symptomatic local progression requiring intervention (34, 35). Moreover, retrospective studies suggest that control of the primary tumor may improve the outcome of men with metastatic disease (36), a fact borne out in randomized trials in men with locally advanced prostate cancer (37, 38), which is in line with observations in other tumor types (39, 40). These data may justify applying consolidative definitive treatment to the primary tumor despite the presence of distant metastases in this patient population.

Our findings confirm the usefulness of clinical criteria for identifying a subset of patients with prostate cancer with an atypical and aggressive clinical course that may also be characterized by sensitivity to platinum-containing combination chemotherapy. They provide the impetus to further study this unique phenotype, which accounts for a considerable proportion of lethal prostate cancers. Parallel efforts to understand the drivers of these variant prostate cancers are under way in model systems that reflect the salient features observed clinically (41, 42). The ongoing clinical and coclinical studies should lead to a reclassification of prostate cancer founded on an understanding its underlying biology.

Disclosure of Potential Conflicts of Interest

J. Kim has a commercial research grant from Merck and is a consultant/advisory board of Dendreon. C.J. Logothetis has commercial research grants from Atellas, Novartis, Bristol-Myers Squibb, Johnson & Johnson, and Pfizer; has honoraria from speakers bureau from Astellas, Novartis, Bristol-Myers Squibb, Johnson & Johnson, and Pfizer; and is a consultant/advisory board for Astellas, Novartis, Bristol-Myers Squibb, Johnson & Johnson, and Pfizer. No potential conflicts of interest were disclosed by the other authors.

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Clinical Cancer Research

Platinum-Based Chemotherapy for Variant Castrate-Resistant Prostate Cancer

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