Management and interpretation of novel toxicities of molecular targeted therapies: Renal toxicities

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Introduction

Over the past years the benefits and risks associated with pharmaceutical agents have received increasing attention from the medical community.

Some doubts have arisen concerning the current approach of drug approval based on clinical trials. In most cases these studies include relatively small numbers of patients, which can lead to an incomplete safety profile assessment of these drugs at the time of approval. In addition, safety profile and effectiveness may change when these drugs are used in a wider, less carefully selected population than patients included in clinical trials.

This phenomenon has been discussed in detail by Giezen and colleagues [1] in a recent publication. In this study of 174 biological products (antibodies, hormones, enzymes) approved from January 1995 through June 2007, including 136 agents approved in the US, 105 approved in the European Union, and 67 approved in both regions, the authors found 82 safety-related regulatory actions. The probability of a biological agent having a first safety-related regulatory action was 14% at 3 years and 29% at 10 years after approval.

This is very important in cancer treatment in which major advances have been made in recent years with new targeted molecules such as antibodies (ABs) and tyrosine kinase inhibitors (TKIs). Most patients will be treated with these compounds for a long period of time and in such circumstances cumulative toxicities will appear. In our opinion, one has to be alert for new signs and symptoms reported by patients who are treated with these drugs.

As an example, kidney cancer treatment has evolved in the last 3 years, and this change has been made thanks to the development of new drugs. During 2006 and 2007, four drugs were approved to treat kidney cancer: bevacizumab, sorafenib, sunitinib and temsirolimus.

Bevacizumab toxicity is better known because many patients have been treated with it for other indications like colon, breast and lung cancer before its approval in renal cell cancer.

However, the approval by the US Food and Drugs Administration (FDA) and the European Medicines Agency (EMEA) of sorafenib, sunitinib and temsirolimus was based on less than 3000 patients. Surprisingly, only 1242 patients have been treated with sorafenib (137 patients in phase I; 202 patients in phase II and 903 patients in one phase III study); 884 patients with sunitinib (28 patients in phase I, 106 in phase II and 750 in phase III studies) and 761 patients with temsirolimus (24 in a phase I study, 111 in phase II and 626 patients in the phase III study). Under such circumstances, little is known about the chronic toxicities of these drugs.

In a recent study, Bhojani and colleagues [2] reviewed the main toxicities reported in phase I, II and III studies of three drugs approved, in different settings, for kidney cancer. The authors found that renal toxicities were rare and included proteinuria and oedema. However, proteinuria may occur after prolonged exposure. Other molecules included were bortezomib, erlotinib and lapatinib.

As previously mentioned, the approval of different inhibitors that target the epidermal growth factor receptor (EGFR) and the vascular endothelial growth factor receptor (VEGFR) has changed the treatment of cancer patients. However, because the same growth factors are expressed in the kidney, these therapeutic agents have renal side effects. In this paper, we will review renal toxicities related to molecular targeted therapies according to their different nephron structural damage. We will also point out the probable pathogenesis, early diagnosis and treatment.

Nephron structure damage

Glomerular lesions

Glomerulonephritis and proteinuria

Different drugs have been reported to cause glomerulonephritis and proteinuria through glomerular damage. Most of the toxicity is related to VEGF inhibition. VEGF is very important in maintaining normal glomerular endothelial function. In an elegant study, Guan and colleagues showed that VEGF can act as a survival factor for podocytes and thereby prevent glomerulonephritis [3]. Shulman and colleagues [4] performed renal biopsies on patients with various glomerular diseases to evaluate the expression of VEGF mRNA and protein by using *in situ* hybridisation and immunohistochemistry. They found that endothelial cells expressing VEGF were decreased or absent in areas of glomerular sclerosis in cases of membranous glomerulonephritis, focal segmental sclerosis, IgA nephropathy, and crescentic glomerulonephritis. The importance of VEGF in glomerular homeostasis is of interest in pregnant women who develop pre-eclampsia and eclampsia disease. Pre-eclampsia is seen in about 5% of pregnant women and is characterised by the initiation of proteinuria and hypertension [5]. Recent studies have demonstrated that patients with eclampsia have elevated levels of soluble VEGFR-1. This soluble receptor binds to VEGF and decreases the VEGF levels in blood [6].

