ANNALES
UNIVERSITATIS MARIAE CURIE-SKŁODOWSKA
LUBLIN – POLONIA
VOL. XXIV, N 4, 11 SECTIO DDD 2011

[1] Department of Chemotherapy, St John's Cancer Center, Lublin, Poland;
[2]Department of Clinical Pathomorphology, Medical University in Lublin, Poland;
[3]St John's Cancer Center, Lublin, Poland;
[4]Occupational Hygiene and Ergonomic Department, Lublin University of Technology, Poland
[5]Radiodiagnostic Department St John's Cancer Center, Lublin, Poland

TOMASZ CISZEWSKI[1], TOMASZ KUBIATOWSKI[1],
JUSTYNA SZUMIŁO[2], ELŻBIETA STAROSŁAWSKA[1],
KRZYSZTOF J. CZARNOCKI[3,4], FRANCISZEK BURDAN[5]

May peripheral blood hemoglobin concentration be a prognostic factor among patients diagnosed with metastatic clear cell renal carcinoma treated with targeted therapies?

Czy stężenie hemoglobiny może być czynnikiem prognostycznym u pacjentów z przerzutowym jasnokomórkowym rakiem nerki poddanych terapii lekami ukierunkowanymi molekularnie?

INTRODUCTION

Metastatic renal cell carcinoma is considered to be a neoplasm of particularly bad prognosis [9]. Because clear cell histopathological subtype of this cancer is chemotherapy resistant, so during recent years the only therapeutic option in disseminated stadium of the disease was immunotherapy based on interleukin-2 or interferon-alfa [5,8]. Advances made in molecular biology area led to introduction of new agents targeting mediators and intracellular pathways influencing angiogenesis. In Poland drugs of such mechanism of action registered in the treatment of metastatic clear cell renal carcinoma include: tyrosine kinase inhibitors – sorafenib, sunitinib and pazopanib; anti-VEGF (vascular endothelial growth factor) monoclonal antibody – bavacizumab and mTOR (mammalian target of rapamycin) inhibitors – temsirolimus and ewerolimus. Third phase randomized clinical trials comparing new agents to interferon-alfa monotherapy proved superiority of antiangiogenic therapy over cytokine treatment [3,7,12]. However, despite constant progress in knowledge concerning renal cell carcinoma therapy, many of the problems are still unresolved. They especially include matters involving estimation of prognosis and prediction of response to applied systemic therapy.

One of the most common symptoms of renal cell carcinoma is anemia that may be associated with dysfunction of erythropoietin production or with bleeding caused by cancer infiltration and destruction of blood vessels [17]. On the other hand, anemia is considered to be one of the most frequent adverse events observed during application of targeted therapies. A lot of data suggest that

unfavourable effects of new molecular agents may be, to some extent, predictors of response to applied therapy and indicators of patient prognosis. Riesenbeck and colleagues [15] demonstrated that hypothyreosis occurring during sorafenib or sunitinib therapy may be an independent prognostic factor and elevated thyroid-stimulating hormone level correlates with longer progression free survival (PFS). Moreover, Bono and colleagues [2] suggest that sunitinib-induced hypertension may be a predictive marker of effective therapy.

The aim of the study is the evaluation of influence of hemoglobin level and degree of anemia observed during different stages of therapeutic process on the treatment outcome and prognosis of patients.

MATERIALS AND METHODS

The retrospective analysis covered medical files of 77 patients treated in St. John's Cancer Center in Lublin from 1.01.2004 to 31.12.2010 diagnosed with histopathologically confirmed metastatic clear cell renal carcinoma. Each patient included to the study received at least one targeted therapy line of treatment. Drugs were applied in the following way: in the first line of treatment (77 patients) – sunitinib, sorafenib, temsirolimus or interferon-alfa, in the second line of treatment (42 patients) – sorafenib, pazopanib, everolimus or sunitinib and in the third line of treatment (14 patients): everolimus, temsirolimus, pazopanib, sorafenib or sunitinib. The drugs were dosed according to the manufacturers' protocols with the possibility to reduce doses in case of intolerance or high grade adverse events connected with the therapy.

