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ORIGINAL ARTICLE

Is early change in systemic inflammatory markers associated with treatment response in patients who received pazopanib?

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Summary

Purpose: *To demonstrate whether early changes in systemic inflammatory markers are related with pazopanib treatment response in soft tissue sarcoma and renal cell carcinoma.*

Methods: *Forty-one patients with metastatic clear cell renal carcinoma (mRCC) (n=22) and advanced stage soft tissue sarcoma (STS) (n=19) were assessed. Systemic inflammatory markers such as neutrophils, lymphocytes, c-reactive protein (CRP), mean platelet volume (MPV), lactate dehydrogenase (LDH) and neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) at both baseline and 1-month of pazopanib treatment were obtained and their relation with the first radiological response about 3-months later after pazopanib treatment was evaluated.*

Results: *Disease control rate (DCR) at the first initial radiological evaluation was 58.5 % for all, it was 77.3% for the RCC group and 36.8% in the STS group. Serum neutrophil, NLR and CRP levels were significantly decreased from baseline in RCC patients who had DCR with pazopanib treatment. Also, serum CRP levels after pazopanib treatment was significantly lower in RCC patients who had DCR (+) rather than those who progressed.*

Conclusions: *Early decline in serum CRP, neutrophil and NLR levels in RCC patients who received pazopanib at the first month was significantly associated with disease control, assuming a predictive role for the first radiological assessment. However, there was no significant association between change in serum inflammatory marker levels and disease control in STS patients.*

Key words: *pazopanib, metastatic renal cell carcinoma, soft tissue sarcoma, disease control, inflammatory markers*

Introduction

Pazopanib is a multitargeted oral tyrosine kinase inhibitor (TKI) targeting anti-VEGFR, stem cell factor receptor and platelet-derived growth factor receptors [1]. Effectiveness and safety of pazopanib was demonstrated in patients with advanced stage renal cell carcinoma (RCC), differentiated thyroid cancer and non-lipogenic soft tissue carcinoma [2-5]. Although its efficacy and safety were identified in different tumor types, no predictive marker was available.

Tumor microenvironment has a critical role in tumor growth and disease progression [6]. Cancer-related inflammation on disease prognosis has been confirmed by many researchers [7]. This inflammation concept consists of local and systemic inflammation associated with tumor-host and systemic inflammatory response and local immune response including tumor-stroma ratio and high or weak immune reaction or density of immune cells. On the other hand, systemic inflammation consists of acute-phase proteins, circulating cytokines and immune cells and small inflammatory proteins that have been associated with prognosis [8]. In addition, the lack of immune cell infiltrating the

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tumor characterizes the tumor as cold or non-inflammed. There is a wide spectrum of cancer types from hot tumors to cold tumors. Local and systemic inflammatory markers have also prognostic and predictive role in treatment efficacy. Angiogenesis together with immune system has complex interaction to promote tumor progression [9]. Although immunomodulatory effect of anti-VEGFR inhibitors has been demonstrated [10], the interplay between systemic inflammation and pazopanib has not been adequately revealed and its importance on treatment markers is unknown.

In this study, we aimed to demonstrate whether early changes in systemic inflammation markers are related with pazopanib treatment response and to compare its efficacy on immune markers between soft tissue sarcoma and renal cell carcinoma.

Methods

Study patients

This was a retrospective descriptive study which was approved by Trakya University ethical board. A total of 41 patients receiving pazopanib for treatment of metastatic clear cell renal carcinoma (mCRC) (n=22) and advanced stage soft tissue sarcoma (n=19) were assessed. Of them, 22 patients had pathologically proven metastatic CRCC and were treated with interferon at the first-line settings while after disease progression, pazopanib was given as second-line option. On the other hand, patients with soft tissue sarcoma were divided as 6 undifferentiated sarcomas, 5 leiomyosarcomas, 4 malignant fibrous histocytomas, 2 alveolar rhabdomyosarcomas, 1 synovial sarcoma and 1 fibrosarcoma and pazopanib was second or above line treatment option. Patients received pazopanib orally 800 mg once daily and continued until no longer clinically benefiting or until unacceptable toxicity.

