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Adverse kidney effects of epidermal growth factor receptor inhibitors

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FULL REVIEW

ABSTRACT

The epidermal growth factor receptor (EGFR) is implicated in various malignancies. The past decade has seen the development and widespread use of EGFR inhibitors for the successful treatment of such cancers. Available EGFR inhibitors include small molecule tyrosine-kinase inhibitors and monoclonal antibodies. Class-related renal adverse events result in dual toxicity including tubular/electrolyte disorders and glomerulopathies. Tubular injury is common and mainly due to monoclonal antibodies while glomerulopathy is rare and related to various anti-EGFR agents. The exact pathogenesis of anti-EGFR agents associated with kidney disorders remains to be elucidated.

Keywords: EGFR, electrolyte, glomerulopathy, hypomagnesemia, onconephrology

INTRODUCTION

The epidermal growth factor receptor (EGFR) is overexpressed in various malignancies such as non-small-cell lung cancer (NSCLC), breast, head and neck, and pancreatic cancer. EGFR activation reduces cancer cell apoptosis and allows progressive tumor growth and metastasis. The past decade has seen the development and widespread use of EGFR inhibitors for the treatment of such cancers [1].

The EGFR is a transmembrane glycoprotein and a member of the erbB family of receptor tyrosine kinases (TKs). The ErbB family includes HER1 (EGFR/erbB1), HER2 (neu/erbB2), HER3 (erbB3), HER4 (erbB4) and 13 polypeptide extracellular ligands. The *EGFR* gene encodes a 170-kDa type I transmembrane growth factor receptor located on the short arm of chromosome 7 [1]. As seen in Figure 1, EGFR binds to multiple ligands [EGF, transforming growth factor-α (TGF-α) or amphiregulin] and forms homodimers as well as three functional heterodimers, and subsequent autophosphorylation of the tyrosine domain leads to downstream signaling of the mitogen-activated protein kinase (MAPK) cascades, Raf-Mek-Erk, PI3K [PI3K-Akt-mammalian target of rapamycin (mTOR) or forkhead box protein O, PLC (PLC-PKC)] and STAT (Jak-Src-STAT) pathways [1], which are associated with cell growth, proliferation, differentiation, survival, adhesion, invasion and angiogenesis [2–4]. Upon EGFR deregulation, these signal transduction pathways are amplified resulting in the development of cancer [5–7].

On the other hand, EGFR activation is a pivotal mediator for renal fibrosis and may interact with TGF-β signaling [8, 9] and delayed EGFR inhibition with a clinically available EGFR inhibitor, even after the onset of acute kidney injury (AKI), was shown to effectively reduce kidney damage and AKI [10]. Furthermore, EGFR activation has a major role in activating pathways that mediate podocyte injury and loss in diabetic nephropathy [11]. Thus, based on this mechanism, one would predict that EGFR inhibitors should be renoprotective. It appears, however, through this anti-EGFR class-related renal toxicity review, that this is not the case.

