Cancer Treatment and Research Communications 19 (2019) 100127

Contents lists available at ScienceDirect

Cancer Treatment and Research Communications

journal homepage: www.elsevier.com/locate/ctarc

Elevated plasma interleukin 6 predicts poor response in patients treated with sunitinib for metastatic clear cell renal cell carcinoma

Martin Pilskog[a,b], Gry Hilde Nilsen[d], Christian Beisland[c,d], Oddbjørn Straume[a,b,*]

[a] Centre for Cancer Biomarkers, University of Bergen, Norway
[b] Department of Oncology, Haukeland University Hospital, Bergen, Norway
[c] Department of Urology, Haukeland University Hospital, Bergen, Norway
[d] Department of Clinical Medicine, University of Bergen, Norway

ARTICLE INFO

Keywords:
Biomarker
Inflammation
ELISA
Kidney cancer
Treatment
Targeted therapy

ABSTRACT

Introduction: Clear cell renal cell carcinoma (ccRCC) is the most common type among renal cell carcinomas, and anti-angiogenic treatment is currently first line therapy in metastatic ccRCC (mccRCC). Response rates and duration of response show considerable variation, and adverse events have major influence on patient's quality of life. The need for predictive biomarkers to select those patients most likely to respond to receptor tyrosine kinase inhibitors (rTKI) upfront is urgent. We investigated the predictive value of plasma interleukin-6 (pIL6), interleukin-6 receptor α (pIL6Rα) and interleukin 6 signal transducer (pIL6ST) in mccRCC patients treated with sunitinib.

Material and methods: Forty-six patients with metastatic or non-resectable ccRCC treated with sunitinib were included. Full blood samples were collected at baseline before start of sunitinib and after every second cycle of treatment during the study time. pIL6, pIL6R and pIL6ST at baseline and week 12 samples were analysed by ELISA. The predictive potential of the candidate markers was assessed by correlation with response rates (RECIST). In addition, progression free survival (PFS) and overall survival (OS) were analysed.

Results: Low pIL6 at baseline was significantly associated with improved response to sunitinib (Fisher's exact test, $p < 0.01$). Furthermore, low pIL6 at baseline was significantly associated with improved PFS (log rank, $p = 0.04$). In addition, patients with a decrease in concentration of pIL6R between baseline and week 12 showed significantly improved PFS (log rank, $p = 0.04$) and patients with high pIL6ST at baseline showed significantly improved OS (log rank, $p = 0.03$).

Conclusion: Low pIL6 at baseline in mccRCC patients treated with sunitinib predicts improved treatment response, and might represent a candidate predictive marker.

Introduction

Renal cell carcinoma (RCC) is the 7th most common cancer type among men and 10th most common among women worldwide [1]. 70–85% of RCC are clear cell RCC (ccRCC). After anti-angiogenic receptor tyrosine kinase inhibitors (rTKIs) showed superior efficacy over interferon and interleukin-2 therapy, currently rTKIs are first line treatment option for ccRCC [2]. Due to the diversity of treatment response and toxicity among patients, the research community investigates potential predictive markers of response to antiangiogenic treatment.

Vascular endothelial growth factor (VEGF) is the most important mediator of tumour-associated angiogenesis in renal cell carcinoma [2]. In addition, some reports suggest a role of systemic inflammation in development and progression of RCC [3–5]. Along with a stimulating effect on tumour associated angiogenesis, VEGF also plays an important role in the local immune response during wound healing as well as in tumours by inducing accumulation of immature dendritic cells, myeloid-derived suppressor cells, regulatory T cells, and VEGF inhibits the migration of T lymphocytes to the tumour [6].

