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RENAL EFFECTS OF MOLECULAR TARGETED THERAPIES IN ONCOLOGY

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Abstract:

One prevalent type of urologic tumor that develops from the extremely diverse renal tubule epithelium is renal cell carcinoma (RCC). Clinical management for RCC has changed during the past ten years due to medications that target renal cancer cells. The idea that renal cancer stem cells (CSCs), which were isolated from renal carcinomas, are what cause tumor growth and resistance to traditional chemotherapy and radiation has recently been put forth. This has given rise to treatments that target this aggressive cell population. Characterization of disease subtypes will be precisely informed by the precise identification of renal CSC populations and the entire cell hierarchy. In the end, this will help provide more individualized and focused treatments.

Tyrosine kinase inhibitors, mammalian target of rapamycin inhibitors (mTOR), interleukins, CSC marker inhibitors, bone morphogenetic protein-2, antibody drug conjugates, and nanomedicine are some of the possible targeted options for renal cancer cells and renal CSCs that we have compiled here. To sum up, targeted therapy for RCC offer fresh avenues for research and clinical study as well as a glimmer of hope for more sophisticated clinical treatment.

Keywords: glomerular filtration rate (GFR), chronic kidney disease (CKD), monoclonal antibodies (Mab), vascular endothelial growth factor (VEGF), nephrectomy, cell death protein 1 (PD-1),

INTRODUCTION

Targeted therapies are defined by the National Cancer Institute (NCI) [25] as medications or other substances that interfere with particular molecules involved in tumor growth and progression in order to prevent the growth and spread of cancer. These medications are the outcome of the last three decades increasing understanding of the mechanisms and processes underlying tumor genesis, growth, and dissemination. These medications often target molecular signaling pathways that control cell division and/or prevent apoptosis. Targeted treatments have the pharmacodynamic effect of blocking these pathways. But in a healthy organism, these signaling pathways are also active. Tumorigenesis is caused by their increasing activity. [26] Renal toxicities are of special relevance among the adverse effects that may emerge from their inhibition.

PREVALENCE OF CHRONIC KIDNEY DISEASE IN CANCER PATIENTS

In recent years, a remarkable number of targeted medicines have shown clinical advantages and efficacy in various tumor types, leading to improved overall and/or progression-free survivals. Patients with solid tumors have been shown to have a high prevalence of chronic kidney disease (CKD), hence it is necessary to determine their renal tolerance. In a cohort of 5000 patients with various solid tumor types, the "IRMA" studies (Insuffisance Rénale et Médicaments Anticancéreux; Renal Insufficiency and Anticancer Medications) in France found that the prevalence of a reduced glomerular filtration rate (GFR < 90

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ml/min/1.73 m2) was 52.9% in IRMA-1 [16] and 50.2% in IRMA-2. With dialysis excluded, the prevalence of stage 3–5 CKD was likewise high, at 12.0% and 11.8%, respectively, in accordance with the worldwide definition and categorization of CKD. In a cohort of 662 patients with a renal cortical tumor awaiting partial or radical nephrectomy, Huang et al. found that 87% of patients with kidney cancer had a GFR less than 90 ml/min/1.73 m2 [5]. A GFR of less than 60 ml/min/1.73 m2 was present in 26% of cases. According to other research, the prevalence of CKD in cancer patients in Belgium [5], the US, and Japan [16] ranged from 16.1% to 25.0%. Around 50% of all tumor types in the IRMA-1 research had chronic kidney disease (CKD), whether they were breast, colorectal, lung, ovarian, or prostate malignancies.

However, those with kidney dysfunction have a higher prevalence of cancer. According to the first study, which had 3654 people, males with at least stage 3 CKD—but not women—had a markedly higher risk of developing cancer as soon as their GFR dropped below 55 ml/min/1.73 m2. For every 10-ml drop in eGFR (aMDRD), the risk of cancer rose by 29% and primarily affected the lung and urinary tract. According to the authors of a Danish registry study [17], during two 8-year periods: The average percentage of cancer prevalence increased gradually from 10.4% (95% CI 8.1–13.3) in 1993–2000 to 14.0% (95% CI 12.8–15.4) in 2001–2008, a rise of 35% (P = 0.0002) [17]. In contrast, the incidence of cancer per year of risk did not change significantly between 1993–2000 and 2001–2008, ranging from 3.1% (95% CI 1.8–5.4) to 2.6% (95% CI 2.1–3.3) (P = 0.4). According to descending order of frequency, the most common cancers in this population were melanoma, breast cancer, cervix uteri cancer, squamous-cell carcinoma of the skin, basal cell carcinoma, and cancers of the colon, respiratory tract, bladder, prostate, and kidney [13]. According to these research, cancer is a risk factor for all CKD patients, not just those receiving dialysis or kidney transplants, as previously demonstrated [11, 3]. It's interesting to note that tumors for which targeted therapies are available and used in clinical practice were among the cancer types for which CKD was highly prevalent (breast, colorectal, lung, ovarian, and skin cancers) and those that were demonstrated to be highly prevalent in CKD (breast, cervix, colon, and kidney). This highlights the significance of these medications' renal safety.