Demographic and clinical characteristics were collected from patient files. Biochemical findings regarding systemic inflammatory markers such as neutrophils, lymphocytes, c-reactive protein (CRP), mean platelet volume (MPV), lactate dehydrogenase and neutrophil and lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) at both baseline and 1-month of pazopanib treatment were obtained and their relation with the first radiological response about 3-months later after pazopanib treatment was evaluated. Radiological response was classified as achieved disease control or progressed disease according to RECIST criteria. Accordingly, 24 patients had achieved disease control, 17 of them in RCC group and 7 in STS group.

Statistics

Statistical analyses were performed using SPSS software, version 22 (Chicago, IL, USA). Data were presented as mean±standard deviation or median and interquartile ranges, as appropriate. Categorical variables were reported as frequencies and group percentages. Differences in systemic inflammatory markers between patients who had disease control and those who had progressed were evaluated by Mann-Whitney U test. The Wilcoxon signed-rank test was used to compare changes in systemic inflammatory values between baseline and 3 months after pazopanib treatment. A p value <0.05 was considered as statistically significant.

Results

Study patients

A total of 41 patients who received pazopanib was analyzed. Twenty-two patients were diagnosed with RCC and 19 of them were diagnosed with STS.

Table 1. Demographic and clinical characteristics of the study subjects

Characteristics	*n (%)*
Age, years	
Median	59
Interquartile range	52-69
Gender	
Female	19 (46.3)
Male	22 (53.7)
ECOG performance score	
0	24 (58.5)
1	16 (39.0)
2	1 (2.4)
Primary disease	
Renal cell cancer	22 (53.7)
Soft tissue sarcoma	19 (46.3)
Metastatic site	
Lung	27 (65.9)
Bone	18 (43.9)
Liver	6 (14.6)
Metastasis number	
1	27 (65.9)
≥2	14 (34.1)
Histopathology	
Clear cell renal cell carcinoma	22 (53.6)
Undifferentiated sarcoma (NOS)	6 (14.6)
Leiomyosarcoma	5 (12.2)
Malignant fibrous histiocytoma	4 (9.7)
Alveolar rhabdomyosarcoma	2 (4.8)
Synovial sarcoma	1 (2.4)
Fibrosarcoma	1 (2.4)
Primary tumor site	
Extremity/Trunk/Nasal cavity	13 (68.4)
Retroperitoneal/Intra-abdominal	3 (15.8)
Uterine	3 (15.8)
Kidney	22 (53.7)

ECOG PS: Eastern Cooperative Oncology Group

Table 1 shows the clinical and demographic characteristics of the study subjects. All RCCs had clear cell histology and STS group included 6 undifferentiated sarcomas, 5 leiomyosarcomas, 4 malignant fibrous histocytomas, 2 alveolar rhabdomyosarcomas, 1 synovial sarcoma and 1 fibrosarcoma. According to NSKCC, 18 of RCC patients had intermediate risk and 4 of them had poor risk at initial diagnosis.

Change in systemic inflammatory markers after pazopanib treatment

Table 2 shows the baseline and after one-month serum inflammatory levels of the study subjects. Serum neutrophil and neutrophil-to-lymphocyte ratio values were changed significantly. In addition, these changes were also significantly observed in the RCC groups, but there were no significant changes in the STS group.

DCR at the first initial radiological evaluation was 58.5% for all, it was 77.3% for the RCC group and 36.8% in the STS group. Serum neutrophil, NLR and CRP levels were significantly decreased from baseline in RCC patients who had DCR with pazopanib treatment. Besides, serum CRP levels after pazopanib treatment was significantly lower in RCC patients who had DCR (+) rather than those who progressed. In addition, serum neutrophil and NLR levels after pazopanib treatment were significantly decreased in STS patients, but there was no significant change from baseline inflammatory marker levels during pazopanib treatment (Table 3).

