Renal effects of molecular targeted therapies in oncology: a review by the Cancer and the Kidney International Network (C-KIN)

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A number of cancer therapy agents are cleared by the kidney and may affect renal function, including cytotoxic chemotherapy agents, molecular targeted therapies, analgesics, antibiotics, radiopharmaceuticals and radiation therapy, and bone-targeted therapies. Many of these agents can be nephrotoxic, including targeted cancer therapies. The incidence, severity, and pattern of renal toxicities may vary according to the respective target of the drug. Here, we review the renal effects associated with a selection of currently approved targeted cancer therapies, directed to vascular endothelial growth factor or VEGF receptor(s) (VEGF/VEGFR), epidermal growth factor receptor (EGFR), human epidermal growth factor receptor2 (HER2), BRAF, anaplastic lymphoma kinase (ALK), programmed cell death protein-1 or its ligand (PD-1/ PDL-1), receptor activator of nuclear factor kappa-B ligand (RANKL), and mammalian target of rapamycin (mTOR). The early diagnosis and prompt treatment of these renal alterations are essential in the daily practice where molecular targeted therapies have a definitive role in the armamentarium used in many cancers.

**Key words:** nephrotoxicity, renal toxicity, kidney disease, renal failure, molecular targeted therapy, cancer

**introduction**

The National Cancer Institute (NCI) defines targeted therapies as ‘drugs or other substances that block the growth and spread of cancer by interfering with specific molecules involved in tumor growth and progression’. These drugs are the result of the growing knowledge regarding the processes and mechanisms that lead to tumor formation, growth, and dissemination that has emerged during the last 3 decades. Molecular signaling pathways targeted by these drugs generally include those regulating cell division and/or those inhibiting apoptosis. The
The pharmacodynamic effect of targeted therapies is to inhibit these pathways. However, such signaling pathways are also active in a healthy organism. Their increased activity drives tumorigenesis. As a result, their inhibition may be accompanied by side-effects, among which renal toxicities are of a particular interest.

**Prevalence of Chronic Kidney Disease in Cancer Patients**

During recent years, an impressive number of targeted therapies have demonstrated efficacy and clinical benefits in different tumor types with increased progression-free and/or overall survival. As the prevalence of chronic kidney disease (CKD) has been demonstrated to be high in solid tumor patients, their renal tolerance needs to be established. In France, the ‘IRMa’ studies (Insuffisance Rénale et Médicaments Anticancéreux; Renal Insufficiency and Anticancer Medications) reported a prevalence of a reduced glomerular filtration rate (GFR < 90 ml/min/1.73 m²) of 52.9% and 50.2% in IRMA-1 [1] and IRMA-2 [2], respectively, in a cohort of 5000 patients with different types of solid tumors. According to the international definition and stratification of CKD [3], the prevalence of stage 3–5CKD, excluding dialysis, was also high: 12.0% and 11.8%, respectively [1, 2]. In patients with kidney cancer, Huang et al. reported 87% prevalence of a GFR lower than 90 ml/min/1.73 m² in a cohort of 662 patients with a renal cortical tumor awaiting partial or radical nephrectomy [4]. The prevalence of a GFR lower than 60 ml/min/1.73 m² was 26%. Other studies reported prevalences of CKD of 16.1% to 25.0% in cancer patients in Belgium [5], United States [6], and Japan [7]. In the IRMA-1 study, the prevalence of CKD was consistently high in different tumor types, around 50%, either in breast, colorectal, lung, ovarian, or prostate cancers.

On the other hand, the incidence of cancers is higher in patients with kidney disease. A first study [8] showed that over a cohort of 3654 participants, men, but not women, with at least stage 3 CKD had a significantly increased risk for cancer as soon as GFR became lower than 55 ml/min/1.73 m² [8]. The risk of cancer mostly involved lung and urinary tract and increased by 29% for each 10-ml decline in eGFR (aMDRD). In a Danish registry study [9], the authors reported that over two 8-year periods of time: 1993–2000 and 2001–2008, the incidence of cancer per year of risk did not change significantly, 3.1% (95% CI 1.8–5.4) versus 2.6% (95% CI 2.1–3.3) (P = 0.4) while the average percentage in cancer prevalence gradually increased, from 10.4% (95% CI 8.1–13.3) in 1993–2000 to 14.0% (95% CI 12.8–15.4) in 2001–2008, resulting in a rise of 35% (P = 0.0002) [9]. The most frequent cancers in this population were basal cell carcinoma, squamous-cell carcinoma of the skin, breast cancer, cancer of cervix uteri, melanoma, and cancers of the colon, respiratory tract, bladder, prostate, and kidney, by descending order of frequency [10]. These studies showed that all CKD patients are at risk for cancer, and not only dialysis or kidney transplant recipients, as shown before [11, 12].

