EDITOR'S PICK

Targeted therapies (vascular endothelial growth factor/vascualar endothelial growth factor receptor targeting agents and/or mammalian target of rapamycin inhibitors) for the treatment of metastatic renal cell carcinoma have changed the treatment landscape of patients suffering from end-stage renal disease requiring dialysis. Data about the pharmacokinetics of these drugs in renal failure are scarce and the timely paper by Guida et al. that follows provides an informative summary of the available literature on this topic. This paper can be highly recommended to nephrologists and oncologists involved in the difficult management of these patients.

Prof Norbert Lameire

TARGETED AGENTS IN PATIENTS WITH METASTATIC RENAL CELL CARCINOMA ON DIALYSIS: MYTHS AND REALITY

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ABSTRACT

Agents targeting the vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR) pathway, as well as mammalian target of rapamycin (mTOR) inhibitors have revolutionised the therapeutic landscape of metastatic renal cell carcinoma (mRCC) in the past decade, greatly improving the survival rates of these patients. However, translating results of registrative Phase III trials into everyday clinical practice is often troublesome, since real-world patients are completely different from those enrolled in randomised controlled Phase III trials. Prospective data on active oncological treatments in mRCC patients on dialysis are dramatically lacking. This literature review summarises and critically comments on available data relative to mRCC patients on dialysis receiving either VEGF/VEGFR-targeting agents, or mTOR inhibitors. Although prospective studies would definitely be warranted in these specific patient populations, all the available data suggest that mRCC patients on dialysis have the same outcome, both in terms of efficacy and safety, as mRCC patients with normal or marginally impaired kidney function, when treated with VEGF/VEGFR-targeting agents and/or mTOR inhibitors.

Keywords: Vascular endothelial growth factor (VEGF), vascular endothelial growth factor receptor (VEGFR) targeting agents, mammalian target of rapamycin (mTOR) inhibitors, dialysis, end-stage renal disease (ESRD).

INTRODUCTION

A number of molecularly targeted therapies (i.e. agents targeting the vascular endothelial growth factor [VEGF]/VEGF receptors [VEGFR] pathway, as well as mammalian target of rapamycin [mTOR] inhibitors) have revolutionised the therapeutic landscape of metastatic renal cell carcinoma (mRCC) in the past decade, greatly improving the survival of these patients[1] irrespective of their baseline prognostic features.[2,3]

However, translating the results of a Phase III trial into everyday clinical practice is often troublesome since real-world patients are completely different from those enrolled in large, global, randomised, controlled Phase III trials, usually characterised by very strict inclusion and exclusion criteria. Indeed, we now know that patients not suitable for consideration for a clinical trial have a very poor prognosis.[4] It is therefore crucial to confirm the efficacy, as well as the safety profile, of these novel agents in specific patient subpopulations, typically excluded from clinical trials.

A better knowledge of the outcome of treatment in these subpopulations may in fact allow us to improve the way we take care of patients with complicated cases, as well as to understand whether the decision to exclude some of these subpopulations from clinical trials is sensible or not.

In this literature review, we summarise and critically comment on the available data relative to mRCC patients on dialysis receiving either VEGF/VEGFR-targeting agents or mTOR inhibitors. Since the available data are scarce, exclusively retrospective, and mainly coming from small series or even single case reports, the derived evidence is highly biased and is endowed with a low level of supporting data. Nevertheless, we strongly believe that, in the absence of reasonable alternatives, these data could be practically quite useful and scientifically hypotheses-generating.[5]

CANCER AND DIALYSIS

Data from cancer registries show a high incidence of cancer in patients with end-stage renal disease (ESRD).[6] In patients undergoing dialysis, a number of pro-carcinogenic conditions are often present, including immune suppression, the presence of uraemic toxins, chronic oxidative stress, and cytokine-mediated inflammatory responses. The development of kidney neoplasms, ranging from adenoma to metastatic carcinoma, is the most serious complication of acquired cystic kidney disease (ACKD). ACKD-associated renal cell carcinoma is seen predominantly in males, occurs approximately 20 years earlier than in the general population, and is frequently bilateral (9%) and multicentric (50%).[7]

ACKD occurs in patients who are on dialysis for ESRD. It is generally accepted that ACKD develops as a consequence of sustained uraemia and can first manifest in stages of chronic kidney disease, even before dialysis is initiated. The prevalence of ACKD is directly related to the duration of dialysis and the risk of cancer is directly related to the presence of cysts.[8]