Discussion

In this retrospective study, we revealed that decreased serum CRP, neutrophil and NLR levels in RCC patients who received pazopanib at the first month was significantly associated with disease control, assuming a predictive role for the first radiological assessment. However, there was no significant association between change in serum inflammatory marker levels and disease control in STS patients.

Tumor microenvironment plays critical role in tumor initiation, growth and progression. Although inflammation is not an essential part of tumorigenesis and many cancers are non-inflammed, tumor itself induces both local and systemic inflammation and may promote immune escape and is associated with treatment resistance. This tumor-related inflammation that may be presented with increased CRP, neutrophil, NLR and decreased lymphocyte levels [11] was demonstrated as prognostic marker in solid cancers [12]. On the other hand, disease progression could lead to production of these inflammatory markers. Conversely, it was demonstrated that reduced NLR in the early phase of the immunotherapy of mRCC patients were associated with improved outcome [13]. There is not enough data about decline systemic inflammation markers during treatment with tyrosine kinase inhibitors and its association between treatment efficacy or outcomes. In this matter, we revealed that decline in systemic inflammatory markers were associated with predicting pazopanib response in the first radiological assessment. One of the most common factors for pathogenesis of RCC is increased hypoxia-inducible factor due to inactivation of von Hippei-Lindau gene which leads to dysregulation of angiogenesis via increased VEGF levels and cell growth. In addition, systemic inflammation markers were also associated with inducing VEGF secretion [14] based on proangiogenic factors secretion, and anti-angiogenic drugs targeting the several receptors of these factors may play crucial role on tumor microenvironment [15], such as possible effect on distribution of immune cells, inhibiting im-

Table 2. Changes in systemic inflammatory markers after pazopanib treatment

	All			*Renal cell carcinoma*			*Soft tissue sarcoma*		
	Baseline	*After*	*p*	*Baseline*	*After*	*p*	*Baseline*	*After*	*p*
Neutrophils	4.1 (2.7-6.3)	3.7 (2.5-4.8)	0.01	4.4 (3.6-6.7)	3.8 (2.7-4.2)	0.008	3.4 (2.4-5.4)	3.6 (2.1-5.5)	0.60
Lymphocytes	1.4 (1.1-1.7)	1.3 (1.1-2.3)	0.22	1.5 (1.1-2.1)	1.5 (1.2-2.4)	0.23	1.2 (0.9-1.6)	1.2 (0.7-1.8)	0.57
N/L ratio	3.2 (1.9-5.3)	2.2 (1.5-3.3)	0.02	3.2 (1.9-4.4)	2.0 (1.6-2.7)	0.01	3.4 (2.2-7.9)	3.2 (1.4-4.3)	0.47
CRP	3.0 (1.1-6.5)	2.6 (1.3-8.3)	0.35	3.1 (2.2-6.7)	2.1 (1.0-4.6)	0.02	1.8 (0.8-4.6)	6.1 (2.5-11.7)	0.26
MPV	8.8 (8.0-9.6)	8.4 (7.8-9.5)	0.04	8.7 (8.0-10.2)	8.5 (7.8-9.7)	0.16	9.2 (8.0-9.6)	8.3 (7.8-9.4)	0.19
Albumin	3.8 (3.5-4.1)	3.8 (3.3-4.1)	0.06	4.0 (3.6-4.1)	4.0 (3.4-4.1)	0.13	3.7 (3.4-4.1)	3.7 (2.7-4.1)	0.18
LDH	251 (210-278)	294 (208-387)	0.69	243 (198-847)	296 (228-397)	0.51	254 (248-258)	220 (165-351)	0.95
OPNI	44.8 (41.2-48.7)	47.0 (40.0-50.9)	0.96	46.4 (42.2-53.3)	47.5 (46.2-53.2)	0.79	44.3 (38.3-46.7)	43.7 (33.5-49.1)	0.75
PLR	188 (125-230)	166 (100-212)	0.34	169 (114-196)	161 (92-186)	0.18	220 (185-327)	198 (100-433)	0.87

