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In-depth Review

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Nephrotoxicity of recent anti-cancer agents

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Abstract
Cancer patients may develop a variety of kidney lesions that impair not only their immediate survival but also limit the adequate treatment of the underlying malignant process. This review summarizes the nephrotoxic potential of some of the most recently developed anti-cancer drugs, focusing on those interfering with the vascular endothelial growth factor and epidermal growth factor receptor pathways and mammalian target of rapamycin inhibitors. Thrombotic microangiopathy (haemolytic-uraemic syndrome), proteinuria, hypertension and magnesium depletion are the most common side effects. Also the risk for developing acute kidney injury in patients with advanced prostate cancer undergoing androgen deprivation therapy is discussed.

Keywords: anti-angiogenesis drugs and cancer; anti-cancer drugs and nephrotoxicity; androgen deprivation therapy and AKI

Introduction

The association between kidney disease and cancer has long been recognized, but has only recently received full attention as a 'new' nephrological subspecialty, called 'onco-nephrology' [1].

Cancer patients may develop a variety of kidney lesions that impair not only their immediate survival but also limit the adequate treatment of the underlying malignant process. These nephrological problems pose a significant challenge for both the oncologist and nephrologist. A list of common clinical issues related to nephrological management in patients with cancer, taken from ref. [1], is provided in Table 1.

Acute kidney problems in cancer patients

Acute kidney injury (AKI) and electrolyte disturbances are the most common forms of renal disease that may occur in a hospitalized patient with cancer. Important factors potentiating AKI in these patients are extracellular volume depletion due to vomiting, diarrhoea, urinary tract obstruction, fluid and electrolyte disturbances, exposure to contrast media, nephrotoxic antibiotics, non-steroidal anti-inflammatory drugs and nephrotoxicity of some of the anti-cancer treatments [2–4]. In the recent analysis of Salahudeen *et al*. [4] of 3558 patients admitted to the Anderson Cancer Centre (Texas, USA) over 3 months in 2006, 12% of them suffered from AKI. In the multivariate model, the odds ratio (OR) for developing AKI was significantly higher for diabetes [OR, 1.89; 95% confidence interval (CI), 1.51–2.36], chemotherapy (OR, 1.61; 95% CI, 1.26–2.05), intravenous contrast (OR, 4.55; 95% CI, 3.51–5.89), hyponatraemia (OR, 1.97; 95% CI, 1.57–2.47) and antibiotics (OR, 1.52; 95% CI, 1.15–2.02). It appears thus that chemotherapy is a lower risk factor for developing AKI than other complications or exposures present in cancer patients before hospital admission.

As in many other AKI populations, reductions in renal function previously considered trivial equally predict a poor outcome in critically ill patients with malignant disease [5]. Increases in serum creatinine (SCr) as small as 10% (0.2 mg/dL–17.6 μmol/L) were associated with prolonged ICU stay and increased mortality. Patients with a 25% rise in SCr during the first 72 h of ICU admission were twice as likely to die in the hospital (14.3 versus 30.1%, $P < 0.001$). The poor outcome in those with rising SCr could not be explained by severity of illness or other risk factors. The frequent comorbidities present in the cancer patient directly influence the care of cancer patients, the selection of initial treatment and the effectiveness of treatment. Comorbidities are also important factors in estimating patient outcome, because they may interact with the cancer to create frequently a more lethal situation than that caused by the cancer alone [6–8].

Limited epidemiological data on AKI in patients with cancer suggest that the incidence is at least 3-fold higher in these patients than those without cancer [4, 5, 9, 10]. Although cancer patients are susceptible to all of the usual causes of AKI in patients without cancer, there are a number of AKI syndromes that occur more frequently or are unique to this patient population. Lymphomatous infiltration of the kidneys, cast nephropathy in multiple myeloma and monoclonal gammopathies, tumour lysis syndrome, particularly occurring in malignancies with high tumour burden and rapid cell turnover, and the

Table 1. Common clinical issues related to nephrological management in patients with cancer

Volume depletion
Acute kidney injury (AKI)
Sepsis and septic shock
Severe fluid and electrolytes derangements
Severe acid–base disorders
Hyponatraemia
Hypokalaemia
Hyperkalaemia
Hypercalcaemia
Renal toxicity of chemotherapeutic agents
Renal toxicity of non-chemotherapeutic drug treatments
Tumour lysis syndrome
Myeloma-related kidney injury
Tumour- or tumour treatment-related microangiopathies and glomerular diseases
Tumour- or tumour treatment-related nephritic syndrome
Stem-cell transplant-associated acute and chronic kidney injuries
Cancer-associated obstructive uropathies
Modifications of dosing of chemotherapy in patients with CKD and ESRD who have cancer
Management of nutrition and dialysis in patients with ESRD-receiving cancer therapy

several causes of AKI in the haematopoietic cell transplant are unique to the cancer population. Recent reviews containing detailed information on these particular forms of AKI are available [3, 11, 12] and a further discussion of these entities is beyond the scope of this review.

Nephrotoxicity of anti-cancer agents

Identifying novel mediators that regulate the growth and death of cancer cells has facilitated the development of more effective anti-cancer agents that have revolutionized treatment options and clinical outcomes in cancer patients [13–16].

However, many of the new agents often carry significant side effects, covering a whole spectrum of body systems, including sometimes serious disturbances of kidney function.

The proliferation in recent years of these novel anti-cancer agents with potential nephrotoxic renal injury has reinforced the need for vigilance amongst all clinicians treating cancer patients. In general, nephrotoxic drugs cause renal injury by inducing a varying combination of intrarenal vasoconstriction, direct tubular toxicity and intratubular obstruction. The vulnerability of the kidney to various potentially nephrotoxic agents can be attributed to several functional properties of the kidney including a rich blood supply (25% of cardiac output), ensuring high levels of toxicant delivery, a high tubular reabsorptive capacity (via specific transporters) leading to high intracellular tubular cell concentrations, and an ability to concentrate toxins to high levels within the medullary interstitium via the renal countercurrent mechanisms. In addition, the kidneys are an important site for xenobiotic metabolism and may transform relatively harmless parent compounds into toxic metabolites. They also have a high metabolic rate and the workload to renal cells results in increased sensitivity to toxicants and a high sensitivity to vasoactive agents [17]. Finally, the kidneys are a major elimination pathway for many antineoplastic drugs and their metabolites. Renal impairment can result in delayed drug excretion and metabolism of chemotherapeutic agents, resulting in increased systemic toxicity. Many drugs require thus dose adjustment when administered in the setting of renal insufficiency [18].

