ORIGINAL ARTICLE

Prognostic value of serum C-reactive protein level prior to second-line treatment in intermediate risk metastatic renal cell carcinoma patients

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Abstract

Background The later-line treatment of metastatic renal cell carcinoma (mRCC) has been drastically changing by the development of immune-oncology drugs and molecular targeted treatment in recent years. Although the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) model is useful for second-line setting, this model has the problem that over 50% patients are classified as intermediate risk group. The aim of this study is to evaluate whether the serum C-reactive protein (CRP) levels prior to second-line treatment could divide intermediate risk group patients.

Methods We retrospectively reviewed 82 consequent intermediate-risk mRCC patients who received second-line molecular targeted therapy. We classified patients who had serum CRP higher than 0.5 mg/dl in elevated CRP group because the median baseline serum CRP level before second-line treatment was 0.51 mg/dl. We assessed the prognostic impact of serum CRP levels prior to second-line treatment initiation to predict overall survival (OS).

Results Thirty-three out of 82 (40%) patients demonstrated elevated baseline CRP levels. The median OS of elevated and non-elevated CRP group was 11.5 (95% CI 5.4–17.5) and 29.4 (95% CI 25.5–33.5) months, respectively ($p = 0.001$). The serum CRP elevation could predict prognosis in intermediate risk patients treated with second-line treatment (HR 2.5, 95% CI 1.4–4.2, $p = 0.001$).

Conclusions The serum CRP levels after first-line treatment termination could divide intermediate risk group mRCC patients into two prognostic subgroups in second-line targeted treatment setting.

Keywords Renal cell carcinoma · Neoplasm metastasis · C-reactive protein · Biomarkers · Prognosis

Introduction

The systemic treatment strategy for metastatic renal cell carcinoma (mRCC) has been drastically changing with the development of molecular targeted therapy (TT) in this decade. These therapies for mRCC target mainly two different pathways, the vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) pathways [1–4]. In recent years, immune-oncology (IO) drugs including programmed cell death 1 (PD-1) antibody: nivolumab and cytotoxic T-lymphocyte associated antigen 4 (CTLA-4) antibody: ipilimumab outperformed other TT drugs [5, 6]. While progress has been achieved in developing new drugs, mRCC has been rarely cured and frequently acquires resistance to the first-line treatment. Therefore, sequential treatment is inevitable for the management of mRCC and this treatment approach is recommended in several guidelines [7, 8]. Currently the choice of drugs depends on what the benefits of the next treatment are supposed to be; however, there is no consensus concerning the selection of second- and later-line agents. Therefore, prognostic indices that

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influence patient survival in those receiving second-line therapy are needed for the selection of optimal agent.

The International metastatic RCC database consortium (IMDC) criteria was reported to predict oncological outcome for mRCC in TT era [9]. Recently, the US Food and Drug Administration (FDA) has approved ipilimumab/nivolumab combination as first-line treatment for intermediate- or poor-risk mRCC patients based on the IMDC model [6]. The limitation of this model is that more than half of patients are categorized into the intermediate-risk group. In this heterogeneous intermediate-risk group with various survival outcomes, some patients show improved response to the therapy, but others demonstrate rapid progression as if they belong to poor-risk group. Therefore, new indices to predict prognosis in intermediate risk group patients have been warranted. The C-reactive protein (CRP) reflects systemic inflammation and was reported to be relevant to prognosis in many cancers [10, 11]. We recently reported CRP could stratify IMDC intermediate risk group patients in the first-line settings [12]. Although the IMDC classification model is also useful as predicting survival outcome before second-line TT [13], there exists no consensus to stratify IMDC intermediate risk group patients in the second-line settings. The objective of this study is to evaluate the prognostic value of serum CRP levels prior to second-line TT on oncological outcome in intermediate risk group mRCC patients.

Patients and methods

A total of 153 mRCC patients treated by second-line TT at our two institutions between 2008 and 2017 were reviewed. We excluded three cases because of lack of data, remaining 150 patients were categorized by the IMDC criteria after first-line TT into favorable (41 cases, 27%), intermediate (82 cases, 55%) and poor risk (27 cases, 18%) group, respectively. In this study 82 intermediate risk mRCC patients treated by second-line TT were included. This study was approved with the ethical board of Keio University Research Ethics Committee (Approval no-20130425). All procedures were performed in compliance of the 1964 Helsinki Declaration and present ethical standards. During targeted therapies, these patients were followed up by physical examination and blood test including serum CRP levels every month and at the timing when treatment is changed. Radiographic evaluation with computed tomography (CT) or/and magnetic resonance imaging (MRI) every 3–4 months. Brain CT/MRI and bone scintigraphy were performed only when clinically indicated. We evaluated the prognostic impact of serum CRP level before second-line TT administration, which was measured more than 2 weeks after first-line treatment was terminated, on overall survival (OS) from second-line TT.