Table 3. Association between early reduced inflammatory markers and disease control rate at first radiological assessment

	Renal cell carcinoma			*Soft tissue sarcoma*		
	DCR (-)	*DCR (+)*	*P*	*DCR (-)*	*DCR (+)*	*p*
Neutrophils						
Baseline	6.7 (4.9-8.4)	4.1 (3.9-4.9)	0.26	5.4 (2.7-6.1)	2.6 (2.4-2.7)	0.05
After	4.0 (3.4-6.0)	3.3 (2.4-4.1)	0.12	5.0 (3.7-6.4)	1.5 (1.0-2.7)	0.007
p value	0.14	0.03		0.88	0.13	
Lymphocytes						
Baseline	1.6 (1.1-2.1)	1.5 (1.0-1.9)	0.73	1.1 (0.9-1.5)	1.1 (1.2-1.7)	0.80
After	1.9 (1.4-2.4)	1.3 (1.2-2.7)	0.66	1.0 (0.7-1.6)	1.3 (1.3-1.8)	0.54
p value	0.46	0.26		0.97	0.22	
N/L ratio						
Baseline	4.4 (2.2-7.2)	3.2 (1.9-4.2)	0.46	5.2 (2.9-7.9)	2.2 (1.3-3.0)	0.25
After	2.5 (2.0-2.9)	1.9 (1.4-2.6)	0.35	4.3 (3.1-4.8)	1.4 (1.1-2.6)	0.03
p value	0.14	0.03		0.85	0.22	
CRP						
Baseline	6.4 (4.4-8.2)	3.1 (2.0-6.7)	0.53	2.1 (0.9-6.2)	1.5 (0.7-2.3)	0.66
After	9.6 (6.7-9.9)	1.6 (0.5-2.4)	0.04	8.3 (3.8-15.1)	2.1 (0.1-4.1)	0.28
p value	0.10	0.002		0.24	0.65	
MPV						
Baseline	9.5 (7.1-10.5)	8.4 (8.0-9.5)	0.64	9.1 (8.7-9.5)	9.6 (8.0-9.7)	0.42
After	9.2 (7.5-10.3)	8.4 (7.8-9.4)	0.64	8.3 (7.9-9.4)	8.3 (7.8-9.4)	0.94
p value	0.97	0.11		0.77	0.07	
LDH						
Baseline	214 (164-364)	243 (200-867)	0.20	258 (256-285)	249 (247-252)	0.07
After	262 (184-347)	297 (282-427)	0.48	165 (164-240)	285 (206-479)	0.85
p value	0.71	0.44		0.50	0.46	
PLR						
Baseline	196 (151-243)	166 (107-188)	0.22	249 (211-327)	185 (102-187)	0.11
After	156 (142-189)	161 (61-186)	0.53	332 (178-450)	109 (92-173)	0.12
p value	0.71	0.23		0.59	0.05	

DCR: Disease control rate

mune escape, local inflammation and potenting the efficacy of subsequent or combination regimens of immunotherapy. Recently, combined regimen of anti-VEGF inhibitors with immunotherapies had favourable outcomes in RCC and HCC patients [16,17].