In the CANDY (Cancer and Dialysis) study, Janus et al.[9] retrospectively analysed a population of 178 patients who developed cancer after initiation of chronic dialysis. The mean period between the beginning of dialysis and cancer diagnosis was 30.8 months, and the main primary cancer sites were genito-urinary (21%), haematologic (15%), lung (13%), gastrointestinal (13%), prostate (8%), and head and neck cancers (7%), while the remaining were miscellaneous malignancies. Only 28% of these patients received active anti-cancer treatments, including agents for which no recommendations in dialysis were available. Seventy-two of the patients received at least one drug that required a dosage adjustment or for which there were no data in dialysis. This lead to the development of iatrogenic toxicity in 44% of the treated patients; 34% related to drugs requiring dosage adjustment, and 17% related to additional drugs with no existing management recommendations in dialysis patients. Overall, 88% of those who received an active oncological treatment needed specific drug management in terms of dose adjustment and/or time of administration according to the dialysis session of at least one anti-cancer drug. Notably, just 11% of the anti-cancer agents administered to studied patients were represented by target therapies, either monoclonal antibody (7%), or tyrosine kinase inhibitors (TKIs) (4%). Fifty-eight percent of the CANDY patients died during the 2-year follow-up period after cancer diagnosis and about half of those cases were due to cancer, with median survival time being 13.5 months after the diagnosis of malignancy. Furthermore, 38% of the CANDY patients died within a period of 2 years after dialysis onset versus 28% in the French Renal Epidemiology and Information

Network (REIN) registry.[10] Notably, in the European Renal Association and European Dialysis and Transplantation Association (ERA-EDTA) registry, mortality from malignancies was 2.9-times higher in dialysis patients than in the general population.[11]

Renal Cell Carcinoma

Renal cell carcinoma represents 2–3% of all malignancies in adults and generally occurs during the sixth and seventh decades of life.[12] Approximately a third of all patients with newly diagnosed renal cell carcinoma present with metastatic disease, and as many as 50% of those completely resected for a localised disease develop a local or distant relapse. Five percent of patients present with a bilateral renal mass with or without a known hereditary renal cancer syndrome.[13]

In regards to surgery, over the years less invasive techniques (compared with radical nephrectomy) have been developed for smaller tumours; indeed, according to the 2015 guidelines of the European Association of Urology (EAU), partial nephrectomy is recommended in patients with T1a tumours (i.e. a tumour ≤4 cm maximum dimension, limited to the kidney), while it is recommended to favour partial nephrectomy over radical nephrectomy in patients with T1b tumours (i.e. a tumour >4 cm but ≤7 cm maximum dimension, limited to the kidney), whenever feasible.[14] These conservative surgical approaches achieved similar oncological outcomes as compared with radical nephrectomy, but allowed the maintenance of an adequate renal function in a larger number of patients. Despite this, in patients with pre-existing kidney disease, especially the elderly and those with relevant cardiovascular comorbidities, the surgical excision (radical or partial) of a renal malignancy may contribute to the development of *de novo* kidney function impairment, or to the worsening of pre-existing chronic kidney disease.

Our improved knowledge of the molecular mechanisms underlying kidney carcinogenesis have led to the development of active systemic therapies, which ultimately improved the natural history of tumours in these patients, expecially when administered sequentially.[15] These novel agents include four VEGFR-TKIs (sorafenib, sunitinib, pazopanib, and axitinib), the anti-VEGF monoclonal antibody bevacizumab (which is given together with interferon-α [IFN-α]), as well as two mTOR inhibitors (everolimus and temsirolimus).[16] More recently, a further two agents have been registered (at least in many parts of the world): cabozantinib,[17] which is a VEGFR/C-Met inhibitor, and the anti-programmed death 1 checkpoint inhibitor, nivolumab.[18]

This review will focus on just the first seven agents, thus excluding cabozantinib and nivolumab; data for patients on dialysis treated with these agents are presently not available, due to their very recent implementation in clinical practice.