Evaluation of kidney function in cancer patients

It is important to remember that the nephrotoxic potential of most anti-cancer agents is dramatically increased in the presence of borderline or overt preexisting chronic kidney disease and the presence of concomitant comorbidities such as heart failure and sepsis. In some cases this may be explained by the altered pharmacokinetics of drugs predominantly excreted by the kidneys, but in other circumstances the reasons for this potentiation are unclear [19].

Evaluation of renal function is therefore of utmost importance in the cancer patient before any treatment is initiated. This is all the more important because of the well-known decline in renal function with age and the increasing prevalence of elderly cancer patients [20]. Primarily for reasons of convenience, the most common method for evaluation of renal function is at present the estimation of the patient's glomerular filtration rate by equations (e.g. Cockcroft-Gault, the abbreviated MDRD and CKD-EPI) based upon a stable SCr concentration. The caveats associated with the use of these formulae in cancer patients have previously been discussed [21]. The SCr concentration may be falsely low in cancer patients owing to cachexia, low muscular mass or fluid overload, which may lead to substantial errors in the estimation of the GFR. Despite these limitations, the abbreviated MDRD formula has become the reference method in cancer patients [22–24].

Using this formula, a study of 4684 adults (mean age 58 years) undergoing treatment for cancer in 15 French centres [the Renal Insufficiency and Anticancer Medications (IRMA) study] found that 50–60% had biochemical evidence of impaired glomerular function [25, 26]. Of the patients who were treated with an anti-cancer drug, 79.9% received at least one drug that required a dosage adjustment or for which there were no data for use in patients with renal insufficiency and 80.1% received at least one drug that was potentially nephrotoxic.

The Belgian Renal Insufficiency and Anticancer Medications (BIRMA) study including 1137 cancer patients with solid tumours and in whom an SCr was available found a prevalence of an elevated SCr $\geq$ 1.2 mg % ($\geq$106 µmol/L) of 14.9%, but 64.0% had an eGFR $\leq$ 90 mL min/per 1.73 m^2 [27]. This apparently 'high' prevalence of 'disturbed kidney function' should be corrected since it is well known that the eGFR estimated by MDRD is not reliable for accurate calculation of GFR above a value of 60 mL/min 1.73 m^2. Classifying only patients with an eGFR < 60 mL/min as having CKD, the prevalence of 'true' CKD in the BIRMA study is thus 196 on a total of 1137 patients (17.2%). In all, 78.6% of treated patients (n = 1087) were receiving at least one drug that needed dosage adjustment and 78.1% received at least one potentially nephrotoxic drug. In several of these patients the dose was not appropriately adjusted to the decreased renal function.

Besides the presence of an unrecognized abnormal GFR, higher rates of renal oxidative stress and excessive levels of angiotensin-II/endothelin, all of which increase drug nephrotoxicity are present in elderly individuals [28, 29]. As summarized by Perazella [18] another important risk factor is the patient's underlying genetic makeup, which is

likely a powerful explanation for the heterogeneous response to chemotherapeutic agents. Gene polymorphisms in the renal cytochrome P450 enzyme system, which favour reduced metabolism and renal excretion, enhance nephrotoxic risk. Other examples are loss of function mutations in apical secretory tubular transporters and mutations in kinases that regulate drug carrier proteins, which can impair drug excretion and induce nephrotoxicity by increasing intracellular drug concentrations. In most cases, the toxic kidney lesions develop from innate toxicity of these medications, but underlying host risk factors and the renal handling of these drugs clearly increase the likelihood of nephrotoxicity [18, 30].

Many recent excellent reviews on the potential nephrotoxicity and the renal handling of cancer chemotherapeutic drugs are available in the literature; abundant information is available on the classical cytotoxic drugs (cisplatin, carboplatin, oxaliplatin), alkylating agents (bendamustine, cyclophosphamide, ifosfamide, nitrosureas, temozolomide, melphalan), anti-tumour antibiotics (mitomycin C, bleomycin), anti-metabolites (methotrexate and its derivative, pemetrexate, capecitabine, gemcitabine),vinca alkaloids (vincristine, vinblastine and vinorelbine), taxanes (paclitaxel, docetaxel, cabazitaxel) and the topisomerase inhibitor (irinotecan). The interested reader is referred to the literature [3, 18, 21, 30–35].

Thrombotic microangiopathy with 'older' anti-cancer drugs

Malignancy itself, outside the use of chemotherpautic agents, may cause thrombotic microangiopathy (TMA). This complication is associated most commonly with lymphoma, thymoma and cancers of the stomach, breast and lung [36, 37].

Mitomycin

Although also described with carboplatin [38], AKI as a consequence of TMA, often manifesting as haemolytic-uraemic syndrome (HUS) occurs more frequently with the anti-tumour antibiotics, mitomycin C and gemcitabine [21, 30]. Acute TMA is characterized by fibrin microthrombi in arteries, arterioles and glomerular capillaries. Other features of acute TMA include mesangiolysis and vascular changes, such as mucoid material in the intima of arteries and arterioles. However, in chronic TMA, remodelling of the capillary walls and mesangium takes place, resulting in double contours and nodular expansion of the mesangium, respectively. In addition, arteries and arterioles show sclerosis and onion skinning of the vessel walls in chronic TMA. It should be kept in mind that there often is overlap of findings in acute and chronic TMA.