Statistical analysis

Differences between elevated and non-elevated CRP groups were compared using the t test and χ^2-test for categorical indices. Survival analysis was assessed using the Kaplan–Meier methodology, and statistical comparison of survival curve was assessed by log-rank test. Multivariate analysis was performed using Cox proportional hazards regression models to determine the risk factor on survival outcome. p values less than 0.05 was judged as statistically significant. We estimated clinical value of these clinicopathological indices; age, gender, the prior nephrectomy, histological type, number of metastasis, the drug type of first-line and second-line TT, time to treatment failure (TTF) of first-line TT and IMDC prognostic factors. Statistical analysis was performed by the SPSS version 25.0 statistical software package (IBM-SPSS Inc, Tokyo, Japan).

Results

### Characteristics and outcomes of patients

The overall survival curve of 150 consequent mRCC patients, received second-line TT, categorized by IMDC prognostic model after first-line TT was shown in Fig. 1. The median OS from second-line TT initiation of whole cohort and favorable, intermediate and poor prognostic risk group was 24.6 (95% confidence interval, 95% CI 18.2–31.0), 40.5 (95% CI 25.6–55.5), 23.6 (95% CI 15.1–32.1) and 8.7 (95% CI 1.2–16.2) months in, respectively. Of these, 82 intermediate-risk cases were included in this study. Median follow-up was 13.8 months (range 0.9–103.3 months) and 55 cases deceased in follow-up period. In total, 50 (61%), 11 (13%), 10 (12%), 6 (7%), and 5 (6%) patients received sunitinib, sorafenib, axitinib, temsirolimus and pazopanib as a first-line TT, respectively. In second-line TT, 48 (59%), 20 (24%), 6 (7%), 5 (6%), 2 (2%) and 1 (1%) patients were treated by everolimus, axitinib, sunitinib, sorafenib, temsirolimus and pazopanib, respectively.

The median baseline serum CRP level before second-line TT was 0.51 mg/dl (range 0.01–20.3), and we defined 0.5 mg/dl as cutoff point in this study, i.e., patients who had serum CRP higher than 0.5 mg/dl were categorized in elevated CRP group. Statistically significant differences were found between elevated and non-elevated CRP groups in gender (male, 88% vs. 55%, $p=0.005$) and the rate of prior nephrectomy (70% vs. 92%, $p=0.017$) (Table 1).

The clinical impact of serum CRP levels before second-line therapy on prognosis in intermediate risk patients

The serum CRP elevation before second-line TT had significantly relevant with shorter OS than non-elevated CRP

Fig. 1 Kaplan–Meier analysis of the overall survival of metastatic renal cell carcinoma patients treated by second-line targeted therapy categorized by IMDC prognostic model
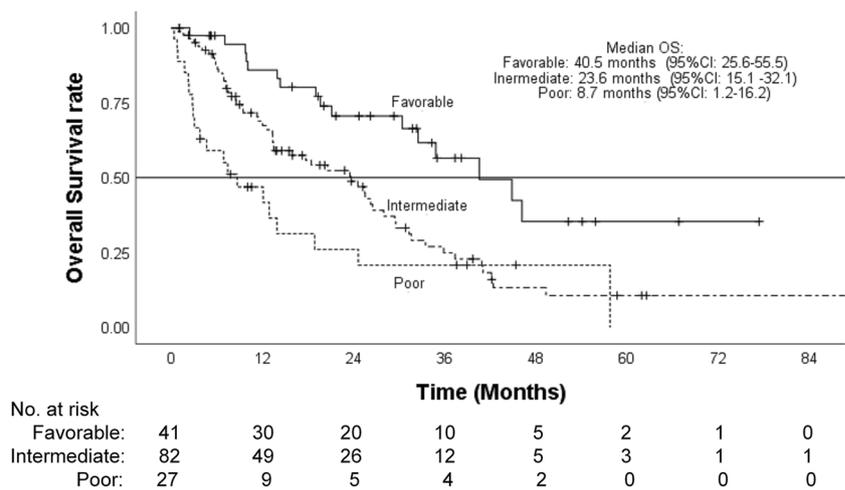
group (median OS, 11.5 vs. 29.4 months, $p = 0.001$) (Fig. 2). The median OS of intermediate risk with elevated-CRP was similar with that of poor-risk group (median OS, 11.5 vs. 8.7 months, $p = 0.926$). The median OS of intermediate risk with non-elevated CRP was shorter than that of favorable risk group but not statistically significant (median OS, 29.4 vs. 40.5 months, $p = 0.080$). We evaluated the relationship with OS of some clinical indices; age, gender, prior nephrectomy, pathology (clear cell RCC or others), number of metastasis (more than 1 organ or 1 organ), type of first-line TT (sunitinib or others), time to treatment failure (TTF) of first-line TT (more than 12 months or shorter), type of second-line TT [tyrosine kinase inhibitor (TKI) or mTOR inhibitor] and each IMDC prognostic factor.

