Is Change in Hemoglobin Level a Predictive Biomarker of Tyrosine Kinase Efficacy in Metastatic Renal Cell Carcinoma? A Turkish Oncology Group Study

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Introduction

- Renal cell carcinoma (RCC) currently accounts for 2–3% of all solid tumors, and this proportion is increasing. Stage IV RCC has poor prognosis, and the 2- and 5-year overall survival (OS) rates do not exceed 20% and 10% respectively. Many different prognostic models have been designed for metastatic RCC (mRCC). However, only a few of these have been validated and assessed for their predictive accuracy.
- Among these models, the two most popular are the French Group of Immunotherapy model, which predicted the progression and survival of patients who were under cytokine-based immunotherapy, and the Memorial Sloan-Kettering Cancer Center (MSKCC) model, which stratified patients into three prognostic groups with five different variables

- The development of hypertension during mRCC treatment with TKIs or bevacizumab-based regimens has been associated with improved outcomes. However, these controversial findings were supported by retrospective analyses as well as some results of occurrence of hypothyroidism.
- In our two unpublished case reports, we observed secondary erythrocytosis during TKI treatment in patients with mRCC. These two patients had a PFS rate higher than 12 months, with perfect clinical and radiological response.

Method

- This study included a total of **308 mRCC** patients recruited from over 15 different oncology clinics. All patients were pathologically confirmed to have RCC. According to our health insurance policies, all mRCC patients were treated with interferon (IFN)-alpha as a first line of choice following either progression or intolerance because of tyrosine-based therapy applied. We usually started TKI therapy with either sunitinib or pazopanib. After progression of disease or intolerance toward TKI, axitinib or everolimus therapy was started according to physician's choice. The following data were obtained from the patient charts: age, gender, body mass index (BMI), histopathology, date of diagnosis, type of TKI, date of progression, date of last visit, response to treatment, and survival.

Study design

- The patients were categorized into “decreased Hb” and “increased Hb” groups. The latter group included patients whose Hb levels decreased in the first month after treatment and then became higher than the baseline. Patients who had a history of bleeding or erythrocyte replacement therapy during the TKI treatment were excluded fromthe study.
- The twomost commonly used TKIs as the first line of choice were sunitinib and pazopanib, the efficacies of which were compared.

Results

Table 1. Demographic and clinical characteristics of the study population.

Characteristics	Hemoglobin decreased group	Hemoglobin increased group	*p* value
Number	150 (48.7%)	158 (51.3%)	
Age (years)	59 ± 12	59 ± 11	.9
Males/females	114/36	108/50	.16
Hemoglobin (gr/dL; baseline)	12.3	11.8	.007
Hemoglobin (gr/dL; first month)	11.3	12.8	.0001
Hemoglobin (gr/dL; third month)	11.1	12.6	.0001
Creatinine (mg/dL)	1.2	1.1	.9
WBC ($mm^3 \times 1000$)	5.5	4.6	.2
PLT ($mm^3 \times 1000$)	202	190	.7
Serum iron (Fe)	65	54	.4
Ferritin	151	142	.6
Sunitinib	115	89	.11
Pazopanib	15	45	.001
Sorafenib	9	10	
Others TKI	11	14	.9
Progression-free survival (months)	6.35	11.5	<.001
Overall survival (months)	11.36	21.0	<.001

TKI: tyrosine kinase inhibitor, PLT: thrombocyte count, WBC: white blood cell count.

- In the survival analyses, the increasedHb group had significantly higher OS than the decreased Hb group (21 vs. 11.3 months; hazards ratio (HR), 0.5; 95% confidence interval (CI), 0.35–0.72; $p < .001$). Similarly, the PFS was significantly higher in the increased Hb group (11.5 vs. 6.35 months; HR, 0.5; 95% CI, 0.3–0.7; $p < .001$).