The propensity of mitomycin C to cause TMA has been well documented, with an incidence of 4–15% [39]. Mitomycin C-induced TMA is dose dependent, usually occurring 4–8 weeks after the last dose [40] but ∼10% of patients may develop adverse renal effects after 5–12 months of mitomycin C therapy. A subacute form may manifest months after treatment without the characteristic haemolysis of the acute form [41]. As with other drugs, a higher cumulative dose of mitomycin C (>60 mg) appears to increase the risk for TMA. In general, although TMA may be renal limited, hypertension and a more generalized microangiopathic haemolytic anaemia with thrombocytopenia also occur. Haematuria and proteinuria along with AKI are common and neurological abnormalities, skin rash and non-cardiogenic pulmonary oedema may occur.

Gemcitabine

Gemcitabine is also a cause of TMA, with a reported incidence ranging from 0.015 to 1.4% [42–44]. Based on a patient exposure of 78 800, Fung *et al.* [42] calculated a crude overall incidence rate of 0.015% (range, 0.008–0.078%), showing that HUS associated with gemcitabine treatment appears to be rare. Nonetheless, as with other cancer treatments, clinicians should weigh the appropriate risk/benefit ratio in using gemcitabine to treat their patients. The series described by Müller *et al.* [43] documented the highest incidence of 1.4%, all after pretreatment with other chemotherapeutic regimens for 4–26 months. These investigators hypothesized that pretreatment with other agents and advanced-stage disease may increase the risk of developing gemcitabine-induced HUS, explaining the increased incidence in their series compared with others. Glezerman *et al.* [45] report that in their patients with gemcitabine-induced HUS, only 21 of 24 patients had schistocytes on peripheral smear. They also note that all patients had anaemia, thrombocytopenia and increased lactate dehydrogenase levels. Furthermore, it is important to note that TMA associated with gemcitabine may present more indolently than acutely [46].

The mechanism of gemcitabine-induced TMA has not been elucidated. Both direct endothelial injury and reduced ADAMTS-13 (von Willebrand factor protease) activity have been hypothesized to have a role [47].

Unlike mitomycin-C, there is no clear-cut relationship between the cumulative dose of gemcitabine and risk of HUS. However, most patients had received gemcitabine for at least 3–5 months before the onset of HUS. A recent report [48] described the development of HUS in six patients suffering from an advanced cancer and treated by protracted (≥4 months) infusions of gemcitabine. Over 4–14 months, the patients received 13–34 infusions delivering a cumulative dose oscillating between 9 and 29 g/m^2. A progressive alteration of renal function preceeded the acute syndrome. After interruption of gemcitabine and symptomatic treatment, the evolution of haemolytic anaemia was generally favourable, but this was not the case for renal dysfunction: two complete and one partial resolution of renal insufficiency were noted, but one case required chronic dialysis. Based on this report, the frequency of an HUS complication after protracted gemcitabine treatment could thus be as high as 2.7%.

The renal toxicity of gemcitabine, represented by TMA, is treated by complete discontinuation of the drug therapy. Therapeutic plasma exchange is not clearly beneficial [49], but case reports have suggested a possible response to rituximab [50, 51] and to eculizimab [52]. Figure 1 illustrates the presence of lesions compatible with haemolytic-uraemic syndrome in a kidney biopsy from a 75-year-old male with carcinoma of the lung and who developed acute hypertension and a rise in SCr during treatment with gemcitabine and TL-32711, a second mitochondrial-derived activator of caspase (SMAC) inhibitor [52]. After stopping the offending drug without improvement of renal function over 4 weeks, the patient received eculizumab resulting in improvement and stabilization of kidney function.

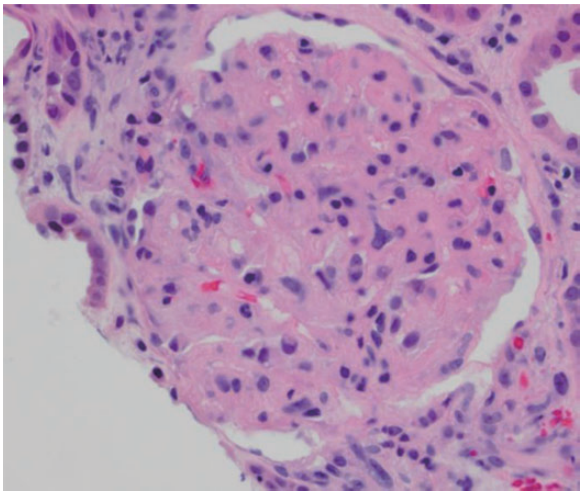

Fig. 1. Microscopic appearance of kidney biopsy showing diffuse segmental thickening of glomerular basement membranes and increased extracellular matrix within the glomeruli. The findings are consistent with thrombotic microangiopathy/antineoplastic drug-induced atypical haemolytic-uraemic syndrome. For more clinical details see text. Figure taken from ref. [52] with permission.

Nephrotoxicity of anti-angiogenesis drugs

In more recent years several studies have been performed in cancer patients with the so-called targeted drugs, mostly molecules interfering with tumour-associated pathways of angiogenesis. Tumour cells communicate with vascular endothelial cells within developing neoplasms via diffusible growth factors, leading to increased vascularization that further facilitates tumour growth. Interrupting pro-angiogenic signalling pathways is a principle objective of novel anti-neoplastic strategies and vascular endothelial growth factor (VEGF) is a main target (for review see [53]).

However, as explained in a number of very instructive recent reviews [54–56], although tumour angiogenesis plays a critical role in tumour growth, invasion and metastasis, in the majority of cancers, vessel growth is not only stimulated, but these vessels are also abnormal in almost all aspects of their structure and function. This results in a hostile tumour microenvironment—characterized by hypoxia, low pH and high interstitial hostile fluid pressure—that can alter the intrinsic characteristics of tumour cells such that malignant tumour clones are selected and the escape of tumour cells through leaky vessels is facilitated. Abnormal tumour vessels can also impede the function of immune cells in tumours, as well as the transport and/ or distribution of chemotherapeutics and oxygen. As a result, the abnormal tumour vasculature can lead to a resistance of tumour cells to radiation therapy and many chemotherapeutics. In addition, hypoxia upregulates the production of angiogenic factors by cancer and stromal cells, which further aggravate vessel disorganization and thereby fuel non-productive angiogenesis in an endless self-reinforcing loop.