Inflammation is one of the hallmarks of cancer, involved in development and maintenance of cancer [7]. In a recent study, we found a significant correlation between low serum C-reactive protein (CRP) and objective response (OR) in mccRCC patients treated with sunitinib [8]. CRP is regarded a relevant biomarker for systemic inflammation [9]. Interleukin-6 (IL6) has a role in inflammation, infection responses and the regulation of metabolic, regenerative and neural processes [10–13]. Tissue and serum levels of IL6 are elevated in RCC and secreted when

* Corresponding author.
E-mail address: Oddbjorn.straume@helse-bergen.no (O. Straume).

https://doi.org/10.1016/j.ctarc.2019.100127

cells are exposed to hypoxia. Enhanced level of IL6 results in RCC cell invasion [10,14]. IL6 is also shown to be closely related to hypoxia-inducible factor 1- α (HIF-1α) as well as increased VEGF activity [15]. The prognostic information of IL6 and IL6-receptor (IL6R) is well known [10,16]. A predictive value of IL6 levels has also been reported for response to immune checkpoint inhibitors [17]. IL6 signals in cells via classic (membrane-bound) and trans-signalling (soluble) pathways [18,19]. The interleukin 6 receptor α (IL6Rα) binds to the interleukin 6 signal transducer (IL6ST), also known as glycoprotein 130 (gp130) protein receptor to transduce the signal. In a recent study, we identified ccRCC tumour cell expression of IL6Rα as a predictive marker of response to sunitinib treatment [20]. The membrane-bound IL6Rα is found on hepatocytes and different leukocytes [21]. In trans-signalling, soluble IL6 binds to soluble IL6R and the complex binds to cells expressing IL6ST [22]. Soluble IL6ST is also detected in the blood and has been shown as an inhibitor of IL6 trans-signalling [23].

In the present work, we investigated the predictive and prognostic value of plasma levels of IL6, IL6R and IL6ST in mccRCC treated with sunitinib.

Material and methods

Patients and treatment

Between 2007 and 2015, forty-six patients with radiologically confirmed progressive mccRCC were enrolled in an open-label, single-arm phase II study at Haukeland University Hospital, Norway. Treatment was given as sunitinib 50 mg/day on schedule four weeks on/ two weeks off until disease progression, significant toxicity or consent withdrawal. The study has previously been reported elsewhere [8,24]. In summary, we observed 1 complete response (CR), 7 partial responses (PR) and 18 patients with stable disease (SD) ≥ 6 months. Twelve patients showed progressive disease (PD). Eight patients stopped treatment before week 12 and were recorded as non-evaluable for response rates and PFS. In response analyses objective response (OR) is CR and PR together versus SD and PD and clinical benefit (CB) is CR, PR and SD together versus PD. Clinical information is provided in Table 1.

Ethics

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonization of Good Clinical Practice. The protocol was approved by the Regional Ethics Committee (REK number 080/07 and REK number 78/05) and the Norwegian Medicines Agency. All participating patients provided signed informed consent before enrolment.

Table 1
Baseline patients characteristics.

	Study cohort (n = 46)
Sex - no. (%)	
Male	29 (63.0)
Female	17 (37.0)
Age, years	
Median	63.1
Range	41.1–84.0
IMDC[a] risk score – No. (%)	
Good	7 (15.2)
Intermediate	16 (34.8)
Poor	21 (45.7)
Missing	2 (4.3)
WHO[b] performance status - No. (%)	
0	30 (65.2)
1	16 (34.8)
Number of disease sites - No. (%)	
1	10 (21.7)
2	11 (23.9)
≥3	25 (54.3)

[a] International Metastatic Renal Cell Carcinoma Database Consortium.
[b] World Health Organization.

Blood samples

Full blood samples were collected at baseline before start of sunitinib and after every second cycle of treatment during the study time. After centrifugation, Na-heparin plasma samples were stored frozen at −80 °C. For ELISA we used the heparin plasma sample tubes, which was de-frozen in room temperature, shaken and then centrifuged for different amount of fibrin precipitation.

Enzyme-linked immunosorbent assay (ELISA)

The antibodies used were human IL6 (P05231), human IL6R (BMS214) and human IL6ST (EHIL6ST). Invitrogen, Thermo Fisher Scientific, Waltham, MA, USA provided all three. For IL6 we used a ready-to-use self-coating system kit (Invitrogen) and an ELISA 96-well flat-bottom plate (Nune MaxiSorp flat-bottom (catalog number 44–2404), Invitrogen). For IL6R we used a ready-to-use sandwich ELISA 96 micro well plate coated kit with human IL6R (Invitrogen). For IL6ST we used a ready-to-use self-coating system kit (Invitrogen). Phosphate buffered saline (PBS); containing 0.05% (v/v) Tween 20 (PBS-T) (Prod.nr. 822,184, Merck, USA) was used as washing buffer. All other buffers used were from the respective ELISA kit. The staining process was performed according to the manufactures manual and was analysed at 450 nm with a microplate reader (Molecular Devices Emax).

