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Pre-treatment neutrophil-to-lymphocyte ratio may be associated with the outcome in patients treated with everolimus for metastatic renal cell carcinoma

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Background: Everolimus is a mammalian target of rapamycin inhibitor approved for the treatment of metastatic renal cell carcinoma (mRCC). We aimed to assess the association between pre-treatment neutrophil-to-lymphocyte ratio (NLR) and the outcome of patients treated with everolimus for mRCC.

Methods: Ninety-seven patients with mRCC were treated with everolimus till April 2013 in our institutions. Patients were stratified in two groups with NLR >3 (Group A) *vs* <3 (Group B). Progression-free survival (PFS) and overall survival (OS) were estimated using Kaplan–Meier method. Gender, age, Motzer prognostic group, PFS on first-line therapy, neutrophilia and NLR were included in the Cox analysis to investigate their prognostic relevance.

Results: Median OS and PFS were 10.6 and 5.3 months, respectively. Median OS was 12.2 months in Group A and 24.4 months in Group B ($P=0.001$). Median PFS was 3.4 months in Group A and 9.9 months in Group B ($P<0.001$). At multivariate analysis, only Motzer prognostic group and NLR were independent prognostic factors for OS and PFS.

Conclusion: Pre-treatment NLR is an independent prognostic factor for patients with mRCC treated with second- or third-line everolimus. This should be investigated and validated in prospective studies.

In recent years, exciting advances have emerged in the treatment of metastatic renal cell carcinoma (mRCC), with the development of targeted agents in addition to immunotherapy-based treatments. This has been achieved primarily through the elucidation of the crucial role of vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) pathways in RCC. However, there is still a great deal of information to be discovered regarding the pathogenesis of this tumour. Increasing evidence suggests that inflammatory cells are an essential component of the tumour microenvironment and have a role in tumour progression (Mantovani *et al*, 2008; Hanahan and Weinberg, 2011). Tumour cells often constitutively produce several inflammatory chemokines, including neutrophil-attracting CXC-chemokines (Mantovani *et al*, 2008). The process of myelopoiesis is profoundly modified during inflammation and cancer, and this leads to the appearance of altered mature myelocytes and myeloid-derived

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suppressor cells, which account for immune suppression in patients with RCC (Mantovani *et al*, 2011).

Markers of inflammation, such as the neutrophil-to-lymphocyte ratio (NLR), and their clinical significance in RCC patients are still under evaluation. NLR is an easily measurable parameter of systemic inflammation. Increased pre-treatment NLR has been demonstrated to be associated with poor outcome for various types of cancers, including gastric cancer (Yamanaka *et al*, 2007), advanced pancreatic cancer (An *et al*, 2010), hepatocellular carcinoma (Gomez *et al*, 2008), colorectal liver metastases (Kishi *et al*, 2009), non-small-cell lung cancer (Sarraf *et al*, 2009), malignant mesothelioma (Kao *et al*, 2010), ovarian cancer (Cho *et al*, 2009) and soft-tissue sarcoma (Szkandera *et al*, 2013). However, to our knowledge, we are the first to investigate the association between pre-treatment NLR and outcome of mRCC patients treated with mTOR inhibitor everolimus as second- or third-line therapy.

The mTOR signalling pathway is crucial for a wide variety of cells including leukocytes, and dysfunction within the mTOR axis may have a role in the pathogenesis of RCC (Thomas *et al*, 2006). Based on the results of the phase III RECORD-1 trial (Motzer *et al*, 2008, 2010), everolimus, a potent mTOR inhibitor, has become the recommended standard of care for patients with mRCC whose disease has progressed after initial TKI therapy (de Reijke *et al*, 2009; Ljungberg *et al*, 2010).

To our knowledge, no study to date has validated molecular predictive and prognostic markers associated with outcome of mRCC patients treated with mTOR inhibitors. In the present study, we aimed at further assessing the prognostic significance of pre-treatment NLR in patients receiving everolimus as second- and third-line therapy for mRCC.

MATERIALS AND METHODS

Patients. The study population consisted of adults (aged 18 years and above) with metastatic clear cell RCC, treated with everolimus after failure of initial one or two TKIs. Treatments were separated by a wash-out period of at least 2 weeks. Patients were treated in three Italian Institutions between January 2005 and April 2013. Data were retrospectively collected from patient's electronic medical records and paper charts.

Patients were ineligible if they had previously received mTOR inhibitor therapy (temsirolimus) or if they presented factors that could influence NLR, such as concurrent infections, chronic inflammatory diseases or recent treatment with steroids.

