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RESEARCH ARTICLE

Assessment of Predictive Biomarker in Metastatic Renal Cell Carcinoma Treated with Pazopanib

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Abstract:

Purpose:

Metastatic renal cell carcinoma is a heterogeneous group of neoplasms with distinctive behavior. Systemic therapy is the treatment of choice in this group of patients. It is important to identify predictive factors to predict response during treatment. In this study we retrospectively evaluate the possible responsive predictors during treatment with pazopanib in metastatic renal cell carcinoma (mRCC).

Materials and Methods:

We retrospectively reviewed 32 patients between 2012 and 2020 who were diagnosed with mRCC and received treatment with pazopanib RECIST (version 1.1) was used to evaluate tumor response and imaging data were re-evaluated by radiologists. Univariate and multivariate cox regression model was used to analyze the predictive factors with clinical outcome.

Results:

Male patient was predominated (65.6%) and most of the patients had prior nephrectomy (71.9%). During treatment 32 (72%) patients experienced elevated liver enzymes and 16 (50%) had diarrhea. Overall response rate and disease control rate were 21.88% and 68.75% respectively. Hemoglobin ≤ 11 g/dl (p=0.001) and NLR ≥ 3.5 (p=0.02) were associated with poor response. Multivariate analysis show increasing age (p=0.008) and level of NLR (p=0.037) were independent factors associated with the response of treatment.

Conclusion:

Increasing age could be a positive predictor of the disease control response of patients with mRCC while leveling NLR ≥ 3.5 represented a poor outcome of treatment with pazopanib.

Keywords: Renal cell carcinoma, Pazopanib, Prognostic marker, Biomarker, Univariate, mRCC.

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1. INTRODUCTION

Renal cell carcinoma (RCC) represents approximately 2-3% of cancer in adults [1]. In Thailand, it is the 20th frequently diagnosed malignancy, accounting for approximately 2,170 new cases and 1,230 deaths in 2020 [2]. Overall incidence and mortality of RCC are 1.6:100,000 and 1.0:100,000, respectively. Worldwide, the incidence changed from 7 per 100,000 to 20 per 100,000 and is expected to increase to 32 per 100,000 in 2035 [3]. Nearly 30% of patients presented with distant metastatic RCC (mRCC) at the time of initial diagnosis. The prognosis of this group of patients was poor, with a 5-year survival rate of less than 5-10% [4, 5]. The standard treatment of mRCC is systemic therapy with or without cytoreductive nephrectomy. In the past decade, systemic treatment for mRCC had rapidly developed, transitioning the cytokine treatment into tyrosine kinase inhibitor (TKI) and immunotherapy (I/O) treatment. Sunitinib and pazopanib have been approved for the treatment of metastatic clear cell RCC [6]. Pazopanib is TKI with both anti-angiogenic and anti-tumor features. It is a standard first-line drug for mRCC and remains the first-line treatment in Thailand. The response rate of pazopanib could be achieved up to 30% [7, 8]. The emerging neoadjuvant treatment has some advantages, including decreasing and shrinkage of primary tumor feasible for nephrectomy and also associated to better outcomes in patients with Memorial Sloan-Kettering Cancer

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Center (MSKCC) intermediate risk scores [9]. The International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic score is commonly used to predict overall survival, but it did not address in response rate. The main objective of this study is to use a pre-systemic treatment biomarker to predict the positive effect of response during treatment with pazopanib in patients with mRCC.

2. MATERIALS AND METHODS

All cases in this retrospective study were treated at Songklanagarind Hospital.This study was conducted at our hospital. Patients were diagnosed with mRCC when they had pathologic confirmation of renal cell carcinoma of the primary site and later or concomitant finding of metastasis from an imaging study. Performance status and laboratory were evaluated. Patients who received pazopanib from the year 2012 to 2020 were included. The exclusion criteria from the collection of cases were patients who were under 18 years of age, patients who had incomplete preoperative data, and patients who could not be evaluated for performance status. The proposal of the study was approved by the Human Research Ethics Committee, Faculty of Medicine, Prince of Songkla University. All data were obtained by reviewing patient history, imaging studies, operative records, as well as discharge summaries. The possible factors which may be related to the response to pazopanib include age at diagnosis, gender, body mass index (BMI), and preoperative blood chemistry. Imaging data were re-evaluated by radiologists to assess the response to treatment. We used RECIST version 1.1 to evaluate tumor response. Progression of the disease means target lesions was increased ≥ 20% (longest diameter) and disease control interpreted as mean patient with complete response, partial response, and stable diseases.