Evaluation of ELISA results

We evaluated the ELISA results in according to the manufactures manual. SoftMax Pro was used to evaluate the ELISA data and then transferred to SPSS for statistical analysis. We categorized the baseline ELISA variables (pIL6, pIL6R, pIL6ST), into low (below median) versus high (above median). The change in pIL6, pIL6R and pIL6ST concentration between baseline and week 12 were divided into three categories (decrease, stable, increase). We tested the decrease group versus the stable and increase groups. The variables referred in the paper are baseline values if not otherwise specified.

Tumour tissue samples and data

Immunohistochemically tumour tissue expression of interleukin-6 receptor α (IL6Rα), interleukin-6 (IL6), jagged1 (JAG1), vascular endothelial growth factor A (VEGF-A), vascular endothelial growth factor 2 (VEGFR2), platelet-derived growth factor receptor β (PDGFRβ) and heat shock protein 27 (HSP27) are previously published [24].

Statistical analyses

Comparisons between categorical variables were performed by using the Fisher's exact test and Pearson chi-square. The Mann–Whitney U test was used to compare the distribution of continuous variables between two groups such as responders and non-responders. Logistic regression analysis was used to test the relative importance of predictive factors for sunitinib response. Sample size calculations (alpha 0.05/ power 80%) indicated that 20 patients per group based on candidate marker expression were needed to detect a difference between 10% and 50% of patients having a response to treatment with sunitinib. Kaplan–Meier estimates were constructed for time-to-event endpoints such as PFS and OS, and log rank-test was applied for testing of differences between groups. All p-values are two-sided. Statistical investigations were done using IBM SPSS Statistics version 24.

Table 2
Plasma biomarkers in relation to response.

Variable	Best overall tumor response (RECIST ver. 1.1)		
	CB[a]	PD[b]	*p* value[c]
	n(%)	*n*(%)	
pIL6[d] baseline			**<0.01**
Low	17(94)	1(6)	
High	8(42)	11(58)	
pIL6R[e] baseline			0.73
Low	15(71)	6(29)	
High	11(65)	6(35)	
pIL6ST[f] baseline			0.48
Low	10(63)	6(38)	
High	16(76)	5(24)	
Change in pIL6 between baseline and week 12			0.54
Decrease	5(71)	28(29)	
Stable	9(90)	1(10)	
Increase	5(71)	2(29)	
Change in pIL6R between baseline and week 12			0.53
Decrease	8(89)	1(11)	
Stable	7(78)	2(22)	
Increase	6(67)	3(33)	
Change in pIL6ST between baseline and week 12			0.26
Decrease	6(86)	1(14)	
Stable	9(75)	3(25)	
Increase	2(40)	3(60)	
	CB	PD	*p* value[g]
pIL6 baseline			**<0.01**
Mean value	6.13	14.82	
pIL6R baseline			0.59
Mean value	189.30	183.47	
pIL6ST baseline			0.21
Mean value	179.43	158.63	

[a] Clinical benefit (Complete + Partial response + Stable disease).
[b] Progressive disease.
[c] Fisher's exact test.
[d] Plasma Interleukin 6.
[e] Plasma Interleukin 6 receptor.
[f] Plasma Interleukin 6 signal transducer.
[g] Mann-Withney U test.