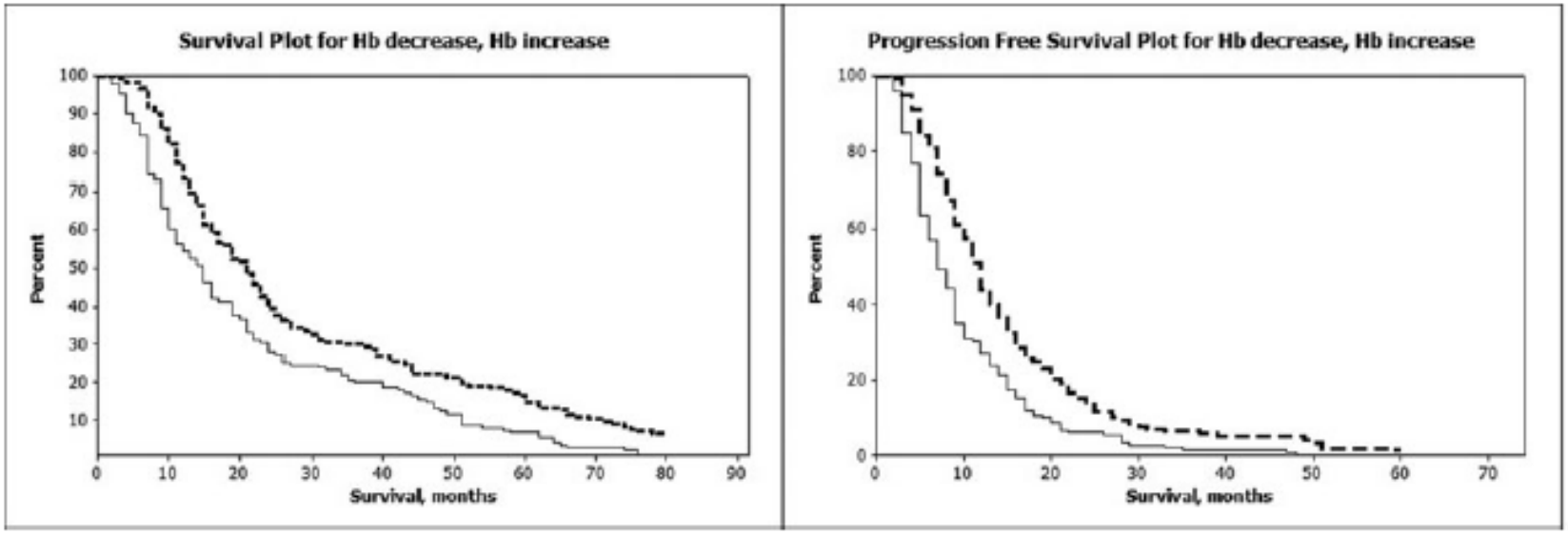

Figure 2. Left panel: Differences in OS between the groups with increased and decreased Hb (median, 21 vs. 11.3 months; $p < .001$). Right panel: Differences in PFS between the groups with increased and decreased Hb (median, 11.5 vs. 6.35 months; $p < .001$). Dashed thick black line determined Hb increased group, and thin constant black line determined Hb decreased group.

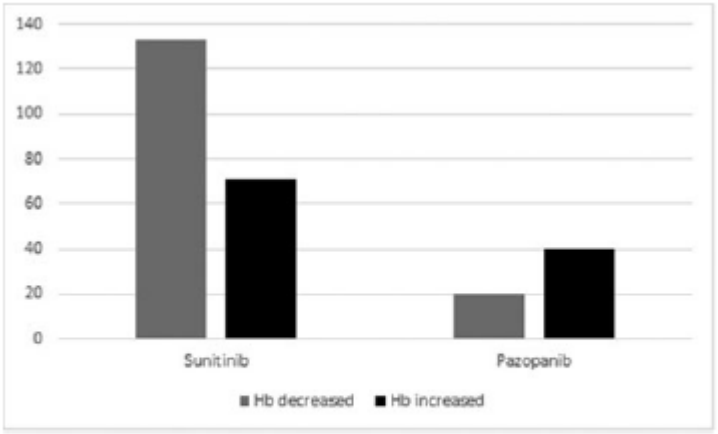

Figure 3. Hb decreased and increased patients in sunitinib and pazopanib groups.

Discussion

- The present study indicated that mRCC patients with increased Hb levels after TKI therapy achieved significantly higher survival rates, including OS and PFS, compared with the patients with decreased Hb levels. Thus, increased Hb levels after TKI treatment may be a good predictive marker in patients with mRCC, given the lack of prognostic and predictive markers at present.