Peripheral blood samples were obtained 1–7 days before the start of everolimus. Patients without available data on pre-treatment NLR and those with baseline comorbidity such as chronic lymphocytic leukemia, chronic inflammatory diseases, previous treatment with mTOR inhibitor temsirolimus and recent therapy with steroids, cytokines or granulocyte colony-stimulating factor were excluded from this analysis.

Treatment regimens and statistical analysis. Everolimus was administered orally, usually at a starting dose of 10 mg once daily. In patients with significant comorbidities, treatment was initiated at a reduced dose, with subsequent dose escalation if well tolerated. On treatment, dose reductions or treatment interruptions were done for the management of adverse events, depending on their type and severity, according to standard guidelines. Treatment was continued until evidence of disease progression on scans, unacceptable adverse events or death. Follow-up generally consisted of regular physical examination and laboratory assessment (haematologic and serum chemical measurements), every 4–6 weeks, and imaging studies by computed tomography or magnetic resonance imaging scans were carried out according to local procedures every 8–12 weeks. The progression of disease was defined as a $\geqslant$20% increase of the long diameter according to the RECIST 1.0 criteria (Therasse *et al*, 2000). Values were expressed as median and interquartile range. Progression-free survival (PFS) was defined as the time from beginning of treatment to progression or to death from any cause, whichever occurred first. Patients without tumour progression or death at the time of the data cutoff for the analysis or at the time of receiving an additional anticancer therapy were censored at their last date of adequate tumour evaluation. PFS and overall survival (OS) were estimated using Kaplan–Meier method with Rothman's 95% confidence intervals (CIs) and compared across the groups using the log-rank test. Patients with a stable disease, partial remission and a complete remission were considered as responders.

Pre-treatment NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count and potential factors associated with outcome were evaluated, including patients' gender, age, Motzer prognostic group, PFS on first-line therapy, neutrophilia and NLR. The value of NLR that best discriminated between good and poor survival, which is with the most significant *P*-value according to the log-rank test, was determined by testing all possible cutoffs.

Cox proportional hazard models were applied to explore patients' characteristics predictors of survival in univariate- and multivariable-adjusted analysis using a stepwise selection approach with type I error of 0.05 for model entry and 0.10 for elimination. Additional elimination was applied to identify significant variables at the level of $P<0.05$. All statistical analysis was done using MedCalc version 11.4.4.0 (MedCalc Software, Broekstraat 52, 9030, Mariakerke, Belgium).

The research was carried out in accordance with the approval by the ethical committee of our institution.

RESULTS

One hundred and seven patients received everolimus till April 2013 in our institutions. Of these, 97 patients (70 males and 27 females) were included in the NLR analysis, whereas 10 patients were excluded for the lack of data on pre-treatment NLR. Median age was 64 years (95% CI = 44–82). Patients' characteristics are summarised in Table 1. Median follow-up time from diagnosis was 46.9 months (95% CI = 39.9–53.9). Thirty-nine patients died during their follow-up.

Twenty-three percent of patients were at favourable risk, 67% at intermediate risk and 10% at poor risk. When stratified by previous therapy, 67% ($n=65$) of patients had received one previous VEGFR-TKI and 33% ($n=32$) of patients had received two previous VEGFR-TKIs. The distribution of sequences is reported in Table 1.

Median neutrophil count was 3620 per mm^3, median lymphocyte count was 1480 per mm^3 and median NLR was 2.2. When NLR was analysed as a dichotomous variable, a cut-point of 3 provided the strongest prognostic value in our data set, therefore, this level was chosen for further study. Patients were further divided depending on NLR into two groups. Thirty-eight patients (40%) had NLR >3 at baseline (Group A), whereas 59 had lower NLR (Group B). In Group A, 15 patients had absolute neutrophilia (defined as >7500 per mm^3 in our institutions). Baseline characteristics and therapy sequences did not significantly differ according to groups: thus in Group A, 25 patients (66%) received everolimus as second line and 13 (34%) as third line, whereas in Group B, 40 patients (68%) received everolimus as second line and 19 (32%) as third line.

Median OS from everolimus was 10.6 months (95% CI = 7.8–13.4) and median PFS was 5.3 months (95% CI = 4.4–6.2). Median OS

was 12.2 months (95% CI = 10.1–14.3) in Group A and 24.4 months (95% CI = 20.9–27.9) in Group B ($P = 0.001$; Figure 1A). Median PFS was 3.4 months (95% CI = 2.6–4.2) in Group A and 9.9 months (7.8–12.0) in Group B ($P < 0.001$; Figure 1B). The relative risk of progression within 6 months from the start of everolimus in Group A *vs* Group B was 1.61 (95% CI = 1.13 to 2.29).