The sample size from studies was 32 subjects. Statistical analysis was used R software Version 3.5.1 that demographic data are demonstrated in mean and standard deviation. Categorical variables were presented as counts and percentages. Analyzed longitudinal data was used to generalize estimating equations. Univariate and multivariate logistic regression analyses were performed to identify predictive factors of pazopanib with estimated odds ratios (OR) and 95% confidence interval (CI). A P value less than 0.05 (P<0.05) was considered statistically significant.

3. RESULTS

3.1. Patient Characteristics

Thirty-two patients were diagnosed with mRCC and received pazopanib for systemic treatment. The characteristics of patients are shown in Table **1**. Overall response rate was 21.88% and the disease control rate was 68.75%. The median age was 61.1 years and 21 patients (65.6%) were male. Most of the patients (56.2%) were classified in the intermediate of IMDC prognostic score; only one patient was classified in favorable risk of IMDC prognostic score. There were 9 patients (28.1%) who received cytoreductive nephrectomy before starting pazopanib; the rest of the patients received pazopanib after confirming with tissue diagnosis. Overall, 30 patients (93.8%) had good performance (ECOG<2). The median BMI was 23.97 kg/m^2.

Table 1. Demographics for patients undergoing treatment with pazopanib.

Baseline Characteristics	Total population (N=32)
Age, mean (SD),y	61.1 (10)
Gender Male Female	21 (65.6) 11 (34.4)
BMI (SD)	23.97 (4.40)
ECOG < 2 ≥ 2	30 (93.8) 2 (6.2)
IMDC Favorable Intermediate poor	1 (3.1) 18 (56.3) 13 (40.6)
Prior nephrectomy Yes No	23 (71.9) 9 (28.1)
Hb, mean (SD)	11.5 (2)
NLR, median (IQR)	2.6 (2,3.8)
PLR, median (IQR)	138.1 (99.7,214.4)

Abbreviation: BMI= body mass index, IMDC = International Metastatic Renal Cell Carcinoma Database Consortium, Hb = hemoglobin, NLR = neutrophil to lymphocyte ratio, PLR = platelet to lymphocyte ratio.

3.2. Pre-treatment Inflammatory-Related Blood Markers, Adverse Events Related, and Factors for Predicting Disease Control

Most of the patients had a complete blood count (CBC) more than one assessment before systemic treatment. We used the last CBC prior to pazopanib to initial analysis. Overall, baseline hemoglobin (Hb) was 11.5 g/dL. In the disease control group, patients had higher baseline Hb than the progression group. (11.9 VS 10.5, p=0.069 respectively), The neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) were 3.6 and 163.1 in the progression group, respectively. The ratio of NLR and PLR were lower in the disease control group (2.6, 123 respectively). 17 patients (77.3%) were treated with surgery before systemic treatment and 5 patients (22.7) with upfront pazopanib in the disease control group. In the progression group, six patients (60%) performed nephrectomy before TKI treatment and 4 patients (40%) received upfront pazopanib. Data is shown in Table **2**. Adverse related events are shown in Table **3**. Twenty-three (72%) had elevated liver enzymes. Half of the patients had diarrhea.

We investigated the association between the level of Hb, NLR, and PLR to predict the effect of pazopanib. On univariate analysis, we identified that Hb > 11 (p=0.01), NLR ≥ 3.5 (P=0.02) were associated with disease control after treatment with pazopanib. On multivariate analysis, age (p=0.008) and level of NLR (p=0.037) were independent factors associated with treatment response (Table **4**).

Table 2. Demonstrate baseline characteristics between disease control group and progression group.

Baseline Characteristics	Disease control (N = 22)	Progression (N =10)	P value
Age, mean (SD),y	62.9 (7.8)	57.1 (13.2)	0.133
Gender Male Female	16 (72.7%) 6 (27.3%)	5 (50%) 5 (50%)	0.252
BMI (SD)	24.7 (4)	22.3 (4.9)	0.145
ECOG < 2 ≥ 2	20 (90.9%) 2 (9.1%)	10 (100%) 0 (0)	1
IMDC Favorable Intermediate poor	1 (4.5%) 12 (54.5%) 9 (40.9%)	0 (0) 6 (60%) 4 (40%)	1
Prior nephrectomy Yes No	17 (77.3%) 5 (22.7%)	6 (60%) 4 (40%)	0.407
Hb, mean (SD)	11.9 (2)	10.5 (1.9)	0.069
NLR, median (IQR)	2.6 (1.9,3.3)	3.6 (2.2, 5.6)	0.118
PLR, median (IQR)	123 (84.5, 205.4)	163.1 (129.7,287.6)	0.161
MLR, median (IQR)	0.2 (0.2,0.3)	0.4 (0.2,0.5)	0.084