Inclusion criteria to the therapy were:

1. Histologically confirmed clear cell renal carcinoma.
2. Metastatic disease confirmed and possible to be objectively monitored by computed tomography or magnetic resonance imaging.
3. Pregnancy exclusion.
4. Adequate organ efficiency measured by basic blood tests.
5. Signed informed consent prior to beginning of the therapy.

Exclusion and discontinuation criteria were:

1. Progression of the disease – defined according to the Response Evaluation Criteria in Solid Tumours [18].
2. Treatment intolerance or unacceptable toxicity.
3. Karnofsky performance status [19] deterioration under 60%.
4. Withdrawal of consent for the treatment.

The analysis of blood morphology was performed before, during (the highest grade of anemia was noted) and after each line of treatment. The patients were divided into groups according to the hemoglobin (Hgb) blood concentration (group 0 – Hgb concentration in reference range of laboratory performing morphology; group 1 – Hgb under reference range but over or equal 10.0 g/dL; group 2 – Hgb < 10.0 g/dL – 8.0 g/dL; group 3 – Hgb < 8.0 g/dL – 6.5 g/dL; group 4 – Hgb <6.5 g/dL).

Physical examination, adverse events and blood tests analysis were performed every patient visit that was not less frequent than once on four weeks.

The evaluation of treatment effectiveness was performed on the basis of the following parameters:

1. Progression free survival (PFS) – defined as time from the beginning of the therapy to the progression of the disease or death of the patient from any cause.
2. Overall survival (OS) – defined as time from the beginning of the therapy to death of the patient from any cause.

The statistical analysis was performed on the basis of the collected medical data. The data were expressed as median, interquartile range. Associations between parameters were defined using Spearman's rank correlation coefficient (p).

The analyses were performed using Statistica 9.1 Stat Soft Inc. software.

Comparison between biochemical parameters of treated group was made using the Kruskal-Wallis test. Kaplan-Meier method with F Cox test were used to compare OS and PFS in subgroups.

RESULTS

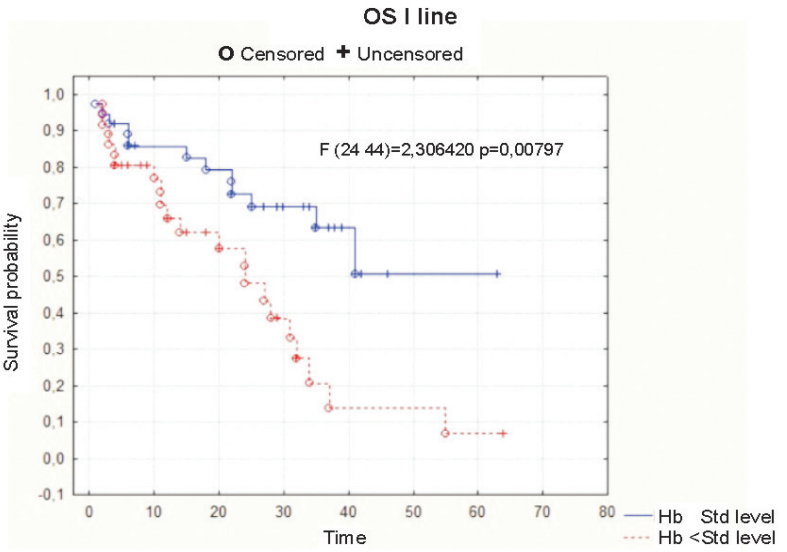

Figure 1 OS probability in 1st line of the treatment determined by the hemoglobin level before beginning of the treatment