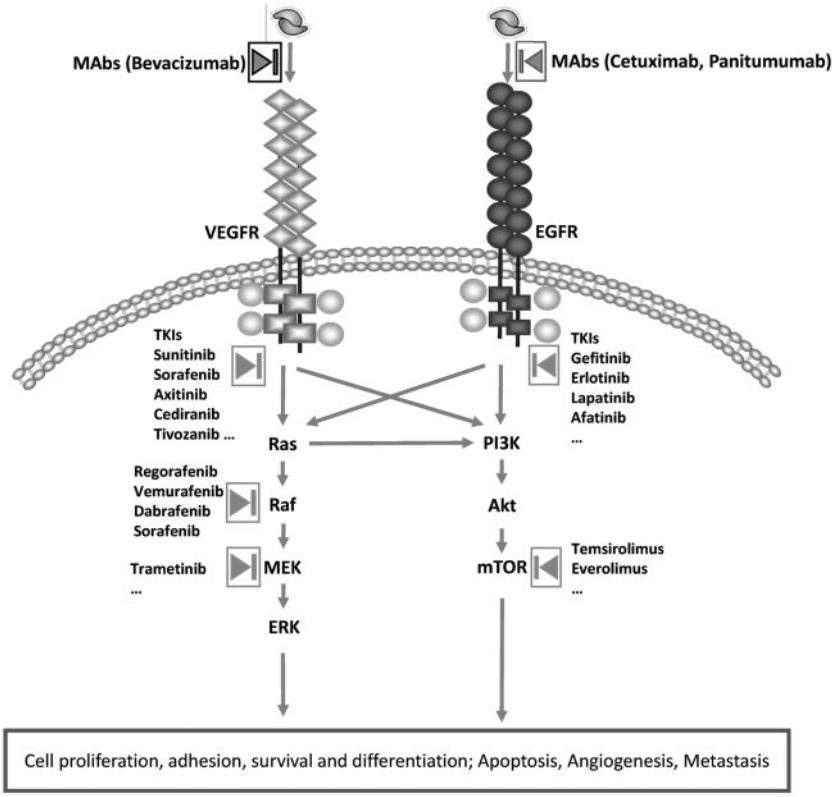

FIGURE 1: Overview of the VEGFR and EGFR signaling pathways and drugs targeting signaling proteins and receptors. EGFR, epidermal growth factor receptor; VEGFR, vascular endothelial growth factor receptor; MAbs, monoclonal antibodies; TKIs, tyrosine kinase inhibitors.

FULL REVIEW

EGFR INHIBITORS

Currently available EGFR inhibitors include small molecule tyrosine-kinase inhibitors (TKIs) [i.e. gefitinib (Iressa™), erlotinib (Tarceva™) and Afatinib], and monoclonal antibodies (MAbs) [i.e. cetuximab (Erbitux™) and panitumumab (Vectibix™)] (Figure 1). The development plan of selected EGFR inhibitors is summarized in Table 1.

EGFR TKIs

First-generation TKIs.

Gefitinib. This is an orally active, reversible EGFR-TKI developed by AstraZeneca. Based on Phase II IDEAL studies [12, 13] and four randomized Phase III trials (WJTOG3405 trial, NEJ002 study, IPASS trial and First-SIGNAL trial [14–17]), it was approved as first-line therapy for the treatment of advanced NSCLC in patients with activating mutations of EGFR. Currently, gefitinib is undergoing a Phase III randomized IMPRESS study (NCT01544179) in NSCLC [1].

Erlotinib. This is an orally active, reversible EGFR-TKI marketed by OSI, Genentech and Roche for stage IIIb/IV NSCLC patients, which was approved worldwide as second- or third-line treatment of advanced NSCLC based on the Phase III, randomized BR.21 study [18], and as a first-line treatment for patients with EGFR exon 19 deletion and L858R mutation based on OPTIMAL [19] and EURTAC studies [20]. Furthermore, in combination with gemcitabine, erlotinib was approved as a treatment for pancreatic cancer [21]. Erlotinib is currently investigated in NSCLC as adjuvant treatment (NCT01456325) for patients with MET-diagnostic-positive NSCLC (NCT01456325), head-to-head against gefitinib in mutant EGFR NSCLC Korean patients and in erlotinib/bevacizumab combination treatment for stage IIIb/IV NSCLC patients [1].

Lapatinib. Originally designed as an EGFR inhibitor, lapatinib failed to demonstrate tumor regression in EGFR-overexpressed NSCLC [22]. Further development concerning lapatinib became HER2-activation and based on a Phase III randomized study comparing lapatinib plus capecitabine versus capecitabine alone in metastatic breast cancer (MBC) patients [23], lapatinib was approved by the FDA for HER2-activated breast cancer [23, 24].

Icotinib. This is an orally available, reversible EGFR-TKI developed by Zhejiang b Pharma, and was approved in China in 2011 [25].

Second-generation TKIs.

Afatinib. Unlike reversible first-generation TKIs, afatinib is an irreversible inhibitor of the TK activity of EGFR through the formation of a covalent bond to the ATP-binding site [26, 27]. This ultimately leads to reduced auto-phosphorylation and cell proliferation. Afatinib was approved by the food and drug administration (FDA) and European Medicines Agency (EMA) on the basis of two Phase III clinical trials comparing afatinib against chemotherapy in the first-line setting in NSCLC [1, 28, 29].