Cancer therapies targeted to VEGF and VEGFR

The circulating vascular endothelial growth factor (VEGF) or its receptors (VEGFR) are the targets of antiangiogenic medications. Aflibercept (VEGF-Trap), a soluble recombinant decoy that binds to circulating VEGF, bevacizumab, which binds and sequesters VEGF, ramucirumab, which targets VEGFR2, and several tyrosine kinase inhibitors (TKI) that act on VEGFR include sunitinib, sorafenib, axitinib, regorafenib, and nintedanib. Podocytes in a healthy kidney produce VEGF, which is expressed at high levels and attaches to the VEGF receptor found on mesangial cells and glomerular and peritubular endothelium. The integrity of the glomerular filtration membrane and the regular operation of these cells are preserved by local VEGF synthesis. Mice with podocyte-specific VEGF gene deletion developed renal dysfunction, as demonstrated by Eremina et al. Endotheliosis, hyaline deposits, and nephrotic-range proteinuria were its defining features. Because of their inherent method of action, all medications that affect the VEGF pathway have the potential to cause renal problems [8].

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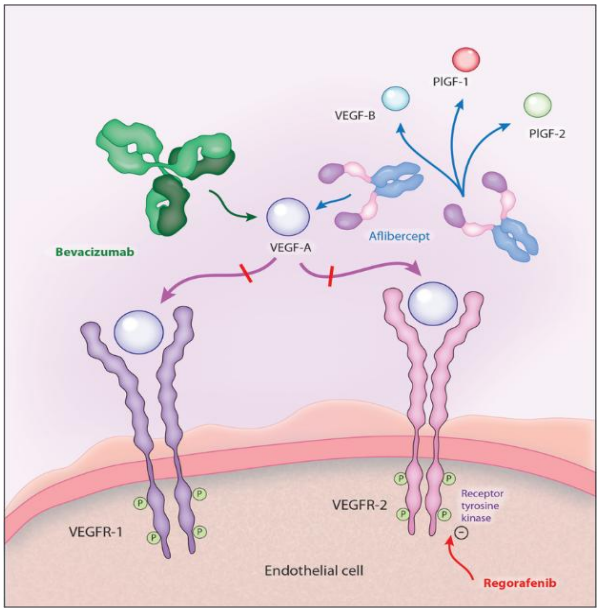

They mostly cause renovascular renal toxicity, which includes thrombotic microangiopathy (TMA), proteinuria, reduced GFR, and hypertension (HTN). The latter is still uncommon. In 1126 patients receiving their first antiangiogenic medication treatment, particularly those with ovarian, lung, and breast cancers receiving bevacizumab, the recent prospective MARS research (management of antiangiogenics' renovascular safety) found no cases of TMA. In the MARS research, 17.1%, 22.1%, and 12.9% of patients treated with bevacizumab for ovarian, lung, and breast cancer, respectively, experienced de novo hypertension, which is defined as hypertension that develops while a patient is receiving treatment and has a normal baseline blood pressure [15]. In every situation, traditional antihypertensive medication may successfully control hypertension. However, there aren't many published data on the clinical sequelae of hypertension in patients receiving antiangiogenic drugs, primarily TKI. These include severe refractory hypertension, malignant hypertension, and HTN-associated reversible posterior leucoencephalopathy syndrome. Notably, the MARS study supported a prior study [17] by showing that baseline HTN may be a risk factor for reduced GFR with antiangiogenic therapy. Additionally, HTN has been proposed as a possible biomarker of efficacy or activity, particularly for anti-VEGF TKI. HTN may be a biomarker of sunitinib action in metastatic renal cell carcinoma, according to information first presented by Azizi et al. Further research is necessary because there is insufficient data to determine whether this biomarker could predict the clinical response to treatment of all antiangiogenic drugs [24]. According to the National Cancer Institute-Common toxicity criteria for adverse events (NCI-CTCAE), de novo proteinuria—defined as proteinuria that develops during treatment in patients who did not have it at baseline—occurred in 36.4%, 72.1%, and 15.0% of patients treated with bevacizumab for ovarian, lung, and breast cancer, respectively. These cases were most often grade 1 [15]. Regarding HTN and proteinuria, Axitinib's renovascular tolerance profile is comparable. But no TMA has been documented as of yet. Since they were just licensed, ramucirumab and nintedanib have not yet been assessed in a standard clinical environment. However, care must be taken because these new medications may have the same renal consequences.