It is also known that VEGF can exert its protective function by different means: firstly, by activating the phosphatidylinositol 3-kinase (PI3K) pathway that in turn activates different antiapoptotic pathways.

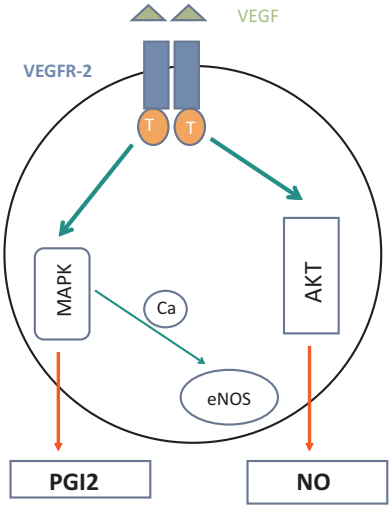

Fig. 1. Mechanisms of action of vascular endothelial growth factor (VEGF).

Secondly, VEGF induces production of nitric oxide and prostacyclin that are potent vasodilators, and lastly by inducing the decay accelerating factor (DAF) expression on endothelial cells. DAF is a protective glycoprotein against complement-mediated injury and is very important in circumstances of infection, inflammation, thrombosis or angiogenesis (Fig. 1).

Several studies have demonstrated that the injury in the glomerulus is related to VEGF inhibition. Podocytes usually secrete VEGF, which modulates the formation of fenestrations in the glomerular endothelium. It has been demonstrated that a loss of VEGF in the glomerulus leads to a loss of the healthy fenestrated phenotype and promotes the development of endotheliosis [7].

Glomerulonephritis is categorised into several different pathological patterns, which are broadly grouped into non-proliferative or proliferative types. Diagnosing the pattern of glomerulonephritis is important because of the outcome and treatment differs among different types. Primary causes are intrinsic to the kidney, whilst secondary causes are associated with certain infections (e.g. bacterial, viral or parasitic pathogens), cancer, systemic disorders or drugs. Different types of glomerulonephritis have been described during the use of molecular targeted therapies including membranoproliferative glomerulonephritis [8], minimal change disease [9], cryoglobulinemic glomerulonephritis [10] and focal segmental glomerulosclerosis [11].

The knowledge on management of proteinuria due to targeted agents is mostly related to bevacizumab. Many patients develop an increased protein excretion during treatment with bevacizumab, but few of them have a proteinuria in the range of nephrotic disease. A recent meta-analysis showed that bevacizumab is associated with a significant risk of developing proteinuria and hypertension in a group of patients with metastatic solid cancers. In this study, for patients receiving low-dose bevacizumab, the incidence of proteinuria ranged from 21% to 41%; and in the high-dose group, the incidence varied from 22% to 63%. Grade III proteinuria (protein 3.5 g/24 h) developed in only 1 of 872 patients in the control group (0.1%). However, 6 of 597 patients (1.0%) developed grade III proteinuria with low-dose and 7 of 381 patients (1.8%) with high-dose bevacizumab. The authors recommended that early detection and effective management of proteinuria and hypertension may allow a safer use of bevacizumab [12].

The identification of factors that confer susceptibility to overt glomerular disease in this subgroup of patients is important. It has been hypothesised

that altered glomerular permeability appears to be a direct consequence of VEGF inhibition and proteinuria may correlate with drug efficacy. However, the underlying mechanism of increased proteinuria related to treatment with angiogenesis inhibitors is unknown. Alternatively, or in parallel, the endothelial cell lining might be disturbed in patients treated with angiogenesis inhibitors, causing an extravasation of plasma proteins into the extracellular matrix or urine. Proteinuria is, in general, reversible after discontinuing the anti-angiogenic agent.

In addition, a clear correlation between the induction of hypertension and the prevalence of proteinuria has been described. In most clinical trials, patients with pre-existing proteinuria were excluded from study entry and, therefore, studies to determine the safety of angiogenesis inhibitors in this category of patients are of major interest.

