available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Kidney Cancer

Editorial by Joaquim Bellmunt and Jeffrey J. Leow on pp. 731–732 of this issue

The Impact of Low Serum Sodium on Treatment Outcome of Targeted Therapy in Metastatic Renal Cell Carcinoma: Results from the International Metastatic Renal Cell Cancer Database Consortium

Fabio A.B. Schutz[a], *Wanling Xie*[a], *Frede Donskov*[b], *Monica Sircar*[c], *David F. McDermott*[d], *Brian I. Rini*[e], *Neeraj Agarwal*[f], *Sumanta Kumar Pal*[g], *Sandy Srinivas*[h], *Christian Kollmannsberger*[i], *Scott A. North*[j], *Lori A. Wood*[k], *Ulka Vaishampayan*[l], *Min-Han Tan*[m], *Mary J. Mackenzie*[n], *Jae Lyun Lee*[o], *Sun-Young Rha*[p], *Takeshi Yuasa*[q], *Daniel Y.C. Heng*[r,†], *Toni K. Choueiri*[a,c,†,*]

[a] *Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA;* [b] *Aarhus University Hospital, Aarhus, Denmark;* [c] *Brigham & Women's Hospital, Harvard Medical School, Boston, MA, USA;* [d] *Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA;* [e] *Cleveland Clinic, Taussig Cancer Institute, Cleveland, OH, USA;* [f] *Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA;* [g] *City of Hope Comprehensive Cancer Center, Duarte, CA, USA;* [h] *Stanford Medical Center, Stanford, CA, USA;* [i] *British Columbia Cancer Agency, Vancouver, BC, Canada;* [j] *Cross Cancer Institute, Edmonton, AB, Canada;* [k] *Dalhousie University, Halifax, NS, Canada;* [l] *Karmanos Cancer Institute, Wayne State University, Detroit, MI, USA;* [m] *National Cancer Centre Singapore, Singapore;* [n] *London Regional Cancer Program, London, ON, Canada;* [o] *Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea;* [p] *Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea;* [q] *Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan;* [r] *Tom Baker Cancer Center, Calgary, AB, Canada*

Article info

Article history:
Accepted October 12, 2013
Published online ahead of print on October 26, 2013

Keywords:
Hyponatremia
Renal cell cancer
Anti-VEGF
Prognostic factors

Abstract

Background: Hyponatremia has been associated with poor survival in many solid tumors and more recently found to be of prognostic and predictive value in metastatic renal cell cancer (mRCC) patients treated with immunotherapy.
Objective: To investigate the influence of baseline hyponatremia in mRCC patients treated with targeted therapy in the International Metastatic Renal Cell Carcinoma Database Consortium.
Design, setting, and participants: Data on 1661 patients treated with first-line vascular endothelial growth factor (VEGF) or mammalian target of rapamycin (mTOR) targeted therapy for mRCC were available from 18 cancer centers to study the impact of hyponatremia (serum sodium level <135 mmol/l) on clinical outcomes.
Outcome measurements and statistical analysis: The primary objective was overall survival (OS) and secondary end points included time to treatment failure (TTF) and the disease control rate (DCR). The chi-square test was used to compare the DCR in patients with and without hyponatremia. OS and TTF were estimated with the Kaplan-Meier method and differences between groups were examined by the log-rank test. Multivariable logistic regression (for DCR) and Cox regression (for OS and TTF) were undertaken adjusted for prognostic risk factors.

† Co-senior authors.
* Corresponding author. 450 Brookline Ave., Boston, MA 02115-5415, USA. Tel. +1 617 632 5456; Fax: +1 617 632 2165.
E-mail address: toni_choueiri@dfci.harvard.edu (T.K. Choueiri).

0302-2838/$ – see back matter
http://dx.doi.org/10.1016/j.eururo.2013.10.013

Results and limitations: Median OS after treatment initiation was 18.5 mo (95% confidence interval [CI], 17.5–19.8 mo), with 552 (33.2%) of patients remaining alive on a median follow-up of 22.1 mo. Median baseline serum sodium was 138 mmol/l (range: 122–159 mmol/l), and hyponatremia was found in 14.6% of patients. On univariate analysis, hyponatremia was associated with shorter OS (7.0 vs 20.9 mo), shorter TTF (2.9 vs 7.4 mo), and lower DCR rate (54.9% vs 78.8%) ($p < 0.0001$ for all comparisons). In multivariate analysis, these effects remain significant (hazard ratios: 1.51 [95% CI, 1.26–1.80] for OS, and 1.57 [95% CI, 1.34–1.83] for TTF; odds ratio: 0.50 [95% CI, 34–0.72] for DCR; adjusted $p < 0.001$). Results were similar if sodium was analyzed as a continuous variable (adjusted $p < 0.0001$ for OS, TTF, and DCR).
Conclusions: This is the largest multi-institutional report to show that hyponatremia is independently associated with a worse outcome in mRCC patients treated with VEGF- and mTOR-targeted agents.

