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ORIGINAL RESEARCH

Prognostic significance of host immune status in patients with late relapsing renal cell carcinoma treated with targeted therapy

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Abstract We aimed to assess the prognostic role of pretreatment neutrophilia, lymphocytopenia, and neutrophil to lymphocyte ratio (NLR) in patients treated with vascular endothelial growth factor-tyrosine kinase inhibitors (VEGFR-TKIs) for late relapsing (>5 years) metastatic renal cell carcinoma (mRCC). Data were collected from 13 Italian centers involved in the treatment of metastatic RCC. Late relapse was defined as >5 years after initial radical nephrectomy. One hundred fifty-one patients were included in this analysis. Among them, MSKCC risk score was favorable in 68 %, intermediate in 29 %, and poor in 3 %. Fifty-six patients (37 %) had NLR ≥3 at the start of VEGFR-TKI therapy (group A), while 95 had lower NLR (63 %, group B). The median overall survival (OS) was 28.8 months in group A and 68.7 months (95 % confidence interval (CI) 45.3–NA) in group B ($p<0.001$). The median progression-free survival (PFS) was 15.8 months in

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group A and 25.1 months in group B (p=0.03). At multivariate analysis, MSKCC risk group and NLR were independent prognostic factors for both OS and PFS. Pretreatment NLR is an independent prognostic factor for patients with late relapsing mRCC treated with first-line VEGFR-TKIs. A better characterization of baseline immunological impairment may optimize the management of this RCC subpopulation.

Keywords Late recurrence · Neutrophil to lymphocyte ratio · Prognosis · Renal cell carcinoma · Tyrosine kinase inhibitors

Introduction

In the last decades, the molecular basis of the pathogenesis of renal cell carcinoma (RCC) has been widely investigated leading to the development of targeted agents in addition to immunotherapy-based treatments. Beyond the well-recognized genetic mechanisms, represented by the inactivation of the von Hippel–Lindau (VHL) tumour-suppressor gene and the consequent abnormal accumulation of hypoxia-inducible factor (HIF), which leads to the dysregulation of cellular growth and angiogenesis [1], the immune sensitiveness of RCC suggested a potential pivotal role of the immune system in RCC carcinogenesis and disease progression.

RCC develops various mechanisms of tumor escape from patient immune response, such as tumor heterogeneity [2, 3] and direct tumor-induced immunosuppression [4, 5].

Late relapsing RCC is not a rare event. Several studies have reported that 4.7 to 11 % of patients developed a recurrence >10 years after initial nephrectomy [6–9]. In addition, this subpopulation shows better response to vascular endothelial growth factor-tyrosine kinase inhibitors (VEGFR-TKIs) compared to patients relapsing within 5 years [10]. However, to our knowledge, no study to date has validated molecular predictive and prognostic markers associated with the outcome of late relapsing metastatic renal cell carcinoma (mRCC).

Several markers of inflammation have been evaluated for their clinical significance in the RCC population and immunological elements have been included in the Heng-validated prognostic model [11]. Previous evidence was provided for the role of neutrophil to lymphocyte ratio (NLR) as a feasible measurable marker of systemic inflammation, demonstrating a correlation with the outcome of RCC patients [12–17]. The ability to predict the disease outcome using the host's immune parameters may allow the preselection of patients with different prognostic profiles and the consequent planning of tailored pathways for treatment and follow-up.

In the present study, we aimed to assess the prognostic role of pretreatment neutrophilia, lymphocytopenia, and NLR in patients treated with VEGFR-TKIs for late relapsing metastatic RCC.

Material and methods

Study population

We retrospectively collected clinical data of patients treated with VEGFR-TKIs for mRCC diagnosed >5 years after initial radical nephrectomy. Patients were treated in 13 Italian Institutions between January 2005 and June 2014. Patients were

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collected consecutively to avoid selection bias. Inclusion criteria were tumor previously surgically treated with radical nephrectomy, disease-free survival (DFS) >5 years, and clear cell histology. All patients included in the analysis were without evidence of metastatic disease at the time of initial nephrectomy. Patients were excluded from this analysis if data on NLR were not available at the time of the start of first line VEGFR-TKI therapy. In addition, patients were ineligible if they presented factors that could influence NLR, such as concurrent infections, chronic inflammatory diseases, recent or chronic treatment with steroids, chronic lymphocytic leukemia (CLL), previous treatment with immunotherapy, or granulocyte colony stimulating factor (G-CSF).