Oedema (fluid extravasation) can also occur as a result of angiogenesis inhibition and may be a direct consequence of proteinuria. When large amounts of proteins are lost in the urine, the balance of the osmotic pressure between the blood and the interstitium is disturbed, causing the extravasation of fluid reflected by oedema (nephrotic syndrome). This complication has only occurred in a few patients during anti-angiogenic therapy but it is one of the dose-limiting toxicities of sunitinib [13]. In a phase I trial of KRN951, a small-molecule VEGFR tyrosine kinase inhibitor, 14 of 15 patients developed hypertension, and grade 3 proteinuria was a dose-limiting toxicity [14]. Also, proteinuria has been reported with vatalanib, vandetanib and axitinib [15].

Another group of targeted agents are the mTOR inhibitors, temsirolimus and everolimus (rad 001), approved in the treatment of poor-prognosis metastatic renal cancer and second-line treatment after anti-angiogenic failure. It has been postulated that this group of drugs is non-nephrotoxic because of their hepatic metabolism while only 5% of the drug is metabolised in the kidney. Temsirolimus is a sirolimus ester that is hydrolysed to sirolimus in patients, resulting in 74% of the circulating drug following weekly temsirolimus administration. Sirolimus and everolimus are also employed in renal transplant and these drugs can cause proteinuria in transplant recipients. Sirolimus is an immunosuppressant with potent antiproliferative actions and represents a major therapeutic advance in the prevention of acute renal allograft rejection and chronic allograft nephropathy. Sirolimus does not share the vasomotor renal adverse effects exhibited by calcineurin inhibitors, and has been classified as a 'non-nephrotoxic drug'. However, clinical reports suggest that, under some circumstances, sirolimus is associated with proteinuria and acute renal dysfunction [16]. The mechanism of sirolimus-associated proteinuria is multifactorial and may be due to an increase in glomerular capillary pressure or directly by increasing glomerular permeability/injury.

Podocyte injury and focal segmental glomerulosclerosis have been related to mToR inhibition in some patients, but the pathways underlying these lesions remain hypothetic [17].

The acute renal dysfunction associated with sirolimus (such as in delayed graft function) may be due to suppression of compensatory renal cell proliferation and survival/repair processes. Although these adverse effects occur in some patients, their occurrence could be minimised by knowledge of the molecular effects of sirolimus on the kidney, the use of sirolimus in appropriate patient populations and close monitoring of proteinuria and renal function.

Proteinuria should be monitored in patients receiving anti-VEGF therapy using the urine protein to creatinine ratio. This index of proteinuria is commonly used in the nephrology literature and correlates well with 24-h protein excretion. Using this ratio also avoids the inaccuracies associated with dipstick urine assays and the inconvenience of 24-h collections. If spot urine protein tests are not available, then dipstick urine assays at regular intervals are useful. The frequency of testing should be every 2 to 8 weeks (before each dose and/or restaging), according to the severity of the previous proteinuria and any other relevant risk factors or considerations. Dipstick values 2 or higher should be confirmed by the ratio of urine protein to creatinine or 24-h collection.

As mentioned above most of the proteinuria management knowledge is related to bevacizumab therapy. It is known that under this medication treatment should be interrupted in patients with proteinuria greater than 2 g/24 h [18,19]. Although this procedure has been followed in most clinical studies with bevacizumab, it is not known if it is applicable to other therapies.

Tubular lesions

Two main syndromes have been described according to the tubular alteration.

Fanconi syndrome or renal tubular acidosis

Fanconi syndrome or renal tubular acidosis (RTA) is a medical condition that involves an accumulation of acid in the body due to a failure of the kidneys to appropriately acidify the urine. The metabolic acidosis

that results from RTA may be caused either by failure to recover sufficient bicarbonate ions from the filtrate in the early portion of the nephron (proximal tubule) or by insufficient secretion of acid into the latter portions (distal tubule). Proximal RTA (pRTA) is caused by a failure of the proximal tubule cells to reabsorb filtered bicarbonate from the urine, leading to urinary bicarbonate wasting and subsequent acidemia. The distal intercalated cells function normally, so the acidemia is less severe than distal RTA and the urine can acidify to a pH of less than 5.3 [20]. pRTA has several causes, and may occasionally be present as a solitary defect, but is usually associated with a more generalised dysfunction of the proximal tubular cells and with phosphaturia, glycosuria, aminoaciduria, uricosuria and tubular proteinuria.