Abbreviation: BMI= body mass index, IMDC = International Metastatic Renal Cell Carcinoma Database Consortium, Hb = hemoglobin, NLR = neutrophil to lymphocyte ratio, PLR = platelet to lymphocyte ratio

Table 3. Adverse events between disease control group and progression group.

Side effect	Overall	Disease control	Progression	P value
Diarrhea Yes No	16 (50%) 16 (50%)	10 (45.5%) 12 (54.5%)	6 (60%) 4 (40%)	0.703
Fatigue Yes No	5 (15%) 27 (85%)	3 (13.6%) 19 (86.4%)	2 (20%) 8 (80%)	0.637
Hypertension Yes No	8 (25%) 24 (75%)	6 (27.3%) 16 (72.7%)	2 (20%) 8 (80%)	1
N/V Yes No	7 (22%) 25 (78%)	6 (27.3%) 16 (72.7%)	1 (10%) 9 (90%)	0.387
Hand –foot syndrome Yes No	8 (25%) 24 (75%)	6 (27.3%) 16 (72.7%)	2 (20%) 8 (80%)	1
Increased Liver enzyme Yes No	23 (72%) 9 (18%)	18 (81.8%) 4 (18.2%)	5 (50%) 5 (50%)	1

Abbreviation: N/V= nausea, vomiting

Table 4. Univariate and multivariate analysis of factors and hematologic scoring for predicting disease control.

	Univariate analysis		Multivariate analysis	
Variable	**HR (95% Cl)**	**P value**	**HR (95%Cl)**	**P value**
Age (cont.var.)	0.94 (0.86,1.02)	0.123	0.85 (0.72,0.99)	0.008
BMI (cont.var.)	1 0.86 (0.7,1.06)	0.145	1 0.82 (0.6,1.11)	0.16
Hb ≤ 11 > 11	1 0.13 (0.02,0.68)	0.011	1 0.15 (0.02,1.4)	0.076

(Table 4) contd.....

Platelet ≤ 350,000 > 350,000	1 4.00 (0.83,19.32)	0.078	-	-
NLR < 3.5 ≥ 3.5	1 6.75 (1.28,35.7)	0.02	1 13.16 (0.88,197.11)	0.037
PLR ≤ 140 >140	1 2.17 (0.47,9.95)	0.315	-	-
Prior nephrectomy Yes no	1 2.27 (0.45,11.35)	0.322		
MLR <0.317 ≥ 0.317	5.1 (1.02,25.54)	0.042		

Abbreviation: BMI= body mass index, IMDC = International Metastatic Renal Cell Carcinoma Database Consortium, Hb = hemoglobin, NLR = neutrophil to lymphocyte ratio, PLR = platelet to lymphocyte ratio

4. DISCUSSION

RCC is a lethal malignancy with a poor prognosis if presented with metastatic disease. Nearly 20-30% of patients present with metastatic renal cell carcinoma, the most common site is pulmonary metastasis, followed by bone, lymph nodes, liver, adrenals gland, and brain. Most mRCC patients had monometastatic disease and 39% had polymetastatic disease [10]. The treatment of choice is systemic treatment with or without cytoreductive nephrectomy. Currently, there are several approved with distinct target agents such as Cabozatinib, Nivolumab, Pembrolizumab, Axitinib, Lenvatinib, and Everolimus, which means we have to choose the right treatment for a specific patient. Basic laboratory data such as CBC, NLR, PLR had shown a significant role as a biomarker for predicting response to pazopanib treatment. Precisely risk stratification and biomarkers are important for making decisions and choosing treatment for patients [11].

The pathogenesis of RCC is the high expression of vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and other substances associated with neovascularization [5]. Pazopanib is an inhibitor of tyrosine kinases, including VEGF and PDGF. Several trials showed clinical benefits to pazopanib as first-line therapy for mRCC with an overall response rate of around 31% [12]. Long-term treatment with VEGF receptor inhibitors results in overexpression of collateral pathways, leading to progression of the disease [10]. The evidence of cancer-related inflammatory response has an important clue in the process of oncogenesis and tumor progression. The systemic inflammatory response leads to changing of the circulating inflammatory environment [13]. A high NLR is associated with a rise in proangiogenic factors and a reduction in systemic immune response, both of which are linked to poor outcomes and all-cause mortality [14].