Interestingly, the types of cancers for which CKD was highly prevalent (breast, colorectal, lung, ovarian, and skin cancers) and those which were shown to be highly prevalent in CKD (breast, cervix, colon, and kidney) included tumors for which targeted therapies are available and used in clinical practice. This emphasizes why the renal safety of these drugs is an important issue.

**Cancer Therapies Targeted to VEGF and VEGFR**

Antiangiogenic drugs are targeted either to the circulating vascular endothelial growth factor (VEGF) or VEGF receptor(s) (VEGFR). They include monoclonal antibodies (Mab); bevacizumab, which binds and sequesters VEGF, and ramucirumab, targeted to VEGFR2; a number of tyrosine kinase inhibitors (TKI), which act on VEGFR: sunitinib, sorafenib, axitinib, regorafenib, and nintedanib; and a soluble recombinant decoy that binds to circulating VEGF: aflibercept (VEGF-Trap).

In the normal kidney, VEGF is produced by the podocytes that normally express VEGF at high levels and binds to the VEGF receptor present on glomerular and peritubular endothelium and mesangial cells. Local VEGF production maintains the normal functioning of these cells and the integrity of the glomerular filtration membrane. Eremina et al. [13] showed that podocyte-specific knockout of the VEGF gene resulted in renal disease in mice. It was characterized by nephrotic-range proteinuria, endotheliosis, and hyaline deposits. As a result, all drugs that act on the VEGF pathway may induce renal abnormalities, as a consequence of their intrinsic mode of action [14]. Their renal toxicity is mainly renovascular in nature, including hypertension (HTN), proteinuria, decreased GFR, and thrombotic microangiopathy (TMA). The latter remains rare. The recent prospective MARS study (management of antiangiogenics’ renovascular safety) reported no case of TMA in 1126 patients treated for the first time with an antiangiogenic drug, especially in ovarian [15], lung [16], and breast [17] cancer patients treated with bevacizumab.

In the MARS study, de novo HTN, defined as HTN occurring under treatment in patients with normal baseline blood pressure, occurred in 17.1%, 22.1%, and 12.9% of patients treated with bevacizumab for ovarian, lung, and breast cancer, respectively [15–17]. In all cases, HTN could be effectively controlled by classical antihypertensive therapy. However, few reports have been published regarding HTN-related clinical complications in patients receiving antiangiogenic agents, mainly TKI, including malignant HTN, severe refractory HTN, and HTN-associated reversible posterior leucoencephalopathy syndrome. Of note, the MARS study demonstrated that baseline HTN could be a risk factor for decreased GFR under antiangiogenic therapy [18], in concordance with a previous study [19]. HTN has also been suggested as a potential biomarker of activity/efficacy, especially for anti-VEGF TKI. Azizi et al. were the first to provide evidence that HTN could be a biomarker of sunitinib activity in metastatic renal cell carcinoma [20]. However, there is a lack of evidence on whether this biomarker could predict the clinical response to treatment of all antiangiogenic agents, and further studies are mandatory [21].

Again in the MARS study, de novo proteinuria, defined as proteinuria occurring under treatment in patients with no proteinuria at baseline, occurred in 36.4%, 72.1%, and 15.0% of patients treated with bevacizumab for ovarian, lung, and breast cancer, respectively, most frequently grade 1, according to the
cancer therapies targeted to EGFR

The cancer therapies targeting the epidermal growth factor receptor-1 (EGFR) include two Mab, cetuximab and panitumumab, and three TKIs, erlotinib, gefitinib, and afatinib.

In one study, it is reported that 13 of 633 patients treated with cetuximab (2%) may develop kidney failure [22]. Another concern regarding the renal tolerance of cetuximab is hypomagnesaemia, which can be problematic in patients with or without CKD. Magnesium reabsorption in the distal convoluted tubule is partly dependent on EGFR activity on the basolateral membrane. This results in the integration of the cation channel transient receptor potential M6 into the apical membrane, which facilitates the reabsorption of magnesium from the urinary space. Cetuximab prevents EGF binding to its receptor causing renal magnesium wasting. In two studies, the authors showed that both from a pharmacokinetic point of view and a biological tolerance point of view, the use of cetuximab appears to be safe, even in patients with end-stage renal disease undergoing hemodialysis [23, 24].