VASCULAR ENDOTHELIAL GROWTH FACTORS AND THEIR RECEPTORS' TYROSINE KINASE INHIBITORS TO TREAT METASTATIC RENAL CELL CARCINOMA

Sorafenib Tosylate

Originally identified as an inhibitor of Raf kinase, sorafenib proved to be endowed with a significant anti-angiogenic activity, characterised by the ability to inhibit, at pharmacological concentrations, all three VEGFRs (VEGFR-1, 2, and 3) along with platelet-derived growth factor receptor (PDGFR)-α and β, in addition to a number of other kinases during its pre-clinical development.[19] Sorafenib is administered orally at the fixed dose of 400 mg twice a day and has a safety profile characterised by a high incidence of fatigue, hypertension, hand–foot skin reaction (HFSR), hypothyroidism, and diarrhoea.[20]

The sorafenib registrative study was a placebo-controlled, Phase III trial comparing this multikinase inhibitor with placebo in patients with treatment-refractory (mainly cytokine-refractory) mRCC. Sorafenib almost doubled progression-free survival (PFS) (the primary endpoint of the study) compared with placebo (5.5 versus 2.8 months), a difference that was not only statistically significant, but also equivalent to a reduction in the risk of progression or death of 56%.[21] Sorafenib is metabolised in the liver by cytochrome CYP3A4; approximately 19% of the administrated dose is recovered in urine as metabolites.[22]

Sunitinib Malate

Sunitinib is an oral multikinase inhibitor selectively directed against all three VEGFRs (VEGFR-1, 2, and 3), against PDGFR-α and β, as well as against a range of other kinases.[23] From Phase I studies, the dose of 50 mg per day within a 4 weeks on,

2 weeks off schedule emerged as the one to be used in later stages of development,[23] although alternative schedules (expecially the 2 weeks on, 1 week off) have been recently proposed to alleviate its toxicity profile,[24] which is characterised mainly by hypertension, diarrhoea, myelotoxicity, skin toxicity (expecially HFSR), hypothyroidism, and fatigue.[25]

The pivotal sunitinib study was a randomised, controlled, Phase III trial, in which 750 treatment-naïve mRCC patients were randomised to receive either sunitinib or IFN-α (given subcutaneously at a loading dose of 9 MU 3-times per week), PFS being the primary endpoint of the study.[26] Median PFS in sunitinib-treated patients was significantly longer than in those treated with IFN-α (11 versus 5 months), corresponding to a reduction in the risk of progression or death of 58%. From a pharmacokinetic (PK) viewpoint, as with all VEGFR-TKIs sunitinib is metabolised by cytochrome CYP3A4, and renal eliminations account for 16% of the administrated dose.[22]

Bevacizumab

Bevacizumab is a recombinant humanised monoclonal antibody directed against VEGF; it is able to selectively bind and neutralise all active isoforms of VEGF (also known as VEGF-A), but not other members of the family of VEGF, i.e. VEGF-B, C, and D.[27] In mRCC, it is administered intravenously at a dose of 10 mg/kg every 2 weeks; its safety profile includes hypertension, proteinuria, wound healing impairment, an increased risk of haemorrhage, intestinal perforation, and thromboembolic events.[28] However, since in mRCC it is administered together with IFN-α, patients treated with this combination usually also experience IFN-α-related adverse events (AEs) such as fever and flu-like syndrome.

In the AVOREN pivotal trial,[29] the combination of bevacizumab plus IFN-α was compared with IFN-α plus placebo, overall survival (OS) being the primary endpoint of the study. The combination was approved based on preliminary results showing a significant benefit in terms of the secondary endpoint PFS (median 10.2 versus 5.4 months; hazard ratio [HR]: 0.63, equivalent to a reduction in the risk of progression or death of 37%). Surprisingly, OS did not differ between the two treatment arms, mainly due to the confounding role of subsequent active treatments.[30] As with all large molecular size monoclonal antibodies, bevacizumab is mainly metabolised by the reticuloendothelial system and has no renal excretion.[22]

Pazopanib

Pazopanib is another oral multikinase inhibitor capable of inhibiting the activation of different tyrosine kinases heavily implicated in the mechanisms of angiogenesis (mainly VEGFR-1, 2, and 3, but also PDGFR-α and β, and others).[31]

The recommended dose resulting from a Phase I study, which showed a correlation between plasma concentrations of pazopanib and development of hypertension, was 800 mg/day.[32] The safety profile of pazopanib is similar to that of sunitinib, but with a less detrimental effect on the quality of life of mRCC patients, as subsequently demonstrated by both the COMPARZ and PISCES studies;[33,34] compared with sunitinib, pazopanib induces more hepatic toxicity, but less myelotoxicity and HFSR.