In our study, NLR ≥ 3.5 and increased age are independent prognostic markers associated with response to treatment. After adjusting for age, Hb, BMI, and NLR, there was a 13.16-times difference in the odds of outcomes between those with NLR ≥ 3.5 and those with NLR < 3.5. Although the chance could not be ruled out as the best explanation for the observed findings (the 95% CI included the null value), the magnitude of the association nonetheless suggested that such association would have been significant given slightly larger sample size. Tanaka *et al*. [15] reported that change in NLR levels might be predictive for prognosis in patients who were treated with a first and second line targeted therapy. Nader Marta *et al*. [16] also reported that NLR >3.5 was an independent prognosis marker in mRCC patients. These results were similar to our study. In the adjuvant setting, the S-TRAC trial demonstrated that patients with NLR ≤ 3 had longer disease-free survival with sunitinib compared to placebo [17]. The hematologic blood markers used in this report are easier to calculate and usually obtained in a pre-treatment setting.

The combination regimen with an immune checkpoint inhibitor (ICI) was approved for first-line treatment in patients with intermediate and poor risk mRCC [18, 19]. Treatment with ICI may need more unique risk stratification due to its mechanism of action. Martini *et al*. [11] proposed a new risk scoring system for patients treated with ICI. They used body mass index (BMI), metastatic site, and monocyte-to-lymphocyte ratio (MLR) to predict survival and found that these risk scoring might be effective predictors. They also mentioned that increasing NLR, MLR, and PLR were associated with poor outcomes. However, there was no consensus on the cutoff level of NLR, PLR, or MLR. The evidence from hematologic biomarkers could be of potential benefit to predict the response of TKI treatment.

Role of cytoreductive nephrectomy (CN) in the TKI era remained controversial, but most of the recent pieces of evidence support CN combined with targeted therapy [9, 20]. The main reasons for prior nephrectomy are mainly due to abdominal discomfort and hematuria. When compared to targeted therapy alone, patient selection is critical to achieve survival benefit [12, 18, 21]. In this study, 23 patients (71.9%) went through cytoreductive nephrectomy before starting pazopanib; however, 18 patients (56.3%) were classified as intermediate IMDC risk group. Unlike result from different studies which reported that IMDC risk group affected in overall survival [22, 23], risk group in this report do not show a significant relation to prognostic factors.

Major side effects were diarrhea, fatigue, nausea, and hypertension in a previous study. Fifteen percent of patients were discontinued due to toxicity [24]. In our study, no patients discontinued medication due to toxicity. D'Aniello C *et al*. [25]

reported that adverse events of angiogenesis therapy may be associated with treatment outcomes. Hypertension, hypothyroidism, hand-foot syndrome, and fatigue were adverse related events with longer progression free survival and overall survival. There was no correlation between adverse events and the disease control cohort in our study.

There are several limitations of our study. It is a retrospective review, a single-institute experience with a small cohort. It is an eight-year retrospective research that relied on a variety of data sources.Comorbidities, such as infection, may influence circulating inflammatory cells in some patients.

CONCLUSION

Increasing age could be a positive predictor of the disease control response of patients with mRCC, while leveled NLR ≥ 3.5 represented a poor outcome of treatment with pazopanib. Biomarker predictors are future potential tools to improve the treatment of patients. There is a need to conduct a high-volume research study to predict the value of the biomarkers in mRCC. Careful selection based on basic chemistry parameters will improve response and overall survival.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Human Research Ethical Committee of the Faculty of Medicine, Prince of Songkla University (Approval number: REC. 63-231-10-3).

HUMAN AND ANIMAL RIGHTS

No animals were used for studies that are the basis of this research. All the humans used were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013 (http://ethics.iit.edu/ecodes/node/3931).

CONSENT FOR PUBLICATION

After the datasheet fill-up, data were anonymously analyzed. All patients' identities were protected in the whole process of analysis and manuscript preparation.

STANDARDS OF REPORTING

STROBE guidelines and methodologies were followed in this study.

AVAILABILITY OF DATA AND MATERIALS

The datasets generated during and/or analyzed during the current study are available from the corresponding author [W.A.] on reasonable request.

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None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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