Univariate analysis showed that Motzer prognostic group (HR = 1.84; 95% CI = 1.10–3.08; $P = 0.02$), neutrophilia (HR = 2.73; 95% CI = 1.50–4.95; $P = 0.001$) and NLR (HR = 2.99; 95% CI = 1.80–4.97; $P < 0.001$) were associated with PFS. At multivariate analysis, only Motzer prognostic group (HR = 1.93; 95% CI = 1.15–3.23; $P = 0.013$) and NLR (HR = 2.66; 95% CI = 1.43–4.94; $P = 0.002$) were predictors of PFS.

As for OS, univariate analysis showed that Motzer prognostic group (HR = 2.54; 95% CI = 1.36–4.76; $P = 0.004$), neutrophilia (HR = 2.08; 95% CI = 1.08–3.99; $P = 0.02$) and NLR (HR = 2.45; 95% CI = 1.40–4.30; $P = 0.002$) were associated with OS. Multivariate Cox regression analysis revealed that only Motzer prognostic group (HR = 2.96; 95% CI = 1.57–5.57; $P < 0.001$) and NLR (HR = 2.27; 95% CI = 1.16–4.30; $P = 0.003$) were independent prognostic factors (Table 2).

Table 1. Patient demographics and disease characteristics

Patients	97 (%)
Gender	
Male Female	70 (72%) 27 (28%)
Age, years	64
Range	44 – 82
Karnofsky performance status	
Score > 70 Score < 70	90 (93%) 7 (7%)
Past nephrectomy	91 (94%)
Motzer risk stratification	
Favourable risk Intermediate risk Poor risk	22 (23%) 65 (67%) 10 (10%)
Common sites of metastasis	
Lymph nodes Lung Bone Liver	43 (44%) 75 (77%) 33 (34%) 18 (19%)
Patients treated with second-line everolimus	65
Sunitinib—everolimus Sorafenib—everolimus Pazopanib—everolimus	54 (83%) 3 (5%) 8 (12%)
Patients treated with third-line everolimus	32
Sunitinib—sorafenib—everolimus Sorafenib—sunitinib—everolimus Bevacizumab + IFN-α—sunitinib—everolimus	19 (59%) 9 (28%) 4 (13%)
Median neutrophil count	3620 per mm^3
Median lymphocyte count	1480 per mm^3
Neutrophil-to-lymphocyte ratio	
Score > 3 Score < 3	38 (39%) 59 (61%)

Abbreviation: IFN = interferon.

DISCUSSION

RCC is considered to be an immunogenic tumour (Tsavaris *et al*, 1996). This evidence is based on several reports, such as the incidence of spontaneous regressions observed in a small number of these patients (De Riese *et al*, 1991) and its response rate to immunotherapy (Alexandrescu and Dasanu, 2006; Motzer and Bukowski, 2006; Yang and Childs, 2006), such as high-dose IL-2, suggesting that host immune response to RCC has a role in the disease control.

However, based on the complexity of the interaction between tumour and host immune responses, there is still a great deal of information to be discovered both on the effects of targeted agents on immune system and, otherwise, on the role of immune cells in tumour response to targeted therapies (Santoni *et al*, 2012). In 2009, Jensen *et al* (2009) observed that the presence of intratumour neutrophils is an independent prognostic factors for short recurrence-free and OS in localised clear cell RCC. In the Heng prognostic model, increased blood neutrophil count was significantly associated with poor prognosis in mRCC patients (Heng *et al*, 2009), but not unanimously in other studies (Patil *et al*, 2011). This may be partially explained by the potential parallel role of lymphocyte-mediated immune response, which has not been taken into account.

These data suggest that NLR may reflect the contribution of immune response on RCC progression and response to treatment, representing a better predictor of outcome. Moreover, the controversial association between blood neutrophil count and RCC development and progression has not considered the existence of different neutrophil subsets (Beyrau *et al*, 2012), identified through expression of specific molecular markers, and their different functional capacities, which have not been elucidated yet in RCC.