Peripheral blood samples were obtained 1 to 7 days before the start of first-line VEGFR-TKI therapy. Pretreatment NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. The value that best discriminated between good and poor survival, that is, with the most significant *p* value according to the log rank test, was determined by testing all possible cutoffs.

Patients were treated with sunitinib (orally at a dose of 50 mg daily, 4 weeks on–2 weeks off), sorafenib (400 mg orally twice daily), or pazopanib (at a dose of 800 mg orally daily) as first-line therapy. Dose reductions or treatment interruptions were performed for the management of adverse events, depending on their type and severity, according to standard guidelines. Treatment with VEGFR-TKIs was continued until evidence of disease progression on scans, unacceptable adverse events, or death. The overall survival (OS) was defined as the time from TKI treatment beginning to death from any cause. The progression-free survival (PFS) was defined as the time from beginning of VEGFR-TKI treatment to progression or to death from any cause, whichever occurred first. Patients with a stable disease, partial remission, and a complete remission were considered as responders.

This study was carried out in accordance with the approval by the ethical committee of the institutions included in this analysis.

Statistical analysis

Survival analysis was conducted via Kaplan–Meier product-limit method and the Mantel–Haenszel log-rank test was employed to compare survival among groups. The chi-square test was used to compare frequency distributions.

A Cox regression model was applied to the data with a univariate and multivariate approach. Variables included in the univariate analysis were gender, age, Memorial Sloan Kettering Cancer Center (MSKCC) risk group, neutrophil and lymphocyte counts, and NLR. Continuous covariates (age, neutrophil, and lymphocyte counts) were grouped into discrete ordinal categories. Variables not fitting at univariate analysis were excluded from the multivariate model. No multicollinearity of the grouped covariates was checked. Significance level in the univariate model for inclusion in the multivariate final model was more liberally set at a 0.2 level [18, 19]. Statistical analysis was conducted with the "R" statistical software version 2.15.2.

Results

Patient characteristics

One hundred and fifty-one patients were included in this analysis. Of them, 99 (66 %) were male; median age was 64 years (range 29–88 years). MSKCC risk score was favorable in 102 patients (68 %), intermediate in 44 patients (29 %), and poor in 5 patients (3 %). Patients' characteristics are summarized in Table 1.

Median neutrophil count was 3790/mm^3, median lymphocyte count was 1370/mm^3 and median NLR was 2.34 (95 %

Table 1 Patient characteristics and differences among NLR groups by chi-square test

Patients	Overall, 151 (%)	NLR ≥3, 56 (37)	NLR <3, 95 (63)	*p* value
Gender				
Male	99 (66)	36 (64)	63 (66)	0.84
Female	52 (34)	20 (36)	32 (34)	
Age, years	64	65	64	0.76
Range	29–88	29–84	31–88	
Karnofsky performance status score				
>70	132 (93)	51 (91)	81 (85)	*0.02*
<70	19 (7)	5 (9)	14 (15)	
MSKCC risk stratification				
Favorable risk	102 (68)	29 (52)	73 (77)	0.08
Intermediate risk	44 (29)	25 (45)	19 (20)	
Poor risk	5 (3)	2(3)	3 (3)	
Common sites of metastasis				
Lymph nodes	41 (27)	17 (30)	24 (25)	0.55
Lung	84 (56)	27 (48)	57 (60)	0.29
Bone	36 (24)	16 (29)	20 (21)	0.34
Liver	22 (15)	13 (23)	9 (9)	0.81
Brain	10 (7)	6 (11)	4 (4)	0.09
Pancreas	31 (21)	10 (18)	21 (22)	0.74
Soft tissues	8 (5)	3 (5)	5 (5)	0.75
Median neutrophil count	3790/mm^3	3400/mm^3	3340/mm^3	0.23
Median lymphocyte count	1370/mm^3	515/mm^3	1790/mm^3	*0.01*