Table 1. Selected EGFR tyrosine kinase inhibitors in NSCLC (and other cancers)

Drug	Indication	Mode	Phase of development	Trial or ID No.
First-generation EGFR TKIs				
Gefitinib	EGFR	Reversible	FDA approved (2003)	IDEAL-1 and -2 studies INTACT-1 and -2 studies IPASS (Iressa Pan-Asia Study) Korean first-SIGNAL study Japanese WJTOG3405 study IMPRESS study (NCT01544179) NCT00054691 (skin) NCT00317772 (ovarian) NCT00229723 (head and neck) NCT00632723 (breast) NCT00212108 (nasopharyngeal carcinoma)
Erlotinib	EGFR	Reversible	FDA approved (2003)	TRIBUTE, TALENT and TORCH studies OPTIMAL and EURTAC studies NCT01456325 NCT01515137 (head and neck) NCT00503841 (breast) NCT00088946 (bladder)
Lapatinib	EGFR, erbB2	Reversible	FDA approved (2007, metastatic breast cancer)	EGF30008
Icotinib	EGFR	Reversible	Approved (2011, China)	NCT01040780
KD019	EGFR, erbB2	Reversible	Phase III	NCT02154529
Varlitinib	EGFR, erbB2/4	Reversible	Phase II (metastatic gastric, cholangiocarcinoma)	Orphan drug designation
Second-generation EGFR TKIs				
Afatinib	EGFR, erbB2/4	Irreversible	FDA approved 2013	LUX-Lung 1 to 8, ASCENT study NCT01345682, NCT01345669
Dacomitinib	EGFR, erbB2/4	Irreversible	Phase III	NCT00548093, NCT00818441 ARCHER1009 (NCT01360554) ARCHER1050 (NCT01774721) BR.26 study (NCT01000025)
Neratinib	EGFR, erbB2	Irreversible	Phase III (metastatic breast cancer)	NCT01808573
Poziotinib	EGFR, erbB2	Irreversible	Phase II	NCT01819428
BMS690514	EGFR, erbB2/4, VEGFR1/2/3	Reversible	Phase II	NCT00743938
CUDC101	EGFR, erbB2, HDAC	Reversible	Phase I (head and neck cancer)	NCT01384799
Third-generation/mutant-selective EGFR TKIs				
CO-1686	Mutated EGFR	Irreversible	Phase I/II	NCT01526928
AZD-9291	Mutated EGFR	Irreversible	Phase I/II	NCT01802632
WZ4002	Mutated EGFR	Irreversible	Preclinical	No clinical trial initiated
TAS-2913	Mutated EGFR	Irreversible	Preclinical	No clinical trial initiated

Dacomitinib (PF00299804). This is an orally available, irreversible, pan-ErbB TKI developed by Pfizer. Several single-arm studies were conducted to explore the efficacy of dacomitinib in NSCLC patients with wild-type KRAS, who were refractory to prior line(s) of chemotherapy and erlotinib or gefitinib (NCT00548093 in USA and NCT00553254 in Korea) [30, 31] and in a first-line dacomitinib A7471017 trial (NCT00818441) [32].

EGFR MAbs

The MAbs approved by the FDA include cetuximab (Erbitux™) in February 2004 and panitumumab (Vectibix™) in September 2006 [33, 34]. These agents continue to be evaluated in treatment of various advanced malignant diseases such as metastatic colorectal cancer (mCRC), NSCLC, and head and neck cancer. Cetuximab is also used in squamous cell carcinomas of the head and neck (together with chemotherapy or radiation therapy).

Cetuximab and panitumumab are most effective in combination with chemotherapy, but also show activity as single agents in chemorefractory mCRC [35]. Both are approved in patients with KRAS wild type refractory metastatic CRC as first- and second-line therapy and monotherapy based on the Phase III randomized CRYSTAL trial [36] and randomized Phase II OPUS trial [37] for cetuximab, and on the randomized Phase III PRIME trial [38, 39] for panitumumab. These two molecules appear to be equally effective, as reported in patients with chemotherapy-refractory wt KRAS exon 2 mCRC in the randomized Phase III ASPECCT trial [40].