Cancer therapies targeted to EGFR

There are three TKIs (erlotinib, gefitinib, and afatinib) and two Mab (cetuximab and panitumumab) that target the epidermal growth factor receptor-1 (EGFR). According to one study, 13 out of 633 patients receiving cetuximab (2%) may get renal failure [4]. Hypomagnesaemia is another issue with cetuximab's renal tolerance that can affect patients with or without chronic kidney disease. EGFR activity on the basolateral membrane is partially responsible for magnesium reabsorption in the distal convoluted tubule. Magnesium is reabsorbed from the urine space more easily as a result of the cation channel transient receptor potential M6 being integrated into the apical membrane. Renal magnesium wasting results from cetuximab's inhibition of EGF's receptor binding. Even in patients with end-stage renal illness receiving hemodialysis, the authors of two trials demonstrated that cetuximab appeared to be safe from the perspectives of pharmacokinetics and biological tolerance [21].

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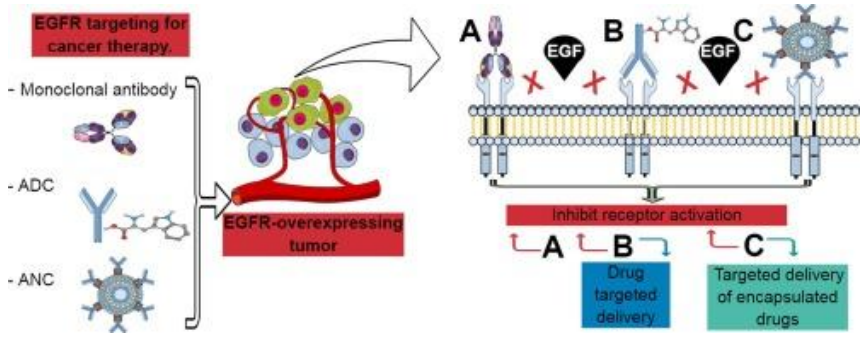

In the initial clinical reports of metastatic renal cell cancer, panitumumab was not linked to renal side effects. However, patients who received panitumumab had higher rates of hypomagnesaemia (12% versus 4% in the control group), hypokalemia (10% versus 7%), and dehydration (5% versus 2%) in the spectrum phase 3, open label, randomized trial of cisplatin and fluorouracil with or without panitumumab in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck. While it has been demonstrated that erlotinib may also cause hypomagnesaemia at high enough doses [2], there are no data indicating any renal side effects associated with the drug in clinical settings. Several authors have also suggested that this effect may be related to the inhibition of EGFR in the kidney and intestine [15]. In order to compensate for hypomagnesaemia, some authors proposed that the oral small molecule erlotinib might include adjuvants such magnesium stearate in its formulation. The authors of a recent preclinical investigation in nephrotic rats also shown that erlotinib might stop salt retention and GFR degradation in rats given doxorubicin with or without erlotinib. However, erlotinib had no discernible effect on proteinuria, and this result was proposed to be independent of EGFR inhibition.

