The Prognostic Value of Hemoglobin Change After Initiating Androgen-Deprivation Therapy for Newly Diagnosed Metastatic Prostate Cancer

A Multivariate Analysis of Southwest Oncology Group Study 8894

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BACKGROUND. The objective of this study was to characterize changes in hemoglobin (HGB) levels after the initiation of androgen-deprivation therapy (ADT) in patients with previously untreated, metastatic prostate cancer who were enrolled in a large clinical trial.

METHODS. The multivariate associations between 3-month change in HGB and baseline characteristics were evaluated with a linear regression model. The associations between 3-month change in HGB level and time-to-event outcomes, including overall survival and progression-free survival, were evaluated by using proportional hazards regression models.

RESULTS. Quartiles of baseline HGB levels were $\leq$12.0 g/dL, from 12.1 to 13.7 g/dL, from 13.8 to 14.7 g/dL, and $>$14.7 g/dL. Overall, 3 months after initiating ADT, the mean HGB level declined 0.54 g/dL (standard deviation [SD], 1.68 g/dL); however, the mean HGB level increased by 0.99 g/dL (SD, 1.83 g/dL) in patients who had baseline HGB levels $<$12 g/dL and decreased 1.04 g/dL (SD, 1.28 g/dL) in patients who had baseline HGB levels $\geq$12 g/dL. After adjusting for potential confounders, including baseline HGB level, a decline in HGB after 3 months of ADT was associated independently with shorter survival (hazards ratio [HR], 1.10 per 1 g/dL decline; $P = .0035$) and shorter progression-free survival (HR, 1.08 per 1 g/dL decline; $P = .013$). An unexpected finding was that the effect of baseline HGB on overall and progression-free survival varied significantly by race.

CONCLUSIONS. In a sample of men with newly diagnosed, metastatic prostate cancer, a decline in HGB level after 3 months of ADT was associated with shorter survival and progression-free survival after adjusting for disease status and other baseline covariates. Although race alone was not a strong predictor of death or disease progression, the effect of the baseline HGB level on overall and progression-free survival varied significantly by race. ***Cancer* 2006;107:489–96.**

KEYWORDS: androgen-deprivation therapy, anemia, prostate cancer, prognosis.

In a previous study, we showed that anemia was common among patients with newly diagnosed, metastatic prostate cancer (25% of patients presented with hemoglobin levels $<$12 g/dL) and that anemia prior to the initiation of treatment was associated with shorter survival, shorter progression-free survival, and lower likelihood of prostate-specific antigen (PSA) normalization after adjusting for disease status and other covariates.[1] Anemia is a described adverse effect of androgen-deprivation therapy (ADT). In a group of patients with largely nonmetastatic prostate cancer and normal mean hemo-

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globin levels at baseline, ADT was associated with a significant decline in hemoglobin after the initiation of therapy.[2] Similar results were reported recently by Japanese investigators.[3]

Relatively little is known about the change in hemoglobin in anemic patients who are starting ADT for advanced prostate cancer. Anemia may be expected to worsen to the extent that therapy-induced hypogonadism reduces red cell production, but it also may improve as a result of successful cancer treatment.

The clinical significance of hemoglobin change after initiation of hormone therapy remains poorly defined. Recently, D'Amico et al. reported that a decline in hemoglobin of $\geq$1 g/dL during the first month of neoadjuvant ADT was a predictor of early recurrence in patients who received neoadjuvant ADT followed by radiation for high-risk, localized prostate cancer.[4] The prognostic or predictive value of hemoglobin change after initiation of hormone therapy for metastatic prostate cancer is not known.

We hypothesized that a change in hemoglobin level after the initiation of therapy may be heterogeneous in patients with advanced prostate cancer and may be an independent prognostic factor in advanced prostate cancer. The objective of the current study was to characterize this change by reviewing hemoglobin levels, relevant covariates, and outcome data from the Southwest Oncology Group (SWOG) 8894 trial, a randomized study that compared orchiectomy alone with orchiectomy plus the antiandrogen flutamide in the initial treatment of metastatic prostate cancer.