Several targeted agents for the treatment of advanced carcinoma are now approved and in clinical use: the anti-VEGF ligand inhibitors (bevacizumab and aflibercept), the anti-angiogenic small-molecule multi-target tyrosine kinase inhibitors (MTKIs) (sunitinib, sorafenib, pazopanib, ponatinib, axitinib, cabozantinib, vandetanib) that target the VEGF-receptor VEGFR-2, the platelet-derived growth factor (PDGF)_ receptor, rat sarcoma (RAS), stem-cell factor receptor c-KIT and the mammalian target of rapamycin (mTOR) inhibitors, temsirolimus and everolimus [57, 58].

The use of these medications has expanded to many different solid tumours, with ongoing clinical trials of newer formulations of these medications. Their use is growing rapidly and they are now the first-line therapy for cancers such as metastatic renal cell carcinoma (RCC) which accounts for 2.5% of all new cancer diagnoses [59, 60].

The receptor tyrosine kinases play a key role in the pathogenesis of clear-cell carcinoma, the predominant type of RRC, through involvement of the von Hippel–Lindau (VHL) gene. VHL is inactivated in up to 80% of sporadic cases of clear-cell carcinoma by deletion, mutation or methylation. This tumour-suppressor gene encodes a protein that is involved in the regulation of the production of VEGF, PDGF and a number of other hypoxia-inducible proteins. Inactivation of the VHL gene causes overexpression of these agonists of VEGFR and PDGFR, and the resulting persistent stimulation of the receptors may promote tumour angiogenesis, tumour growth and metastasis [61–64]. RCC has high VEGF expression and all these considerations make the receptors for VEGF and PDGF rational targets, particularly in the treatment of clear-cell RCC.

Yang *et al*. [65] demonstrated that bevacizumab, an anti-VEGF antibody, has efficacy in RCC, and over the past several years, there has been an increase in progression-free survival and quality of life in patients with metastatic RCC, which was attributed to the advent of the MTKIs [66, 67]. Although the advent of novel molecular-targeted agents such as sunitinib and sorafenib represents a substantial advance in the treatment of metastatic RCC, the spectrum of adverse effects may be broader than initially predicted.

As VEGF-targeted therapies entered practice, it became clear that hypertension and proteinuria were major toxicities of this drug class—both the biologics and the small molecules. Both side effects, hypertension and proteinuria, as a consequence of VEGF inhibition are discussed in recent major reviews [18, 30, 53, 68–72].

The renal side effects of anti-VEGF inhibition are not surprising because VEGF is produced by renal visceral epithelial cells and binds to VEGF receptors located on glomerular podocytes, endothelium and mesangium, as well as peritubular capillaries [73]. Figure 2a illustrates a model of VEGF signalling in the glomerulus and Figure 2b shows how several anti-cancer drugs may at several levels interfere with the VEGF pathway.

Hypertension occurs in up to 80% of patients on some forms of these medications [74] and nearly all patients taking these drugs experience an increase in blood pressure, even if not to hypertensive levels. The development of hypertension can serve as a biomarker because there is increasing evidence that an increase in blood pressure in patients on these medications may predict better tumour response [75]. The rationale is that hypertension is a mechanism-dependent effect of the VEGF signalling pathway (VSP) inhibition (i.e. it reflects effective *in vivo* inhibition of the VSP pathway) [76]. This raises a natural question: are cancer patients who do not develop hypertension on these drugs being underdosed? In patients with metastatic colorectal cancer with induced arterial hypertension, 84.6% achieved a complete or partial response, when compared with 42.6% of patients who did not show this side effect and Kaplan–Meier analysis showed a statistically significant improvement in median