Cancer therapies targeted to HER2

Some aggressive types of breast and stomach cancers overexpress the membrane receptor known as human epidermal growth factor receptor-2 (HER2), which belongs to the EGFR family. Two Mab, trastuzumab and pertuzumab (see below), as well as the TKI lapatinib, are available anti-HER2 treatments. Recombinant humanized monoclonal antibody trastuzumab targets the extracellular domain of HER2 and has not been shown to have any effect on the kidneys. Although new results indicate that the cardiac tolerance of trastuzumab in combination with epirubicin may be within an acceptable range, the use of this medication in conjunction with anthracyclines can result in cardiorenal syndrome [31]. Lapatinib has demonstrated the similar pattern of renal tolerance. When lapatinib is used with anthracyclines or other chemotherapy, its cardiac tolerance is identical to that of trastuzumab. Additionally, a recent study revealed that patients with CKD may have higher levels of trastuzumab cardiotoxicity [18]. The authors contrasted the 369 patients who did not develop cardiotoxicity with the 130 individuals who did in their retrospective analysis of 499 consecutive patients who had received adjuvant trastuzumab for early HER2-positive breast cancer. Among the variables where there were significant group differences, patients who experienced cardiotoxicity had a considerably lower eGFR than those who did not. Additionally, compared to patients whose eGFR was ≥90 ml/min/1.73 m2, the prevalence of trastuzumab cardiotoxicity was substantially greater in the groups of patients with eGFRs within 15–29 and 30–89, at 38%, 28%, and 15%, respectively. 78 ml/min/1.73 m2 was the best predictive cutoff value for both cardiotoxicity and eGFR, indicating that patients with lower eGFR were at a much higher risk for cardiotoxicity.

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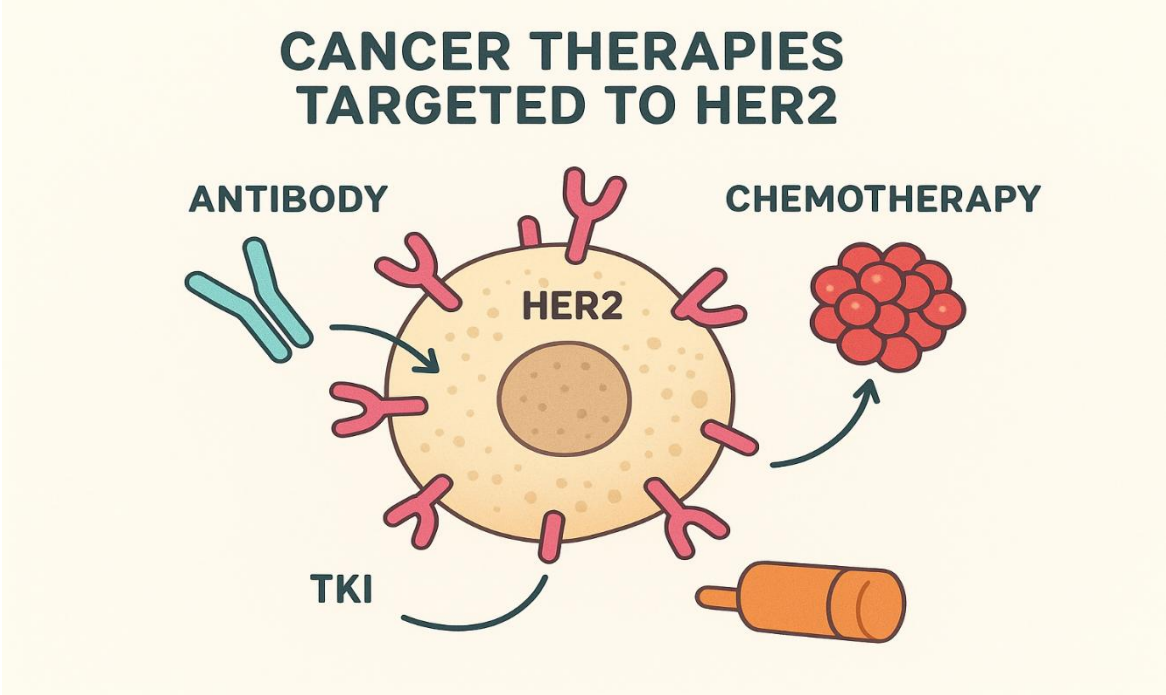

It's interesting to note that every patient in this trial had previously had chemotherapy, which included 5-fluorouracil, cyclophosphamide, anthracyclines, and taxanes. Considering the research population's GFR, none of these chemotherapeutic drugs needed their dosages changed. This possible increase in cardiotoxicity cannot be linked to overdosing because trastuzumab does not require dose change. The authors stress the significance of a cardiorenal syndrome that may arise and/or be exacerbated by the presence of CKD in a different article that discusses the preceding one. Because CKD may have a pharmacodynamic rather than a pharmacokinetic influence on trastuzumab cardiotoxicity, this possible risk should be considered while using other anti-HER2 treatments.

