

ORIGINAL ARTICLE

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

Bulent Erdogan¹, Osman Kostek², Muhammet Bekir Hacioglu¹, Ali Gokyer¹, Ahmet Kucukarda¹, Erkan Ozcan¹, Ivo Gokmen¹, Sernaz Uzunoglu¹, Irfan Cicin¹

¹Trakya University, School of Medicine, Department of Medical Oncology, Edirne, Turkey; ²Sultan I. Murat State Hospital, Clinic of Medical Oncology, Edirne Turkey.

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

Corresponding author: Bulent Erdogan, MD. Trakya University, School of Medicine, Department of Medical Oncology, Kosasinan Mahalesi 22030, Edirne, Turkey.

Tel: +90 505 213 7335; Email: berdoga@hotmail.com

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tumor characterizes the tumor as cold or non-inflamed. 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 histiocytomas, 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 histiocytomas, 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-inflamed, 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 Hippel-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

| | <i>Renal cell carcinoma</i> | | | <i>Soft tissue sarcoma</i> | | |
|--------------------|-----------------------------|---------------|------|----------------------------|---------------|-------|
| | 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

immune escape, local inflammation and potentiating 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 dendritic 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-inflamed 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.

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