Results

pIL6

Forty-five of 46 (98%) cases had heparin plasma available for quantification of pIL6 at baseline. Median value was 6.90 pg/ml (range 0.9–36.5 pg/ml). Twenty-six of 46 (56%) cases had heparin plasma available for quantification of pIL6 at week 12. Median value was 8.90 pg/ml (range 1.0–18.8 pg/ml). Low baseline pIL6 was significantly associated with clinical benefit (CB) (Fisher's exact test, $p = <0.01$) (Table 2). Similarly, the continuous values of pIL6 was significantly associated with CB (Mann–Whitney *U* test, $p = <0.01$) (Table 2). Logistic regression analysis was used to test the relative importance of the following candidate predictive factors for clinical benefit to sunitinib; International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk groups, baseline CRP, baseline European Organization for Research and Treatment of Cancer Quality of Life (EORTC QoL) symptom scale and pIL6. Of these, pIL6 was the only significant predictive factor for CB in the final model, with an odds ratio of 23.4 ($p = <0.01$). Low pIL6 was significantly associated with improved PFS (median 14.7 months vs 5.3 months, log rank, $p = 0.04$) (Table 3). Low pIL6 was not significantly associated with OS (Tables 2 and 3).

Low pIL6 was significantly associated with normal CRP (Pearson chi-square, $p = 0.05$), but not with tumour tissue expression of IL6 or IL6Rα (Supplementary Table 1).

pIL6R

Forty-six of 46 (100.0%) cases had significant heparin plasma for quantification of pIL6R at baseline. Median value was 190.40 ng/ml (range 115.0–288.9 ng/ml). Twenty-eight of 46 (60.9%) cases had significant heparin plasma for quantification of pIL6R at week 12. Median value was 164.13 ng/ml (range 94.7–248.4 ng/ml). pIL6R was not significantly associated with CB (Table 2). Low pIL6R tended to be associated with improved OS (median 26.3 months vs 13.7 months, log rank, $p = 0.06$) and not with PFS (Table 3).

Low pIL6R at baseline was significantly associated with age under median (Pearson chi-square, $p = 0.04$)). pIL6R was not significantly associated with s-CRP or tumour tissue expression of IL6 or IL6Rα (Supplementary Table 2).

pIL6ST

Forty-five of 46 (98.0%) cases had significant heparin plasma for quantification of pIL6ST at baseline. Median value was 170.94 ng/ml (range 102.2–260.84 ng/ml). Twenty-nine of 46 (63.0%) cases had significant heparin plasma for quantification of pIL6ST at week 12. Median value was 161.84 ng/ml (range 120.58–291.84 ng/ml). pIL6ST was not significantly associated with CB (Table 2). High pIL6ST was significantly associated with improved OS (median 25.2 months vs 12.7 months, log rank, $p = 0.04$) and tended to be associated with improved PFS (median 12.9 months vs 8.4 months, log rank, $p = 0.06$) (Table 3). pIL6ST was not significantly associated with s-CRP or tumour tissue expression of IL6 or IL6Rα (Supplementary Table 3).

Change in candidate biomarkers between baseline and week 12

Twenty-five of 46 (54.3%) cases had significant heparin plasma for quantification of pIL6 from baseline and week 12. Median value of the change in pIL6 between baseline and week 12 was 1.99 pg/ml (range: −13.4 to +11.9 pg/ml). The change in pIL6 was not significantly associated with PFS or OS (Table 3).

Twenty-eight of 46 (60.9%) cases had significant heparin plasma for quantification of change in pIL6R between baseline and week 12. Median value of the change in pIL6R between baseline and week 12 was −24.63 ng/ml (range −63.8 to 17.5 ng/ml). The cases with decrease had significantly better PFS than cases with stable or increased change of pIL6R between baseline and week 12 (median missing vs 8.7 months, log rank, $p = 0.04$). We found no association with OS (Table 3).

Twenty-nine of 46 (63.0%) cases had significant heparin plasma for quantification of change in pIL6ST between baseline and week 12. Median value of the change in pIL6ST between baseline and week 12 was −2.40 ng/ml (range −108.68 to 137.87 ng/ml). We found no association with PFS or OS (Table 3).