Statistically significant values are Italicized

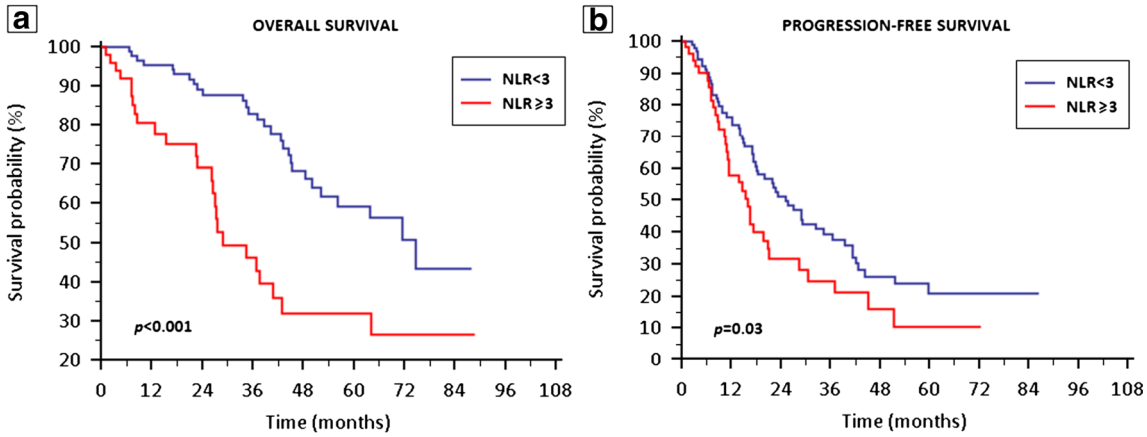

Fig. 1 OS (**a**) and PFS (**b**) in patients with late relapsing RCC according to NLR at time of recurrence

confidence interval (CI) 1.64–5.49). When NLR was analyzed as a dichotomous variable, a cut-point of 3 provided the strongest prognostic value in our dataset; therefore, this level was chosen for further study.

Patients were further divided based on NLR <3 or ≥3. Fifty-six patients (37 %) had NLR ≥3 at the start of VEGFR-TKI therapy (group A), while 95 had lower NLR (63 %, group B).

In group A, the median NLR was 6.97, 51 patients (91 %) had absolute neutrophilia (defined as >7500/mm^3 in our institutions), and 17 patients (30 %) had absolute lymphocytopenia (defined as <1500/mm^3 in our institutions). In group B, the median NLR was 1.79, 2 (2 %) had absolute neutrophilia, and 21 patients (22 %) had absolute lymphocytopenia.

The differences between group A and group B were evaluated, and the results are reported in Table 1.

Outcome analyses in the overall population and based on NLR status

All these patients received VEGFR-TKIs as first-line therapy; 107 (71 %), 32 (21 %), and 12 (8 %) were treated with sunitinib, sorafenib, and pazopanib, respectively.

The median OS was 63.9 months (95 % CI 45.2–NA), with a median follow-up of 51.6 months (95 % CI 5.7–NA). Fifty-three patients (35 %) died during follow-up. The median OS was 28.8 months (95 % CI 16.9–NA) in group A and 68.7 months (95 % CI 45.3–NA) in group B ($p<0.001$) (Fig. 1a). The median PFS was 20.7 months (95 % CI 11.3–NA) in the overall population, with 92 patients (61 %) progressed during first-line therapy. The median PFS was 15.8 months (95 % CI 7.1–31.3) in group A and 25.1 months (95 % CI 11.7–NA) in group B ($p=0.03$) (Fig. 1b). In addition, significant differences in terms of OS (17.3 vs

Table 2 Univariate and multivariable analysis of predictors of PFS and OS of patients treated with everolimus for mRCC

	Univariate Cox regression		Multivariable Cox regression	
	HR (95 % CI)	*p* value	HR (95 % CI)	*p* value
OS				
Gender (M vs F)	1.15 (0.69–1.27)	0.312		
Age (<65 vs ≥65 years)	1.06 (0.87–1.43)	0.276		
MSKCC prognostic group	2.29 (1.34–3.91)	*0.002*	1.90 (1.1–3.27)	*0.019*
Neutrophilia (Y/N)	3.22 (1.27–8.17)	*0.014*		
Lymphocytopenia (Y/N)	1.05 (0.61–1.80)	0.872		
NLR >3 vs <3	3.04 (1.76–5.22)	*<0.001*	2.21 (1.21–4.04)	*0.010*
PFS				
Gender (M vs F)	1.16 (0.76–1.78)	0.495		
Age (<65 vs ≥65 years)	0.98 (0.79–1.13)	0.541		
MSKCC prognostic group	2.02 (1.37–3.00)	*<0.001*	2.11 (1.41–3.17)	*<0.001*
Neutrophilia (Y/N)	3.82 (1.90–5.68)	*0.001*		
Lymphocytopenia (Y/N)	1.10 (0.73–1.67)	0.650		
NLR >3 vs <3	1.56 (1.02–2.39)	*0.04*	2.21 (1.21–4.04)	*0.014*

Statistically significant values are Italicized

63.9 months, $p=0.009$) and PFS (4.1 vs 21.8 months, $p<0.001$) were found between patients with or without neutrophilia at time of late relapsing, respectively (Fig. S1).

