Prognostic Impact of the Neutrophil-to-Lymphocyte Ratio in Men With Metastatic Castration-Resistant Prostate Cancer

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Abstract

This retrospective analysis of a phase III trial comparing prednisone combined with sunitinib or placebo following docetaxel for metastatic castration resistant prostate cancer demonstrated the prognostic impact of peripheral blood neutrophil-lymphocyte ratio (NLR) independent of known prognostic factors. NLR warrants external validation, given its ready and inexpensive availability, and the potential role of the host immune in modulating tumor biology.

Background: We retrospectively evaluated the prognostic impact of neutrophil-lymphocyte ratio (NLR) as a marker for inflammatory and immune state in men with progressive metastatic castration resistant prostate cancer (mCRPC) following docetaxel. **Methods:** The SUN-1120 phase III trial comparing prednisone combined with sunitinib (n = 584) or placebo (n = 289) for mCRPC following docetaxel-based chemotherapy was evaluated. The arms were combined for analysis, since no difference was observed in the primary endpoint of overall survival (OS). A logarithmic transformation was applied to non-normal factors. The Kaplan-Meier method was used for OS estimation. To identify an optimal prognostic model for survival, we used a Cox proportional hazards regression method with forward stepwise selection, stratifying for ECOG PS, progression type (prostate specific antigen [PSA] or radiographic) and treatment group. Patients were categorized into risk groups. **Results:** Complete data was evaluable for 784 men. The factors used in the model that remained individually significant for OS in multivariable analysis were: log-lactate dehydrogenase level (LDH) level (HR 2.86 [95% CI = 2.29, 3.56], $P < .001$), hemoglobin (0.80 [0.74, 0.85], $P < .001$), > 1 organ involved by metastatic disease (1.49 [1.21, 1.84], $P < .001$), log-alkaline phosphatase (1.13 [0.99, 1.28], $P = .074$), log-number of prior cycles of docetaxel (0.84 [0.71, 0.98], $P = .031$), progression on docetaxel (1.35 [1.00, 1.81], $P = .049$), log-PSA (1.06 [1.00, 1.12], $P = .075$) and log-NLR (1.55 [1.32, 1.83], $P < .001$). NLR increased the c-statistic of the prognostic model from 0.703 to 0.715. **Conclusion:** High NLR may be associated with an independent poor prognostic impact in post-docetaxel patients with mCRPC. These data warrant external validation.

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Introduction

The recent demonstration of improved survival with immunotherapy in men with metastatic castration-resistant prostate cancer (mCRPC) suggests the prognostic importance of immune function in the presence of metastatic disease.[1] An emerging and readily available measure of the immune state, the neutrophil-to-lymphocyte ratio (NLR) may be a crude measure of the inflammatory and immune state of the host. High NLR has been associated with adverse outcomes in a variety of malignancies, eg, mesothelioma, bladder cancer, renal cancer, colon cancer, ovarian cancer, and gastric cancer.[2-9] Additionally, neutrophilia is a validated independent poor prognostic factor in some malignancies, eg, renal cell carcinoma.[10] Therefore, we hypothesized that NLR may confer an independent prognostic impact in men with mCRPC.

The influence of NLR on outcomes needs to be determined independent of the impact of other recognized clinical prognostic factors. Previous studies have reported the prognostic stratification of men with mCRPC on the basis of baseline clinical and laboratory parameters and, more recently, the number of circulating tumor cells (CTCs).[11-15] A retrospective analysis of the TAX327 trial comparing docetaxel and mitoxantrone first-line chemotherapy has demonstrated several pretreatment factors to be associated with survival: pain level, performance status, alkaline phosphatase level, number of sites of metastatic disease, presence of liver metastases, hemoglobin level, PSA level, and time since diagnosis. In the postdocetaxel setting, in addition to the presence of visceral metastases, pain level, performance status, and anemia, the number of progression factors (PSA level, pain level, and tumor size), the duration of first-line chemotherapy, whether progression occurred during chemotherapy, and the time from diagnosis to second-line chemotherapy independently predicted postprogression survival.[16] A recent presentation identified changes in number of CTCs and baseline lactate dehydrogenase (LDH) level as prognostic indicators in patients receiving abiraterone acetate following docetaxel.[17] Given the relatively modest accuracies of existing prognostic models in men with mCRPC, additional biomarkers are needed that may better help in risk assessment in this disease. Such biomarkers may allow for improved treatment selection based on prognosis or may help in ensuring homogenous groups across a clinical trial (stratification). In addition, such immune biomarkers may then be evaluated for a predictive role in the context of treatments that modulate inflammation or immunity.

