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Pretreatment Neutrophil-to-Lymphocyte Ratio in Metastatic Castration-Resistant Prostate Cancer Patients Treated With Ketoconazole: Association with Outcome and Predictive Nomogram

DANIEL KEIZMAN,[a] MAYA GOTTFRIED,[a] MAYA ISH-SHALOM,[a] NATALIE MAIMON,[a] AVIVIT PEER,[b] AVIVIT NEUMANN,[b] ELI ROSENBAUM,[c] SVETLANA KOVEL,[d] ROBERTO PILI,[e] VICTORIA SINIBALDI,[f] MICHAEL A. CARDUCCI,[f] HANS HAMMERS,[f] MARIO A. EISENBERGER,[f] AVISHAY SELLA[d]

[a]Genitourinary Oncology Service, Institute of Oncology, Meir Medical Center and the Sackler School of Medicine, Tel Aviv University, Kfar-Saba, Israel; [b]Department of Oncology, Rambam Medical Center, Haifa, Israel; [c]Department of Oncology, Rabin Medical Center, Petah Tikvah, Israel; [d]Department of Oncology, Asaf Harofe Medical Center, Zerifin, Israel; [e]Roswell Park Cancer Institute, Buffalo, New York, USA; [f]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, Maryland, USA

ABSTRACT

Background. The neutrophil-to-lymphocyte ratio (NLR), an inflammation marker, is prognostic in several cancers. We assessed the association between the pretreatment NLR and outcome of patients with metastatic castration-resistant prostate cancer (mCRPC) treated with the CYP17 inhibitor ketoconazole.

Methods. This was an international, retrospective study of 156 mCRPC patients treated with ketoconazole. The independent effect of the pretreatment NLR and factors associated with treatment outcome were determined by multivariate analysis.

Results. Seventy-eight patients (50%) had a ≥50% decline in prostate-specific antigen (PSA). The median progression-free survival (PFS) time was 8 months. Excluded from the analysis were 23 patients without available data on their NLR and those with a recent health event or treatment associated with a blood count change. Sixty-two patients (47%) had a pretreatment NLR >3. Risk factors associated with the PFS outcome were a pretreatment NLR >3 and PSA doubling time (PSADT) <3 months and a prior response to a gonadotropin-releasing hormone agonist of <24 months or to an antiandrogen of <6 months. The number of risk factors was used to form a predictive nomogram by patient categorization into favorable (zero or one factor), intermediate (two factors), and poor (three or four factors) risk groups.

Conclusions. In mCRPC patients treated with ketoconazole, the pretreatment NLR and PSADT, and prior response to androgen-deprivation therapy, may be associated with the PFS time and used to form a risk stratification predictive nomogram. *The Oncologist* 2012;17: 1508–1514

INTRODUCTION

Prostate cancer is the most common cancer affecting men and the second leading cause of male cancer mortality in the western world [1]. The initial treatment of metastatic prostate cancer consists of androgen deprivation therapy (ADT), usually using a gonadotropin-releasing hormone (GnRH) agonist and an antiandrogen [2]. Most patients respond for 18–48 months and eventually progress to a castration-resistant state [3].

Activation of the androgen receptor (AR) is central in the pathogenesis of prostate cancer. In the castration-resistant

state, the AR is exquisitely sensitive to low levels of androgens through its gene amplification, overexpression, and activating mutation as well as enhancement of its responses and signaling by stimulation of kinases [4–6]. The source of androgens activating the AR in the castration-resistant state is the adrenal gland, where 10%–30% of total serum androgens are produced. More recently, the role of intratumoral production of androgens through overexpression of enzymes, including cytochrome P450 (CYP)17A1, a key enzyme for de novo steroid and androgen biosynthesis, has been emphasized [4–10].

The imidazole antifungal agent ketoconazole, which inhibits several CYP enzymes, including CYP17A1, suppresses adrenal and intratumoral steroidogenesis by inhibiting the conversion of cholesterol to pregnenolone [6–7, 11]. It has been used for >30 years in the treatment of castration-resistant prostate cancer, with reported prostate-specific antigen (PSA) decline rates of 20%–75% and progression-free survival (PFS) times of 3–10 months [5–7, 12–17].