Pazopanib is a tyrosine multikinase inhibitor that limits tumor growth via angiogenesis inhibition by inhibiting VEGFR-1, VEGFR-2i, VEGFR-3, PDGFR-alpha and-beta, FGFR-1 and-3, cKIT, interleukin-2 receptor inducible T-cell kinase, lymphocyte-specific protein tyrosine kinase (Lck), and transmembrane glycoprotein receptor tyrosine kinase (c-Fms). Anti-angiogenic TKIs have immunomodulatory effect. Pazopanib does exert both anti-angiogenesis and immunomodulatory effects. Pazopanib affects neutrophil migration, immune cell metabolism and improves differentiation and performance of dentritic cells, and increases T-cell proliferation [8]. In addition, pazopanib treatment enhances a circulating CD4+ T-cell population that expresses CD137 and may convert a cold tumor to a hot one, so immunotherapy combinations are more effective [18]. A meta-analysis revealed that elevated NLR predicted poorer OS (HR=1.82, 95% CI 1.51 to 2.19) and PFS (HR=2.18, 95% CI 1.75 to 2.71) [19]. Donskov et al demonstrated that increased neutrophil value was associated with shorter survival in mRCC patients [11]. Besides, early change in systemic inflammation markers was associated with improved outcomes in mRCC patients who received immunotherapy [13]. One of the possible mechanisms of higher tumor immunogenicity leading to high cancer-related inflammation presented with elevated systemic inflammation markers. Early systemic inflammatory change after immunotherapy showed longer OS and better ORR in this population. Our study showed decline

of inflammatory markers in the early period, predicting treatment response as well.

Pazopanib is an effective option for non-adipocytic soft-tissue sarcomas after previous chemotherapy [3]. Data regarding the immunologic profiles of STS are limited [20] and generally accepted as non-inflammed tumor. Not only for mRCC but also for STS patients there is a lack of predictive markers for anti-angiogenic drugs. Mirili et al showed that lower NLR and decreased NLR after pazopanib treatment was associated with longer overall survival in univariate analysis, whereas in multivariate analysis only baseline lower NLR was shown as an independent risk factor. Besides, patients whose baseline NLR was above 3.1 had lower DCR [21]. In another study, it was revealed that STS patients who had increased baseline NLR had poor prognosis [22]. In our study, although there was no significant change in NLR in patients with STS compared to the baseline in patients with and without pazopanib disease control, the NLR ratios of patients whose disease control was achieved at the end of the 1st month were found to be lower than those who did not. As in all cancers, STS are also associated with inflammation, but inflammation is not prominent in renal cell carcinoma. Presumably, the immune modulatory effect of pazopanib on mRCC is more prominent than those in STS. While CRP values decrease after treatment in RCC patients with disease control, the fact that there is no change in STS patients might be related with tumor immunogenicity or inflammatory features.

There are some major limitations in our study. First, clinical data based on the retrospective data collection medical records of patients with STS and RCC has some disadvantages to control for bias of all potential confounding factors. Second, the study was performed on a small number of patients. In addition, systemic inflammatory marker measurements were performed twice: at baseline and at first outpatient visit after new-onset of treatment. Also, data about toxicity profile may be missing due to incomplete identification of adverse events. There were no data on the change in quality of life scores in the baseline and under treatment. Despite these limitations, it has been an outstanding strength of the study to conclude that early decline in serum CRP, neutrophil and NLR levels in RCC patients who received pazopanib at the first month was significantly associated with disease control, assuming a predictive role for the first radiological assessment. Further larger sample size studies are needed to clarify the possible association between effect of pazopanib on systemic inflammatory markers and its predictive role on treatment response in solid malignancies.

In conclusion, change in NLR, CRP and neutrophil values at first measurement during therapy are predictive of disease control at first radiological assessment in patients with mRCC. No same association between change in serum inflammatory marker levels and disease control was observed in STS patients.

Conflict of interests

The authors declare no conflict of interests.