Recently, a phase III trial compared the combination of prednisone with sunitinib or placebo for men with mCRPC progressing following docetaxel-based chemotherapy.[18] Given the setting of a large phase III trial, this trial affords an excellent opportunity to discover novel prognostic factors. Therefore, we conducted a retrospective analysis of this trial to investigate the independent impact of NLR.

Methods

Patient Population

The SUN-1120 trial (n = 873) compared the combination therapy of prednisone with sunitinib (n = 584) and the combination of prednisone with placebo (n = 289) in men with mCRPC with disease progression following docetaxel-based chemotherapy.[18] This trial reported no improvement in overall survival (OS) in patients who received sunitinib in addition to prednisone; however, a significant improvement in progression-free survival (PFS) was observed in these patients. In this multicenter, double-blind study, eligible men were stratified by ECOG (Eastern Cooperative Oncology Group) performance status (PS) and progression type (prostate-specific antigen [PSA] or radiographic). Patients were required to have disease for which 1 prior docetaxel-based chemotherapy regimen had failed (defined as disease progression or drug intolerance). In the event both disease progression and drug intolerance were observed during prior docetaxel therapy, disease progression was considered the dominant entry criterion. Patients were randomized (2:1) to receive prednisone 5 mg twice per day (b.i.d.) and either sunitinib 37.5 mg or placebo on a continuous once-daily dosing schedule. OS was the primary endpoint, and secondary endpoints included radiographic PFS and improvement in pain. No maximum number of cycles was stipulated, and imaging was performed every 2 cycles (8 weeks) or earlier if required. Patients who discontinued the trial for reasons other than disease progression were followed for OS but not for progression. Urinary N-telopeptide (NTx) and bone-specific alkaline phosphatase (BSAP) levels were measured in a subset of patients.

Statistical Methods

This is a retrospective, nonprespecified analysis of a prospective phase III trial database. Descriptive statistics are presented for baseline characteristics and outcomes. The Kaplan-Meier method was used to estimate OS outcomes. Variables evaluated for model development included age, number of prior cycles of docetaxel, hemoglobin level, alkaline phosphatase level, PSA level, LDH level, months from diagnosis, whether the patient progressed on docetaxel, Prostate Cancer Clinical Trials Working Group 2 (PCWG-2) subtype, number of metastatic organ sites, Gleason score ($\geq$ 8 vs. $\leq$ 7), and baseline measurable disease.[19] Trial stratification factors (ECOG PS 0 vs. 1 and progression by PSA criteria or radiographic imaging) along with treatment group were included in all models as strata. Baseline BSAP, urine NTx and pain levels were assessed separately in subgroups of patients because of large numbers of missing data. A logarithmic transformation was applied to nonnormally distributed continuous factors for regression modeling. No formal statistical test was performed to determine normality, which was evaluated by visual inspection.

Both arms of the trial were combined for this retrospective analysis as no difference in OS was identified between the arms; however, treatment group and study stratification factors (ECOG PS and type of disease progression) were included as strata in regression models. Furthermore, supportive analyses were conducted whereby univariate and multivariate analyses were performed separately in each arm of the trial. The comparison of patient characteristics between subgroups based on NLR was performed using χ^2 tests and Wilcoxon rank sum tests. The prognostic impact of selected variables on OS was studied using univariate Cox proportional hazards regression methods. An optimal multivariate Cox proportional hazards regression model was constructed using forward stepwise selection with entry criteria set to the 0.15 level. Because the primary focus of this analysis was to investigate the prognostic ability of NLR, neutrophils and lymphocytes were excluded from potential entry into the optimal model. The