Discussion

Recently, an inverse response relationship was reported for VEGF inhibitor (VEGFi) treatment and immune checkpoint inhibitor treatment according to IMDC risk groups [25], and new predictive biomarkers are needed to further optimize treatment for individual patients. The ongoing search for biomarkers to optimize VEGFi treatment in renal cell carcinomas has so far been unsuccessful in finding predictive biomarkers useful for clinical practice. In a previous paper, we presented results suggesting a predictive role of CRP [8]. This might indicate that the immunomodulating effect of anti VEGF therapy plays an important role in treatment response in addition to the effect on angiogenesis. In the follow-up investigation, we found that low tumour cell expression of IL6Rα was significantly associated with improved objective response to sunitinib and low tumour cell expression of IL6 was significantly associated with PFS and OS [24]. In our present work, we investigated the plasma level of baseline IL6, IL6R and IL6ST in the

Table 3
Survival analyses according to pIL6, pIL6R and pIL6ST.

Variable	PFS[a] Median	95% CI[c]	*p*-value[d]	OS[b] Median	95% CI	*p*-value
pIL6[e] baseline			**0.04**			0.11
Low	14.7	1.9–27.6		25.2	15.6–34.8	
High	5.3	1.8–8.8		8.3	3.0–13.6	
pIL6R[f] baseline			0.12			0.06
Low	14.7	1.6–27.8		26.3	4.7–47.9	
High	8.7	7.6–9.8		13.7	11.0–16.5	
pIL6ST[g] baseline			0.06			**0.04**
Low	8.4	3.0–13.8		12.7	8.3–17.2	
High	12.9	5.9–20.0		25.2	15.7–34.7	
Change in pIL6 between baseline and week 12			**0.03**			0.63
Decrease	8.4	0.5–16.2		25.2	9.5–40.9	
Stable/Increase	17.0	9.0–25.0		19.7	03–39.2	
Change in pIL6R between baseline and week 12			**0.04**			0.40
Decrease	–[h]	–[h]		26.0	24.3–27.6	
Stable/Increase	8.7	7.4–9.9		17.5	7.2–27.7	
Change in pIL6ST between baseline and week 12			0.30			0.95
Decrease	16.5	1.9–32.2		19.7	9.0–30.5	
Stable/Increase	8.4	6.0–10.7		13.9	9.3–18.5	

[a] Progression free survival.
[b] Overall survival.
[c] Confidence interval.
[d] Log rank test.
[e] Plasma interleukin 6.
[f] Plasma interleukin 6 receptor.
[g] Plasma interleukin 6 signal transducer.
[h] Median survival cannot be calculated, due to less than 50% censored.

same cohort with established metastatic ccRCC. Low baseline level of pIL6 was significantly associated with clinical benefit of sunitinib treatment and improved PFS.

Tissue and serum levels of IL6 are elevated in RCC, and high levels of IL6 have been associated with elevated CRP in RCC patients [26,27]. IL6 signals cells via membrane-bound (classic) and soluble (trans-signalling) pathways [18,19]. The trans-signalling pathway is considered to be pro-inflammatory [28]. Elevated IL6 has been associated with poor survival in renal cell carcinoma and resistance to TKI treatment [29–32]. Tumour cells produce IL6 in response to cellular stress such as hypoxia, and enhanced levels of IL6 is associated with increased tumour cell invasion [10,14]. Kwon et al. found a stimulating effect of elevated IL6 on endothelial cells, which might represent a resistance mechanism to anti-VEGF therapy [33]. As a response to cellular stress, IL6 activation of the transcription factor STAT3 drives angiogenesis by inducing expression of VEGF and fibroblast growth factor (bFGF) by tumour cells, and thereby supports vascularization required for tumour growth and metastasis [34,35]. Our results are in support of previous reports indicating that high levels of inflammation-associated cytokines are negative for the outcome of treatment [13]. Elevated levels of IL6 among patients with poor response was also found in a recent work of Mizuno, investigating angiogenic, inflammatory and immunologic markers of sunitinib treatment in 56 patients with metastatic RCC [31]. However, they did not include patients with poor IMDC prognostic score. Our findings may therefore show that we can include this group as well. Tran et al. found opposite results, where a significantly increase in PFS in patients treated with another rTKI (pazopanib) versus placebo, in patients with high serum IL6 [36].