MATERIALS AND METHODS

Patients

SWOG Study S8894 (Intergroup Study 0105) examined orchiectomy with or without antiandrogen (flutamide) in men with metastatic prostate carcinoma in a randomized, double-blinded, Phase III trial. Between 1989 and 1994, 1286 patients were enrolled. Inclusion criteria were histologically proven diagnosis of adenocarcinoma of the prostate with bone or distant soft tissue metastases. Adequate hematologic, hepatic, and renal functions were required. Eligible patients were required to have a SWOG performance status of 0 to 3, although a performance status of 3 was allowed only if bone pain was the cause of incapacitation. Measurable disease was not required. Prior or concomitant hormone therapy, chemotherapy, or biologic response, modifiers were not allowed.

Baseline studies included evaluations of renal, hepatic and hematologic function as well as history, physical examination, serum PSA measurement, and central pathologic review with Gleason grading of biopsy specimens. On study, physical examinations and laboratory tests, including hemoglobin measurements, occurred after 1 month and after 3 months of treatment and every 3 months thereafter. At baseline and at 6-month intervals up to 2 years, the extent of disease was evaluated by bone scan. After 2 years, a bone scan was performed only if the PSA level increased by $\geq$25 ng/mL during any 3-month period. Patients were followed for survival. Results of the primary treatment plan were reported previously by Eisenberger and colleagues.[5] All patients signed an Institutional Review Board-approved informed consent form.

Statistical Methods

Associations between 3-month changes in hemoglobin levels and various baseline characteristics were evaluated by using multivariate linear regression. The baseline characteristics examined included baseline hemoglobin level (g/dL), the presence of bone pain (yes vs. no), performance status (0–1 vs. 2–3), extent of disease (minimal disease was defined as metastases to lymph nodes and/or to the axial skeleton, extensive disease was defined as metastases to viscera or the appendicular skeleton), Gleason sum ($\leq$5 vs. 6–7 vs. 8–10), treatment assignment (flutamide vs. placebo), age, PSA, prior local radiation therapy, prior prostatectomy, and race. In addition, *t* tests were used to evaluate the association of change in hemoglobin with treatment assignment (flutamide vs. placebo), race (African American vs. other), and baseline anemia (hemoglobin $<$12 g/dL).

The associations between 3-month change in hemoglobin level and time-to-event outcomes, including overall survival and progression-free survival, were evaluated by using proportional hazards regression models with adjustment for the baseline characteristics detailed above. Day 0 in these survival models was defined as 3 months postregistration. Patients who died or progressed within the 3 months postregistration were excluded from the analysis. To explore whether the correlation between hemoglobin level and outcome differed by race, interaction terms were added to these models.

RESULTS

Anemia Prevalence and Patient Characteristics

Of 1286 patients registered to this study, 827 patients were eligible and had data available for all of the variables analyzed. Of these, 2 patients died within 3 months of registration, and 8 experienced disease progression/recurrence before their follow-up hemo-

TABLE 1
Descriptive Table of 817 Patients from S8894 Included in This Analysis

Characteristic	All patients
African American (%)	19.8
Bone pain (%)	48.0
Performance status 2–3 (%)	15.2
Extensive disease (%)	79.4
Gleason score (%)	
<5	8.5
6–7	33.9
8–10	57.6
Age at study entry, y (mean ± SD)	69.6 ± 8.0
PSA at study entry (mean ± SD)	637 ± 1251
Prior radiation to the primary tumor (%)	18.7
Prior radical prostatectomy (%)	13.5
Baseline Hgb	
Mean ± SD	13.3 ± 2.1
Median	13.7
Hgb at 3 months postregistration	
Mean ± SD	12.7 ± 1.6
Median	12.8
3-Month Hgb change (mean ± SD)	− 0.54 ± 1.68

SD indicates standard deviation; Hgb, hemoglobin.