Cancer therapies targeted to the dimerization of HER2

Similar to trastuzumab, pertuzumab is a recombinant humanized monoclonal antibody that targets a distinct epitope in the extracellular domain of HER2. Pertuzumab prevents HER2 from dimerizing, which is necessary for cell division and activation. Clinical results in HER2-positive breast cancer demonstrated improved overall and progression-free survival when combined with trastuzumab and docetaxel. This led to approval and marketing authorization in the metastatic setting in Europe and in both the metastatic and (neo) adjuvant settings in the United States [20]. Pertuzumab has not yet been associated with any renal adverse effects in clinical trials. Since the medication has just recently become available, patient data from the routine clinical practice is lacking.

Cancer therapies targeted to BRAF

Vemurafenib and dabrafenib are medications that have demonstrated effectiveness in treating metastatic melanoma in persons with a certain BRAF enzyme mutation (the V600 BRAF mutation). The European summary of product characteristics (SmPC) does not include any information regarding kidney toxicity. However, a number of kidney failure findings while using vemurafenib have recently been documented in two papers and as abstracts [10]. Patients with concomitant conditions like diabetes and/or hypertension are more likely to experience renal damage, which can occasionally be quite severe. After stopping treatment, renal function usually improved, but in certain cases, vemurafenib caused kidney failure to return. Research is required to determine risk factors and to look into the mechanism behind these kidney toxicities.

Cancer therapies targeted to ALK

For patients with non-small cell lung cancer (NSCLC) who have ALK fusions, crizotinib, an inhibitor of the anaplastic lymphoma kinase (ALK), is recommended. Hypophosphatemia is listed by the SmPC as a frequent adverse occurrence (3% for all grades, 2% for grade 3). Although renal failure has not been documented, less than 1% of people in clinical trials may develop renal

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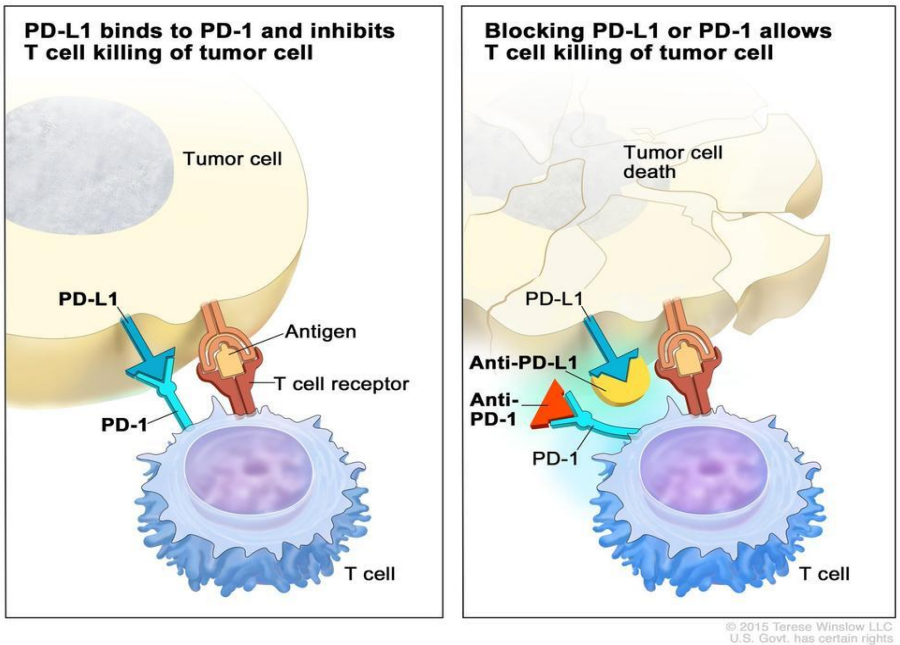
cysts. However, even with ongoing treatment, these cysts may be reversible. The first-in-human phase 1 study has not reported any renal adverse events. Notably, 39% and 50% of the patients, respectively, had vomiting and diarrhea, which put them at risk for functional renal insufficiency and dehydration. The open label phase 3 research of crizotinib versus chemotherapy and the phase 1–2 investigation of crizotinib in patients with ALK-rearranged advanced non-small cell lung cancer [19] both validated the favorable renal tolerance profile. However, a patient using crizotinib experienced abrupt renal failure, according to a recent paper. After three weeks of crizotinib treatment, serum creatinine increased from 0.8 to 2.6 mg/dl. When crizotinib was stopped, renal function partially improved to 1.6 mg/dl, and when it was resumed, it increased to 3.8 mg/dl. Hematuria and proteinuria accompany acute renal failure.