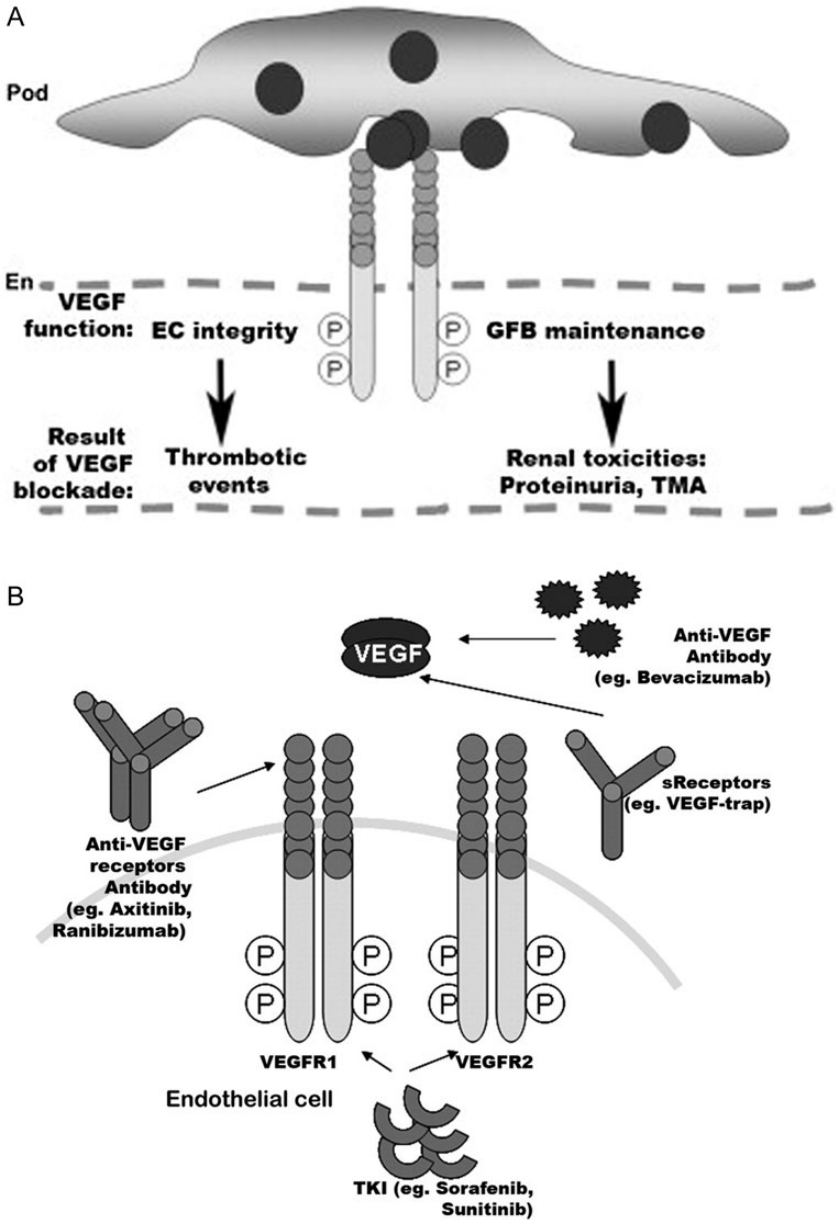

Fig. 2. (**a**) Model of VEGF signalling in the glomerulus. VEGF is released by podocytes and acts on VEGF receptors on endothelial cells (EC), causing receptor phosphorylation and signal transduction that is required to maintain endothelial cell integrity and the glomerular filtration barrier. TMA, thrombotic microangiopathy. (**b**) Targeting the VEGF pathway at a number of levels. Anti-VEGF antibodies and VEGF-trap bind VEGF ligand; anti-VEGF-receptor antibodies block at the level of the receptors, whereas TKIs inhibit intracellular pathways activated by VEGF. TKI, tyrosine kinase inhibitors. Both figures are taken from [69] with permission.

progression-free survival for patients with induced arterial hypertension (15.1 versus 8.3 months, P = 0.04) [77]. This observation should prompt clinicians to continue therapy and control blood pressure with anti-hypertensive agents rather than discontinuing anti-angiogenic therapy.

The most important mechanisms of the hypertension are explained by the VEGF blockade inducing endothelial dysfunction resulting in the inhibition of VEGF-dependent vasodilatory pathways such as nitric oxide and prostacyclin, as well as the possible up-regulation of vasoconstrictive pathways such as endothelin-1. Together with the loss of microvascular capillary density through capillary rarefaction, these mechanisms cause systemic vasoconstriction, resulting in increased afterload and hypertension. Endothelial dysfunction and VEGF blockade also reset the pressure–natriuresis relationship, resulting in inadequate renal sodium excretion in the face of increased blood pressure. Finally, VEGF blockade also may block VEGFR-3 expressed on endothelial cells, decreasing lymphangiogenesis and reducing the capacity of the lymphatic network to buffer sodium and extracellular fluid volume. Both of these latter two mechanisms contribute to volume overload and exacerbate blood pressure increase [73]. Active monitoring of the blood pressure throughout treatment is required because this toxicity is so common. Anti-hypertensive therapy should be initiated when blood pressure increases above 140/90 mm Hg, as a general rule, but in high-risk groups such as patients with diabetes or chronic kidney

disease, the threshold is lower (130/80 mm Hg). Choice of anti-hypertensive agent should be individualized, but angiotensin-converting enzyme inhibition or calcium channel blockers are reasonable first-line options. Diuretics, direct vasodilators and beta-blockers may be added to adequately control blood pressure [53].

Mild proteinuria is reported to occur in up to 63% of patients and the incidence increases with increasing dose of the inhibitor (for review see [69]). More serious toxicity to full-blown nephrotic syndrome is less frequent, but has been reported to occur in 1–7% of patients depending on the trial. Importantly, many of the early trials excluded patients with comorbidities or any degree of renal insufficiency, which should be kept in mind as enrolment and indications for these drugs increase. Furthermore, tests of renal function (such as GFR) are not reported consistently in all of the trials and in the early trials quantitative urine protein determinations were not performed, making it difficult to calculate the true incidence of renal injury.

Given the large number and differences between agents, one obvious question arises: are there different risks of renal toxicity associated with different anti-VEGF drugs? To date, clinical experience is greatest with bevacizumab because it was the first agent approved for clinical use. Most clinical studies with bevacizumab report mild proteinuria, with only 3–4% of patients developing Grade 3 and 4 proteinuria.

However, RCC patients have a higher incidence of high-grade proteinuria, up to 7–8% [65, 78]. The increased risk observed in patients with RCC may reflect changes in GFR in patients who have undergone nephrectomy.

Generally, clinical trials with MTKIs, such as sunitinib or sorafenib, report lower rates of proteinuria, although no head-to-head comparisons have been performed. However, this is not always the case; for example, 32% of patients with RCC developed Grade 2 or higher proteinuria when treated with axitinib—an oral TKI that inhibits VEGF receptors 1, 2 and 3 [79]. Although Grade 3 and 4 proteinuria reflects glomerular injury, milder grades of proteinuria may reflect either tubular or glomerular defects. A number of renal biopsies performed in patients who have received anti-VEGF agents confirm that the glomerular microvasculature is a major target of injury.

Of the cases with induced nephrotoxicity presented in the literature, by far the most common renal lesion is TMA, which is characterized by profound endothelial swelling known as endotheliosis and may be associated with both nephrotic and subnephrotic levels of proteinuria (for review see [18, 30, 53, 68–72]). Although endotheliosis is a consistent feature of all thrombotic microangiopathies, the degree and prominence of endothelial swelling observed in patients on VEGF inhibitors is most similar to the TMA of preeclampsia. When multiple anti-VEGF drugs are combined, the rates of high-grade proteinuria increase.

In the spring of 2008, Health Canada issued a warning to all physicians to avoid combinations of VEGF inhibitors because of TMA. In another case series, six of seven patients on combined TKI therapy (sunitinib and sorafenib) developed proteinuria of varying degrees and hypertension [80]. In addition to TMA, a number of other glomerular lesions have been reported in patients but at a less frequent rate (for review see [69]). Given the low number of other glomerular lesions, it is not clear whether they are the direct result of VEGF inhibition or simply reflect exacerbation of an underlying disorder that was exposed as a result of the addition of a glomerulotoxic agent.

Although management of the proteinuria has not been tested in prospective trials, it is recommended to screen for the presence of proteinuria and renal function before and during the treatment with these agents. In case of appearance of nephrotic syndrome the therapy should be interrupted. Changing to another anti-VEGF therapy that targets the pathway at a different level might not result in recurrence of proteinuria.

