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Change in Neutrophil-to-lymphocyte Ratio in Response to Targeted Therapy for Metastatic Renal Cell Carcinoma as a Prognosticator and Biomarker of Efficacy

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Abstract

Background: Neutrophil-to-lymphocyte ratio (NLR), if elevated, is associated with worse outcomes in several malignancies.
Objective: Investigation of NLR at baseline and during therapy for metastatic renal cell carcinoma.
Design, setting, and participants: Retrospective analysis of 1199 patients from the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC cohort) and 4350 patients from 12 prospective randomized trials (validation cohort).
Intervention: Targeted therapies for metastatic renal cell carcinoma.
Outcome measurements and statistical analysis: NLR was examined at baseline and 6 (± 2) wk later. A landmark analysis at 8 wk was conducted to explore the prognostic value of relative NLR change on overall survival (OS), progression-free survival (PFS), and objective response rate using Cox or logistic regression models, adjusted for variables in IMDC score and NLR values at baseline.
Results and limitations: Higher NLR at baseline was associated with shorter OS and PFS (Hazard Ratios [HR] per 1 unit increase in log-transformed NLR = 1.69 [95% confidence interval {CI} = 1.46–1.95] and 1.30 [95% CI = 1.15–1.48], respectively). Compared with no change (decrease < 25% to increase < 25%, reference), increase NLR at Week 6 by 25–50% and > 75% was associated with poor OS (HR = 1.55 [95% CI = 1.10–2.18] and 2.31 [95% CI = 1.64–3.25], respectively), poor PFS (HR = 1.46 [95% CI = 1.04–2.03], 1.76 [95% CI = 1.23–2.52], respectively), and reduced objective response rate (odds ratios = 0.77 [95% CI = 0.37–1.63] and 0.24 [95% CI = 0.08–0.72], respectively). By contrast, a decrease of 25–50% was associated with improved outcomes. Findings were confirmed in the validation cohort. The study is limited by its retrospective design.
Conclusions: Compared with no change, early decline of NLR is associated with favorable outcomes, whereas an increase is associated with worse outcomes.
Patient summary: We found that the proportion of immune cells in the blood is of prognostic value, namely that a decrease of the proportion of neutrophils-to-lymphocytes is associated with more favorable outcomes while an increase had the opposite effect.

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1. Introduction

With the advent of targeted treatments, treatment options for metastatic renal cell carcinoma (mRCC) have changed dramatically [1,2]. The International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic criteria (also known as Heng criteria) based on clinical (performance status, diagnosis-to-treatment interval) and laboratory (hypercalcemia, anemia, thrombocytosis, neutrophilia) variables are currently used to stratify patients into three risk groups [3].

Inflammation has been recognized as a hallmark of cancer [4] and elevated markers of systemic host inflammation such as C-reactive protein [5] or the neutrophil-to-lymphocyte ratio (NLR) have been shown to be associated with a poor prognosis in several solid tumors [6–8] including RCC [9–11]. The mechanism by which inflammation leads to worse outcomes is not known. Neutrophilia is considered to occur as an inflammatory response and may lead to suppression of cytolytic activity of immune cells such as lymphocytes, natural killer cells, and activated T cells [12,13].

We aimed to confirm that higher NLR is associated with worse prognosis in patients with mRCC and hypothesized that an early decline of NLR during treatment with targeted therapies would indicate a more favorable prognosis independent of established prognostic factors at baseline and that an increase of NLR would be associated with the opposite effect.

2. Patients and methods

Criteria for Reporting Recommendations for Tumor Marker Prognostic Studies were followed where appropriate [14].

2.1. Study populations and data collection

Patients with mRCC receiving targeted therapy at IMDC sites for which NLR data were available prior to first-line treatment, and 6 wk thereafter (±2 wk) were eligible and were analyzed first (IMDC cohort). Patients treated in studies (Supplementary Table 1) conducted or sponsored by Pfizer Inc (New York City, NY, USA) were subsequently analyzed to assess the robustness of the results (validation cohort).