The principal feature of Fanconi's syndrome is bone demineralisation due to phosphate wasting. This syndrome has been reported with different TKIs like imatinib [21].

Distal tubular alteration

This alteration is characterised by hypomagnesaemia. This phenomenon is one of the most frequent toxicities described with antibodies against EGFR and is potentially a class effect.

Hypomagnesaemia was first described in patients treated with cetuximab and it has been reported in around 20% of patients but only 3–5% of patients develop grade 3–4 toxicity.

In the kidney, about 80% of total plasma magnesium (Mg^{2+}) is filtered in the glomeruli, of which the majority is reabsorbed along the nephron. Mg^{2+} reabsorption occurs in different nephron segments: 10% to 20% of Mg^{2+} is reabsorbed in the proximal tubule, and 50% to 70% is reabsorbed in the afferent loop by passive paracellular reabsorption processes. But in the distal convoluted tubule, 10% of the Mg^{2+} reabsorption is a highly regulated process. Different genetic studies in families with hypomagnesaemia and secondary hypocalcemia (HSH) have identified a critical region on chromosome 9q21. The pathophysiology of HSH is largely unknown, but physiological studies have shown that there are defects in both intestinal Mg^{2+} absorption and renal Mg^{2+} reabsorption. Subsequent analysis of this critical region pointed to a gene, *TRPM6* (transient receptor potential cation channel, subfamily M, member 6), which was mutated in patients with HSH. TRPM6 is localised along the apical membrane of the loop of Henle and the distal convoluted tubule, as well as in the small intestine. EGFR is also highly expressed in these regions suggesting the hypothesis that blockade of EGFR in the nephron reversibly impairs the function of the proteins involved in the active transport of extracellular Mg^{2+} [22]. However the possibility of effects of EGFR blockade on Mg^{2+} absorption from the gut cannot be excluded. An important study of monogenic disorders to understand this process has been conducted by Groenestege and colleagues [23]. They have demonstrated that a point mutation in pro-EGF gene in isolated autosomal recessive renal hypomagnesaemia leads to impaired basolateral sorting of pro-EGF. Thus, the renal EGFR is inadequately stimulated, with consequent insufficient activation of the epithelial Mg^{2+} channel TRPM6 and thereby Mg^{2+} loss. Of note, Mg^{2+} is involved in physiological enzymatic reactions such as nucleic acid metabolism, protein synthesis and energy production. In cancer biology, it seems to be involved in the regulation of oxidative stress, carcinogenesis, tumour progression and angiogenesis. Moreover, it has been suggested that the interaction between anti-EGFR agents and Mg^{2+} homeostasis could be partially responsible for the anticancer activity of these agents. For example, one of the mechanisms could be that low Mg^{2+} inhibits endothelial migration and proliferation, late events absolutely required for the formation of new vessels, by desensitising endothelial cells to the effects of angiogenic factors. Also, the effect on cell motility is so striking that Mg^{2+} has been proposed to serve as a chemotactic factor for endothelial cells. In conclusion, hypomagnesaemia could contribute to the antitumoural effect of cetuximab both by an antiangiogenetic (direct action on endothelial cells) effect and by an indirect influence in EGFR signalling and production of angiogenic molecules.

Surprisingly, hypomagnesaemia has not been reported with TKIs that act at the same receptor and could have the potential to impair Mg^{2+} metabolism in the nephron. It has been hypothesised by Altundag and colleagues [24] that among the inactive excipients in gefitinib and erlotinib tablets is Mg^{2+} stearate and this Mg^{2+} may balance the deficiency produced by the EGFR blockage.

Because symptoms may be rapidly ameliorated with supplementation, it has been suggested that during anti-EGFR antibodies therapy, in addition to baseline assesment, serum Mg^{2+} level should be measured when fatigue or hypocalcaemia is encountered, and repleted as necessary [25].

Interstitial lesions

Interstitial lesions are often associated to and commonly difficult to distinguish from tubular injury.