Panitumumab was not associated with renal side-effects in the first clinical reports in metastatic renal cell carcinoma [25]. However, in the spectrum phase 3, open label, randomized trial of cisplatin and fluorouracil with or without panitumumab in recurrent or metastatic squamous-cell carcinoma of the head and neck, patients who received panitumumab showed higher frequencies of hypomagnesaemia (12% versus 4% in the control group), hypokalemia (10% versus 7%), and dehydration (5% versus 2%) [26].

There are no data reporting any renal side-effect related to erlotinib in the clinic while it has been shown that, at high enough doses, it may also induce hypomagnesaemia [27], several authors further suggesting that this effect could be related to the inhibition of EGFR in the intestine and the kidney [28]. Other authors suggested that erlotinib, which is an orally administered small molecule, might contain in its formulation, adjuvant substances such as magnesium stearate, which could compensate for hypomagnesaemia [29]. In a recent preclinical study conducted in nephrotic rats, the authors further showed that erlotinib could prevent GFR deterioration and salt retention in rats receiving doxorubicin with or without erlotinib. This effect was suggested to be independent of the inhibition of EGFR, and erlotinib had, however, no significant effect on proteinuria [30].

Available anti-HER2 therapies include two Mab, trastuzumab and pertuzumab (see below), and the TKI lapatinib. Trastuzumab is a recombinant humanized monoclonal antibody directed against the extracellular domain of the HER2 and has not been reported to induce any renal effect. However, cardiorenal syndrome can occur with the use of this agent in combination with anthracyclines [31], although recent data suggest that the cardiac tolerance of trastuzumab in combination with epirubicin could be of an acceptable range [32]. The same pattern of renal tolerance has been shown for lapatinib. The cardiac tolerance of lapatinib in combination with anthracyclines or other chemotherapy does not differ from that of trastuzumab. Furthermore, a recent study showed that the cardiotoxicity of trastuzumab might be increased in patients present with CKD [33]. The authors retrospectively studied 499 consecutive patients who had received adjuvant trastuzumab for early HER2-positive breast cancer, and they compared the 130 patients who experienced cardiotoxicity to the 369 who did not. Among items that significantly differed between groups, the eGFR was significantly lower in patients who developed cardiotoxicity as compared with patients who did not. Furthermore, the prevalence of trastuzumab cardiotoxicity was significantly higher in the group of patients with an eGFR within 15–29, and 30–89, as compared with patients whose eGFR was ≥90 ml/min/1.73 m², respectively 38%, 28%, and 15%. The best prognostic cutoff value for eGFR and cardiotoxicity was 78 ml/min/1.73 m² meaning that patients who had a lower eGFR had a significantly increased risk for cardiotoxicity [32]. Interestingly, all patients in this study had been previously treated with chemotherapy, including anthracyclines, cyclophosphamide, taxanes, and 5-fluorouracil. None of these chemotherapeutic agents required dosage modification given the level of GFR of the study population [34]. Since trastuzumab does not require dose modification, neither this potentially increased cardiotoxicity cannot be related to overdosage. In another article, discussing the previous one, the authors emphasize the importance of a cardiorenal syndrome that could occur, and/or be amplified by the presence of CKD [35]. As a result, the potential effect of CKD on trastuzumab cardiotoxicity being pharmacodynamic rather than pharmacokinetic, this potential risk should be also observed with other anti-HER2 therapies.

cancer therapies targeted to the dimerization of HER2

Pertuzumab also is a recombinant humanized Mab directed to the extracellular domain of HER2, but to a different epitope as compared with trastuzumab. Pertuzumab blocks the dimerization of HER2, which is essential for cell activation and proliferation. In combination with trastuzumab and docetaxel, the clinical results in HER2-positive breast cancer showed improved progression-free and overall survival, which led to approval and marketing authorization in the metastatic setting in Europe and both in metastatic and (neo) adjuvant settings in the United States [36]. No renal side-effect has been reported to date with pertuzumab in clinical trials. Data from patients in the daily clinical practice are missing since the drug has only been made available recently.