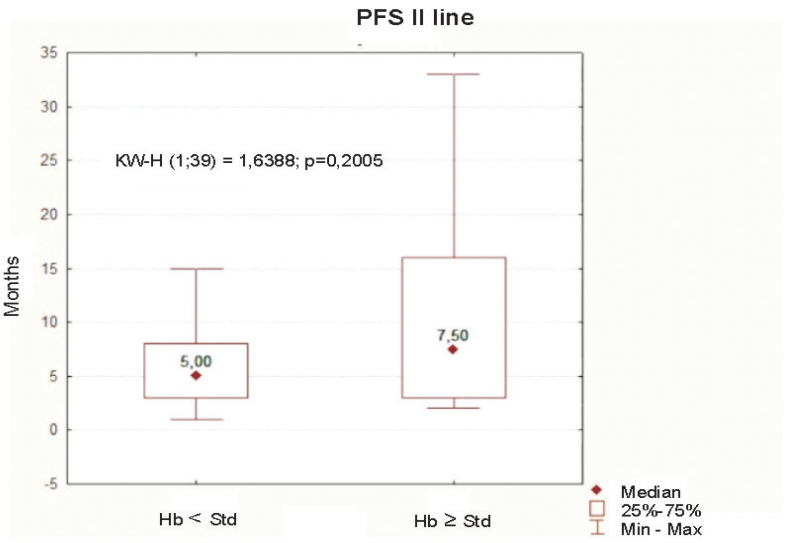

Figure 2 Comparison of PFS medians during 2nd line of treatment in patients subgroups determined by the hemoglobin level before beginning of the 2nd line treatment

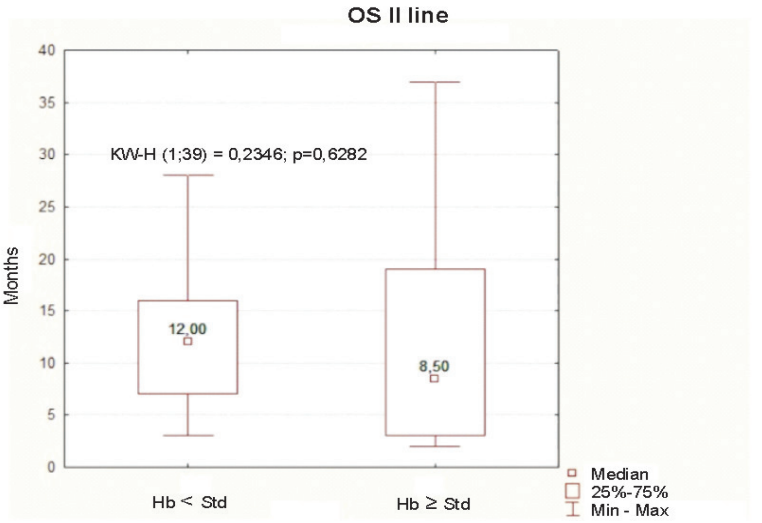

Figure 3 Comparison of OS medians in 2nd line of the treatment determined by the hemoglobin level before beginning of the 2nd line treatment

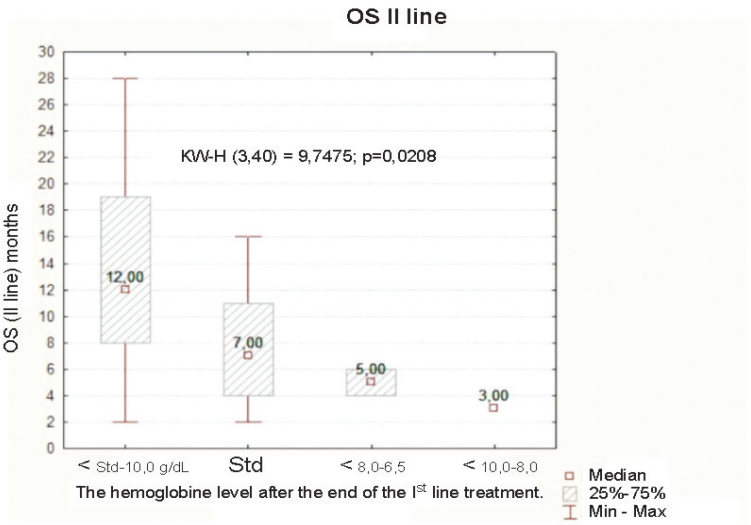

Figure 4 OS median in 2nd line of treatment determined by the peripheral blood hemoglobin concentration measured after 1st line treatment termination