Univariate and multivariate analyses

As for OS, univariate analysis showed that MSKCC risk group (hazard ratio (HR) 2.29; 95 % CI 1.34–3.91, $p=0.002$), neutrophilia (HR 3.22; 95 % CI 1.27–8.17, $p=0.014$), and NLR (HR 3.04; 95 % CI 1.76–5.22, $p=0.002$) were associated with OS. Multivariate Cox regression analysis revealed that MSKCC risk group (HR 1.90; 95 % CI 1.1–3.27, $p=0.019$) and NLR (HR 2.21; 95 % CI 1.21–4.04, $p=0.010$) were independent prognostic factors (Table 2).

Univariate analysis showed that MSKCC risk group (HR 2.02; 95 % CI 1.37–3.00, $p<0.001$), neutrophilia (HR 3.82; 95 % CI 1.90–5.68, $p=0.001$), and NLR (HR 3.04; 95 % CI 1.02–2.39, $p=0.042$) were associated with PFS. At multivariate analysis, MSKCC risk group (HR 2.11; 95 % CI 1.41–3.17, $p<0.001$) and NLR (HR 2.21; 95 % CI 1.21–4.04, $p=0.014$) were predictors of PFS.

Discussion

In recent years, markers of the systemic inflammatory response have demonstrated independent prognostic value across different cancer populations, including RCC [12, 20, 21]. RCC is considered to be an immunogenic tumour [22], and host inflammatory response has an important role in carcinogenesis and disease progression [23, 24]. Immunological parameters such as blood neutrophils, blood lymphocytes, intratumor neutrophils, and other inflammatory serum markers, such as procalcitonin or C reaction protein (CRP), were significantly associated with the prognosis of mRCC patients [11, 25–28]. However, at present, only neutrophil count [11] and CRP [27, 28] have been validated in this setting. The relevance of absolute neutrophilia and the prognosis of RCC has been highlighted by the validated Heng score; on the other hand, the lymphocyte-mediated immune response has been suggested to have some correlation with the disease outcome. With these premises, previous studies has been performed examining pretreatment and posttreatment NLR in RCC, with some encouraging results: NLR demonstrated to be a prognostic factor in nonmetastatic RCC, after surgical approach, but other evidence have been subsequently purchased also in the metastatic setting [13–17, 29, 30].

In our study, we considered late relapsing RCC patients, treated with first-line VEGFR-TKIs; this population has been recently considered in a small sample size study by Sejima et al. [31], who showed that lower values of NLR and FasL expression positivity in late recurrence compared with different metastatic timings underlies a strong host immune activity and may be associated with relatively long survival.

In this study, we showed that increased pretreatment NLR was significantly associated with worse PFS and OS at the univariate and multivariate analyses. Interestingly, a subgroup of 56 patients (37 %) presented pretreatment NLR ≥3, associated with worse outcome than NLR<3 late relapsing patients. Moreover, NLR status was not associated with the sites of metastatic spread and with MSKCC risk group. This selection could allow a selective and more in-depth immunological characterization of the disease in this subgroup of patients, in order to identify prognostic factors that could be potentially used as therapeutic targets in the future.

At multivariate analysis, NLR was an independent prognostic factor of OS and PFS; also, the prognostic role of MSKCC group was reported, while neutrophilia was associated to the outcome only at univariate analysis. The Heng group was taken in consideration, but was not included in the multivariate analysis to avoid the bias of considering more than once the prognostic value of neutrophilia in the overall RCC population.

With the limit of a retrospective analysis, the present study has the strength of a relative large sample size (151 patients), an element that can reduce the potential bias attributable to clinical variables influencing NLR (infections, drugs, others). In addition, the short follow-up of patients who started their treatment in 2014 (3 %) does represent a limit of this analysis.

In conclusion, our results showed that NLR should be considered an independent factor for OS and PFS in patients with late relapsing RCC treated with first-line sunitinib, sorafenib, or pazopanib. The altered balance between host immunity and cancer-related inflammation may reflect the contribution of immune response on RCC outcome and response to targeted agents.

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