Retrospective studies identified several clinical factors that are associated with the outcome of patients with metastatic castration-resistant prostate cancer (mCRPC) who are treated with ketoconazole, including prior response to hormonal therapy, pretreatment PSA doubling time (PSADT), and disease extent (limited versus extensive) [17].

Data suggest that inflammation plays a role in the tumorigenesis process and progression of many cancers, by promoting cancer cell proliferation and survival, angiogenesis, and tumor metastasis, and impacting tumor response to systemic therapies [18]. This is mediated by interaction among proinflammatory cytokines, oncogenes (*RAS*, *MYC*, *RET*), and pathways, including the nuclear factor kB and signal transducer and activator of transcription 3 pathways [18–19]. In patients with advanced prostate cancer, molecular signaling triggered by inflammatory mediators may evolve in disease progression [20].

The neutrophil-to-lymphocyte ratio (NLR) is an easily measured, reproducible, and inexpensive marker of systemic inflammation [21–24] that is associated with outcome in different cancer types. The pretreatment NLR was found to be an independent predictor of outcome in patients treated with systemic therapies for malignant mesothelioma [21], colorectal liver metastases [22], advanced pancreatic cancer [23], ovarian cancer [24], gastric cancer [25], and renal cell carcinoma [26].

In the present study, we sought to determine association of the pretreatment NLR with the response rate and PFS interval of patients with mCRPC who are treated with ketoconazole.

MATERIALS AND METHODS
The study group consisted of an unselected cohort of all patients with evidence of mCRPC who were treated with ketoconazole and followed by medical oncologists in 1999–2011 at four centers across two different countries: the U.S. (Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD) and Israel (Institute of Oncology, Meir Medical Center, Kfar Saba; Department of Oncology, Asaf Harofe Medical Center, Zerifin; Department of Oncology, Rambam Medical Center, Haifa). Before initiation of ketoconazole

treatment, all patients had objective biochemical (PSA) and/or clinical (scans) disease progression on gonadal suppression (orchiectomy or GnRH agonist), antiandrogen, and antiandrogen withdrawal. All patients had an Eastern Cooperative Oncology Group performance status score of 0–2 and pretreatment serum testosterone level <50 ng/mL [27]. Patient data were retrospectively and personally collected by one of the investigators (D.K.) from electronic medical records and paper charts. Outcome data were frozen on December 31, 2011.

Ketoconazole Treatment
Patients were maintained on gonadal suppression (orchiectomy or GnRH agonist), staged with a computed tomography scan and bone scan, and treated with ketoconazole, 200 or 400 mg orally 3× per day, with replacement doses of hydrocortisone (30 mg morning and 10 mg night). The initial dose of ketoconazole was left at the treating physician's discretion. Antacids, H_2 blockers, and proton pump inhibitors were avoided but not explicitly prohibited. Patients were evaluated for adverse events and response to therapy with a history, physical examination, and laboratory analysis, including liver function tests and PSA assessment, initially around the first month and then every 3 months. Treatment was continued until evidence of biochemical (PSA) and/or clinical (scans) disease progression or unacceptable adverse events. Scans were repeated upon symptoms or biochemical progression. An increase from 200 mg 3× per day to 400 mg 3× per day was deemed acceptable (left at the discretion of the treating physician) if a PSA decrease was not noted at 3 months or at the time of biochemical and/or clinical progression on the 200 mg 3× per day dose. Patients on 400 mg 3× per day had their treatment discontinued at the time of progression. Upon ketoconazole discontinuation, hydrocortisone was tapered and discontinued after 3 weeks, followed by clinical (scans) and biochemical (PSA) evaluations after 4 weeks. Toxicity was defined according to the National Cancer Institute Common Toxicity Criteria, version 3.0 (http://ctep.info.nih.gov). Treatment was held for any grade 3 or 4 toxicity (except for hepatotoxicity, see below), at which point patients were followed until toxicity resolved to grade ≤1 and then restarted. Treatment was discontinued upon occurrence of dose-limiting toxicity, defined as recurrence of the same grade 3 or 4 toxicity event or grade 3 or 4 hepatotoxicity at any time.