Pazopanib's pivotal trial was conducted in a population of mRCC patients who were either treatment-naïve, or cytokine pre-treated. The study was placebo-controlled, and its primary endpoint was once again PFS.[35] A significant benefit in terms of PFS in favour of pazopanib was observed in both groups of patients, with a median PFS of 11.1 months in treatment-naïve patients (versus 2.8 months for placebo-treated subjects, hazard ratio [HR]: 0.4), and 7.4 months (versus 4.2, HR: 0.54) in cytokine pre-treated patients.[35] Like all VEGFR-TKIs, pazopanib is metabolised by cytochrome CYP3A4; renal eliminations are particularly low at <4% of the administered dose.[22]

Axitinib

Axitinib is a so-called third-generation VEGFR-TKI,[36] characterised by a particular selectivity of action for all three VEGFRs, and a high power. Commonly observed axitinib-related AEs include hypertension, diarrhoea, and fatigue.[37] The pivotal Phase III axitinib trial[38] was conducted in a second-line setting, in patients pre-treated with a variety of first-line treatment, and was the very first study on renal cell carcinoma which compared two active drugs head-to-head, sorafenib having been chosen as the control arm. In this study (AXIS study), axitinib proved to be superior in terms of PFS (primary endpoint of the study) to sorafenib; indeed, median PFS was 6.7 months with axitinib compared with 4.7 months with sorafenib, equivalent to a 33.5% reduction in the risk of progression.[38] The biggest advantage of axitinib over sorafenib was

evidenced in patients pre-treated with cytokines; however, when just sunitinib pre-treated patients were considered, both drugs performed quite well, axitinib maintaining an advantage over the older agent.[37,39] Again, as a VEGFR-TKI, axitinib is metabolised by cytochrome CYP3A4, with renal eliminations accounting for 23% of the administrated dose.[22]

MAMMALIAN TARGET OF RAPAMYCIN INHIBITORS TO TREAT METASTATIC RENAL CELL CARCINOMA

Temsirolimus

Temsirolimus, a water-soluble derivative of sirolimus, is a highly selective inhibitor of mTOR; binding the FKBP1 domain of mTOR, it inhibits kinase activity, preventing phosphorylation of substrate proteins such as 4E-BP1 and S6K1, and consequently blocking the cell cycle in the G1 phase.[40] Furthermore, inhibition of mTOR by temsirolimus leads to a suppression of various other proteins involved in the processes of angiogenesis, such as the hypoxia-inducible factor-1α, and ultimately also VEGF.[41] Temsirolimus-induced AEs include fatigue, stomatitis, anaemia, dyslipidaemia, hyperglycaemia, drug-induced pneumonitis, as well as an increased risk of infections.[42]

Its registrative study was a randomised, Phase III trial, aimed at investigating the efficacy of temsirolimus alone or in combination with IFN-α, compared with IFN-α alone in patients with poor prognosis features, according to the Memorial Sloan-Kettering Cancer Center (MSKCC) classification,[2] OS being the primary endpoint of the study. Treatment with temsirolimus was associated with a reduction in the risk of death by 27%, with an OS of 7.3 months in the group treated with IFN-α alone, 8.4 months in the group treated with the combination of the two drugs, and 10.9 months in the group treated with temsirolimus alone.[43] Temsirolimus is metabolised by cytochrome CYP3A4, with renal eliminations accounting for 4.6% of the administrated dose.[22]

Everolimus

Everolimus is another derivative of rapamycin, endowed with inhibitory activity on the mTOR, developed, unlike temsirolimus, as an oral medication.[44] Its safety profile is similar to that of temsirolimus, more common AEs being anaemia, hyperglycaemia, dyslipidaemia, stomatitis, drug-induced pneumonitis, and an increased risk of infection.[45] RECORD-1, everolimus' registrative Phase III trial was a randomised (2:1), placebo-controlled, Phase III study, in which mRCC patients who had failed treatment with sunitinib, sorafenib, or both, were enrolled; the majority of patients treated within this study had also failed other previous treatments, mainly (but not exclusively) cytokines.[46]