Human epidermal growth factor receptor-2 (HER2) is a membrane receptor, member of the EGFR family, which is overexpressed in some aggressive forms of breast and gastric cancers.
cancer therapies targeted to BRAF

Vemurafenib and dabrafenib are drugs that showed efficacy in metastatic melanoma in patients carrying a specific mutation on the BRAF enzyme (V600 BRAF mutation). There is no report of renal toxicity in the European summary of product characteristics (SmPC). However, several observations of kidney failure under treatment with vemurafenib have been recently reported as abstracts and in two publications [37, 38]. Renal toxicity may be severe in some cases, and often occurs in patients who present with comorbidities such as hypertension and/or diabetes. In most cases, renal function recovered upon treatment discontinuation, but in some instances, kidney failure recurred when vemurafenib was reintroduced. Studies are mandatory to investigate the mechanism of these renal toxicities, and to identify risk factors.

Vandetanib is a multikinase inhibitor. According to the SmPC, it has been reported that electrolyte disturbances can occur in less than 1% of the patients in clinical trials. In the adverse events section, hypophosphatemia is reported in 7% of patients included in the clinical trials, more than half of them (4% of total) with grade 3 in severity (NCI—CTC). It is therefore recommended that patients should be routinely monitored for serum creatinine and electrolytes while treated with dabrafenib, and treatment interruption is recommended when serum creatinine increases or electrolyte disturbance occurs.

cancer therapies targeted to ALK

Crizotinib is an inhibitor of the anaplastic lymphoma kinase (ALK) indicated in patients with non-small cell lung cancer (NSCLC) harboring ALK fusions. The SmPC reports hypophosphatemia as a common adverse event (3% all grades, 2% grade 3). Renal failure has not been reported; however, renal cysts may occur in less than 1% of the patients in clinical trials. These cysts might be reversible despite continuous treatment, however [39]. No renal adverse event has been reported in the first-in-human phase 1 study [40]. Of note, diarrhea and vomiting were highly frequent, with 50% and 39% of the patients affected, respectively, thus exposing patients to dehydration and functional renal insufficiency. The good renal tolerance profile has been confirmed in the phase 1–2 study of crizotinib in patients with ALK-rearranged advanced NSCLC [41], and in the open label phase 3 study of crizotinib versus chemotherapy [42]. However, a recent publication reported acute renal failure in a patient receiving crizotinib [43]. Serum creatinine rose from 0.8 to 2.6 mg/dl over 3 weeks of crizotinib treatment. Renal function recovered partly to 1.6 mg/dl upon crizotinib discontinuation, and rose again to 3.8 mg/dl when crizotinib was reintroduced. Acute renal failure was accompanied by proteinuria and hematuria.

Vandetanib was reintroduced. Acute renal failure was accompanied by proteinuria and hematuria. The good renal tolerance profile has been confirmed in the phase 1–2 study of crizotinib in patients with ALK-rearranged advanced NSCLC [41], and in the open label phase 3 study of crizotinib versus chemotherapy [42]. However, a recent publication reported acute renal failure in a patient receiving crizotinib [43]. Serum creatinine rose from 0.8 to 2.6 mg/dl over 3 weeks of crizotinib treatment. Renal function recovered partly to 1.6 mg/dl upon crizotinib discontinuation, and rose again to 3.8 mg/dl when crizotinib was reintroduced. Acute renal failure was accompanied by proteinuria and hematuria.

cancer therapies targeted to VEGFR, EGFR, and RET

Vemurafenib and dabrafenib are drugs that showed efficacy in metastatic melanoma in patients carrying a specific mutation on the BRAF enzyme (V600 BRAF mutation). There is no report of renal toxicity in the European summary of product characteristics (SmPC). However, several observations of kidney failure under treatment with vemurafenib have been recently reported as abstracts and in two publications [37, 38]. Renal toxicity may be severe in some cases, and often occurs in patients who present with comorbidities such as hypertension and/or diabetes. In most cases, renal function recovered upon treatment discontinuation, but in some instances, kidney failure recurred when vemurafenib was reintroduced. Studies are mandatory to investigate the mechanism of these renal toxicities, and to identify risk factors.