1. Introduction

Renal cell cancer (RCC) is the sixth most common cancer in United States [1], accounting for an estimated 64 770 new cases and 13 570 deaths in 2012. Patients can present with metastatic disease or recur after nephrectomy. Currently, patients with advanced RCC are stratified into three different risk groups based on the two prognostic models used most [2,3]. These prognostic models take into account several baseline clinical and laboratory values, and capture the natural history of metastatic RCC (mRCC).

Hyponatremia is one of the most common electrolyte disorders observed in hospitalized patients [4], and it is probably highly underestimated. According to the studied populations and the definition of hyponatremia, its reported frequency varies greatly, from <1% to >40% [5]. Hyponatremia can be caused by either dilution of the serum sodium by excess retained free water or by excessive sodium losses.

Hyponatremia has been associated with poor survival in several nonmalignant diseases, such as congestive heart failure, liver cirrhosis, and infectious diseases (pneumonia, childhood meningitis, necrotizing soft-tissue infection) [6–8]. Serum sodium has been analyzed in mRCC patients treated with cytokines [9], and hyponatremia was found to be associated with a worse outcome. Similar observations have been made in malignancies, such as advanced hepatocellular carcinoma [10], advanced gastric cancer [11], advanced small cell lung cancer [12], and localized RCC [13]. However, the role of hyponatremia in mRCC patients treated with targeted therapies is not well defined. One study including 87 mRCC patients treated with sunitinib or sorafenib showed that hyponatremia was significantly associated with cancer-specific survival [14]. Since serum sodium levels are routinely measured and, therefore, widely available most of the time, we sought to investigate the association of hyponatremia on treatment outcomes in mRCC patients treated with contemporary targeted therapies.

2. Methods

2.1. Patient population

The International Metastatic Renal Cell Cancer Database Consortium (IMDC) includes 20 academic cancer centers from Canada, the United States, Japan, South Korea, Singapore, and Denmark. As of October 10, 2012, a total of 2370 patients who had received first-line targeted therapy between 2003 and 2012 were included. For this study, 1661 patients from 18 centers had baseline serum sodium level information readily available.

All patients were diagnosed with mRCC of any pathologic subtype with no prior vascular endothelial growth factor (VEGF)-targeted therapy. Prior treatment with immunotherapy (interleukin-2 or interferon) was allowed. The majority of patients were treated with a first-line anti-VEGF agent: sunitinib, sorafenib, axitinib, bevacizumab, pazopanib, or tivozanib; and a small proportion of patients were treated with mammalian target of rapamycin (mTOR)-targeted agents: temsirolimus and everolimus.

Baseline demographic, clinical, and laboratory data, including those previously found to have prognostic value, were collected retrospectively on all patients by using uniform database templates to ensure consistent data collection [2]. Laboratory values were standardized against institutional upper limit of normal (ULN) and lower limit of normal (LLN) values when appropriate. Hyponatremia was defined as a serum sodium level <135 mmol/l, which is a widely used laboratory cut point. Outcome data on response rate, time to treatment failure (TTF), and overall survival (OS) were collected from patient charts. This study received institutional review board approval from each participating center.

2.2. Statistical analysis

The primary objective was to investigate whether baseline hyponatremia was associated with OS, and secondary end points included TTF and the disease control rate (DCR). OS was defined as time between targeted therapy initiation and the date of death, or it was censored at the date of the last follow-up visit. TTF was defined as time between treatment initiation and progression, drug cessation, death, or it was censored at the last follow-up visit. Progression was determined according to clinical criteria that made continuation of treatment impossible or radiographic criteria using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. DCR included complete response, partial response, and stable disease to targeted therapy per the RECIST criteria, which has been used as an inverse measure of refractory disease (progressive disease as best response).

Patient and tumor characteristics, and DCR were compared between patients with and without hyponatremia using the chi-square test. OS and TTF were estimated with the Kaplan-Meier method and differences between groups were examined by the log-rank test. Multivariable logistic regression (for DCR) and Cox regression (for OS and TTF) were undertaken, adjusted for the IMDC prognostic risk factors [2]. Subgroup analyses were performed according to the IMDC favorable-, intermediate-, and poor-risk groups, respectively. Serum sodium level was also analyzed as a continuous variable in both univariate and multivariable models adjusted for the IMDC prognostic risk factors.

All statistical computations were performed using SAS v.9.2 (SAS Institute Inc., Cary, NC, USA) and a p value (two-sided) <0.05 was considered statistically significant.