The RECORD-1 study showed, at an interim analysis, a statistically significant improvement in median PFS (primary endpoint of the study) in favour of everolimus. Indeed, median PFS was 4 months in the everolimus arm, and just 1.9 months in the placebo arm, with a percentage of patients free of progression at 6 months of 26% (compared with 2%), again in favour of everolimus.[46] Regarding OS, the high percentage of patients who crossed-over from the placebo to the active drug precluded any chance to observe a significant difference between the two arms, even though a subsequent statistical analysis, used to correct the estimate of the effect of treatment taking into account the bias generated by cross-over, showed an OS 1.9-times longer in favour of everolimus-treated patients.[47] Everolimus renal excretion accounts for just 2% of the administered dose.[22]

TARGETED THERAPIES FOR METASTATIC RENAL CELL CARCINOMA AND DIALYSIS

When treated for their cancer, patients with mRCC on dialysis are usually treated as patients without renal impairment, but data about the PKs of these drugs in this context are extremely scarce, at best. Our treatment decisions in this setting thus rely solely on small retrospective series, or even on single case reports. The following is a summary of current literature regarding VEGF/VGFR targeting agents and mTOR inhibitors.

Vascular Endothelial Growth Factor/Vascular Endothelial Growth Factor Receptor Inhibitors in Dialysis

Among VEGF/VEGFR-targeting agents, sorafenib and sunitinib are more frequently used in dialysis and more thoroughly described in the literature, being the very first agents to be registered for the treatment of mRCC, back in 2005/2006.

Kennoki et al.[48] examined PK parameters in patients on dialysis treated with sorafenib for mRCC. In this study, 10 patients received 200 mg of sorafenib once daily (i.e. one-quarter of the standard dose) as the initial dose. Regarding treatment activity, the authors observed one complete response, two partial responses, and disease stabilisation in four more patients. The median PFS and OS were 6.3 and 14.9 months, respectively. AEs were also collected and were generally serious; when the incidence of the AEs observed in patients on dialysis were compared with that of patients with normal renal function from the same institution, the authors found that the incidence of serious AEs was higher in patients on dialysis, the most common being hypertension, thrombocytopenia, and haemorrhagic events. They also reported a Grade 5 subarachnoid haemorrhage, and a Grade 4 cerebellar haemorrhage (in patients without brain metastasis). The PK study was performed in just six of these patients. The geometric mean of C_{max} (maximum level concentration of the day), C_{min} (minimum level concentration of the day), and AUC_{0-10} (area under the curve from 0–10 hours after taking 200 mg of sorafenib) on haemodialysis as compared with non-haemodialysis days was related to the objective responses observed and with the number of AEs of Grade 3 or higher; no significant relationship between the PK parameters and the occurrence of serious AEs, and between PK parameter and clinical efficacy was observed.[48] The authors therefore suggested that the higher incidence of sorafenib-related serious AEs in patients on dialysis is likely associated with the compromised general conditions of these patients, and not with the high plasma exposure of sorafenib. They concluded that sorafenib treatment is also effective in patients on dialysis, but suggested the use of lower sorafenib doses due to the particularly high incidence of AEs, especially cardiovascular ones.[48] This study was performed on Japanese mRCC patients, who, like all Asian populations, are known to poorly tolerate VEGFR-targeting agents.

A retrospective analysis conducted in several centres in the UK and USA in 2010, Josephs et al.[49] reported the outcome of sunitinib treatment in terms of both efficacy and safety. Nineteen patients were included, 10 of whom were undergoing haemodialysis. Of the nine nondialysis-dependent patients at drug initiation, the median estimated glomerular filtration rate was 27 mL/min/1.73 m^2 (range 23–29). The estimated median PFS of the whole cohort was 43 weeks (range 7 to >158), progression having not yet been reached in six patients at the time of publication. Partial response or stable disease was observed as best response in 15 patients, while the most common treatment-related AEs included fatigue, diarrhoea, HFSR, nausea/vomiting, and rash. Grade 3 treatment-related AEs including fatigue (seven patients), HFSR (two patients), diarrhoea (one patient), rash (one patient), and stomatitis (one patient) occurred in a total of 12 patients. Only one patient experienced a Grade 4 AE (HFSR). Diarrhoea, HFSR, and neutropenia were more common in patients undergoing haemodialysis compared with nondialysis-dependent patients. Three haemodialysis, and four nondialysis-dependent patients started at a dose of 50 mg; whereas five and two of the patients undergoing haemodialysis started at doses of 37.5 mg and 25 mg daily, respectively, compared with four and one of the nondialysis-dependent patients. Dose reductions during treatment were performed in eight patients but only one patient required complete discontinuation.[49]