TABLE 2
Multivariate Analysis Predicting 3-Month Change in Hemoglobin

Variable	Coefficient (SE)*	*P*
African-American	− 0.64 (0.12)	<.0001
PSA (ng/mL) in 20-unit increments	8.1E-4 (7.2E-4)	.26
Bone pain	0.071 (.090)	.43
Performance status 2–3 vs. 0–1	− 0.36 (.13)	.0057
Extensive disease	0.060 (.11)	.58
Age in 5-y increments	− 0.073 (0.027)	.0080
Prior RT to primary tumor	− 0.25 (.12)	.031
Prior RP	− 0.22 (.13)	.093
Gleason score		
<5	0 (Reference)	
6–7	− 0.13 (.17)	.45
8–10	− 0.14 (.16)	.38
Flutamide treatment	− 0.54 (.09)	<.0001
Baseline hemoglobin (g/dL)	− 0.56 (.02)	<.0001

SE indicates standard error; PSA, prostate-specific antigen; RT, radiotherapy; RP, radical prostatectomy.
* Coefficients are the 3-month change in hemoglobin associated with a 1-unit increase in the corresponding variable.

TABLE 3
Association of Change in Hemoglobin with Cross-Classification of Baseline Hemoglobin, Race, and Flutamide Treatment

	3-Month change in hemoglobin			
Variable	Baseline < 12 g/dL	*P*	Baseline ≥ 12 g/dL	*P*
Race				
Black	+ 0.69 (1.76)	.039*	− 1.04 (1.40)	.97*
Not black	+ 1.20 (1.86)		− 1.05 (1.26)	
Flutamide treatment				
Yes	+ 0.84 (1.87)	.18*	− 1.38 (1.26)	<.001*
No	+ 1.16 (1.78)		− 0.71 (1.21)	
Overall	+ 0.99 (1.83)	—	− 1.04 (1.28)	<.001†

* Within baseline hemoglobin group.
† Across baseline hemoglobin groups.

globin measurement. Those 10 patients were excluded, leaving 817 patients available for the current analysis. Overall survival and progression-free survival were comparable between patients who were included and patients who were excluded from the analysis, suggesting that covariate data were missing at random. Hemoglobin and Gleason score measurements were missing most frequently. The patients who were included in the analysis are described briefly in Table 1.

The median pretreatment hemoglobin level was 13.7 g/dL. Quartiles of baseline hemoglobin were distributed as follows: first quartile (Q1), ≤12.0 g/dL; Q2, 12.1 to 13.7 g/dL; Q3, 13.8 to 14.7 g/dL; and Q4, >14.7 g/dL. After 3 months of treatment, the median hemoglobin level was 12.8 g/dL, with the following quartile distribution: Q1, ≤11.8 g/dL; Q2, 11.9 to 12.8 g/dL; Q3, 12.9 to 13.8 g/dL; and Q4, >13.8 g/dL. The baseline hemoglobin level was not correlated with the baseline serum testosterone level (testosterone data were available for 599 patients).

Change in Hemoglobin after 3 Months of Therapy

Overall, the mean change in hemoglobin between baseline and 3-month follow-up was a decrease of 0.54 g/dL (standard deviation, 1.68 g/dL). There was considerable variability with regard to hemoglobin change after the initiation of therapy, as indicated by the standard deviation. A multivariate linear regression model was fit with 3-month change in hemoglobin level as the outcome. Higher baseline hemoglobin concentration (g/dL), flutamide treatment, black race, worse performance status, increasing age, and prior radiation therapy were associated with a 3-month decline in hemoglobin level. The remaining covariates had no significant effect, and no covariate was associated with an increase in hemoglobin level (Table 2).