NLR data (the ratio of the absolute neutrophil count to absolute lymphocyte count measured in peripheral blood) were retrospectively collected in the IMDC dataset. In the validation cohort, neutrophil and lymphocyte counts were captured prospectively.

2.2. Statistical analysis

Descriptive statistics for continuous variables are reported as medians and interquartile ranges, and categorical variables as frequencies and percentages. We first analyzed the impact of baseline NLR (log-transformed [lnNLR]) on overall survival (OS) and progression free survival (PFS), defined as time from targeted therapy initiation to death from all causes (for OS) and to progression, treatment cessation, and death (for PFS), censored at last follow-up for those still alive or who have not progressed. Objective response rates (ORRs) were assessed using computed tomography and categorized using Response Evaluation Criteria in Solid Tumors [15,16].

We hypothesized that NLR changes by 6 wk (±2 wk) are of prognostic value. A landmark analysis at 8 wk was done to assess the role of NLR changes, calculated as % change (calculation = [{NLR wk 6/NLR wk 0} – 1]*100) and subsequently grouped into five groups (>75% decrease, 25–75% decrease, no change [<25% decrease to <25% increase], 25–75% increase, >75% increase) with calculation of the hazard ratio (HR) per group. For the landmark analysis, OS and PFS were calculated from 8 wk after targeted therapy initiation. Cox regression models were adjusted for lnNLR at baseline and the six variables in the IMDC score, namely Karnofsky Performance Status < 80%, time from diagnosis to treatment start < 1 yr, corrected calcium > upper limit of normal (ULN), platelet count > ULN, neutrophil count > ULN, hemoglobin < lower limit of normal (for all variables, yes vs no) [3]. Martingale residuals plots were used to verify the linear assumption of the Cox model. Logistic regression models with the same adjustments were used to assess the association of baseline NLR and change in NLR on ORRs. A landmark analysis at 8 wk was also done similarly for "NLR conversion," that is, a change from above to below (or vice-versa) median NLR at baseline rounded to the nearest full integer.

The analyses were subsequently repeated in data from an independent cohort of patients (validation cohort).

Analyses were carried out using SPSS version 20 (IBM Corp. Chicago, IL, USA) and with SAS version v9.2 (Cary, NC, USA). All statistical tests were two sided, and statistical significance was defined as $p < 0.05$. No corrections for multiple significance testing were applied.

3. Results

3.1. Patients

The IMDC cohort comprised a total of 1199 patients who commenced targeted therapy between 2004 and 2013 at nine Consortium sites in the USA, Canada, New Zealand, and Singapore. Baseline characteristics are presented in Table 1. The median age of patients in the IMDC cohort was 62 yr, the majority were men (75%) and treated with sunitinib (74%). Around half of the patients were in the intermediate IMDC prognostic group. One thousand one hundred and sixty six, 1076, and 1058 patients were included in the landmark analysis at wk 8 of OS, PFS, and ORR, respectively.

3.2. Prognostic role of NLR at baseline

Martingale residual plots confirmed linearity of lnNLR and therefore, the Cox model was fitted with lnNLR (Supplementary Fig. 1). Estimated 1-yr and 2-yr survival rates from univariable Cox regression based on the continuous lnNLR are presented in Figure 1A.

Higher NLR at baseline was associated with shorter OS (adjusted HR per 1 unit increase in lnNLR = 1.69, 95% CI = 1.46–1.95, $p < 0.001$), shorter PFS (adjusted HR per 1 unit increase in lnNLR = 1.30, 95% CI = 1.15–1.48, $p < 0.001$), and lower ORR (adjusted OR per 1 unit increase in lnNLR = 0.69, 95% CI = 0.52–0.90, $p = 0.007$).

3.3. Early change in NLR

In the landmark analysis at wk 8, NLR change from baseline to wk 6 (±2 wk) during targeted therapy was an independent prognostic factor for OS and PFS ($p < 0.001$).

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