Vandetanib is a multikinase inhibitor. According to the SmPC, it has been reported with a number of electrolyte disturbances, such as hypocalcemia (very common, ≥10%), hypokalemia, hypercalcaemia, and hyponatremia (common, 1%–10%). HTN also occurred in more than 10% of the patients. Vandetanib has been reported to be a potent inhibitor of 2 different renal transporters MATE1 and MATE2K, which might explain why both decreased creatinine clearance and increased cisplatin nephrotoxicity can be associated with vandetanib administration [44]. Renal adverse events are frequent and include several manifestations, such as proteinuria and nephrolithiasis (≥10%), dysuria, hematuria, pollakiuria, and renal failure (1%–10%), and hypomagnesemia and anuria (0.1%–1%). Data from a phase 2, double-blind, randomized trial of vandetanib in locally advanced or metastatic differentiated thyroid cancer confirmed that HTN is frequent (34%) and electrolyte disturbances with 4% of grade 3–4 hypokalemia and 4% of grade 3–4 hypercalcaemia [45]. The randomized, double-blind phase 3 trial confirmed HTN is frequent (32%) but no electrolyte disturbances were reported in this trial (only adverse events, which incidence was ≥10% being reported) [46]. It is worthwhile to mention that electrolytes must be frequently checked because some of these imbalances can predispose to QTc alterations and arrhythmias.

cancer therapies targeted to PD-1 and PDL-1

Drugs targeting programmed cell death protein 1 (PD-1) or its ligand (PDL-1) have very recently demonstrated their potential efficacy in different tumor types in preclinical and phase 1–2 clinical studies. Activated T cells are carrying PD1, the receptor, at the surface of their membrane (as well as B cells and myeloid cells). Inhibition of T cell proliferation and IL-2 production occurs when PDL-1 interacts with its receptor PD-1. Tumor cells carrying PDL-1 are, thus protected from immune reactions. The objective of blocking the PD1-PDL-1 system is, thus to restore or generate the activation of the immune system, directed to tumor cells. There are several Mab currently developed, among which BMS-936558/MDX-1106 (nivolumab) and MK6475 (pembrolizumab), directed to PD-1, and MPDL-3280A, directed to PDL-1. Nivolumab has not been associated with renal side-effects; however, hypophosphatemia occurred in 3% of patients (1% grade 3–4) [47]. HTN and proteinuria have been previously reported in a phase 1 study. HTN occurred in 16.7% (grade 2, one patient out of six) of patients treated at the lowest dose of 0.3 mg/kg, while no patient among those who received higher doses developed HTN. Grade 2 proteinuria occurred with the same frequency, 16.7% (one patient out of six treated at the dose of 1 mg/kg) [48]. One case of pembrolizumab-associated rhabdomyolysis and acute kidney failure has been reported [49] and renal failure occurred in 2% of the patients in a review [50].

There is no data to date on MPDL-3280A renal safety. In recent published reports on the safety and efficacy of another Mab, MDX1105-01, no renal adverse event has been reported [51].

cancer therapies targeted to RANKL

Denosumab is a Mab that inhibits the osteoprotegerin/RANKL by blocking RANKL. Its clinical efficacy has been established in the prevention of skeletal-related events in patients with bone metastases. Data from three-phase 3 clinical trials comparing denosumab to zoledronic acid in a head-to-head...
fashion, reported on renal adverse events. The renal tolerance was carefully studied in these trials since nephrotoxicity is one of the most frequent side-effects of zoledronic acid. These trials were conducted in breast [52] and prostate [53] cancer patients with bone metastases and in a variety of solid tumors other than breast and prostate, or multiple myeloma patients [54]. Denosumab was better tolerated than zoledronic acid in breast cancer patients, with fewer renal side-effects (4.9% versus 8.5% for denosumab and zoledronic acid, respectively) and fewer cases of renal failure (0.2% versus 2.5%, \( P < 0.05 \)). In castration-resistant prostate cancer and in other solid tumors and myeloma, there was no statistical difference in terms of renal tolerance, between denosumab and zoledronic acid. The combined analyses of these trials reported frequencies of renal adverse events of 9.2% in denosumab-treated patients versus 11.8% in zoledronic acid-treated patients [55]. Furthermore, denosumab does not require any dosage adjustment in case of preexisting renal insufficiency whereas zoledronic acid does.