The association of change in hemoglobin with baseline hemoglobin, race, and flutamide treatment is illustrated in detail in Table 3. Briefly, hemoglobin increased in patients with baseline anemia and decreased in patients without baseline anemia. In patients without anemia at baseline, treatment with flutamide was associated with a greater decline in

TABLE 4
Multivariate Analysis of Prognostic Factors for Overall Survival

Variable	HR for death	95% CI	*P*
African American	0.81	0.63–1.03	.081
PSA (ng/mL) in 20-unit increments	1.00	0.999–1.001	.53
Bone pain	1.55	1.33–1.80	<.0001
Performance status 2–3 vs. 0–1	1.18	0.96–1.46	.12
Extensive disease	1.50	1.25–1.80	<.0001
Age in 5-y increments	1.04	1.00–1.10	.076
Prior RT to primary tumor	0.97	0.80–1.18	.74
Prior RP	0.70	0.56–0.88	.0021
Gleason score			
<5	1.0	Reference	
6–7	1.26	0.94–1.68	.12
8–10	1.68	1.27–2.22	.0002
Flutamide treatment	0.86	0.74–0.99	.040
Baseline hemoglobin centered at 13.7 g/dL (1-unit increment)	0.88	0.83–0.93	<.0001
3-Month hemoglobin change (g/dL) (1-unit decrement)	1.10	1.03–0.16	.0035
African American baseline hemoglobin	0.90	0.82–0.98	.017

HR indicates hazard ratio; 95% CI, 95% confidence interval; PSA, prostate-specific antigen; RT, radiotherapy; RP, radical prostatectomy.

TABLE 5
Multivariate Analysis of Prognostic Factors for Progression-Free Survival

Variable	HR for disease progression or death	95% CI	*P*
African American	0.79	0.62–1.00	.051
PSA (ng/mL) in 20-unit increments	0.999	0.998–1.000	.25
Bone pain	1.52	1.30–1.77	<.0001
Performance status 2–3 vs. 0–1	1.06	0.86–1.32	.58
Extensive disease	1.53	1.28–1.84	<.0001
Age in 5-y increments	1.01	0.96–1.06	.73
Prior RT to primary tumor	0.93	0.77–1.14	.49
Prior RP	0.75	0.60–0.93	.011
Gleason score			
<5	1.0	Reference	
6–7	1.23	0.92–1.64	.16
8–10	1.74	1.32–2.30	<.0001
Flutamide treatment	0.86	0.74–1.00	.043
Baseline hemoglobin centered at 13.7 g/dL (1-unit increment)	0.87	0.83–0.92	<.0001
3-Month hemoglobin change (g/dL) in 1-unit decrement	1.08	1.02–1.15	.013
African American baseline hemoglobin	0.91	0.84–1.00	.038

HR indicates hazards ratio; 95% CI, 95% confidence interval; PSA, prostate-specific antigen; RT, radiotherapy; RP, radical prostatectomy.

hemoglobin. Black race had no effect on change in hemoglobin in patients without anemia at baseline but was associated with less recovery of hemoglobin in patients who were anemic at study entry.

Association between Hemoglobin Change in the First 3 Months and Clinical Endpoints

We previously reported that baseline anemia is an important adverse prognostic factor for both overall and progression-free survival in patients with newly diagnosed metastatic prostate cancer. The current analysis showed that 3-month change in hemoglobin is a new prognostic factor in a multivariate analysis that included baseline hemoglobin and a number of other traditional risk factors, including performance status, Gleason score, and disease extent. In this analysis, a decline in hemoglobin after 3 months of ADT was independently associated with shorter survival (hazards ratio [HR], 1.10 per 1 g/dL decline; $P = .0035$) and shorter progression-free survival (HR, 1.08 per 1 g/dL decline; $P = .013$). Thus, both baseline hemoglobin and 3-month hemoglobin change are prognostic, even after taking into account these other risk factors. Compared with Q4 (an increase in hemoglobin by >0.3 g/dL), patients in Q1 (a drop in hemoglobin by ≥1.6 g/dL) had a 31% higher risk of death. Thus, the impact of hemoglobin change on the risk of death and early progression was moderate but was sufficiently large to be important clinically (Tables 4, 5).