The baseline value of soluble IL6R in plasma was not significantly associated with response variables in this study, though low pIL6R tended to be associated with improved OS. In our previous paper, low tumour cell expression of IL6Rα was beneficial for treatment response. The prognostic value of IL6R expression have previously been presented, where Costes et al. found a significant association between IL6R expression and OS in patients with primary RCC tumours [16]. The complexity of membranous and soluble IL6R is well discussed in several reviews [10,34,37].

Membranous IL6ST is ubiquitous expressed in human tissue [38]. IL6ST and IL6R form a buffer for pIL6 in the blood, and is purposed to be a mechanism by which the organism protects itself from unspecific overstimulation by IL6ST [37]. Soluble IL6ST is an inhibitor of IL6. Even though the range of pIL6ST in our cohort was lower than a normal cohort, the group with under median level of pIL6ST level had worse OS (Table 3), in line with previous findings [29]. This may support the idea of a well-functioning buffer to protect against unspecific overstimulation by IL6-trans-signaling [37].

The cases with sunitinib induced reduction of pIL6R after two rounds of treatment had improved PFS. A reduction of pIL6R might be supported by the theory that trans-signaling pathways mediates cancer development [28,39]. Our results suggest that this might be used as a marker of beneficial on-treatment response, and suggest a relation between IL6Rα in tumour cells and level of circulating pIL6R.

In addition to the lack of a control group, our study has some weaknesses. First, the number of patients included is low and thereby the study lacks the statistical power to detect minor differences in response rates between groups based on the biomarkers under investigation. Thus, our findings should be validated in an independent and larger cohort of patients. Still, our data strongly suggest that biomarkers associated with tumour immune responses might be important in patients treated with anti-VEGF therapy.

Conclusion

Low level of plasma IL6 provides significant predictive information about response to sunitinib, and our data thereby suggest that up-regulation of IL6 might represent an important mechanism of resistance. Baseline measurement of this biomarker might guide clinical decision making in treatment of patients with mccRCC.

Clinical practice points

The anti-angiogenic receptor tyrosine kinase inhibitor sunitinib is first line treatment in metastatic renal cell carcinoma. Today there are no established predictive markers in clinical use. Inflammation is an

important part of cancer. In our study, we find that low level of interleukin 6 in plasma may predict treatment response of sunitinib and guide clinicians in making better treatment plans in renal cell carcinoma. The results suggest that up-regulation of plasma IL6 might represent an important mechanism of resistance. If validated in independent patient cohorts, the biomarker can easily be implicated into routine practice for a low cost using ELISA.

Conflict of interest

Pilskog, M has received consultation fees from Novartis and Pfizer. The other authors declare no conflicts of interest.

MicroAbstract

Anti-angiogenic treatment is first line treatment in metastatic renal cell carcinoma. There are presently no clinically useful predictive markers. In this study, we evaluate markers of tumor immune responses and angiogenesis. We find that low level of plasma interleukin-6 may predict response to sunitinib treatment. These results might represent an important mechanism of resistance.

Acknowledgments

The study was supported by grants from The Norwegian Research Council and The Norwegian Cancer Society. The authors alone are responsible for the content and writing of the paper. This work was partly supported by the Research Council of Norway through its Centres of Excellence funding scheme, project number 223250.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ctarc.2019.100127.