Cetuximab is a recombined, chimeric (mouse/human) IgG1 MAb whereas Panitumumab is a fully human IgG2 MAb, both directed against the extracellular domain of EGFR [41, 42]. Panitumumab binds to EGFR with an 8-fold higher affinity than cetuximab [43], and panitumumab and cetuximab bind to different sites on the domain III of EGFR, which may support reports suggesting treatment efficacy of panitumumab after failure of cetuximab [44–49]. Panitumumab may also induce

Table 2. Grading scale of electrolyte disorders

Adverse event	Grades				
	1	2	3	4	5
Hypokalemia	<LLN–3.0 mmol/L	<LLN–3.0 mmol/L; symptomatic; intervention indicated	<3.0–2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences	Death
Hypomagnesemia	<LLN–1.2 mg/dL; <LLN–0.5 mmol/L	<1.2–0.9 mg/dL; <0.5–0.4 mmol/L	<0.9–0.7 mg/dL; <0.4–0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L; life-threatening consequences	Death
Hyponatremia	<LLN–130 mmol/L	–	<130–120 mmol/L	<120 mmol/L; life-threatening consequences	Death
Hypocalcemia	Corrected serum calcium of <LLN–8.0 mg/dL; <LLN–2.0 mmol/L; ionized calcium <LLN–1.0 mmol/L	Corrected serum calcium of < 8.0–7.0 mg/dL; <2.0–1.75 mmol/L; Ionized calcium <1.0–0.9 mmol/L; symptomatic	Corrected serum calcium of < 7.0–6.0 mg/dL; <1.75–1.5 mmol/L; ionized calcium <0.9–0.8 mmol/L; hospitalization indicated	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; ionized calcium <0.8 mmol/L; life-threatening consequences	Death

LLN, lower limit of normal.
Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 Published: May 28, 2009 (v4.03: June 14, 2010) US DEPARTMENT OF HEALTH AND HUMAN SERVICES, National Institutes of Health, National Cancer Institute http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf (last accessed 12/14/2016).

antibody-dependent cell-mediated cytotoxicity via myeloid-derived cells, which has been suggested to be an additional panitumumab action mechanism [50].

RENAL TOXICITY OF EGFR INHIBITORS

Class-related nephrotoxicity of EGFR inhibitors results in a dual toxicity including tubular and electrolyte disorders and glomerulopathies. Tubular and electrolyte disorders are common and mainly a complication of MAbs while glomerular lesions are unusual and related to various anti-EGFR agents. Table 2 defines the grades of electrolyte disorders. The exact pathogenesis of anti-EGFR-associated kidney-related disorders is unclear and requires further study. It should be pointed out that the two anti-EGFR MAbs cetuximab and panitumumab are commonly employed along with cytotoxic chemotherapy, the latter potentially being able to contribute, directly or through the induction of adverse events such as vomiting and diarrhea, to kidney injury [51].

TUBULAR AND ELECTROLYTE DISORDERS

Anti-EGFR MAbs

Wang *et al.* [52] conducted a meta-analysis including 16 411 patients from 25 randomized controlled trials (RCTs) of published randomized controlled trials to evaluate the incidences and overall risks of all-grade and grade 3/4 electrolyte disorder events associated with anti-EGFR MAbs. Various electrolyte disturbances are reported, mainly hypomagnesemia. Both the incidence and severity of electrolyte disorders appear to be higher with panitumumab as compared with cetuximab. In subanalysis of different tumor types, the addition of cetuximab augmented notably the incidence of grade 3/4 events in colorectal cancer [relative risk (RR) 2.7, 95% confidence interval (95% CI) 0.8–8.3] and NSCLC (RR 5.7, 95% CI 2.9–10.9). For the panitumumab treatment group, colorectal cancer patients received an obviously higher incidence of grade 3/4 events than those in controls (7.2 versus 2.1%, $P < 0.001$) [52].

Hypomagnesemia. The all-grade incidence of hypomagnesemia related to anti-EGFR MAbs was 34.0% compared with 9.7% in controls (95% CI 28.0–40.5%, $P < 0.001$). The incidence of grade 3/4 hypomagnesemia events compared with controls was 4.8 versus 0.7% with an increased RR of grade 3/4 hypomagnesemia events (RR 6.10, 95% CI 4.37–8, 52, $P < 0.001$) in all cancers types [52]. Colorectal cancer patients had the highest risk of grade 3/4 hypomagnesemia events among cancer patients: compared with chemotherapy alone, addition of cetuximab increased the risk of grade 3/4 hypomagnesemia with RRs of 7.14 (95% CI 3.13–16.27, $P < 0.001$) while panitumumab cases were more vulnerable to grade 3/4 hypomagnesemia (RR 18.29, 95% CI 7.29–48.41, $P < 0.001$) [52].