References

1. Hutson TE, Davis ID, Machiels JP et al. Efficacy and safety of pazopanib in patients with metastatic renal cell carcinoma. J Clin Oncol 2010;28:475-80.
2. Sternberg CN, Davis ID, Mardiak J et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol 2010;28:1061-8.
3. van der Graaf WT, Blay JY, Chawla SP et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2012;379:1879-86.
4. Bible KC, Suman VJ, Molina JR, Smallridge RC et al. Efficacy of pazopanib in progressive, radioiodine-refractory, metastatic differentiated thyroid cancers: results of a phase 2 consortium study. Lancet Oncol 2010;11:962-72.
5. Köstek O, Yilmaz E, Hacıoğlu MB et al. Changes in skeletal muscle area and lean body mass during pazopanib vs sunitinib therapy for metastatic renal cancer. Cancer Chemother Pharmacol 2019;83:735-42.
6. Quail DF, Joyce JA. Microenvironmental regulation of tumor progression and metastasis. Nat Med 2013;19:1423-37.
7. Richards CH, Mohammed Z, Qayyum T, Horgan PG, McMillan DC. The prognostic value of histological tumor necrosis in solid organ malignant disease: a systematic review. Fut Oncol 2011;7:1223-35.
8. Diakos CI, Charles KA, McMillan DC, Clarke SJ. Cancer-related inflammation and treatment effectiveness. Lancet Oncol 2014;15:e493-503.
9. Santoni M, Berardi R, Amantini C et al. Role of natural and adaptive immunity in renal cell carcinoma response to VEGFR-TKIs and mTOR inhibitor. Int J Cancer 2014;134:2772-7.

10. Lin JC, Liu CL, Lee JJ et al. Sorafenib induces autophagy and suppresses activation of human macrophage. Int Immunopharmacol 2013;15:333-9.
11. Donskov F. Immunomonitoring and prognostic relevance of neutrophils in clinical trials. Semin Cancer Biol 2013;23:200-7.
12. Wang YQ, Jin C, Zheng HM et al. A novel prognostic inflammation score predicts outcomes in patients with ovarian cancer. Clin Chim Acta 2016;456:163-9.
13. Lalani AA, Xie W, Martini DJ, Steinharter JA et al. Change in neutrophil-to-lymphocyte ratio (NLR) in response to immune checkpoint blockade for metastatic renal cell carcinoma. J Immunother Cancer 2018;6:5.
14. Ishii K, Sasaki T, Iguchi K, Kajiwara S et al. Interleukin-6 induces VEGF secretion from prostate cancer cells in a manner independent of androgen receptor activation. Prostate 2018;78:849-56.
15. Amann A, Zwierzina M, Koeck S et al. Development of a 3D angiogenesis model to study tumour - endothelial cell interactions and the effects of anti-angiogenic drugs. Sci Rep 2017;7:2963.
16. Lee MS, Ryoo BY, Hsu CH et al. Atezolizumab with or without bevacizumab in unresectable hepatocellular carcinoma (GO30140): an open-label, multicentre, phase 1b study. Lancet Oncol 2020;21:808-20.
17. Choueiri TK, Motzer RJ, Rini BI et al. Updated efficacy results from the JAVELIN Renal 101 trial: first-line avelumab plus axitinib versus sunitinib in patients with advanced renal cell carcinoma. Ann Oncol 2020;31:1030-9.
18. Motzer RJ, Penkov K, Haanen J et al. Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med 2019;380:1103-15.
19. Hu K, Lou L, Ye J, Zhang S. Prognostic role of the neutrophil-lymphocyte ratio in renal cell carcinoma: a meta-analysis. BMJ Open 2015;5:e006404.
20. Pollack SM, He Q, Yearley JH et al. T-cell infiltration and clonality correlate with programmed cell death protein 1 and programmed death-ligand 1 expression in patients with soft tissue sarcomas. Cancer 2017;123:3291-304.
21. Mirili C, Paydaş S, Guney IB et al. Assessment of potential predictive value of peripheral blood inflammatory indexes in 26 cases with soft tissue sarcoma treated by pazopanib: a retrospective study. Cancer Manag Res 2019;11:3445-53.
22. Chan JY, Zhang Z, Chew W et al. Biological significance and prognostic relevance of peripheral blood neutrophil-to-lymphocyte ratio in soft tissue sarcoma. Sci Rep 2018;8:11959.