References

[1] B. Escudier, C. Porta, M. Schmidinger, et al., Renal cell carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up, Ann. Oncol. 27 (2016) v58–v68.
[2] R.J. Motzer, T.E. Hutson, P. Tomczak, et al., Sunitinib versus interferon alfa in metastatic renal-cell carcinoma, N. Engl. J. Med. 356 (2007) 115–124.
[3] O. Dalpiaz, T. Luef, M. Seles, et al., Critical evaluation of the potential prognostic value of the pretreatment-derived neutrophil-lymphocyte ratio under consideration of C-reactive protein levels in clear cell renal cell carcinoma, Br. J. Cancer (2016).
[4] P. Fox, M. Hudson, C. Brown, et al., Markers of systemic inflammation predict survival in patients with advanced renal cell cancer, Br. J. Cancer 109 (2013) 147–153.
[5] A. Mantovani, P. Allavena, A. Sica, F. Balkwill, Cancer-related inflammation, Nature 454 (2008) 436–444.
[6] T. Voron, E. Marcheteau, S. Pernot, et al., Control of the immune response by pro-angiogenic factors, Front. Oncol. 4 (2014) 70.
[7] D. Hanahan, R.A. Weinberg, Hallmarks of cancer: the next generation, Cell 144 (2011) 646–674.
[8] M. Pilskog, C. Beisland, L.A. Akslen, et al., Predictive value of C-reactive protein in patients treated with sunitinib for metastatic clear cell renal cell carcinoma, BMC Urol. 17 (2017) 74.
[9] A. Casamassima, M. Picciariello, M. Quaranta, et al., C-reactive protein: a biomarker of survival in patients with metastatic renal cell carcinoma treated with subcutaneous interleukin-2 based immunotherapy, J. Urol. 173 (2005) 52–55.
[10] K. Kaminska, A.M. Czarnecka, B. Escudier, F. Lian, C. Szczylik, Interleukin-6 as an emerging regulator of renal cell cancer, Urol. Oncol. 33 (2015) 476–485.
[11] K. Middleton, J. Jones, Z. Lwin, J.I. Coward, Interleukin-6: an angiogenic target in solid tumours, Crit. Rev. Oncol. Hematol. 89 (2014) 129–139.
[12] J. Scheller, A. Chalaris, D. Schmidt-Arras, S. Rose-John, The pro- and anti-inflammatory properties of the cytokine interleukin-6, Biochim. Biophys. Acta 1813 (2011) 878–888.
[13] J. Wolf, S. Rose-John, C. Garbers, Interleukin-6 and its receptors: a highly regulated and dynamic system, Cytokine 70 (2014) 11–20.
[14] J.P. Fitzgerald, B. Nayak, K. Shanmugasundaram, et al., Nox4 mediates renal cell carcinoma cell invasion through hypoxia-induced interleukin 6- and 8- production, PLoS One 7 (2012) e30712.
[15] Q. Xu, J. Briggs, S. Park, et al., Targeting Stat3 blocks both HIF-1 and VEGF expression induced by multiple oncogenic growth signaling pathways, Oncogene 24 (2005) 5552–5560.
[16] V. Costes, J. Liautard, M.C. Picot, et al., Expression of the interleukin 6 receptor in primary renal cell carcinoma, J. Clin. Pathol. 50 (1997) 835–840.
[17] H. Tsukamoto, K. Fujieda, A. Miyashita, et al., Combined Blockade of IL6 and PD-1/PD-L1 signaling abrogates mutual regulation of their immunosuppressive effects in the tumor microenvironment, Cancer Res. 78 (2018) 5011–5022.
[18] S. Rose-John, P.C. Heinrich, Soluble receptors for cytokines and growth factors: generation and biological function, Biochem. J. 300 (Pt 2) (1994) 281–290.
[19] S. Rose-John, G.H. Waetzig, J. Scheller, J. Grotzinger, D. Seegert, The IL-6/sIL-6R complex as a novel target for therapeutic approaches, Expert Opin. Ther. Targets 11 (2007) 613–624.
[20] M. Pilskog, L. Bostad, R.J. Edelmann, L.A. Akslen, C. Beisland, O. Straume, Tumour cell expression of interleukin 6 receptor alpha is associated with response rates in patients treated with sunitinib for metastatic clear cell renal cell carcinoma, J. Pathol. Clin. Res. 4 (2018) 114–123.