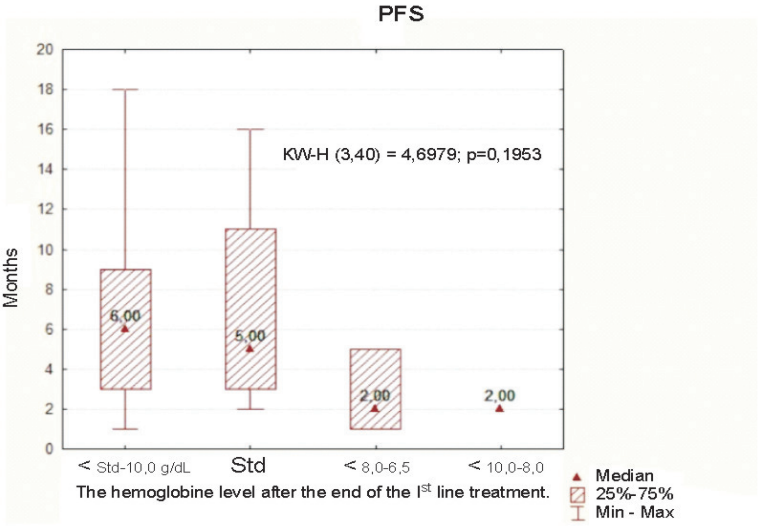

Figure 5. PFS median during 2nd line of treatment determined by the hemoglobin level measured after 1st line treatment termination

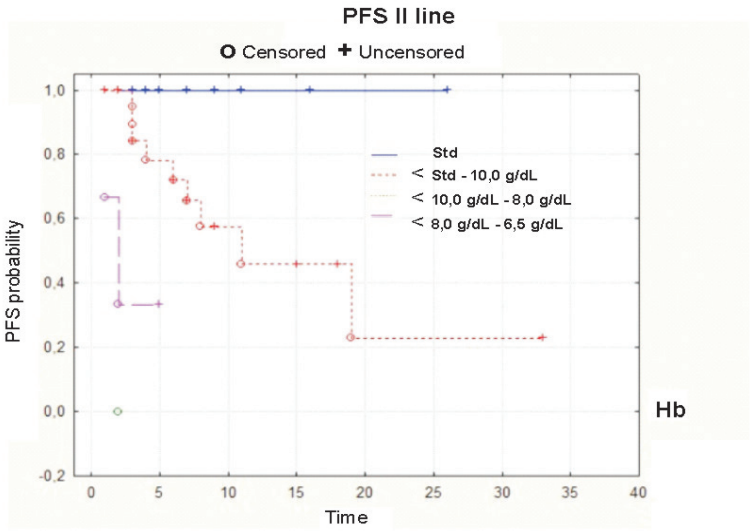

Figure 6 Comparison of PFS probability in 2nd line treatment determined by the hemoglobin level measured before beginning of 2nd line treatment

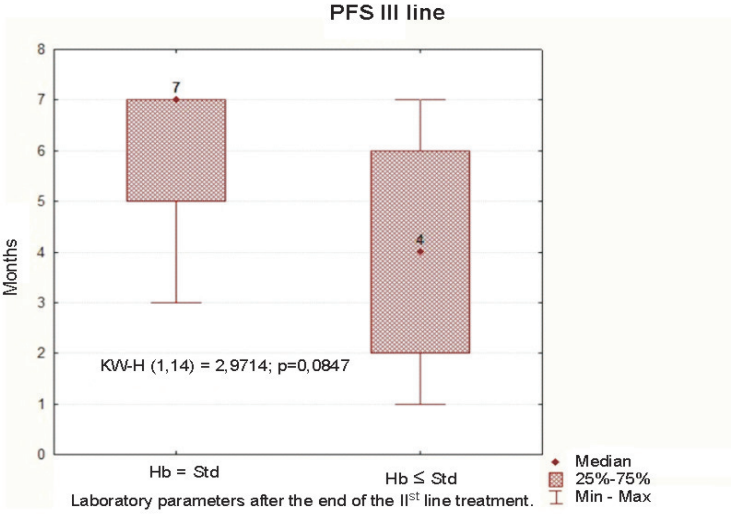

Figure 7 PFS median during 3rd line of treatment determined by the hemoglobin level measured after 2nd line treatment termination