Moreover, preclinical studies suggest that the osteoprotegerin/RANK/RANKL pathway might be imbalanced in patients with CKD or kidney failure [56, 57]. This taken together with the fact that RANKL mRNA and protein have been detected in the mouse kidney throughout development [58], strongly suggest that, as for all patients with cancer, those who receive denosumab should have their renal function monitored before and during therapy. Calcium should also be closely monitored since hypocalcaemia is often associated with the use of denosumab.

cancer therapies targeted to mTOR

Everolimus and temsirolimus are drugs that inhibit the mammalian target of rapamycin (mTOR). They have demonstrated potential interest in solid organ transplantation, in the prevention of graft rejection, before potential benefits in treating cancers have emerged. The phosphoinositide 3-kinase (PI3K)/Akt pathway is activated in a number of cancers. The mTOR kinase is one important mediator of this signaling pathway and mTOR inhibitors can block signal transduction.

In a recent phase 1–2 study in renal cell carcinoma, everolimus was associated with HTN and proteinuria in 22% and 23% of the patients, respectively (NCI—CTC Grade 2–3). Hypophosphatemia was also retrieved in 12%, hyponatremia

<table>
<thead>
<tr>
<th>Table 1. Targeted cancer therapies and the kidney</th>
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<tbody>
<tr>
<td><strong>Targeted therapy</strong></td>
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<tr>
<td>Crizotinib</td>
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<tr>
<td>Dabrafenib</td>
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<tr>
<td>Vemurafenib</td>
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<tr>
<td>Cetuximab</td>
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<tr>
<td>Erlotinib</td>
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<tr>
<td>Panitumumab</td>
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<td>Lapatinib</td>
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<td>Trastuzumab</td>
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<tr>
<td>Pertuzumab</td>
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<tr>
<td>Everolimus</td>
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<tr>
<td>Temsirolimus</td>
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<tr>
<td>Nivolumab (BMS-936558)</td>
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<tr>
<td>Pembrolizumab</td>
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<td>MDX1105-01</td>
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<td>MPDL-3280A</td>
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<tr>
<td>Denosumab</td>
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<td>Bevacizumab</td>
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<tr>
<td>Afatinib</td>
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<td>Axitinib</td>
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<tr>
<td>Sorafenib</td>
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<tr>
<td>Sunitinib</td>
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<tr>
<td>Vandetanib</td>
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</tbody>
</table>

RI, renal insufficiency; Yes, dosage adjustment is required in case of RI; No, no dosage adjustments required in case of RI, the usual dose should be used; ND, there are no data in the literature allowing recommendation; GFR, glomerular filtration rate.
in 4%, and one patient had grade 3 acute renal failure [59]. However, no case of HTN and/or proteinuria appears in a previous report on the safety of everolimus in the same tumor type within an expanded access program [60]. In another phase 2 trial in nonclear-cell renal cell carcinoma, hypophosphatemia in one patient required dose reduction or delay [61]. In the phase 3 trial in metastatic renal cell carcinoma, only increases in serum creatinine are reported as renal adverse events, in 50% of the patients in the everolimus arm [62]. Finally, in a phase 2 trial of daily oral everolimus in metastatic clear cell renal cell carcinoma, hypophosphatemia was the only renal side-effect reported, with an incidence of 30.8% (2.6% grade 3, one patient) [63].

The first phase 2 study reported in the literature for temsirolimus, at that time known only under the name CCI-779, was conducted in patients with advanced refractory renal cell carcinoma [64]. No renal adverse events were reported. However, the threshold for study drug-related adverse event reporting was 20%, so less frequent toxicities were not reported. Grade 3–4 hypophosphatemia, related to the study drug, occurred in 6% to 18% of the patients, depending on the dosage administered. The frequency of hypophosphatemia was not correlated with the dose: 14% at 25 mg, 18% at 75 mg, and 6% at 250 mg. In a phase 1 study on the safety and pharmacokinetics of temsirolimus, one patient presented with grade 3 neutropenia, thrombocytopenia, and hypophosphatemia, at an intermediate dose (34.0 mg/m²) among those tested in the escalation (range: 7.5–220 mg/m²) [65]. One case of temsirolimus-associated glomerulopathy has been reported [66].

Both drugs have also been studied in pancreatic cancer. Two phase 2 studies, one with intravenous temsirolimus and the other with oral everolimus have been reported in the literature [67]. Temsirolimus was not reported with renal adverse events and everolimus was associated only with hyponatremia (grade 3–4) in one patient.