Khosravan et al.[50] published data from a Phase I, open-label study aimed at evaluating PK data relative to sunitinib and its metabolite SU12662. Twenty-four patients were enrolled, eight for each of the following groups: normal renal function (creatinine clearance >80 mL/min/1.73 m^2), severe impairment renal function (creatinine clearance <30 mL/min/1.73 m^2), and ESRD requiring dialysis. PKs in subjects with severe renal impairment appeared similar to those with normal renal function. Indeed, plasma exposure to sunitinib and SU12662 was lower in subjects with ESRD compared with subjects with normal renal function or severe renal impairment. Notably, in haemodialysis patients, the incidence of AEs was quite low, with no drug discontinuations due to AEs. Considering the above data, the authors concluded that sunitinib, given at standard dose and schedule, seems to be an effective and safe option for patients with mRCC undergoing dialysis, yielding results in line with those observed in patients without renal impairment.[50]

In 2012 Masini et al.[51] reported a multicentre, retrospective study on 24 patients with mRCC and ESRD requiring haemodialysis treated with sorafenib (n=8) and sunitinib (n=16), aimed at retrospectively describing targeted agents' administered doses, treatment-related AEs, and clinical response. Sunitinib was administered at the dose of 50 mg daily, 4 weeks on, 2 weeks off, in six

patients; at 37.5 mg daily, 4 weeks on, 2 weeks off, in seven patients (one of them subsequently increased the dose to 50 mg daily); at 25 mg daily, 4 weeks on, 2 weeks off, in two patients; and finally at 12.5 mg daily, 4 weeks on, 2 weeks off, in one patient. Among the eight patients treated with sorafenib, four patients received 800 mg daily (400 mg twice daily), three patients 400 mg daily, and one patient 200 mg daily, all with a continuous schedule. The estimated median PFS and OS in this cohort of patients was 10.3 months and 22.6 months, respectively. With regard to tolerability and safety, no unexpected AEs were registered and no Grade 4 haematological or nonhaematological toxicities were reported. In this series, sunitinib and sorafenib proved to be not contraindicated in patients with mRCC undergoing dialysis, the outcome of this patient population being similar to that observed in patients with normal renal function treated with VEGFR-TKIs.[51]

In another retrospective study, Shetty et al.[52] reported the outcome of 14 mRCC patients on dialysis treated sequentially with different targeted therapies in the USA. The median number of targeted agents received per patient was three (range: 1–4), resulting in a median time on treatment (for all the agents used) of 28 months. Eighty-eight percent of all toxicities were Grade 1–2, without cases of Grade 4 AEs; treatment discontinuations included three patients treated with sorafenib (due to HFSR, intolerable fatigue, and squamous cell skin cancer development, respectively), two patients treated with pazopanib (due to intolerable fatigue and increased transaminase levels), and one patient treated with everolimus (due to non-bacterial pneumonitis).

Table 1: Summary of literature reports on the safety and efficacy of vascular endothelial growth factor/vascular endothelial growth factor receptor-targeting agents in metastatic renal cell cancer.

Author (year)	No. of patients	VEGFR/VEGFR-targeting agents	Dose reductions required	Toxicities observed (Grades ≥3)
Garnier-Viougeat et al.[54] (2006)	1	Bevacizumab*	No	None
Maroto Rey, Villavicencio[55] (2008)	2	Sunitinib (1 patient) Sorafenib (1 patient)	No Yes	None
Ruppin et al.[56] (2008)	1	Sorafenib	No	None
Zastrow et al.[57] (2009)	2	Sunitinib	No (1 patient), Yes (1 patient)	Increase in amylase and lipase (1 patient)
Ferraris et al.[58] (2009)	2	Sorafenib	No (1 patient), Yes (1 patient)	Asthenia, gastritis, dyspnoea (1 patient)
Hilger et al.[59] (2009)	2	Sorafenib	Yes (2 patients)	Not reported
Vickers et al.[60] (2009)	2	Sunitinib	Yes (1 patient), No (1 patient)	Hypothyroidism and fatigue (1 patient)
Park[61] (2009)	1	Sunitinib	No	None
Reckova et al.[62] (2009)	1	Sunitinib	Yes	Thrombocytopenia, hypertension, decreased LVEF
Izzedine et al.[63] (2009)	1	Sunitinib	No	None
Castagneto et al.[64] (2010)	1	Sorafenib	Yes	None
Shinsako et al.[65] (2010)	1	Sorafenib	No	None
Yoon et al.[66] (2010)	2	Sunitinib	No†	None
Park et al.[67] (2010)	6	Sunitinib	Yes	Mucositis, anorexia, fatigue
Khosravan et al.[50] (2010)	8	Sunitinib	No	None
Josephs et al.[49] (2011)	10	Sunitinib	Yes	Fatigue, stomatitis, HFSR, diarrhoea
Kennoki et al.[48] (2011)	10	Sorafenib	Yes	Subarachnoid and cerebellar haemorrhage
Casper et al.[68] (2011)	21	Sunitinib	Yes	Asthaenia, nausea, vomiting, diarrhoea, thrombocytopenia, hypertension, hypotension, decreased LVEF