Cancer therapies targeted to VEGFR, EGFR, and RET

Vandetanib is an inhibitor of several kinases. Numerous electrolyte abnormalities, including hypocalcemia (extremely common, ≥10%), hypokalemia, hypercalcaemia, and hyponatremia (common, 1%–10%), have been linked to it, according to the SmPC. Additionally, almost 10% of the patients experienced HTN. Vandetanib has been shown to be a strong inhibitor of two distinct renal transporters, MATE1 and MATE2K. This may help to explain why administration of vandetanib may result in both increased cisplatin nephrotoxicity and lower creatinine clearance. Proteinuria and nephrolithiasis (≥10%), dysuria, hematuria, pollakiuria, and renal failure (1%–10%), as well as chromaturia and anuria (0.1%–1%), are among the many symptoms of renal adverse events, which are common. HTN is common (34%) and electrolyte abnormalities with 4% of grade 3–4 hypokalemia and 4% of grade 3–4 hypocalcemia, according to data from a phase 2, doubleblind, randomized study of vandetanib in locally advanced or metastatic differentiated thyroid carcinoma. HTN is common (32%) according to the randomized, double-blind phase 3 trial, although no electrolyte abnormalities were noted; only adverse events, with an incidence of ≥10%, were observed [23]. Notably, several of these imbalances can predispose to QTc changes and arrhythmias, hence electrolyte levels need to be regularly monitored.

Cancer therapies targeted to PD-1 and PDL-1

Recently, preclinical and phase 1–2 clinical studies have shown the potential usefulness of drugs that target programmed cell death protein 1 (PD-1) or its ligand (PDL-1) in many tumor types. The receptor, PD1, is present on the membrane surface of activated T cells, B cells, and myeloid cells. When PDL-1 interacts with its receptor PD-1, T cell proliferation and IL-2 production are inhibited. PDL-1-carrying tumor cells are hence immune response-protected. Therefore, restoring or generating immune system activation directed towards tumor cells is the goal of inhibiting the PD1-PDL-1 pathway. Currently under development are a number of Mabs, including MPDL-3280A, which is directed to PDL-1, BMS-936558/MDX-1106 (nivolumab), and MK6475 (pembrolizumab), which is addressed to PD-1.



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Although hypophosphatemia happened in 3% of individuals (1% grade 3–4), nivolumab has not been linked to renal adverse effects. A phase 1 trial has already documented HTN and proteinuria. No patient developed HTN among those who received greater dosages, but 16.7% (grade 2, one patient out of six) of patients treated at the lowest dose of 0.3 mg/kg experienced HTN. The prevalence of grade 2 proteinuria was 16.7%, with one patient out of six receiving treatment at a dose of 1 mg/kg. A review found that 2% of individuals experienced renal failure, and there has been one incidence of pembrolizumab-associated rhabdomyolysis and acute kidney failure [49,]. The renal safety of MPDL-3280A is currently unknown. There have been no reports of renal adverse events in the most recent published data on the safety and effectiveness of another Mab, MDX1105-01.

Cancer therapies targeted to RANKL

By blocking RANKL, the Mab denosumab inhibits the osteoprotegerin/RANK/RANKL pathway. In patients with bone metastases, its therapeutic effectiveness in preventing skeletal-related events has been demonstrated. Data on renal adverse events were published from three phase 3 clinical trials that compared denosumab and zoledronic acid head-to-head. Given that nephrotoxicity is one of the most common side effects of zoledronic acid, the renal tolerance was closely examined in these trials. These trials were performed on individuals with multiple myeloma, a range of solid tumors other than breast and prostate cancer, including breast and prostate cancer patients with bone metastases. With fewer renal side effects (4.9% versus 8.5% for denosumab and zoledronic acid, respectively) and fewer incidences of renal failure (0.2% versus 2.5%, $P < 0.05$), denosumab was better tolerated than zoledronic acid in patients with breast cancer. There was no statistically significant difference in renal tolerance between denosumab and zoledronic acid in castration-resistant prostate cancer, other solid tumors, and myeloma. According to the combined analyses of these trials, the frequency of renal adverse events was 9.2% in patients treated with denosumab and 11.8% in patients treated with zoledronic acid [12]. Additionally, unlike zoledronic acid, denosumab does not require a dosage modification in the event of underlying renal impairment. Furthermore, preclinical research indicates that patients with renal failure or chronic kidney disease may have an imbalance in the osteoprotegerin/RANK/RANKL pathway. Given this and the fact that RANKL mRNA and protein have been found in the mouse kidney throughout development [58], it is highly recommended that patients receiving denosumab, like all cancer patients, have their renal function assessed both before and during treatment. Additionally, as denosumab use is frequently linked to hypocalcemia, calcium levels should be regularly checked.