A meta-analysis demonstrated an overall incidence of all-grades hypomagnesemia of 17% (RR 5.83), whereas the RR of developing hypomagnesemia was 3.87 and 12.55 in cetuximab- and panitumumab-treated patients, respectively [53].

The major risk factor for the development of hypomagnesemia was the duration of treatment: grade 3 and 4 hypomagnesemia ranging from 6% to 47% in relation to the duration of treatment time <3 months or >6 months, respectively [51, 54]. Other risk factors included age and magnesium values at baseline [55]. Due to conflicting data, it is unclear if hypomagnesemia is a biological marker of therapeutic effectiveness [56, 57].

Renal magnesium wasting underlies the development of hypomagnesemia. Pro-epidermal growth factor (pro-EGF) and magnesium permeable transient receptor potential cation channel (TRPM6 channel, subfamily M, member 6 and TRPM7) were both shown to be involved in transepithelial Mg^{2+} transport in the distal convoluted tubule [58], which is the main site of active renal Mg^{2+} reabsorption. *In vitro*, cetuximab abolished the stimulatory effect of EGF on TRPM-6 activity, thus affecting Mg^{2+} transport and leading to hypomagnesemia [55, 59–62].

Careful management of hypomagnesemia is indicated in patients receiving EGFR antibodies. Particular caution should be taken in elderly and frail patients with a history of myocardial infarction or arrhythmias, as hypomagnesemia might lead to severe cardiac events [63, 64].

Treatment of hypomagnesemia involves the temporary discontinuation of anti-EGFR therapy and replacement with either oral or intravenous magnesium [51, 54, 60, 65, 66].

Hypokalemia and hypocalcemia. As hypomagnesemia is also associated with reduced parathyroid hormone (PTH) secretion and renal potassium wasting effect, both hypocalcemia and hypokalemia, respectively, must be monitored for and treated. Unlike hypomagnesemia, clinically significant hypocalcemia is rare and resolves after discontinuation of anti-EGFR MAbs [52]. In the Wang meta-analysis, the all-grade incidence of hypokalemia and hypocalcemia related to anti-EGFR MAbs was 14.5% (95% CI 8.2–24.4%) and 16.8% (95% CI 14.2–19.7%), respectively, which was significantly higher than in controls ($P < 0.001$ for both) [52]. MAbs also obviously increased RR of grade 3/4 hypokalemia and hypocalcemia events with the value of 1.68 and 1.88, respectively [52]. Again, colorectal cancer patients were more prone to have grade 3/4 hypokalemia events than others: compared with chemotherapy alone, addition of cetuximab increased the risk of grade 3/4 hypokalemia with RRs of 2.19 (95% CI 1.14–4.23, $P = 0.019$), whereas panitumumab cases were more vulnerable to grade 3/4 hypokalemia (RR 3.3, 95% CI 1.32–8.25, $P = 0.011$) [52].

In a meta-analysis of prospective Phase II–III clinical trials of patients (11 trials; $n = 2254$) with advanced malignancies treated with cetuximab, Cao *et al.* [67] reported an 8 and 6.2% incidence of all grades and grade 3/4 hypokalemia, respectively. The FDA review of panitumumab demonstrated a 34 and 10% incidence of all grades and grade 3/4 hypokalemia, respectively [68].

The exact mechanism of anti-EGFR MAbs-induced hypokalemia is unclear, but is probably multifactorial: (i) due to a direct toxic effect on the kidney [66] through TRPM6 [69]. Increasing potassium is required to repair Na/K-ATPase due to the magnesium deficiency. Then, over-intracellular transport of potassium could result in hypokalemia, (ii) as a result of hypomagnesemia [70] or (iii) could be related to an increased risk of diarrhea and dehydration with these agents [53]. Whether hypokalemia induced by cetuximab therapy is related to impaired renal handling or intestinal loss needs to be clarified by further studies.

Human TRPM6 also gives rise to hypomagnesemia with secondary hypocalcemia [71]. Although the mechanism responsible for development of hypocalcemia is unclear, several explanations are proposed [51] such as: (i) 'hypomagnesemic hypocalcemia' related to PTH resistance due to hypomagnesemia and which usually responds to Mg replacement, (ii) end-organ unresponsiveness to PTH with altered release of PTH or (iii) an impaired formation of 1, 25-dihydroxy vitamin D3.