Common types of tubulointerstitial injury that can occur secondary to therapeutic agents include allergic interstitial nephritis, acute tubular necrosis, crystal nephropathy, tubular atrophy, and interstitial fibrosis.

Although some cases of reversible acute tubular necrosis have been reported following treatment with sirolimus, especially in combination with tacrolimus, no cases have been comunicated with other mTOR inhibitors such as temsirolimus or everolimus. Acute tubular necrosis has been reported in association with interstitial damage as the predominant lesion secondary to TKI.

Allergic interstitial nephritis

Only a couple of cases of allergic interstitial nephritis have been reported as secondary to novel targeted therapies. Barakat and colleagues [26] reported the case of a 26-year-old man diagnosed with metastatic rectal leiomyosarcoma who was treated with intravenous bevacizumab. The patient was noted to have elevated creatinine levels after two doses and developed acute renal failure requiring haemodialysis after the third dose. A renal biopsy revealed interstitial nephritis. Renal failure was resolved with cessation of the drug. Khurana [27] reported the case of a 69-year-old woman with a history of metastatic renal cell carcinoma after left radical nephrectomy who developed progressive kidney dysfunction with proteinuria, together with peripheral eosinophilia and eosinophiluria during the first cycle of sunitinib therapy. The clinical picture worsened with the second course and resolved after sunitinib discontinuation. In this case confirmatory renal biopsy was not performed due to clinical improvement, a solitary remaining kidney and thrombocytopenia. When subsequently treated with sorafenib, the patient experienced a worsening of serum creatinine and increasing eosinophilia, similar to that noted with sunitinib, suggesting that this event may be a class effect.

Recently, two more cases of acute interstitial nephritis related to sunitinib and sorafenib, both of them proven by biopsy, have been reported [28].

These cases are quite representative of the clinical picture offered by acute intertitial nephritis (AIN). It usually begins 2 weeks after exposure to a drug but may occur sooner if the patient has been previously sensitised to the same or a chemically similar agent.

Patients may present with fever (27% of patients), rash (15% of patients), and enlarged kidneys, eosinophilia (23%), eosinophiluria (sensitivity 65% and specificity 83%), and elevated immunoglobulin E (IgE) levels. In mild cases, clinical presentation may consist of subtle tubular function abnormalities, such as Fanconi syndrome. Proteinuria is usually absent or modest. Urinalysis may show microscopic haematuria and/or sterile pyuria (with or without eosinophils). Although the clinical presentation is often sufficient to make the diagnosis, renal biopsy is required to make a definitive diagnosis (but it may be avoided in mild cases or when clinical improvement is rapid after removal of an offending agent or medication).

The pathogenesis of the majority of cases of AIN is thought to involve a cell-mediated hypersensitivity reaction to a drug. This is supported by the observation that T cells are the predominant cell type comprising the interstitial infiltrate (accompanied by plasma cells with occasional histiocytes and a variable number of, and sometimes predominant, eosinophils). Factors that are likely to play a role include drugs acting as haptens, molecular mimicry, and an individual's immune response genes [29].

Regardless of the severity of the damage to the tubular epithelium, the renal dysfunction is generally reversible after removal of the causing drug, possibly reflecting the regenerative capacity of tubules with preserved basement membrane. Corticosteroids appear to provide some benefit in terms of clinical improvement and return of renal function, but no controlled clinical trials have been conducted to confirm this. If dialysis is necessary, it is usually only required for a short time.

Interestingly, it is recognised that growth factors and their receptors play a fundamental role in the regeneration and repair of injured renal tubule cells and it might be postulated that TKIs therefore interfere with this process [30].

Although the are currently no guidelines regarding this kind of side effect in patients treated with new targeted drugs, it is advisable to monitor serum creatinine levels, and maybe urine and serum leukocytes with differential cell count, closely at the beginning of the treatment and periodically thereafter.