Statistical Analysis
Data were analyzed retrospectively. The follow-up time was defined as the time from initiation of ketoconazole treatment to December 31, 2011. The PSADT prior to ketoconazole treatment was calculated as the natural log of 2 (0.693) divided by the slope of the relationship between the log of PSA and time of PSA measurement for each patient [28], using all PSA values >0.1 ng/mL, which confirmed progressive castration-resistant prostate cancer by PSA progression before initiating ketoconazole. Disease extent was defined as limited if it involved only the axial skeleton and/or lymph nodes and as extensive if it involved the appendicular skeleton and/or visceral

organs [3, 17]. The PFS interval was the primary clinical endpoint of the present study. The response rate was the secondary endpoint. The PFS time was defined as the time from ketoconazole treatment initiation until evidence of biochemical or clinical disease progression. Biochemical progression was defined as a PSA increase $\geq$25% and $\geq$2 ng/mL from baseline or nadir as defined by the Prostate Cancer Clinical Trials Working Group (PCWG-2) criteria [29]. Clinical progression was defined as new findings on physical examination or scans. For the evaluation of measurable disease response and progression, the Response Evaluation Criteria In Solid Tumors, version 1.1, was applied [30]. Bone scan progression (nonmeasurable disease) was defined as two or more new lesions on a bone scan [17]. Scan response was assessed by independent radiologists and treating physicians, and was personally reviewed by one of the investigators (D.K.). Patients who did not progress by December 31, 2011 were censored in the PFS analysis. Regression tree analysis for censored data was used to find the best NLR cutoff value [26]. Patients without available data on their pretreatment NLR and those with a recent ($\leq$1 month) health event (e.g., fracture) or treatment (e.g., radiation, steroids) known to be associated with a change in blood count were excluded from the NLR analysis [26, 31]. A univariate analysis (unadjusted) of the association between the pretreatment NLR (calculated by dividing the neutrophil count by the number of lymphocytes) and potential factors associated with PSA response and disease progression, including prior response to an antiandrogen, pretreatment PSADT, and disease extent [17], was performed using logistic regression for the response rate and the Cox regression model for the PFS time. Factors with a significant association in the univariate analysis were included in a multivariate Cox proportional hazards regression model to determine their independent effects. The PFS probability and median PFS time were estimated from a Kaplan–Meier curve. Data were analyzed using S-Plus 8.0 for Windows Enterprise Developer (Insightful Corporation, Seattle, WA).

Regulatory Considerations

The research was carried out in accordance with approval by the institutional review board committee of our institutions.

RESULTS

Study Group

One hundred fifty-six patients with mCRPC who were treated with ketoconazole in 1999–2011 were included in the present study. Fifteen patients (10%) received chemotherapy (docetaxel, $n = 13$; mitoxantrone, $n = 2$) prior to ketoconazole treatment. Baseline patient characteristics are listed in Table 1. The median age at initiation of ketoconazole treatment was 69 years. The median baseline PSA level was 15.8 ng/mL and median pretreatment PSADT was 2.71 months. Thirty-one percent ($n = 49$) of patients had limited disease and 69% ($n = 107$) had extensive disease. One hundred thirty-three patients (85%) were included in the pretreatment NLR analysis, from which 23 patients were excluded as a result of no data available