Table 1 continued.

Author (year)	No. of patients	VEGFR/VEGFR-targeting agents	Dose reductions required	Toxicities observed (Grades ≥3)
Thiery-Vuillemin et al.[69] (2011)	1	Sunitinib	No	None
Masini et al.[51] (2012)	24	Sunitinib (16 patients), sorafenib (8 patients)	No	Nausea, diarrhoea, symptomatic cardiac ischaemia
Yildiz et al.[70] (2014)	2	Sunitinib	No	Acute pulmonary oedema, hypertension
Shetty et al.[52] (2014)	14	Sunitinib, sorafenib, pazopanib (plus everolimus and temsirolimus)‡	Yes (9 patients)	HFSR, fatigue, and squamous cell skin cancer leading to treatment discontinuation in 3 patients; intolerable fatigue and increased transaminases in 2 patients leading to pazopanib discontinuation
Czarnecka et al.[53] (2015)	9	Sunitinib (3 patients), sorafenib (4 patients), pazopanib (1 patient), (plus everolimus in 1 patient)§	Yes (1 patient)	Hypertension, anaemia, fatigue
Bersanelli et al.[71] (2016)	1	Pazopanib	Yes	Diarrhoea, hypertension

*Bevacizumab was administered as a single-agent at the dose of 5 mg/kg, every 14 days.
†An intermittent schedule was used from the beginning.
‡Authors analysed and reported different sequences of targeted agents.
§Two patients received also a second-line targeted agent.
VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor; LVEF: left ventricular ejection fraction; HFSR: hand–foot skin reaction.

Median OS from initiation of targeted therapies and from time of diagnosis were 28.5 and 35 months, respectively. Once again, the authors concluded that targeted agents were safe, well tolerated, and able to produce an anti-tumour response in patients with mRCC and ESRD receiving dialysis, at the expense of mild-to-moderate AEs consistent with those reported in previous studies conducted in patients not on dialysis.[52]

More recently, Czarnecka et al.[53] retrospectively analysed a large number of consecutive mRCC patients treated with VEGFR-TKIs. Out of a total of 679 patients, 464 (i.e. 68%) were treated with VEGFR-TKIs, and among those just 9 (1.3 and 1.9%, respectively) were treated while on dialysis due to ESRD; 5 of these 9 patients were treated with sunitinib, 3 with sorafenib, and 1 with pazopanib. After first-line treatment, two of them received second-line therapy. PFS of this cohort was within the range reported in the literature for a typical mRCC patient population not on dialysis, i.e. 8–8.5 months. A partial response or a disease stabilisation was observed in one and five patients, respectively; with regard to safety, most AEs were Grade 1 or 2, with no Grade 5 AEs observed. For one patient the dose was decreased, and for another treatment was discontinued; this patient was already hypertensive at the start of treatment. As a whole, the results supported the authors' statement that VEGFR-TKIs treatment in dialysis is safe and effective.[53]

All the above series, together with other case reports and small series published in the literature[54-71] are summarised in Table 1, ultimately supporting the concept that dialysis patients do not differ dramatically from a typical population of mRCC in terms of activity and safety of VEGF or VEGFR-targeting agents.