Univariate analysis showed the elevation of serum CRP levels prior to second-line treatment was significantly associated with shorter OS ($p = 0.002$) and patients who were younger ($p = 0.087$), received nephrectomy ($p = 0.088$), had longer TTF of first-line TT ($p = 0.059$) and had hemoglobin level less than the lower limit of normal ($p = 0.097$), had tendency of association with longer OS (Table 2).

Multivariate analysis revealed the CRP elevation [hazard ratio (HR) 2.5, 95% confidence interval CI 1.4–4.2, $p = 0.001$] was the independent prognostic factor for OS in intermediate risk mRCC patients treated with second-line TT (Table 2).

Discussion

The widespread use of molecular targeted drugs has contributed to survival benefit for patients with mRCC [14]. However, sequential treatment is necessary for optimizing mRCC management because most cases eventually become resistant to first-line treatment. Currently axitinib, nivolumab, cabozantinib, and everolimus plus lenvatinib are recommended

(category 1) as second-line treatment for mRCC by the NCCN guideline [8]. But the selection of appropriate second-line drug is often difficult because direct comparison between these agents is lacking.

In this study we demonstrated that the elevation of baseline CRP levels could predict poor prognosis for intermediate-risk group patients even in the second-line setting, as we previously reported in the first line [12]. This finding was not surprising since high serum CRP level has been reported as the prognostic marker in both localized and metastatic RCC [15–20]. In previous reports, elevated CRP levels at baseline could predict poor response to TT agents as well as shorter survival [18, 20–22]. CRP is the well-known acute inflammation marker, which is produced in liver induced by inflammatory cytokines, such as interleukin (IL)-6. One possible explanation for the relationship between elevated CRP and poor response to TT would be that the elevation of CRP could reflect tumor aggressiveness. Another possible explanation might be the involvement of IL-6 in the angiogenesis cascade.

Our model can stratify heterogeneous intermediate risk group patients into two subgroups and can modify the classical IMDC model, namely elevated CRP (median OS: 11.5 months) is similar to poor risk group (median OS: 8.7 months), and non-elevated CRP (median OS: 29.4 months) may rank between favorable (median OS: 40.5 months) and poor risk group. Finally, our CRP-based model could re-categorize our whole cohort into favorable (27%), intermediate-CRP non-elevation (33%), and poor plus intermediate-CRP elevation (40%) at the initiation of second line treatment. Based on the stratification results, one can speculate tumor aggressiveness because our model could identify patients with shorter OS. Previous study results would be useful for physicians in choosing optimal second-line agents, even if they are not strictly applicable. For example, the Checkmate 025 phase 3 trial

Table 1 Patient characteristics

| | Intermediate risk group n = 82 | | | |
| | Elevated CRP, n = 33 | | Non-elevated CRP, n = 49 | | p value |
	n	%	n	%	
Age, years, median (range)	64.3	32.3–89.2	69.9	22.5–83.8	0.082[a]
Gender, male	29	88	27	55	0.005
Prior nephrectomy, yes	23	70	45	92	0.017
Prior immunotherapy, yes	5	15	9	18	0.439
Histology					0.238
Clear	24	73	41	84	
Others	9	27	8	16	
No. of metastasis				0	0.229
1	13	39	24	49	
≥ 2	20	61	25	51	
Type of first-line targeted therapy					0.815[b]
Sunitinib	19	58	31	63	
Sorafenib	7	21	4	8	
Axitinib	1	3	9	18	
Temsirolimus	3	9	3	6	
Pazopanib	3	9	2	4	
TTF of first-line targeted therapy, ≥ 12 months	9	27	15	31	0.625
Type of second-line targeted therapy					0.332[c]
Everolimus	17	52	31	63	
Axitinib	8	24	12	24	
Sunitinib	3	9	3	6	
Sorafenib	3	9	2	4	
Temsirolimus	2	6	0	0	
Pazopanib	0	0	1	2	
IMDC prognostic factors					
Karnofsky performance status, < 80	0	0	1	2	0.598
Time from diagnosis to treatment, < 1 year	18	55	18	37	0.206
Hemoglobin, < LLN	26	79	39	80	0.571
Corrected calcium, > ULN	4	12	2	4	0.214
Neutrophils, > ULN	4	12	6	12	0.633
Platelets, > ULN	0	0	2	4	0.513

TTF time to treatment failure, *CRP* C-reactive protein, *LLN* the lower limit of normal, *ULN* the upper limit of normal, *mTOR* mammalian target of rapamycin

[a] Student's *t* test

[b] Sunitinib vs. others

[c] Tyrosine kinase inhibitor vs. mTOR inhibitor

subgroup analysis revealed that patients in poor risk group who received nivolumab had greater survival benefit rather than everolimus [21]. The Checkmate 214 phase 3 trial subgroup analysis revealed that patients in favorable risk group who received sunitinib demonstrated prolonged survival compared with ipilimumab plus nivolumab in the first-line setting. Patients in poor-risk group showed poorer survival in axitinib settings [22]. Of course, further study is needed to confirm the optimal treatment strategy in the CRP-based stratification.