Epidermal growth factor receptor family (for review [81])

The epidermal growth factor receptor (EGFR) belongs to a family of receptor tyrosine kinases that includes three other members (erbB2/HER-2, erbB3/HER-3 and erbB4/HER-4). These receptors are anchored in the cytoplasmic membrane and share a similar structure that is composed of an extracellular ligand-binding domain, a short hydrophobic transmembrane region and an intracytoplasmic tyrosine kinase domain (reviewed in refs [82–84]. Animal and human studies showed that EGFR was expressed mainly in distal, collecting and proximal tubules. It also was detected in glomerular capillary walls, mesangial and parietal epithelial cells, and peritubular capillaries and arterioles (for review see [85]).

As illustrated in Figure 3, several strategies are available to target the EGFR pathway in cancer therapeutics [81]. The EGFRs/Her1/ErbB1 receive this attention due to their abnormal expression in many epithelial tumours and their influence on the growth and survival in malignant states. Evidence suggests that the overexpression of HER2 is an early event in tumourigenesis. It occurs in ∼20% of breast cancers and is associated with aggressive and poor prognosis. Overexpression of HER1 appears to be a later event in the evolution of the cell phenotype and is found in about 40% of breast cancers. It also portends a poor prognosis.

Advances in genetic engineering and understanding of the EGFR signalling pathways in cancer have led to the development of many therapeutic agents including monoclonal antibodies (mAbs), small-molecule tyrosine kinase inhibitors (TKIs), antisense oligonucleotides, antibody-based immunoconjugates and other agents like FR-18, peptides, affi- bodies, nanobodies etc.

mAbs bind to the extracellular domain of EGFR and compete with endogenous ligands to inhibit the ligand-induced EGFR tyrosine kinase activation by blocking the ligand-binding region. The TKIs have a partially different activity profile than mAbs as they act on the intracellular domain to inhibit enzyme tyrosine kinase, which is responsible for signal transduction cascade and downstream activation of many proteins.

Two EGFR-targeted pharmacological approaches showed clinical activity in cancer patients. The first approach involves mAbs, such as cetuximab (Erbitux®—a chimeric anti-EGFR antibody), panitumumab (Vectibix—a fully humanized anti-EGFR antibody), raised against the extracellular domain of EGFR to block ligand binding and receptor activation, and trastuzumab (Herceptin®), a recombinant humanized mAb also targeted against the extracellular domain of HER2. The second approach includes small-molecule inhibitors of EGFR tyrosine kinase, such as gefitinib and erlotinib, which prevent EGFR autophosphorylation and downstream signalling. Several other compounds were

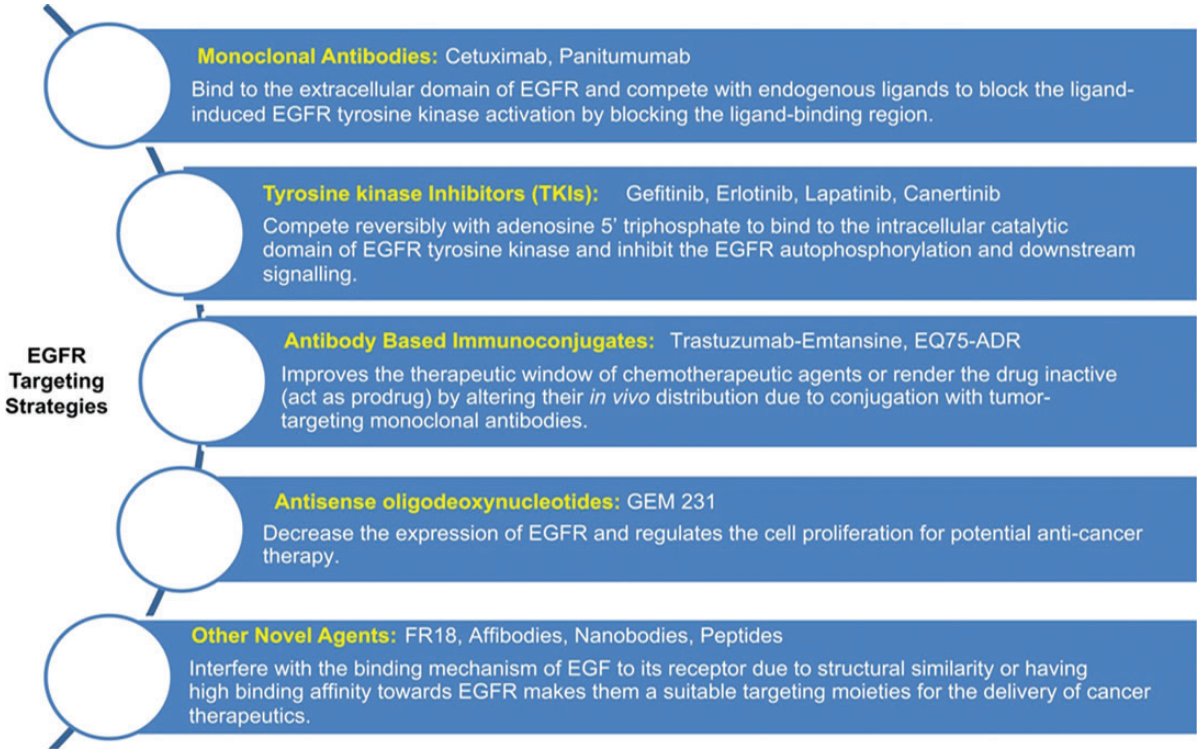

Fig. 3. Different types of agents used to target EGFR with their mechanism of action. Figure taken from ref. [81] with permission.

developed that have broad anti-HER activity like lapatinib (GW572016), pertuzumab (2C4) and canertinib (CI-1033).

Cetuximab (Erbitux/C225; Imclone, New York, NY) is approved for patients with refractory colon cancer alone or in combination with irinotecan and for locally advanced head-and-neck cancer.

Cetuximab was well tolerated in early clinical studies. As summarized by Izzedine *et al*. [70], the most frequently occurring adverse events included fever and chills, asthenia, transaminase level increase, nausea and skin toxicities. Hypertension or proteinuria was not reported, although 13 of 633 patients (2%) experienced kidney failure.