Cancer therapies targeted to mTOR

Drugs that block the mammalian target of rapamycin (mTOR) include temsirolimus and everolimus. Prior to the discovery of possible advantages in the treatment of cancer, they showed a possible interest in solid organ transplantation and the prevention of graft rejection. Many malignancies have activated phosphoinositide 3-kinase (PI3K)/Akt pathways. One significant modulator of this signaling pathway is the mTOR kinase, and signal transmission can be stopped by mTOR inhibitors. Everolimus was linked to HTN and proteinuria in 22% and 23% of patients, respectively, in a recent phase 1–2 research in renal cell carcinoma (NCI—CTC Grade 2–3). Additionally, one patient experienced grade 3 acute renal failure, 12% had hypophosphatemia, and 4% had hyponatremia. A prior publication on the safety of everolimus in the same tumor type under an extended access program, however, did not include any cases of HTN and/or proteinuria [22]. One patient's hypophosphatemia necessitated a dose decrease or delay in a different phase 2 trial for nonclear-cell renal cell cancer. Only increases in blood creatinine are recorded as renal adverse events in 50% of participants in the everolimus arm of the phase 3 study for metastatic renal cell cancer. Lastly, hypophosphatemia was the only renal side-effect documented in a phase 2 trial of daily oral everolimus in metastatic clear cell renal cell carcinoma, with an incidence of 30.8% (2.6% grade 3, one patient) [1].

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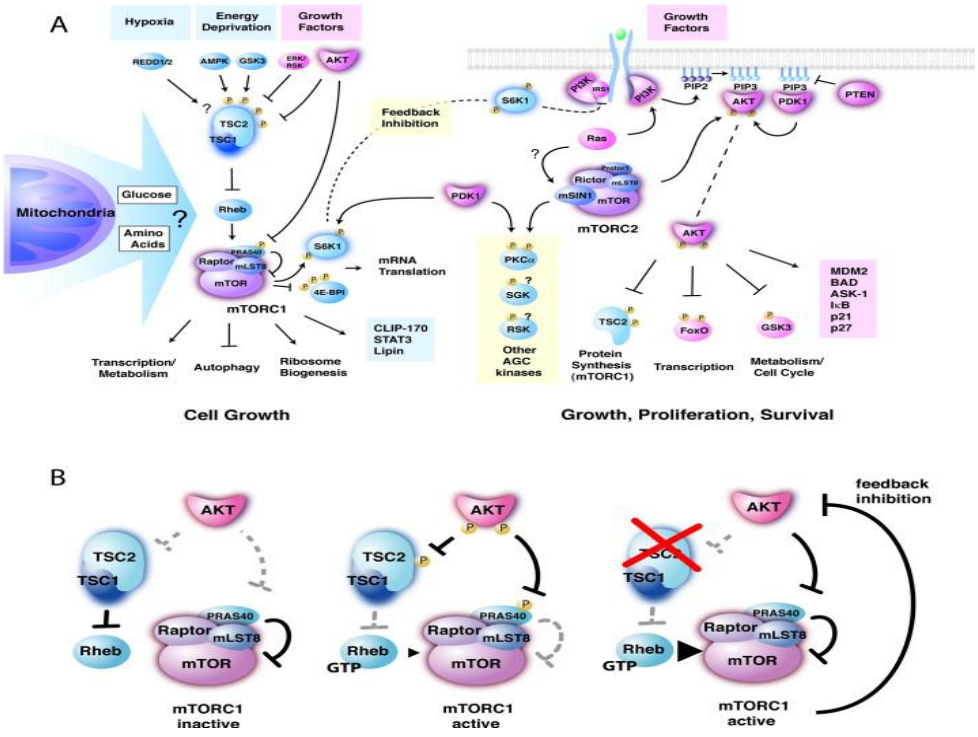