MAMMALIAN TARGET OF RAPAMYCIN INHIBITORS IN DIALYSIS

In 2008/2009, Lunardi[72,73] demonstrated that temsirolimus concentration assessed immediately before haemodialysis was similar to that assayed 1 hour after the treatment, without unexpected or severe AEs.

Table 2: Summary of literature reports on the safety and efficacy of mammalian target of rapamycin inhibitors in metastatic renal cell carcinoma.

Author (year)	No. of patients	VEGFR/VEGFR-targeting agents	Dose reductions required	Toxicities observed (Grade ≥3)
Lunardi et al.[72,73] (2008 and 2009)	2	Temsirolimus	No	None
Thiery-Vuillemin et al.[74] (2012)	2	Everolimus	Yes*	Asthaenia, hyperglycaemia
Guida et al.[75] (2015)	11	Everolimus	Yes	Thrombocytopenia, anaemia, skin rash, dyspnoea, and non-bacterial pneumonitis
Syrios et al.[76] (2013)	2	Everolimus	No	None
Miyake et al.[77] (2013)	10	Temsirolimus	No	Asthaenia, anaemia (1 patient each), thrombocytopenia (2 patients)
Shetty et al.[52] (2014)	9	Everolimus temsirolimus (plus sunitinib, sorafenib, and pazopanib)†	Yes (1 patient)‡	1 patient discontinued everolimus due to pneumonitis
Omae et al.[78] (2016)	4	Everolimus (4 patients) Temsirolimus (2 patients)	No (3 patients), yes (1 patient) No (1 patient), yes (1 patient)	None

*Everolimus starting dose was 5 mg/day with the possibility of escalation according to the tolerance after the first PK assessment; patient n=1 experienced escalation to 10 mg/day, but required dose reduction to 5 mg/day due to Grade 3 AEs (asthaenia).
†Authors analysed and reported different sequences of targeted agents.
‡Treated with everolimus.
VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor; AEs: adverse events.

In 2012, Thiery-Vuillemin et al.[74] for the first time reported PK data relative to everolimus treatment during haemodialysis in two mRCC patients pre-treated with sunitinib; in these two patients everolimus was administered at the reduced dose of 5 mg daily. From a PK viewpoint, dialysis did not modify everolimus blood concentrations, as they were close to the predialysis level; moreover, no everolimus was detected in the dialysate, confirming its lack of adhesion to the dialysis membrane.[74]

In 2012, Guida et al.[75] retrospectively collected data on 11 mRCC patients treated with everolimus. Everolimus was administered at the dose of 10 mg daily in 10 patients, and at the reduced dose of 5 mg daily in 1 patient only. Only five Grade 3 AEs were reported: thrombocytopenia, anaemia, cutaneous rash, dyspnoea, and non-bacterial pneumonitis (in the same patient). In this cohort of patients, the estimated PFS was 9 months, while estimated median OS was 15.7 months.[75]

In the already mentioned study from Shetty et al.[52] six patients were treated with everolimus, all at the dose of 10 mg daily. Four everolimus-related AEs were reported, only one severe (Grade 3). One patient discontinued everolimus due to pneumonitis, but overall the median duration of treatment was just 1.9 months.[52] Taking into account a few other cases reported in the literature[76-78] and summarised in Table 2, mTOR inhibitors' efficacy and safety does not significantly differ in mRCC patients on dialysis from those observed in non-dialytic patients.

CONCLUSION

One of the more challenging areas of onco-nephrology is the appropriate management of cancer patients requiring dialysis. Beyond the ethical aspect related to the choice of whether or not to initiate an active oncological treatment in a patient on dialysis (or vice versa),[79]

to date decisions about anti-cancer drug choices and dosing are too often not supported by PK or pharmacodynamic data, making therapeutic decisions extremely difficult.[80] An accurate understanding of the effects of dialysis on general drug clearance (e.g. volume of distribution, protein binding, and molecular size) is mandatory to reasonably estimate the safety of anti-cancer drugs in patients on dialysis.[80]

The above review of the scarce literature available could be useful to drive our everyday clinical decisions in a very complicated patient population such as that of patients undergoing dialysis. Although prospective studies would definitely be warranted in specific patient populations, such as those with chronic kidney disease and on dialysis, all the available data suggest that mRCC patients on dialysis have similar outcomes, both in terms of efficacy and safety, as mRCC patients with normal or marginally impaired kidney function, when treated with VEGF/VEGFR-targeting agents and/or mTOR inhibitors.

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