This study has several limitations. The retrospective design, small population size, only two institutional studies and the lack of central pathology review were famous biases. Nevertheless, this study revealed serum CRP levels, which are easily reproducible and less-costly testable indicator and was the predictor of prognosis for intermediate-risk group mRCC patients in second-line setting. Our findings might be helpful to physician for treatment decision.

Fig. 2 Kaplan–Meier analysis of the overall survival of intermediate risk metastatic renal cell carcinoma patients treated by second-line targeted therapy categorized by serum CRP levels prior to second-line targeted treatment
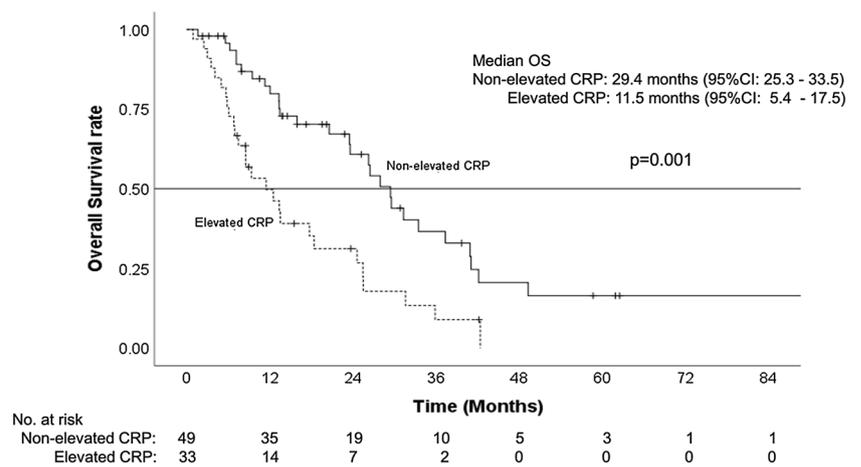

Table 2 Univariate and multivariate cox regression analyses for overall survival in intermediate risk mRCC patients

Overall survival from second-line TT	Univariate analysis	Multivariate analysis		
Predictive factor	p	HR	95% CI	p
Age	0.087		Removed	0.410
Gender (male vs. female)	0.245			
Prior nephrectomy (no vs. yes)	0.088		Removed	0.626
Pathology (others vs. clear cell RCC)	0.138			
Number of metastatic sites (≥ 2 vs. 1)	0.358			
Type of first-line targeted therapy (others vs. sunitinib)	0.990			
TTF of first-line targeted therapy (> 12 vs. ≤ 12 months)	0.059		Removed	0.065
Type of second-line targeted therapy (mTOR-I vs. TKI)	0.507			
Karnofsky performance status (< 80 vs. ≥ 80)	0.687			
Time from diagnosis to treatment (< 1 year vs. ≥ 1 year)	0.215			
Hemoglobin ($<$ LLN vs. $\geq$ LLN)	0.097		Removed	0.093
Corrected calcium ($>$ ULN vs. $\leq$ ULN)	0.872			
Neutrophils ($>$ ULN vs. $\leq$ ULN)	0.900			
Platelets ($>$ ULN vs. $\leq$ ULN)	0.283			
Presecond-line CRP (> 0.5 vs. ≤ 0.5 mg/dl)	0.001	2.5	1.4 4.2	0.001

TT targeted therapy, *Suni* sunitinib, *TTF* time to treatment failure, *mTOR-I* mammalian target of rapamycin inhibitor, *LLN* the lower limit of normal, *ULN* the upper limit of normal, *TKI* tyrosine kinase inhibitor, *CRP* C-reactive protein, *HR* hazard ratio, *CI* confidence interval

In conclusion, baseline serum CRP levels could divide intermediate risk group mRCC patients into two prognostic subgroups in second-line settings.

Compliance with ethical standards

Conflict of interest Ryuichi Mizuno MD has received honoraria from Bristol, Novartis, and Pfizer. Mototsugu Oya MD has received honoraria from Bayer, Bristol, Novartis, and Pfizer. Other authors declare that they have no conflict of interest.

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