Another novel observation of the current analysis is that there was a modest but important difference between the races with regard to the observed associations between hemoglobin and clinical outcomes. Although we did not observe that race modified the association between 3-month hemoglobin change and either overall survival or progression-free survival, the interaction between race and baseline hemoglobin was significant for both outcomes ($P < .04$).

This model suggests that the difference in overall survival across races depended on baseline hemoglobin levels. In Table 4, the HR for death of 0.81 between blacks and nonblacks was among patients who had baseline hemoglobin levels of 13.7 g/dL. Among patients who had baseline hemoglobin levels of 11.7 g/dL, the HR for death may be calculated as $0.81*0.90^{(11.7-13.7)} = 1.0$, where 0.90 is the interaction effect shown in Table 4. Below this level of baseline hemoglobin, black patients had worse overall survival than their nonblack counterparts, although this difference was significant only at hemoglobin levels <7.8 g/dL. At hemoglobin levels >11.7 g/dL, black patients had better overall survival than their nonblack counterparts, but this difference was significant only at hemoglobin levels >14.2 g/dL. This interaction also was observed for progression-free survival, for which the black:nonblack HR was 1.0 at a baseline hemoglobin level of 11.1 g/dL. Below this level,

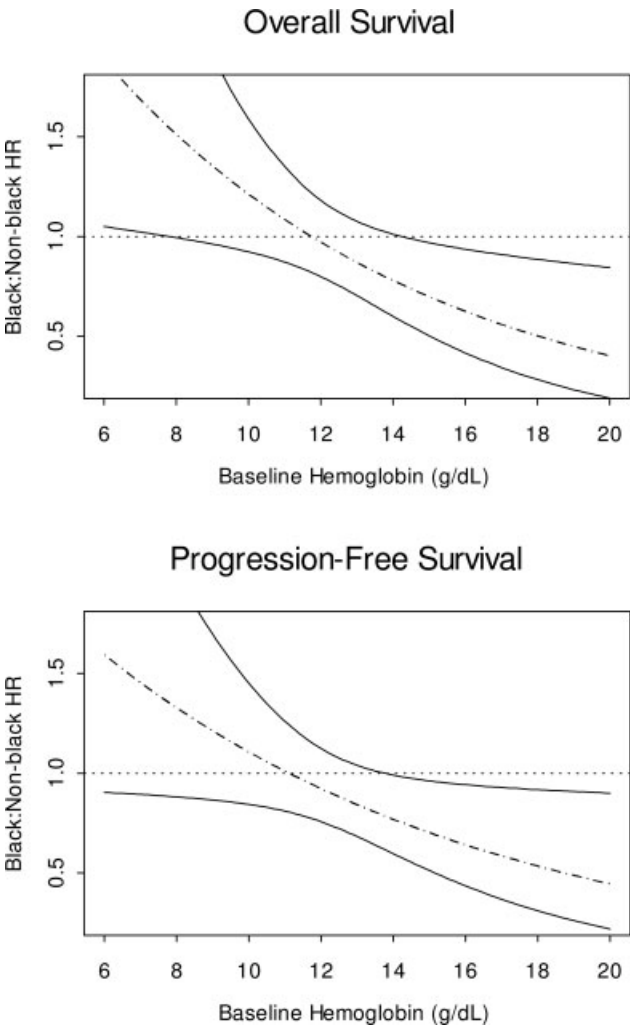

FIGURE 1. Hazards ratio (HR) estimates (dotted-and-dashed line) are shown for black patients versus nonblack patients (with all other predictive variables the same) across the range of baseline hemoglobin levels seen in this data set. The 95% confidence interval bands (solid lines) also are given, and a reference HR of 1.0 is shown with a dotted line. Regions in which the bands do not include 1.0 indicate a significant race effect.

black patients had worse progression-free survival than their nonblack counterparts, although this difference never achieved significance. At hemoglobin levels >11.1 g/dL, progression-free survival among black patients was better than that among nonblack patients, and this difference became significant at baseline hemoglobin levels >13.7 g/dL. These complex correlations are illustrated in Figure 1.