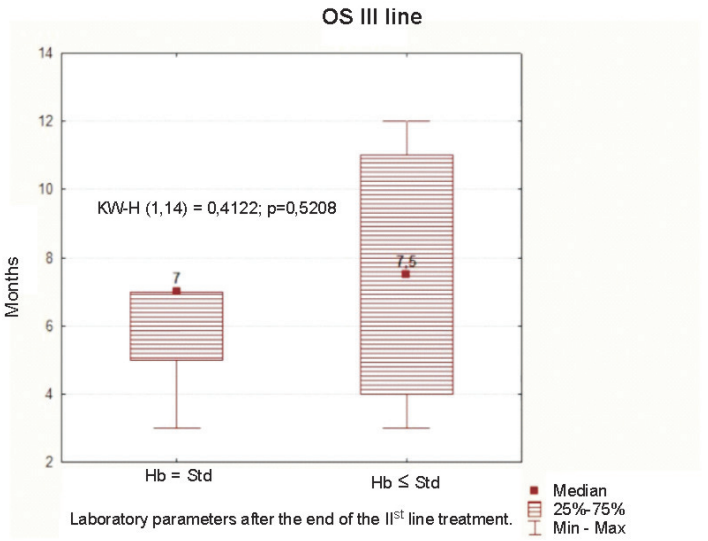

Figure 8 OS median during 3rd line of treatment determined by the hemoglobin level measured after 2nd line treatment termination

DISCUSSION OF THE RESULTS

Memorial Sloan-Kettering Cancer Center (MSKCC) scale was the tool that was most widely used to stratify metastatic renal cell carcinoma patients into three different groups of distinct prognosis in the immunotherapy era [10, 11]. After application of modifications its utility was confirmed in multicenter research evaluating its prognostic value in patients treated with targeted therapies [6]. Moreover, significant role of MSKCC classification was remarked in smaller groups of patients treated with sunitinib [1, 14]. One of the components of the mentioned scale is peripheral blood hemoglobin concentration before beginning of the systemic therapy. On the basis of performed analysis, we observed that patients with correct level of Hgb at that moment are characterized with significantly higher probability of OS comparing to those with anemia (Fig. 1). Moreover, patients with anemia detected before introducing the second line treatment had tendency to shorter PFS during second line therapy than patients with correct Hgb concentration (Fig. 2). On the other hand, median OS for the group treated with second line therapy was longer among patients with anemia (Fig. 3). However, associations that were mentioned were not statistically significant. Additionally, Hgb level after first line treatment termination seems to be an important prognostic factor for the patients treated with the second line therapy. Patients that were included to the first grade anemia group were characterized with the longest second line median OS (12 months), which was statistically significant (Fig. 4). However, this parameter is not valuable for the prediction of second line PFS (Fig. 5). Kaplan-Meier analysis revealed that hemoglobin level measured before second line treatment can be a useful marker of PFS probability during second line therapy (Fig. 6). Moreover, anemia after second line

therapy termination may be, to some extent, the factor that predicts PFS in patients who would receive third line treatment (Fig. 7). OS is however comparable in both groups of patients (Fig. 8).

Prognostic role of hemoglobin level measurement before beginning of targeted therapy was noticed by study group from University of California. The researchers noticed associations between higher hemoglobin concentration and better sunitinib, axitinib or bevacizumab treatment outcome, which seems to be consistent with our analysis [16]. Similarly, third phase clinical trial of everolimus revealed lower hemoglobin level as an independent parameter associated with shorter OS [13]. Additionally, anemia detected before nephrectomy is also proposed as a marker of shorter time to recurrence of the disease or progression as well as parameter influencing survival in renal cell carcinoma group of patients [4].

Our study confirmed anemia observed before the start of systemic treatment as one of the factors associated with shortened survival among patients with metastatic clear cell renal carcinoma treated with targeted therapies. Moreover, measurement of peripheral blood Hgb concentration after termination of the therapy may be an important parameter influencing survival in subsequent line of treatment however these findings require confirmation on wider and better characterized group of patients.