Currently, trastuzumab is the only HER-2-targeted therapy approved for the treatment of patients with metastatic breast cancer.

The mechanism of action of trastuzumab is not completely known, although it is clear that at least some of its effect is caused by complement- and antibody-dependent cell-mediated cytotoxicity. Hypertension or proteinuria was not reported. However, renal disorders are common with trastuzumab use as mentioned in the drug product information (European Medicines Agency (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000278/WC500074922.pdf, consulted 9 September 2013).

One of the clear examples of cancer therapy cardiotoxicity occurs in patients with breast cancer over-expressing the HER2 receptor, which is currently treated with anthracyclines or taxanes and with trastuzumab. Anthracyclines and trastuzumab are both associated with cardiotoxicity [86]. Anthracyclines, taxanes or trastuzumab alone, at present, are not considered to be nephrotoxic, and current guidelines do not require dose reduction in patients with renal dysfunction. Russo *et al*. [87] recently reported that renal dysfunction determined by estimation of GFR with the simplified MDRD equation, assessed at baseline (prior to trastuzumab therapy, after other chemotherapies) is associated with an increased risk of cardiovascular toxicity and complications following trastuzumab. This study suggests that renal function, determined by estimation of GFR, should be assessed prior to the start of trastuzumab therapy.

Urinary magnesium wasting is the major adverse renal effect of anti-EGFR agents. As explained in two excellent recent reviews [18, 88] and illustrated in Figure 4, the hypomagnesaemia is due to the induction of a loss of function mutation in the epithelial Mg2+ channel TRPM6 (transient receptor potential cation channel, subfamily M, member 6), one of the main tubular magnesium channels in the distal collecting tubular cells. Groenestege *et al*. [89] found that EGF markedly increases TRPM6 activity, and a baseline activity of basolateral EGFR activation is required for TRPM6 activity and apical Mg2+ entry. Analysis of data from cetuximab-related clinical trials with renal hypomagnesaemia suggests the hypothesis that blockade of EGFR induced a mutated-like TRPM6 syndrome (for review see [88]). Diagnosis is based on showing an increased fractional excretion of magnesium (15% in the setting of hypomagnesaemia). Oral and intravenous magnesium supplementation are often required to reduce cramping, arrhythmias and other related electrolyte disturbances (hypokalaemia) [89]. In a phase III trial, panitumumab was associated with magnesuria because 36% of treated patients developed hypomagnesaemia, with rather severe symptomatic hypomagnesaemia in 3% [90].

A recent meta-analysis estimated a 5.6% rate of Grade 3–4 hypomagnesaemia and a 36.7% rate of all-grade hypomagnesaemia in patients treated with cetuximab [91]. While periodic monitoring of electrolyte levels is recommended at least

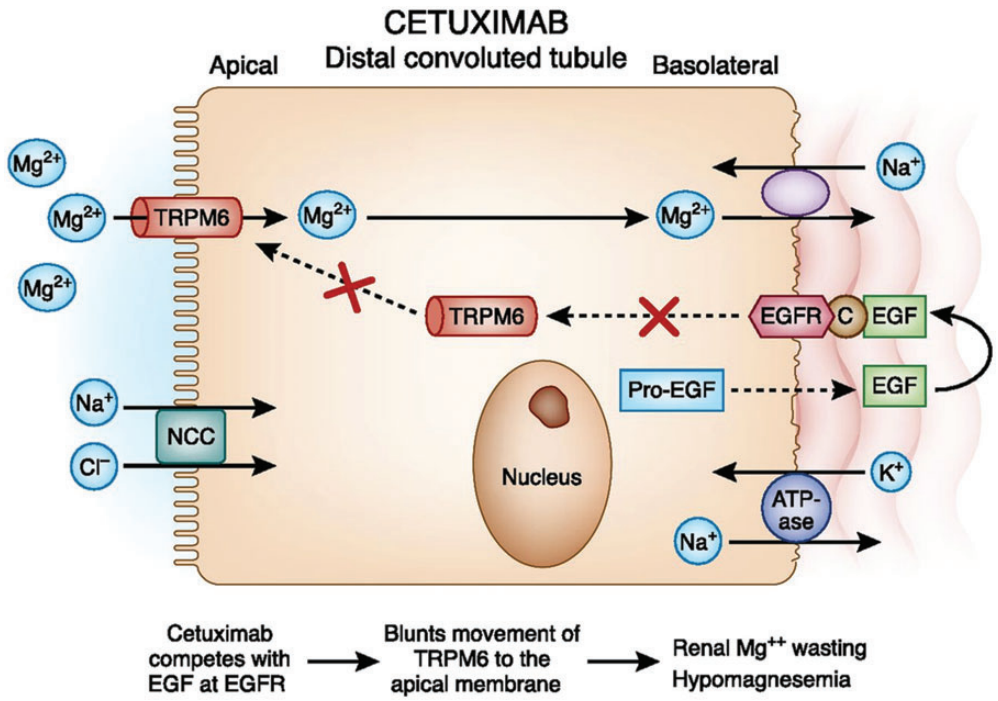

Fig. 4. Cetuximab (C), a chimeric s against EGF receptor (EGFR), competitively inhibits EGF binding to its receptor, thereby blunting the placement of transient receptor potential M6 (TRPM6) into the apical membrane. Normally, EGF binds its receptor (EGFR) and stimulates magnesium reabsorption in the distal convoluted cell. An EGFR antibody causes renal magnesium wasting by competing with EGF for its receptor. NCC, sodium chloride cotransporter. Figure taken from ref. [18] with permission.

in patients treated for more than 4–8 weeks [92], 15–42% of the patients had no Mg determination during treatment with EGFR-targeting antibodies. A recently published 2-year retrospective study on the incidence of hypomagnesaemia in patients treated with either cetuximab or panitumumab for head and neck or colorectal cancer also revealed an overall risk of all-grade hypomagnesaemia of 58.82% (40/68), distributed as 63.46% (33 patients) in the cetuximab group and 43.75% (seven patients) in the panitumumab group and again a lack of sufficient magnesium monitoring was observed. Based on this and previous studies it is thus recommended that serum magnesium determinations should be done every 4–8 weeks in patients treated with EGFR-targeting antibodies, as it is a useful surrogate marker for both toxicity and efficacy [93]. In fact, patients treated with cetuximab and with a decrease in serum Mg concentration >20% from the basal level showed a significantly better tumour response rate and longer time to progression [94] and those with reductions >50% also showed a significantly longer overall survival [95]. Besides hypomagnesaemia, hypophosphataemia, hypokalaemia and hypocalcaemia are other electrolyte disorders related to EGFR-targeting drugs [88].