Patients with advanced refractory renal cell carcinoma were the subjects of the first phase 2 study of temsirolimus, which was then only known by the name CCI-779, that was published in the literature. There were no reported adverse kidney effects. Less common toxicities were not reported, nevertheless, because the reporting threshold for adverse events related to study drugs was 20%. Depending on the dosage, 6% to 18% of patients experienced grade 3–4 hypophosphatemia linked to the study medication. There was no correlation between the frequency of hypophosphatemia and dose: 14% at 25 mg, 18% at 75 mg, and 6% at 250 mg. Among those examined in the escalation (range: 7.5–220 mg/m2), one patient with grade 3 neutropenia, thrombocytopenia, and hypophosphatemia presented at an intermediate dose (34.0 mg/m2) in a phase 1 investigation on the safety and pharmacokinetics of temsirolimus. There has been one documented instance of glomerulopathy linked to temsirolimus [6]. Both medications have also been researched in relation to pancreatic cancer. The literature has documented two phase 2 trials, one including oral everolimus and the other with intravenous temsirolimus. Everolimus was only linked to hyponatremia (grade 3–4) in one patient, while temsirolimus was not linked to any renal adverse effects. The renal effects of the targeted treatments examined in this paper are compiled in Table 1. Table 2 presents a concept for routine monitoring in patients receiving targeted therapy. Since preexisting abnormal eGFR is a known risk factor for medication effects on the kidneys, eGFR determination before to treatment initiation is required in all situations to (i) alter dosage when necessary and/or (ii) raise awareness of renal safety.

DISCUSSION

Because of its resistance to traditional chemotherapy and radiation, renal cell carcinoma (RCC), a physiologically complex cancer that develops from the renal tubular epithelium, has important therapeutic ramifications. The creation of tailored medicines that target particular biochemical pathways linked to tumor growth and progression has propelled therapeutic advancements within the last ten years. Therapeutic resistance is still a significant problem, even though tyrosine kinase inhibitors (TKIs) and mTOR inhibitors are effective in extending survival and slowing the course of disease. The existence of renal cancer stem cells (CSCs) seems to be one of the main causes of resistance. Because of their capacity for self-renewal and tumor induction, CSCs are an aggressive subpopulation that is challenging to remove with conventional treatments. The significance of creating tactics that target CSCs specifically is highlighted by the identification of these cells as causes of tumor recurrence and treatment failure. More accurate disease subtype categorization and individualized treatment strategies may be made possible by developments in

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the identification of renal CSC populations and the mapping of their cellular hierarchy. To get past resistance and target both bulk tumor cells and CSCs, a number of innovative approaches are being investigated. Antibody–drug conjugates, bone morphogenetic protein-2, and CSC marker inhibitors are among the agents that show promise in eradicating CSCs specifically while preserving healthy tissue. Additionally, by improving drug distribution and improving specificity, nanomedicine techniques may reduce systemic toxicity. The therapeutic landscape is further expanded by immunomodulatory techniques, such as the use of interleukins, which have the ability to activate the immune system against CSCs and tumor cells. Even though these methods are significant advancements, careful assessment through well planned clinical studies is necessary before they can be implemented into clinical practice. Combination regimens that combine CSC-directed therapy with well-established targeted medicines like TKIs and mTOR inhibitors may be necessary to overcome therapeutic resistance and produce long-lasting effects. Furthermore, to guarantee that the appropriate treatment is given to the appropriate patient at the appropriate time, further advancements in molecular profiling and biomarker discovery will be essential.

CONCLUSION

Renal toxicity is a common side effect of targeted treatments. The majority of the time, these kidney consequences are not severe. However, a variety of chemotherapies may be nephrotoxic, and targeted cancer treatments are frequently employed in conjunction with chemotherapy or successively following. Therefore, there is a chance that both chemotherapy and targeted treatments could have an additional harmful effect on the kidney. Therefore, renal surveillance is essential before starting treatment to enable differential investigation of the cause of the renal event as well as throughout treatment to detect renal changes as soon as possible. Evaluation of the GFR is also required prior to medication delivery since certain targeted treatments may require dosage changes to renal function [14]. Guidelines that have been validated and supported by data should be followed when making dosage modifications. Patients who are at risk of having renal consequences and have preexisting renal dysfunction are routinely excluded from clinical studies. Such renal effects may occur in ordinary practice but are rarely documented in trials, which may be explained by the high prevalence of CKD in cancer patients in clinical practice. In order to give doctors evidence-based clinical practice guidelines on how to handle renal disorders and maximize the care of cancer patients, such topics will be researched and addressed as part of the Cancer & the Kidney International Network (C-KIN).

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