[21] A. Chalaris, C. Garbers, B. Rabe, S. Rose-John, J. Scheller, The soluble Interleukin 6 receptor: generation and role in inflammation and cancer, Eur. J. Cell Biol. 90 (2011) 484–494.
[22] J. Scheller, N. Ohnesorge, S. Rose-John, Interleukin-6 trans-signalling in chronic inflammation and cancer, Scand. J. Immunol. 63 (2006) 321–329.
[23] T. Jostock, J. Mullberg, S. Ozbek, et al., Soluble gp130 is the natural inhibitor of soluble interleukin-6 receptor transsignaling responses, Eur. J. Biochem. 268 (2001) 160–167.
[24] M. Pilskog, L. Bostad, R.J. Edelmann, L.A. Akslen, C. Beisland, O. Straume, Tumour cell expression of interleukin 6 receptor α is associated with response rates in patients treated with sunitinib for metastatic clear cell renal cell carcinoma, J. Pathol. (2018) n/a-n/a.
[25] R.J. Motzer, N.M. Tannir, D.F. McDermott, et al., Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma, N. Engl. J. Med. 378 (2018) 1277–1290.
[26] J.Y. Blay, J.F. Rossi, J. Wijdenes, et al., Role of interleukin-6 in the paraneoplastic inflammatory syndrome associated with renal-cell carcinoma, Int. J. Cancer 72 (1997) 424–430.
[27] S. Negrier, D. Perol, C. Menetrier-Caux, et al., Interleukin-6, interleukin-10, and vascular endothelial growth factor in metastatic renal cell carcinoma: prognostic value of interleukin-6–from the Groupe Francais d'Immunotherapie, J. Clin. Oncol. 22 (2004) 2371–2378.
[28] C. Garbers, S. Aparicio-Siegmund, S. Rose-John, The IL-6/gp130/STAT3 signaling axis: recent advances towards specific inhibition, Curr. Opin. Immunol. 34 (2015) 75–82.
[29] J.Y. Blay, S. Negrier, V. Combaret, et al., Serum level of interleukin 6 as a prognosis factor in metastatic renal cell carcinoma, Cancer Res. 52 (1992) 3317–3322.
[30] M. Hrab, K. Olek-Hrab, A. Antczak, Z. Kwias, T. Milecki, Interleukin-6 (IL-6) and C-reactive protein (CRP) concentration prior to total nephrectomy are prognostic factors in localized renal cell carcinoma (RCC), Rep. Pract. Oncol. Radiother. 18 (2013) 304–309.
[31] R. Mizuno, G. Kimura, S. Fukasawa, et al., Angiogenic, inflammatory and immunologic markers in predicting response to sunitinib in metastatic renal cell carcinoma, Cancer Sci. 108 (2017) 1858–1863.
[32] C. Porta, C. Paglino, I. Imarisio, et al., Changes in circulating pro-angiogenic cytokines, other than VEGF, before progression to sunitinib therapy in advanced renal cell carcinoma patients, Oncology 84 (2013) 115–122.
[33] K.A. Kwon, S.H. Kim, S.Y. Oh, et al., Clinical significance of preoperative serum vascular endothelial growth factor, interleukin-6, and C-reactive protein level in colorectal cancer, BMC Cancer 10 (2010) 203.
[34] D.T. Fisher, M.M. Appenheimer, S.S. Evans, The two faces of IL-6 in the tumor microenvironment, Semin. Immunol. 26 (2014) 38–47.
[35] L.H. Wei, M.L. Kuo, C.A. Chen, et al., Interleukin-6 promotes cervical tumor growth by VEGF-dependent angiogenesis via a STAT3 pathway, Oncogene 22 (2003) 1517–1527.
[36] H.T. Tran, Y. Liu, A.J. Zurita, et al., Prognostic or predictive plasma cytokines and angiogenic factors for patients treated with pazopanib for metastatic renal-cell cancer: a retrospective analysis of phase 2 and phase 3 trials, Lancet Oncol. 13 (2012) 827–837.
[37] S. Rose-John, The soluble interleukin-6 receptor and related proteins, Best Pract. Res. Clin. Endocrinol. Metab. 29 (2015) 787–797.
[38] M. Hibi, M. Murakami, M. Saito, T. Hirano, T. Taga, T. Kishimoto, Molecular cloning and expression of an IL-6 signal transducer, gp130, Cell 63 (1990) 1149–1157.
[39] J. Scheller, C. Garbers, S. Rose-John, Interleukin-6: from basic biology to selective blockade of pro-inflammatory activities, Semin. Immunol. 26 (2014) 2–12.