DISCUSSION

The baseline hemoglobin level was an independent determinant of 3-month change in hemoglobin after initiation of ADT, as we hypothesized. Although overall hemoglobin levels declined with ADT initiation, this masked the finding that hemoglobin levels increased in patients who were anemic prior to therapy and decreased in patients with no anemia at baseline. We cannot exclude the possibility that a portion of this observation represents regression to the mean, but this observation also is consistent with the hypothesis that, in patients with more severe, cancer-associated anemia, the salutatory effects of successful cancer treatment exceed the reduction in hemoglobin level caused by androgen loss. In addition to baseline hemoglobin, a multivariate analysis identified flutamide treatment, black race, worse performance status, increasing age, and prior radiation therapy as statistically significant factors ($P < .05$) that were associated with a 3-month decline in hemoglobin level. It is not surprising that elderly patients or those with a poor performance status may be at greater risk of treatment-associated anemia. Similarly, prior radiation therapy may reduce the bone marrow reserves needed to maintain hemoglobin in a hypogonadal state. Flutamide may be associated with a greater drop in hemoglobin caused by greater suppression of androgen signaling. Hemolotic anemia also rarely has been reported in association with flutamide therapy (Eulexin Prescribing Information).

The current results provide additional evidence of a link between anemia and poorer outcomes in patients with advanced prostate cancer. In addition to pretreatment anemia, which was identified previously as an adverse prognostic factor, this is the first report to our knowledge demonstrating that a decline in hemoglobin after 3 months of hormone therapy independently predicts a shorter survival and progression-free survival. It is noteworthy that our results are consistent with the findings of D'Amico et al., who showed that a decline in hemoglobin during the first month of neoadjuvant ADT was associated with a higher risk of early disease recurrence after combined treatment with ADT and radiation therapy.[4] Thus, a change in hemoglobin level after the initiation of ADT may be a clinical sign of more aggressive disease, or it may contribute to resistance to therapy not only in early stages but also in metastatic prostate cancer.

The pathophysiology behind this observation merits further study. Anemia may lead to therapy resistance either directly or by association. Anemia-related tumor hypoxia may contribute to treatment resistance. An association between anemia and tumor hypoxia has been demonstrated in breast cancer,[6] cervical cancer,[7] and others. In addition, hypoxia has been observed in the prostate of rats that received ADT.[8] Tumor hypoxia has been impli-

cated in prostate cancer resistance to apoptosis[9] as well as resistance to radiation therapy [10] and chemotherapy.[11] Cellular response to hypoxia may mediate resistance to androgen deprivation. Thus, a possible interpretation of these results is that androgen resistance in these patients is influenced by anemia-related tumor hypoxia.

Another possible explanation is that anemia and androgen resistance share a common pathophysiology. Several cytokines have been associated with anemia of chronic disease, including interleukin 1 (IL-1), IL-6, IL-12, tumor necrosis factor (TNF), transforming growth factor β (TGFβ), interferon-α, interferon-β, and interferon-γ.[12,13] Many of the same cytokines also may promote androgen resistance and the growth of prostate cancer metastases in the bone microenvironment.[14] One example is IL-6, which may contribute to the development of androgen resistance.[15] IL-6 is secreted by androgen-independent prostate cancer (AIPC) cells, is found at elevated levels in the blood of patients with AIPC,[16] and produces an autocrine mitogenic signal in these cells.[17] Similarly, it has been shown that TGFβ1, IL-1, and IL-8 induce changes that may be related to androgen independence.[14,18,19]

Furthermore, we identified a thought-provoking correlation between race and anemia. In a multivariate analysis, African-American race alone was not a strong predictor of death or disease progression. However, our results suggest that the effect of baseline hemoglobin level on overall and progression-free survival varied significantly by race. Overall, anemic African Americans fared worse than anemic Caucasians, and African Americans with high baseline hemoglobin fared better than Caucasians with similar hemoglobin levels.