Table 1. Baseline patient characteristics

Parameter	Value
Age at initiation of ketoconazole, yrs	
Median (range)	69 (50–89)
Mean ± SD	68.9 ± 9.3
Combined Gleason grade, n (%)	
Low risk ($\leq$6)	11 (7%)
Intermediate risk (7)	49 (32%)
High risk (8–10)	80 (51%)
Unknown	16 (10%)
Primary treatment, n (%)	
Radical prostatectomy	76 (49%)
Radiation therapy	34 (21%)
Primary androgen deprivation therapy	40 (26%)
Unknown	6 (4%)
Prior response to gonadotropin-releasing hormone agonist or orchiectomy as primary androgen deprivation for metastatic disease, mos	
Median (range)	14 (2–108)
Mean ± SD	19 ± 18
Prior response to antiandrogen as second-line androgen deprivation for metastatic disease, mos	
Median (range)	4 (1–36)
Mean ± SD	7 ± 6.3
Baseline PSA doubling time before initiation of ketoconazole, mos	
Median (range)	2.71 (0.4–29.3)
Mean ± SD	3.8 ± 4.18
Baseline PSA level before initiation of ketoconazole, ng/mL	
Median (range)	15.8 (0.4–4418)
Mean ± SD	143 ± 473
Disease extent, n (%)	
Limited (axial skeleton and/or lymph nodes)	49 (31%)
Extensive (appendicular skeleton and/or visceral organs)	107 (69%)
Eastern Cooperative Oncology Group performance status score	
0–1	143 (92%)
2	13 (8%)
Alkaline phosphatase, units/L	
Median (range)	86 (31–825)
Mean ± SD	123 ± 118
Anemia, n (%)	102 (65%)
Pretreatment neutrophil to lymphocyte ratio >3, n (%)	62/133 (47%)

Abbreviations: PSA, prostate-specific antigen; SD, standard deviation.

on their pretreatment NLR ($n = 13$), a recent ($\leq$1 month) health event (fracture, $n = 1$), and treatment (steroids, $n = 6$; radiation, $n = 3$) associated with a change in blood count. The NLR cutoff was found to be $\leq$3 versus >3. Sixty-two patients (47%) had a pretreatment NLR >3.

Table 2. Univariate and multivariate analyses of the association between clinicopathologic and prognostic factors and the progression-free survival interval

Parameter	Univariate analysis	Multivariate analysis
Age	Nonsignificant	
Combined Gleason score	Nonsignificant	
Primary treatment (surgery vs. radiation vs. androgen deprivation therapy)	Nonsignificant	
Prior response to gonadotropin-releasing hormone agonist or orchiectomy of ≥24 mos	HR, 0.606; p = .018	HR, 0.513; p = .035
Prior response to antiandrogen of ≥6 mos	HR, 0.392; p < .0001	HR, 0.445; p = .003
Baseline PSA doubling time ≥3 mos	HR, 0.47; p < .0001	HR, 0.449; p = .007
Baseline PSA level	Nonsignificant	
Limited disease extent	HR, 0.451; p < .0001	Nonsignificant
Absence of baseline pain	HR, 0.581; p = .006	Nonsignificant
Baseline alkaline phosphatase within the normal range	HR, 0.466; p < .0001	Nonsignificant
Anemia	Nonsignificant	
Pretreatment neutrophil to lymphocyte ratio ≤3	HR, 0.354; p < .0001	HR, 0.353; p < .0001

Abbreviations: HR, hazard ratio; PSA, prostate-specific antigen.

Ketoconazole Treatment, PSA Response, and Disease Progression

The median follow-up time was 40 months (range, 12–144 months; mean ± standard deviation [SD], 50 ± 29.6 months). The starting ketoconazole dose was 200 mg 3× per day in 116 patients (74%), of whom 53 (46%) subsequently had their dose increased to 400 mg 3× per day (lack of PSA response at 3 months, n = 17; disease progression, n = 36). Forty patients (26%) were initiated on treatment at a dose of 400 mg 3× per day. Overall, 78 patients (50%) had a ≥50% decline in PSA from baseline. Sixteen patients (30%) treated initially at 200 mg 3× per day and subsequently increased to 400 mg 3× per day had a subsequent decline ≥50% in PSA from the level before the dose increase. The overall median PFS interval was 8 months (range, 1–144 months). Sixty-one patients progressed biochemically (PSA only), 82 progressed clinically (PSA plus scans), and 13 remained progression free with a median treatment time of 24 months (range, 12–144 months; mean ± SD, 45 ± 44 months). The PFS duration was ≥12 months in 55 patients (35%) and ≥24 months in 22 patients (14%). Fifty-four patients (35%) were refractory to ketoconazole treatment (PFS time, ≤3 months). The median PFS times were 5 months in patients on 200 mg 3× per day, 8 months in patients who started with 200 mg 3× per day and then increased to 400 mg 3× per day, and 8 months in patients treated with 400 mg 3× per day initially (not statistically significant). A ketoconazole withdrawal effect was noted in 17% (n = 25) of the 143 patients who discontinued treatment. On follow-up 4 weeks after ketoconazole discontinuation, 9% (n = 13) of patients had PSA stabilization (no rise ≥25% and ≥2 ng/mL from the level before ketoconazole cessation) and 8% (n = 12) had a PSA decline. Three of those patients were kept on steroids for >3 weeks for pain control. The median duration of the ketoconazole withdrawal effect was 4 months (range, 1–55 months; mean ± SD, 6.8 ± 9 months) before subsequent PSA progression (rise ≥25% and ≥2 ng/mL from the nadir level after discontinuation of ketoconazole) or initiation of another systemic treatment. Regarding ketoconazole-associated toxicity, 17% of the patients (n = 27) had severe grade 3 or 4 treatment-related toxicity, including mainly fatigue, abdominal discomfort, nausea, and dizziness. Four patients (3%) had grade 3 or 4 hepatotoxicity. Fourteen patients (9%) discontinued treatment because of dose-limiting toxicity. There were no treatment-related fatal or irreversible toxicities.