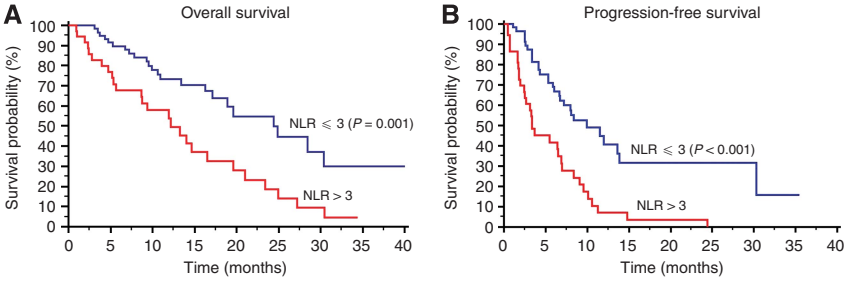

Figure 1. OS (**A**) and PFS (**B**) in patients treated with everolimus for mRCC.

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
PFS				
Gender	0.67 (0.45–1.33)	0.36		
Age	1.00 (0.98–1.02)	0.89		
Motzer prognostic group	1.84 (1.10–3.08)	0.02	1.93 (1.15–3.23)	0.013
PFS on first-line therapy	1.21 (0.69–2.12)	0.50		
Neutrophilia (Y/N)	2.73 (1.50–4.95)	0.001		
NLR >3 *vs* <3	2.99 (1.80–4.97)	<0.001	2.66 (1.43–4.94)	0.002
OS				
Gender	0.85 (0.45–1.60)	0.63		
Age	0.98 (0.95–1.00)	0.16		
Motzer prognostic group	2.54 (1.36–4.76)	0.004	2.96 (1.57–5.57)	<0.001
PFS on first-line therapy	1.08 (0.57–2.03)	0.322		
Neutrophilia (Y/N)	2.08 (1.08–3.99)	0.02		
NLR >3 *vs* <3	2.45 (1.40–4.30)	<0.001	2.27 (1.16–4.43)	0.003

Abbreviations: CI = confidence interval; HR = hazard ratio; N = no; NLR = neutrophil-to-lymphocyte ratio; OS = overall survival; PFS = progression-free survival; Y = yes.

Previous groups have examined pretreatment NLR in RCC patients. Ohno *et al* (2010, 2012) have demonstrated the prognostic role of pre- and post-treatment NLR in non-metastatic and mRCC who underwent radical nephrectomy and the association between post-operative NLR and recurrence-free survival. In 2012, Keizman *et al* (2012) has published the results of a retrospective analysis in mRCC patients treated with sunitinib as first-line therapy. In this study, low NLR $\leqslant 3$ (HR = 0.285, $P < 0.001$), past nephrectomy (HR = 0.38, $P = 0.035$), sunitinib dose reduction/treatment interruption (HR = 0.6, $P = 0.014$) and the use of angiotensin system inhibitors (HR = 0.537, $P = 0.008$) were significantly associated with PFS, whereas low NLR $\leqslant 3$ was associated with OS (HR = 0.3, $P = 0.043$). In 2013, NLR has been validated as prognostic factor in non-metastatic clear cell RCC patients (Pichler *et al*, 2013). Recently, Kobayashi *et al* (2013) revealed that changes in NLR during the early phase of targeted therapy may be a powerful discriminator of who will benefit from the subsequent treatment with molecular-targeted therapy. They observed that Th1/Th2 ratio was not associated with PFS in any targeted therapy, whereas lower pre-treatment NLR was associated with longer PFS in 58 patients treated with sorafenib, sunitinib, everolimus or temsirolimus (Kobayashi *et al*, 2013).

In our study, we first demonstrate that increased pre-treatment NLR was significantly associated with worse PFS and OS in the overall population and in the cohorts of patients treated with second- or third-line everolimus after VEGFR-TKI therapy. At multivariate analysis, neutrophilia was not an independent prognostic factor for PFS and OS, whereas the prognostic role of Motzer prognostic group and NLR were confirmed. Differently from previous studies, PFS on first-line therapy did not result an independent prognostic factor for OS (Iacovelli *et al*, 2013).

However, there are some limitations to this study. First, this is a retrospective study, which is susceptible to bias in data selection and analysis. The total number of patients analysed is relatively small and not included patients with non-clear cell RCC. Other inflammatory markers, such as procalcitonin or CRP, which has demonstrated to be an independent prognostic factor in patients with RCC (Steffens *et al*, 2012; de Martino *et al*, 2013), are not routinely measured in our institutions. Also, NLR differs among individuals and can be influenced by concurrent infection and drugs that cannot be accounted for in this study.

Despite these limitations, our study suggests that pre-treatment NLR may be associated with PFS and OS of patients treated with everolimus for mRCC and should be introduced in clinical practice. Prospective studies are needed to determine the immunogenic mechanisms underlying NLR variations and to adequately assess the potential role of NLR in guiding treatment decisions, patient selection and clinical trials design.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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