The racial disparity in prostate cancer outcomes is well described. African Americans are at greater risk of being diagnosed with the disease,[20] have higher risk disease at diagnosis,[21,22] and, overall, have a higher risk of dying from prostate cancer.[20] Generally, it is believed that the differences in prostate cancer outcomes are explained by disease-related factors. After correcting for stage, grade, and other known prognostic factors, race generally is not predictive of worse outcomes in men with prostate cancer. This has been demonstrated in studies of clinically localized prostate cancer[23–25] and metastatic disease. Analyses of 5284 men with newly diagnosed, primarily distant-stage disease[26] and of 1183 patients with metastatic, hormone-refractory disease[27] showed no independent effect of race on survival. Although a previous analysis of SWOG 8894 identified a significant race effect,[28] hemoglobin data were unavailable at that time. In the current analysis of SWOG 8894, we observed that, after adjusting for both baseline hemoglobin and 3-month change in hemoglobin, race no longer was an adverse prognostic factor.

Thus, the complex relation between baseline anemia, race, and survival identified here is unexpected and novel. Although our study was not designed to determine the underlying cause for the observed anemia-race interaction, several hypotheses may be considered. Prior analyses showed that African-American men who presented with either hormone-naive or hormone-resistant, metastatic prostate cancer had lower hemoglobin concentrations than their Caucasian counterparts.[1,27] Healthy African Americans also had significantly lower mean concentrations of hemoglobin than Caucasians.[29] These discrepancies may be explained by a higher prevalence of hemoglobinopathies[30,31] and by a higher incidence of folate deficiency[32] among African Americans.

The prevalence of sickle cell trait among African Americans is between 8% and 10%.[33] Although this is a clinically benign carrier trait, little is known about the impact of sickle cell trait on tumor hypoxia. A single case study of a sickle trait carrier with squamous cell carcinoma of the cervix demonstrated extensive intratumoral sickling and tumor hypoxia.[34] To the best of our knowledge, no other studies have examined the possibility that otherwise benign hemoglobin abnormalities may exacerbate tumor hypoxia and, consequently, promote tumor resistance to therapy. Another hypothesis worthy of consideration is that there may be race-specific differences in prostate cancer hypoxic response. For example, in a study of 223 patients, the patterns of expression of N-myc downstream-regulated gene-1 (*NDRG1*), a hypoxia-related and androgen-regulated gene, differed significantly between African Americans and Caucasians.[35]

It also is possible that the pathophysiology of cancer-related anemia may differ across races. For example, if African Americans were less susceptible to developing cancer-associated anemia, then it would be expected that the same degree of anemia would be associated with more severe disease in African Americans. We are not aware of data that address this question, although functional polymorphisms of many of the cytokines that are important in the anemia of chronic disease have been described. A number of investigators have found differences in racial distributions of these polymorphisms. For example, Ness et al. reported that polymorphisms known to increase expression of proinflammatory cytokines IL-1A, IL-1B, IL-18, and IL-6 were significantly more likely to be expressed in

African-American women than in white women.[36] In another study, it was observed that individuals of African descent predominantly carried low-producing IL-10 alleles and high-producing IL-6 alleles.[37] If differences in the racial distribution of gene polymorphisms that regulate the development of cancer-associated anemia exist, then such differences may explain the complex relation between anemia, race, and outcome observed in this study.

In summary, our data extend previous findings that link anemia with poor outcomes in men with advanced prostate cancer. We observed that, in addition to baseline anemia, a decline in hemoglobin after 3 months of ADT was associated independently with shorter progression-free and overall survival. Furthermore, we identified an unexpected, complex interaction between race, anemia, and progression-free and overall survival in men with advanced prostate cancer. Although these findings provide important new information about prognosis in patients with advanced prostate cancer, they should not be interpreted as supportive of the therapeutic correction of anemia to improve outcome. It is not known whether anemia-directed interventions in these patients can modify the association between baseline anemia, 3-month hemoglobin decline, and patient outcomes. Further investigation of anemia and outcomes in patients with prostate cancer should be pursued, and prospective clinical trials of anemia correction during hormone therapy should be considered.

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