Hyponatremia. No obvious higher risk of hyponatremia events related to MAbs was discovered. The overall incidence of grade 3/4 and all-grade hyponatremia events was 7.8% (95% CI 2.1–25.0%) and 9.4% (95% CI 7.0–12.5%), respectively [52].

EGFR TKIs

The EGFR TKIs usually cause less hypomagnesemia as compared with the anti-EGFR MAbs, probably due to a different potency of the two classes of agents on magnesium metabolism [72]. Despite this, magnesium levels should be monitored also in patients treated with EGFR TKIs [51, 73].

For both gefitinib and erlotinib, there are no specific data relative to the incidence of electrolyte disorders; however, in the INTEREST gefitinib study an incidence of 6.6% of fluid retention (all grades) was reported, without further details [51, 74]. As for afatinib, a 34 and 3% incidence of hypokalemia of all grades and of grade 3/4, respectively, has been reported [51, 75]. In the literature, one case of AKI [76] occurred on the 16th day of gefitinib use for lung adenosquamous carcinoma. Kidney function was recovered within 2 days after adequate hydration and gefitinib withdrawal [76].

GLOMERULOPATHY

Seven patients with anti-EGFR-induced nephrotic/nephritic syndrome (NS) were reported in the literature [77–83]. As shown in Table 3, glomerular disease occurred after 2–24 weeks of therapy with gefitinib (three), cetuximab (two) and panitumumab and erlotinib (one each) [77–83]. These cases highlight the variable and often prolonged time course between drug exposure (2 weeks to 6 months) and clinical recognition of kidney injury. In these cases, anti-EGFR therapy was prescribed for various cancers [bronchopulmonary (four), digestive (two) and head and neck (one)]. Six patients obtained renal histology with a diagnosis of minimal change nephropathy (MCN) (gefitinib; two cases), proliferative IgA crescentic glomerulonephritis (GN) (gefitinib and cetuximab, one case each) or pauci-immune crescentic GN (erlotinib, one case) and immune complex GN (panitumumab). Two of the three patients on gefitinib had additional interstitial damage such as severe tubulointerstitial involvement (in case of proliferative IgA crescentic GN) or mild inflammatory interstitial infiltrate (associated with MCN).

Response to therapy has been reported for six patients: four of them received treatment with glucocorticoids coupled with discontinuation of anti-EGFR agent, resulting in complete or partial improvement in proteinuria in three and one patients, respectively. Two patients (cetuximab and erlotinib, one case each) required transient hemodialysis (3 weeks for cetuximab, unknown for erlotinib). In one case of MCN with gefitinib withdrawal alone, without immunosuppressive use, complete remission of NS was observed 8 weeks later. A few months after remission, the patient developed recurrent lung tumors. Following the rechallenge with initiation of erlotinib, the patient achieved remission without proteinuria suggesting that erlotinib is a potential treatment option in patients with NS associated with gefitinib therapy [82]. The remaining patient with NS who did not receive corticosteroids while maintaining gefitinib had no improvement in renal parameters. Sixteen months later, the patient continued to have proteinuria and microhematuria, while renal dysfunction remained unchanged [79].

Table 3. Clinicopathological features of cancer patients with glomerular diseases associated with EGFR inhibitor use