Univariate Analysis of Factors Associated with PSA Response and Disease Progression

An NLR ≤3 prior to ketoconazole treatment (odds ratio [OR], 6.5; p = .011), limited disease (OR, 1.8; p < .0001), a prior response to a GnRH agonist or orchiectomy of ≥24 months (OR, 8.7; p = .001), a prior response to an antiandrogen of ≥6 months (OR, 9; p < .0001), and an alkaline phosphatase level within the normal range prior to ketoconazole treatment (OR, 7.1; p = .009) were associated with a PSA response (decrease ≥50%) to ketoconazole (Table 2). An NLR ≤3 prior to ketoconazole treatment (hazard ratio [HR], 0.354; p < .0001), limited disease (HR, 0.451; p < .0001), a prior response to a GnRH agonist or orchiectomy of ≥24 months (HR, 0.606; p = .018), a prior response to an antiandrogen of ≥6 months (HR, 0.392; p < .0001), the absence of pain prior to ketoconazole treatment (HR, 0.581; p = .006), an alkaline phosphatase level within the normal range prior to ketoconazole treatment (HR, 0.466; p < .0001), and a pretreatment PSADT ≥3 months (HR, 0.47; p < .0001) were associated with the PFS time. Age, primary treatment modality (surgery, radiation, androgen deprivation), Gleason score of the primary tumor, the presence of anemia, baseline PSA level, and initial dose or subsequent increase in dose were not found to be associated with PSA response or disease progression.
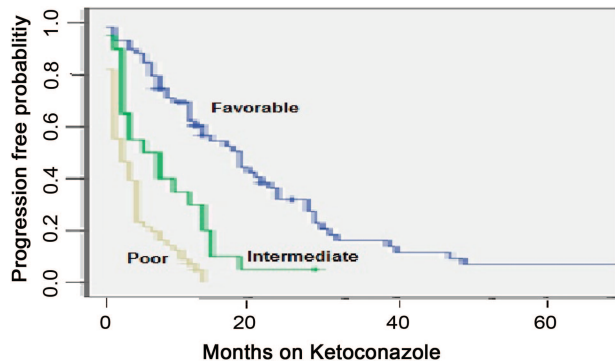
Figure 1. Progression-free survival probability stratified by risk group.

Multivariate Analysis of Factors Associated with PSA Response and Disease Progression

An NLR ≤3 prior to ketoconazole treatment (OR, 3.4; p = .016), a prior response to a GnRH agonist or orchiectomy of ≥24 months (OR, 4.5; p = .001), and a prior response to an antiandrogen of ≥6 months (OR, 5.2; p = .01) were associated with a PSA response (decrease ≥50%) to ketoconazole (Table 2). An NLR ≤3 prior to ketoconazole treatment (HR, 0.353; p < .0001), a prior response to a GnRH agonist or orchiectomy of ≥24 months (HR, 0.513; p = .035), a prior response to an antiandrogen of ≥6 months (HR, 0.445; p = .003), and a pretreatment PSADT ≥3 months (HR, 0.449; p = .007) were associated with the PFS time. The median PFS times were 14 months versus 4 months in patients with a baseline NLR ≤3 versus >3, 12 months versus 5 months in patients with a prior response to a GnRH agonist or orchiectomy of ≥24 months versus <24 months, 18 months versus 3 months in patients with a prior response to an antiandrogen of ≥6 months versus <6 months, and 14 months versus 4 months in patients with a pretreatment PSADT ≥3 months versus <3 months.