Vascular lesions

Renal thrombotic microangiopathy

Thrombotic microangiopathy (TMA) had been previously described after treatment with sirolimus in transplanted patients, preferentially in kidneys with concomitant endothelial injury. Analysis of VEGF has shown that renal VEGF expression during sirolimus-induced TMA was significantly lower than VEGF expression in normal transplanted kidneys, and this decreased expression of VEGF seemed to be a consequence of sirolimus treatment since analysis of biopsies performed after removal of sirolimus showed

reappearance of VEGF expression. Therefore, the potential role of sirolimus (and possibly other mTOR inhibitors)-induced downregulation of VEGF as a predisposing factor to the development of TMA should be taken into account [31].

Also, several cases of TMA have been reported secondary to bevacizumab administration [32] and more recently, as a secondary effect of sunitinib treatment in a patient with a malignant skin hydradenoma [33].

In this last case report, the patient developed hypertension after 2 weeks and low-grade proteinuria after 4 weeks while renal function remained normal, and biological signs of TMA were absent. A renal biopsy was performed 6 months later as proteinuria persisted, demonstrating typical features of TMA while immunohistochemistry showed a normal pattern of expression of VEGF by podocytes (as expected by the mechanism of action of sunitinib). The patient was given irbesartan, and sunitinib was continued for 3 months after diagnosis. Over this period, blood pressure and renal function remained stable and proteinuria became undetectable. This case highlights the possible discrepancy between mild clinical manifestations on one hand and severe TMA features on renal biopsy on the other hand.

These reports suggest that sunitinib and bevacizumab (and probably all drugs inhibiting the VEGF signalling pathway) share a similar risk for developing renal adverse events, including TMA (Table 1). It has been hypothesised that disruption of VEGF signalling through drugs or genetic deletion in podocytes has been shown to lead to the loss of the healthy-fenestrated phenotype of glomerular capillaries, microvascular injury and TMA [32]. Why only a subset of patients receiving anti-VEGF therapy develops TMA remains unclear. Recent advances provided evidence that defective regulation of the complement alternative pathway (CAP) causes defective protection of endothelial cells and TMA [34]. Moreover, mutations in genes encoding CAP proteins (Factor H, Factor I, CD46/MCP, C3) were recently identified in pregnancy-associated haemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome with normal levels of CAP proteins [35]. Of note, in this setting, glomerular lesions are also induced by low levels of biologically available VEGF (and placental growth factor (PIGF)) due to increased sFlt1 production by the ischaemic placenta. Further studies should determine whether CAP genes mutations are a predisposition factor to anti-VEGF-induced TMA.

Usually, withdrawal of the causing drug results in complete recovery or at least significant improvement of hypertension and renal involvement. But, as limited therapeutic options are often the case, the alternative of maintaining treatment while blocking the renin–angiotensin system could be a good strategy for hypertension and proteinuria control.

Table 1
Summary of secondary effects

Monoclonal antibodies	
Bevacizumab	Proteinuria Nephrotic syndrome Glomerulonephritis Interstitial nephritis Thrombotic microangiopathy
Cetuximab	Hypomagnesaemia
Panitunimab	Hypomagnesaemia
Tyrosine kinase inhibitors	
Sunitinib	Interstitial nephritis Thrombotic microangiopathy
Sorafenib	Interstitial nephritis
Vatalanib	Proteinuria
Vandetanib	Proteinuria
Axitinib	Proteinuria
Imatinib	Fanconi Syndrome
mTOR inhibitors	Proteinuria Acute renal dysfunction Focal glomerulosclerosis Acute tubular necrosis Thrombotic microangiopathy

Combinations and interactions with other neprohotoxic drugs

Most of the experience of targeted therapies in combination with chemotherapy has been gained with bevacizumab and cetuximab.

In a recent phase III study, bevacizumab when combined with cisplatin in non-small cell lung cancer (NSCLC) prolongs survival and the incidence of grade 3 or greater adverse events was similar between both arms [36]. Safety results are also very similar to that observed in prior clinical studies of bevacizumab in NSCLC [37,38].

Cetuximab has also been combined with a cisplatin-based regimen in NSCLC. In a recent study there was a better progression-free survival for the group treated with cetuximab but toxicities were very similar [39]. Similar toxicity results have been recently published in another study in Annals of Oncology. In that study [40] the primary endpoint was not reached; however, toxicities between both treatment arms did not differ.

Erlotinib and gefitinib have also been tested in combination with cisplatin-based chemotherapy as first-line treatment in NSCLC and in both phase III trials no increased renal toxicity has been observed [41,42].