REFERENCES

1. Bamias A. et al.: Prognostic stratification of patients with advanced renal cell carcinoma treated with sunitinib: comparison with the Memorial Sloan-Kettering prognostic factors model. BMC Cancer, 10, 45, 2010
2. Bono P. et al.: Hypertension as predictor of sunitinib treatment outcome in metastatic renal cell carcinoma. Acta Oncol., 50, 569, 2011
3. Escudier B. et al.: Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. Lancet, 370, 2103, 2007
4. Fernández Gómez J.M. et al.: Significance of anemia as an independent prognostic factor in patients with renal cell carcinoma. Med. Clin. (Barc.), 133, 407, 2009
5. Fisher R.I., Rosenberg S.A., Fyfe G.: Long-term survival update for high-dose recombinant interleukin-2 in patients with renal cell carcinoma. Cancer J. Sci. Am., 6 Suppl. 1, 55, 2000
6. Heng D. et al.: Prognostic Factors for Overall Survival in Patients With Metastatic Renal Cell Carcinoma Treated With Vascular Endothelial Growth Factor–Targeted Agents: Results From a Large, Multicenter Study. J. Clin. Oncol., 27, 5794, 2009
7. Hudes G. et al.: Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N. Engl. J. Med., 356, 2271, 2007
8. Medical Research Council Renal Cancer Collaborators: Interferon-alpha and survival in metastatic renal carcinoma: early results of a randomised controlled trial. Lancet, 353, 14, 1999
9. Motzer R., Bander N.H., Nanus D.M.: Renal-cell carcinoma. N. Engl. J. Med., 335, 865, 1996
10. Motzer R. et al.: Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. J. Clin. Oncol., 17, 2530, 1999
11. Motzer R. et al.: Interferon- alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. J. Clin. Oncol., 20, 289, 2002

12. Motzer R. et al.: Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N. Engl. J. Med., 356, 115, 2007
13. Motzer R. et al.: Phase 3 Trial of Everolimus for Metastatic Renal Cell Carcinoma. Cancer, 116, 4256, 2010
14. Patil S. et al.: Prognostic factors for progression-free and overall survival with sunitinib targeted therapy and with cytokine as first-line therapy in patients with metastatic renal cell carcinoma. Ann. Oncol., 22, 295, 2011
15. Riesenbeck L.M. et al.: Hypothyroidism correlates with a better prognosis in metastatic renal cancer patients treated with sorafenib or sunitinib. World J. Urol., 29, 807, 2011
16. Rini B.I. et al.: Clinical response to therapy targeted at vascular endothelial growth factor in metastatic renal cell carcinoma: impact of patient characteristics and Von Hippel-Lindau gene status. BJU Int., 98,756, 2006
17. Sunela K.L., Kataja M.J., Kellokumpu-Lehtinen P.L.: Changes in symptoms of renal cell carcinoma over four decades. BJU Int., 106, 649, 2010
18. Therasse P. et al.: New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J. Natl. Cancer Inst., 92, 205, 2000
19. Yates J.W., Chalmer B., McKegney F.P.: Evaluation of patients with advanced cancer using the Karnofsky performance status. Cancer, 45, 2220, 1980

ABSTRACT

Molecular targeted agents that are registered for the treatment of metastatic clear cell renal carcinoma significantly improved prognosis of patients with such diagnosis. Because the treatment costs are high, the problem of predicting the response to applied therapy and objective estimation of patient prognosis seems to be very important at present. The aim of the current study was the evaluation of peripheral blood hemoglobin concentration – parameter measured on different stages of treatment, as a prognostic factor. The analysis that was performed revealed that hemoglobin level may be useful in determining prognosis among patients diagnosed with metastatic clear cell renal carcinoma. Measurements performed before beginning of targeted therapy as well as after its termination seem to have prognostic value.

Keywords: metastatic clear cell renal carcinoma, targeted therapies, anemia, prognostic factors

STRESZCZENIE

Leki ukierunkowane molekularnie zarejestrowane w leczeniu przerzutowego jasnokomórkowego raka nerki poprawiły w znacznym stopniu rokowanie pacjentów z tym rozpoznaniem. Z uwagi na wysokie koszty terapii bardzo istotne są problemy przewidywania odpowiedzi na zastosowane leczenie oraz obiektywnego określenia rokowania pacjentów. Celem niniejszej pracy była ocena przydatności stężenia hemoglobiny – parametru oznaczanego na różnych etapach leczenia, jako czynnika prognostycznego. Przeprowadzona analiza wykazała, że stężenie hemoglobiny może być przydatne w określeniu rokowania pacjentów z przerzutowym jasnokomórkowym rakiem nerki, a wartość prognostyczną mają oznaczenia wykonane zarówno przed rozpoczęciem terapii celowanej, jak również po jej zakończeniu.

Słowa kluczowe: przerzutowy jasnokomórkowy rak nerki, terapie celowane, niedokrwistość, czynniki prognostyczne