Drug [ref]	Cancer type | prior systemic therapy and potential nephrotoxins	Timing of glomerular disorders	Renal findings and Δ in kidney function	Kidney pathological findings	Clinical course
MAbs anti-EGFR					
Cetuximab [77]	Oral floor SCC | radiation cisplatin and docetaxel	4 months	AKI: SCr from 0.6 to 3.4 mg/dL NS: SAlb 2.4 g/dL, UPCR 7.1 g/g	Diffuse proliferative and focally crescentic GN with IgA-dominant immune-complex deposition	Kidney function improved after discontinuation of cetuximab therapy and a short course of cyclophosphamide and steroid
Cetuximab [78]	mRC | mFOLFOX6 + BVZ	3 weeks	NS: SAlb from 3.9 to 1.3 g/dL, UPCR from 0.0 to 8.92 g/g, SCr 0.9 mg/dL	Not performed	No response despite cetuximab discontinuation + oral prednisolone (0.6 mg/kg/day)
Panitumumab [79]	mCRC	2 weeks	NS: SAlb from 4.0 to 2.0 g/dL, UPCR from 0.0 to 6.0 g/g, SCr 49 µmol/L	Immune complex GN	Complete response 4 weeks after panitumumab withdrawal + oral prednisolone (proteinuria <0.5 g/day, SAlb 4.0 g/dL)
TKIs anti-EGFR					
Gefitinib [80]	mLC	6 months		Proliferative crescentic GN with IgA-dominant deposition and severe tubulointerstitial involvement	Unchanged renal parameters 16 months later in gefitinib maintenance without immunosuppressive agent
Gefitinib [81]	adSCC	5 months	NS: SAlb 2.4 g/dL, UPCR >4.0 g/g	MCN with mild interstitial infiltration of lymphocytes	Not available
Gefitinib [82]	mLC	6 months	NS: SAlb 1.8 g/dL, UPCR 8.0 g/g, SCr 0.61 mg/dL	MCN	Complete response after 2 months of discontinuation of gefitinib alone, without corticosteroid administration
Erlotinib [83]	adNSCLC | Carboplatin, docetaxel, paclitaxel, irinotecan, gemcitabine	1 month	AKI: SCr from 88 to 1228 µmol/L NS: Pu 0 to 3+, SAlb 21 g/L	Pauciimmune crescentic GN (autopsy)	Despite erlotinib discontinuation and supportive therapy with hemodialysis, anuria persisted, and patient died of pneumonia

SCC, squamous cell carcinoma; SCr, serum creatinine level; SAlb, serum albumin level; UPCR, urine protein/creatinine ratio; mRC, metastatic rectal cancer; mLC, metastatic lung adenocarcinoma; adSCC, advanced squamous cell carcinoma; adNSCLC, advanced non-small-cell lung cancer; Pu, proteinuria.

The mechanisms of NS related to anti-EGFR agent are unclear. In fact, experimental data regarding these drugs are moving toward a potential renal protective effect. EGFR is widely expressed in the mammalian kidney, including the glomeruli, proximal tubules and cortical and medullary collecting ducts [84–86]. EGFR was also detected in glomerular parietal epithelial cells [87] and in the connective tissue of fibrocellular crescents in primary glomerulonephritis and lupus nephritis [87]. In addition, there have been several cases of leukocytoclastic vasculitis during treatment with erlotinib [88] or gefitinib [89] and one case report of ANCA-negative pauci-immune crescentic glomerulonephritis during erlotinib [83] therapy.

Members of the EGF peptide growth factor-related family [90], such as EGF, amphiregulin, TGF-α, betacellulin and epiregulin, heparin binding-epidermal growth factor (HB-EGF) are produced as transmembrane proteins that are cleaved by metalloproteinases, especially ADAMs, to release a soluble active moiety that can activate EGFR [91]. Using a mouse model of anti-glomerular basement membrane disease in which the mice developed severe crescentic glomerulonephritis and loss of renal function, Bollée *et al.* [10] demonstrated that mice with genetic deletion of HB-EGF show markedly decreased functional and structural injury. They also confirmed increased expression of HB-EGF in podocytes and parietal epithelial cells in wild-type mice with rapidly progressive glomerulonephritis (RPGN), showing substantially increased glomerular immunoreactive HB-EGF in human biopsies of individuals with RPGN [10]. Thus, the authors postulated that inhibitors of the EGFR cascade may actually be useful for preventing severe renal damage and renal failure [10].

However, simultaneously combined nephrotic syndrome due to minimal change disease associated with interstitial lymphoplasmacytic infiltration was noted with gefitinib therapy [80, 81], as has already been reported with nonsteroidal anti-inflammatory drugs (NSAIDs) and amoxicillin [92]. This drug-induced dual pathology may be caused by hypersensitivity and heavy proteinuria related to lymphokines produced as a result of the immunological response [93]. Anti-EGFR therapy may then promote, via speculative aberrant pathways, a migration of effector T-cells into the kidney and an inflammatory response leading to interstitial infiltration of lymphocytes. Thus, pathogenic mechanisms of these renal adverse events require more investigation.

CONCLUSION

The use of EGFR inhibitor agents is expected to increase in the coming years. Since kidney toxicity is not uncommon with these agents, it is mandatory for clinicians to become familiar with these renal effects and to carefully weigh the benefits of drug withdrawal versus the risks of ongoing tumor progression.

CONFLICT OF INTEREST STATEMENT

None declared.

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