Patient Risk Stratification and Predictive Nomogram

The number of clinical risk factors found to be significantly associated with a shorter PFS duration (NLR >3 prior to ketoconazole treatment, prior response to GnRH agonist or orchiectomy of <24 months, prior response to an antiandrogen of <6 months, and baseline PSADT <3 months) was used to categorize patients into three risk groups: favorable (zero of one factors), intermediate (two factors), and poor (three or four factors). The median PFS times were 14 months, 7 months, and 3 months in the favorable, intermediate, and poor risk groups, respectively—HR, 0.35 (p < .0001) in the favorable versus intermediate risk groups; HR, 0.64 (p < .0001) in the intermediate versus high risk groups) (Fig. 1). The median PFS interval was not significantly different between patients with no risk factors and those with one risk factor and between patients with three risk factors and those with four risk factors.

DISCUSSION

The present study suggests that the pretreatment NLR may be associated with the response rate and PFS duration of patients treated with ketoconazole for mCRPC. In this retrospective study, patients with a pretreatment NLR ≤3 had a higher response rate and longer PFS interval after adjustment for other previously described predictive factors. Furthermore, the pretreatment NLR and other factors found to be associated with the PFS time (i.e., prior response to a GnRH agonist or orchiectomy, prior response to an antiandrogen, and pretreatment PSADT) may be used to categorize patients into predictive risk groups and to identify patients who are more likely to benefit from sequential CYP17 inhibition therapy.

Existing preclinical and clinical data suggest that inflammation plays a role in the tumorigenesis process and progression of many cancers, including prostate cancer [18–20]. Molecular signaling triggered by inflammatory mediators may promote cancer cell proliferation and survival, angiogenesis, and tumor metastasis, impacting the tumor response to systemic therapies [18–20]. Furthermore, data suggest that, in patients with metastatic prostate cancer receiving ADT and in those with mCRPC, markers of inflammation, such as C-reactive protein (CRP), may predict a poor outcome [32–34]. The association between the NLR and outcome is complex and remains to be elucidated. A high NLR may reflect both a heightened neutrophil-dependent inflammatory reaction and a lesser lymphocyte-mediated antitumor immune response that contribute to aggressive tumor biology, cancer progression, and a poor prognosis [22–23]. Circulating neutrophils have been shown to produce cytokines, such as tumor necrosis factor, interleukin (IL)-1, and IL-6, which contributes to cancer progression, and to secrete the angiogenic factor vascular endothelial growth factor [23]. A relative lymphocytopenia may reflect a lower count of $CD4^+$ T-helper lymphocytes, resulting in a suboptimal lymphocyte-mediated immune response to malignancy [23].

The present study summarizes the clinical experience with ketoconazole therapy for mCRPC at four centers across two different countries. The efficacy and safety of ketoconazole treatment in the present study were similar to what was described previously [5, 12, 17]. The incidence and severity of adverse drug-related reactions were usually modest and reversible, and indicate that long-term treatment is feasible. The ketoconazole withdrawal effect observed in 17% of patients suggests that a period of observation after discontinuation of treatment is warranted before the initiation of subsequent treatment, especially if this involves a clinical trial.