We would like to point out that decreased efficacy or increased toxicity with other potential nephrotoxic drugs has to be taken in account.

- The Advanced Colorectal Cancer Evaluation study (PACCE) trial, a phase III study in which the addition of panitumumab, a human monoclonal anti-EGFR antibody, to chemotherapy [bolus 5-fluorouracil (5-FU) plus folinic acid plus oxaliplatin (FOLFOX) or 5-FU plus folinic acid plus irinotecan (FOLFIRI)] and bevacizumab, was prematurely discontinued due to an excess of grade 3–4 diarrhoea (21% versus 11%), dehydration (14% versus 4%) and infection (15% versus 7%) in the panitumumab-containing treatment arm, which was accompanied by a significantly inferior progression-free survival (9.0 months versus 10.5 months) [43].
- A year ago, toxicity of the first 400 patients included in the CAIRO2 study was reported. Results showed that the addition of cetuximab to capecitabine, oxaliplatin and bevacizumab did not result in excessive or unexpected toxicity. However, hypomagnesaemia was observed more frequently in the cetuximab-bevacizumab arm (15% versus 37%; $P < 0.001$). It was predominantly grade 1 toxicity (serum Mg^{2+} <0.70 mmol/l and >0.50 mmol/l, in 13% versus 33% of the patients) [44]. Recently, the final results of this study have been reported, and the addition of cetuximab to capecitabine, oxaliplatin and bevacizumab resulted in a significant decrease in progression-free survival and a poorer quality of life [45]. The authors recognised that the reduction in progression-free survival was unexpected and could not be related to an increase in adverse events since such events were manageable and the percentage of patients who discontinued treatment was similar in the two treatment groups, as had been previously reported with the first 400 patients. The results of the trials which combine cetuximab and bevacizumab might translate as an antagonic interaction between both drugs. As reported before, hypertension correlated with clinical outcome in patients with colorectal cancer. In the CAIRO2 study hypertension was less frequent in the cetuximab-bevacizumab group suggesting a decreased efficacy of bevacizumab when administered in combination with cetuximab.

In conclusion, combination of targeted therapies with potential nephrotoxic drugs does not seem to increase renal toxicities.

Patients with renal impairment

Different antibodies have been approved in recent years for cancer treatment. These include bevacizumab, cetuximab, trastuzumab, panitumumab and palifermin. Renal insufficiency per se is not a contraindication to receive different monoclonal antibodies for cancer treatment.

Haemodialysis does not influence cetuximab and bevacizumab clearance. Inauen and colleagues [46] observed no effect of haemodialysis on cetuximab concentrations but the small number of blood samples did not allow them to estimate cetuximab pharmacokinetics parameters. These preliminary data indicate that treating dialysed patients with monoclonal antibodies may be safe. Further prospective studies are warranted to elucidate the pharmacokinetics and pharmacodynamics of monoclonal antibodies.

It has been reported that the increased systemic exposure to imatinib in patients with renal failure could be due to decreased cytochrome P450 (CYP) activity [47]. We have to point out that after many years of treating oncologic patients with chemotherapy we also know, for example, that clearance of paclitaxel is impaired in patients with end-stage renal failure [48], but not in an anephric patient on dialysis [49]. One possible explanatory mechanism is that increased circulating concentrations of uremic toxins associated with renal failure could directly impact on the extent of hepatocellular uptake of different drugs. This interaction has to be taken in account in patients with renal failure that take TKIs which are metabolised by the CYP P450. In this situation renal failure can dramatically impact the pharmacokinetics of agents whose elimination is critically dependent on liver metabolism. Future studies should further evaluate the hypothesis that increased systemic concentrations of uremic toxins can directly inhibit the hepatic uptake of several anticancer agents, and that consideration of this type of interaction could guide the design and interpretation of dose-finding studies in patients with renal dysfunction.

Conclusion

Although the incidence of kidney injury among patients receiving VEGF inhibitors and other molecular targeted therapies has not been fully described, it is prudent to monitor patients receiving these new drugs closely for possible renal toxicity.

Conflict of interest statement

None declared.

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