Anthracyclines, taxanes or trastuzumab alone, are at present not considered to be nephrotoxic, and current guidelines do not require dose reduction in patients with renal dysfunction. However, renal dysfunction is associated with an increased risk of cardiovascular toxicity and complications following trastuzumab [87]. This study suggests that renal function determined by estimation of GFR using creatinine clearance (eGFR) with the simplified MDRD equation should be assessed prior to the start of trastuzumab therapy.

The mTOR protein kinase inhibitors

mTOR, a serine/threonine protein kinase, is ubiquitously expressed in cells, and enhanced activity of the mTOR pathway is frequently observed in malignant cells, including RCC. Several lines of evidence implicate mTOR as a valid target for treatment of RCC [96, 97] and inhibition of this kinase has become an attractive strategy. The importance of mTOR in health and diseases has promoted the development of molecules that inhibit mTOR signalling, including rapalogs (sirolimus, temsirolimus, everolimus and deforolimus), which complex with FK506-binding protein 12 to inhibit mTOR complex 1 activity, or the more recent ATP competitive mTOR inhibitors (mTORi), which target the catalytic site of the enzyme. Rapamycin and its analogues temsirolimus, everolimus and ridaforolimus referred to as 'rapalogs' have demonstrated promising efficacy against RCC and are under investigation for the treatment of other malignancies. However, these mTOR inhibitors produced side effects that could be unpredictably serious and/or debilitating. Their most common side effects included stomatitis, rash, hyperglycaemia and dyslipidaemia, fatigue and pneumonitis. Although in the phase 3 trial, mTORis were associated with mild-to-moderate vomiting and diarrhoea, no significant difference in the increase in SCr was observed between the everolimus and placebo groups of patients [98].

Despite these reassuring observation and that acute tubular necrosis (ATN) has not been reported with mTOR inhibitor use, Izzedine *et al.* [99] recently described four cases of AKI after starting mTOR inhibitor therapy. A kidney biopsy showed ATN with prominent tubular dysfunction. Withdrawal of the drug led to a rapid recovery in two cases. However, a fixed renal dysfunction was noted

in the other two cases, one of which remained dialysis dependent. These cases demonstrated a potentially new and serious adverse consequence occurring with the use of an mTOR inhibitor, of which physicians need to be aware.

Anti-B cell mAbs

Rituximab, (MabThera®, Roche Pty Ltd, Basel, Switzerland), a first-in-class chimeric monoclonal antibody (MoAb) targeting CD 20 molecule, is widely accepted and administered globally to treat B-cell non-Hodgkin lymphoma (NHL), chronic lymphocytic leukaemia (CLL). Rituximab has been associated with electrolyte imbalance and AKI in patients with high circulating tumour cells (>25 000/mm^3) or a high tumour burden. This generally occurs within 12–24 h of the first dose and is presumably the result of tumour lysis syndrome. Prophylaxis should be considered for patients at high risk. Several of these cases suffering tumour lysis syndrome with rituximab have recently been summarized in ref. [100].

MoAbs targeting CD 19 molecule are also rapidly moving through clinical trials [101]. In recent times, Bruton's tyrosine kinase (BTK), a crucial terminal kinase enzyme in the B-cell antigen receptor signalling pathway has emerged as a novel target [102]. This downstream signal transduction protein is a critical effector molecule that governs normal B-cell development, differentiation and functioning, and has also been implicated in initiation, survival and progression of mature B-cell lymphoproliferative disorders [103]. As recently reviewed, ibrutinib, a novel BTK-targeting inhibitor, and many other BTK inhibitors have shown significant activities across a variety of B-cell neoplastic disorders and autoimmune diseases in preclinical models and clinical trials [104]. The most common treatment-related side effects were dry mouth, constipation and diarrhoea. To the best of my knowledge, no specific nephrotoxicity has been reported in the many preclinical and current clinical trials [104].

Androgen deprivation therapy and AKI

Androgen deprivation therapy (ADT) is the mainstay treatment for patients with advanced prostate cancer. While this therapy has been traditionally reserved for patients with advanced disease, ADT is increasingly being used in patients with less severe forms of the cancer, such as in patients with biochemical relapse who have no evidence of metastatic disease [105]. Although ADT has been shown to have beneficial effects on prostate cancer progression, serious adverse events can occur during treatment [106]. With respect to the renal system, by lowering testosterone to castration levels, ADT may antagonize the vasodilating effects of testosterone on renal vessels [107] while also creating an oestrogen deficiency, which can negatively affect renal tubular function [108]. It is possible that through these mechanisms, the use of ADT may increase the risk of AKI.

Although there is one case report associating the use of the oral anti-androgen flutamide with AKI [109], a recent observational study [110] revealed that in a cohort of 10 250 patients with newly diagnosed non-metastatic prostate cancer over a mean follow-up of 4.1 (SD, 2.9) years, 232 incident cases of AKI were identified (rate, 5.5/1000 person-years).

Overall, the current use of any ADT was associated with an increased risk of AKI when compared with never use [OR, 2.48 (95% CI, 1.61–3.82)], generating a rate difference of 4.43/1000 persons per year (95% CI, 1.54–7.33). The highest OR was observed in patients taking combination therapies, such as those concurrently using gonadotropin-releasing hormone agonists with oral anti-androgens. This finding suggests a possible additive effect exerted by ADT on both receptor antagonism and reduction of testosterone excretion. Furthermore, the highest OR of AKI was also observed in the earliest period of treatment, though the OR remained continuously elevated with longer durations of use.

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