Table 1 summarizes the renal effects of targeted therapies reviewed in this article. A proposal for routine monitoring in patients treated with targeted therapies is presented in Table 2. eGFR determination before the start of treatment is mandatory in all cases in order to (i) adjust dosage when required and/or (ii) draw attention to renal safety since preexisting abnormal eGFR is a known risk factor for renal effects of drugs.

**Table 2. Routine monitoring in patients treated with targeted therapies**

<table>
<thead>
<tr>
<th>Targeted therapy</th>
<th>eGFR</th>
<th>Serum</th>
<th>Urine</th>
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<tbody>
<tr>
<td>Crizotinib</td>
<td>Yes</td>
<td>Phosphorus, creatinine</td>
<td>Search for renal cysts in case of AKI</td>
</tr>
<tr>
<td>Dabrafenib</td>
<td>Yes</td>
<td>Phosphorus, creatinine</td>
<td>Renal biopsy can be indicated in case of AKI</td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>Yes</td>
<td>Creatinine</td>
<td>–</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>Yes</td>
<td>Magnesium, creatinine</td>
<td>–</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>Yes</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Panitumumab</td>
<td>Yes</td>
<td>Magnesium, potassium</td>
<td>–</td>
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<tr>
<td>Lapatinib</td>
<td>Yes</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Trastuzumab</td>
<td>Yes</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Pertuzumab</td>
<td>Yes</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Everolimus</td>
<td>Yes</td>
<td>Phosphorus, creatinine, sodium</td>
<td>Urinary dipstick, when positive: protein/creatinine ratio in urine</td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>Yes</td>
<td>Phosphorus</td>
<td>–</td>
</tr>
<tr>
<td>Nivolumab (BMS-936558)</td>
<td>Yes</td>
<td>Phosphorus</td>
<td>Urinary dipstick, when positive: protein/creatinine ratio in urine</td>
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<tr>
<td>Pembrolizumab</td>
<td>Yes</td>
<td>Creatinine</td>
<td>–</td>
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<tr>
<td>MDX1105-01</td>
<td>Yes</td>
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<tr>
<td>Denosumab</td>
<td>Yes</td>
<td>Creatinine, potassium</td>
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<tr>
<td>Bevacizumab</td>
<td>Yes</td>
<td>Creatinine</td>
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<td>Afatinib</td>
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<tr>
<td>Axitinib</td>
<td>Yes</td>
<td>Creatinine</td>
<td>Urinary dipstick, when positive: protein/creatinine ratio in urine</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>Yes</td>
<td>Creatinine</td>
<td>Urinary dipstick, when positive: protein/creatinine ratio in urine</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>Yes</td>
<td>Creatinine</td>
<td>Urinary dipstick, when positive: protein/creatinine ratio in urine</td>
</tr>
<tr>
<td>Vandetanib</td>
<td>Yes</td>
<td>Calcium, potassium, sodium, creatinine</td>
<td>Urinary dipstick, when positive: protein/creatinine ratio in urine. Hematuria, lithiasis</td>
</tr>
</tbody>
</table>

*Table 2: Routine monitoring in patients treated with targeted therapies.*

**eGFR, estimated glomerular filtration rate; AKI, acute kidney injury (serum creatinine increase of 25% or more from baseline).**

**Conclusion**

The majority of targeted therapies are associated with renal toxicity. These renal effects are most often mild in severity. However, targeted cancer therapies are often used in combination with chemotherapy, or sequentially after, and a number of chemotherapies may be nephrotoxic. There is, thus a potential risk of an additional toxic effect on the kidney, from both chemo- and targeted therapies. Renal monitoring is, therefore, crucial, both during treatment to identify renal alterations at the earliest, and also before initiation to allow differential analysis of the origin of the renal event. Furthermore, some targeted therapies may require dosage adjustments to renal function [68], which makes evaluation of the GFR mandatory before...
treatment administration. Dosage adjustments should be carried out according to validated and evidence-based guidelines [69, 70, 34]. Clinical trials systematically exclude patients with pre-existing renal dysfunction, who are at risk of developing renal effects. Due to the high prevalence of CKD in cancer patients in clinical practice, this may explain why such renal effects are not often reported in trials, whereas they may occur in routine practice. Such issues will be studied and addressed as part of the Cancer & the Kidney International Network (C-KIN) in order to provide physicians with evidence-based clinical practice guidelines on how to deal with renal issues to optimize the care of cancer patients.

disclosure
The authors declare no competing interest related to this article.

References