Our study has some limitations. First, this is a retrospective study of a widely varied patient population. We are unable to exclude the possibility that unequal distribution of unidentified clinicopathologic parameters in our patient cohort may have biased the observed results. Second, the total number of 133 patients analyzed for the NLR is relatively small. Other clinicopathologic factors that were not found to be significantly associated with outcome in the present study might have been important in a larger patient cohort. Third, neutrophil and lymphocyte counts may be influenced by concurrent infection and drugs that cannot be accounted for in this analysis. However, we expect these influences to be small. Fourth, because other inflammatory markers, such as CRP, and prognostic markers,

such as lactate dehydrogenase [35] and circulating tumor cells [36], are not routinely measured in our institutions, we could not analyze their association with outcome. Furthermore, the presence of visceral metastases might be associated with a worse outcome in patients with mCRPC [37]. However, in the present study, only 13 patients (8%) had visceral metastases. This number was too small to be included as a separate variable in the analysis. Instead, and based on previous literature, the presence of visceral metastases was used to define a patient as having extensive disease [3, 17]. Fifth, the PFS interval is not a validated endpoint in mCRPC patients. The overall survival time would be a better clinical endpoint. However, in the present study, the NLR was not directly correlated with the overall survival duration but rather with the surrogate endpoint PFS time because the median follow-up time was relatively short and we therefore could not examine clinical factors influencing the overall survival outcome. Sixth, time to castration-resistant prostate cancer, PSADT, and the NLR might not be specific as predictive markers in ketoconazole treatment but rather a reflection of a less lethal phenotype, that is, a longer natural history of the disease. For example, time to castration-resistant prostate cancer has been identified as a predictor of outcome independent of treatment [38]. Seventh, because this is a retrospective study, different criteria might have been followed in the different institutions to define progression. Furthermore, clinical progression as defined in the present study (that includes patient treated in 1999–2011) does not follow the PCWG-2 criteria [29], which were published in 2008 and do not recommend using biochemical progression alone to define treatment failure. Finally, whether our findings are specific to ketoconazole or generalizable to CYP17 inhibitors, including abiraterone acetate, is not known.

Despite these limitations, our preliminary clinical observations that the pretreatment NLR may be associated with the response rate and PFS time and that the clinical factors associated with disease progression may be used for predictive risk grouping of patients treated with ketoconazole for mCRPC may be of both pathophysiological and clinical significance. This may contribute to treatment decisions, patient selection, and clinical trial design. Given the increasing number of treatment choices for mCRPC, a clinical risk stratification nomogram may help in the selection of patients who are more likely to benefit from sequential CYP17 inhibition therapy. The NLR is an easily measured, reproducible, and inex-

pensive marker from a CBC that can easily be incorporated into routine clinical practice. External validation of our preliminary results by further studies is required to test and confirm our hypothesis-generating observation in larger patient cohorts, to elucidate the underlying molecular mechanisms (such as the cytokine balance) determining the NLR and the influence of the inflammatory response on ketoconazole treatment, and to reveal whether or not our results are generalizable to all CYP17 inhibitors, including abiraterone acetate.

CONCLUSIONS

In mCRPC patients treated with ketoconazole, the pretreatment NLR, a prior response to hormonal therapy, and the pretreatment PSADT are associated with the PFS interval and may be used to categorize patients into predictive risk groups and to identify patients who are more likely to benefit from sequential CYP17 inhibition therapy.

AUTHOR CONTRIBUTIONS

Conception/Design: Daniel Keizman, Maya Ish-Shalom, Avivit Peer, Michael A. Carducci, Mario A. Eisenberger, Avishay Sella

Provision of study material or patients: Daniel Keizman, Maya Gottfried, Natalie Maimon, Avivit Peer, Avivit Neumann, Eli Rosenbaum, Svetlana Kovel, Roberto Pili, Victoria Sinibaldi, Michael A. Carducci, Hans Hammers, Mario A. Eisenberger, Avishay Sella

Collection and/or assembly of data: Daniel Keizman, Natalie Maimon, Avivit Peer, Michael A. Carducci

Data analysis and interpretation: Daniel Keizman, Maya Ish-Shalom, Roberto Pili, Michael A. Carducci, Hans Hammers, Mario A. Eisenberger, Avishay Sella

Manuscript writing: Daniel Keizman, Maya Ish-Shalom, Natalie Maimon, Eli Rosenbaum

Final approval of manuscript: Daniel Keizman, Maya Gottfried, Maya Ish-Shalom, Natalie Maimon, Avivit Peer, Avivit Neumann, Eli Rosenbaum, Svetlana Kovel, Roberto Pili, Victoria Sinibaldi, Michael A. Carducci, Hans Hammers, Mario A. Eisenberger, Avishay Sella

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