




CKJ REVIEW

Anaplastic lymphoma kinase inhibitors and their effect on the kidney

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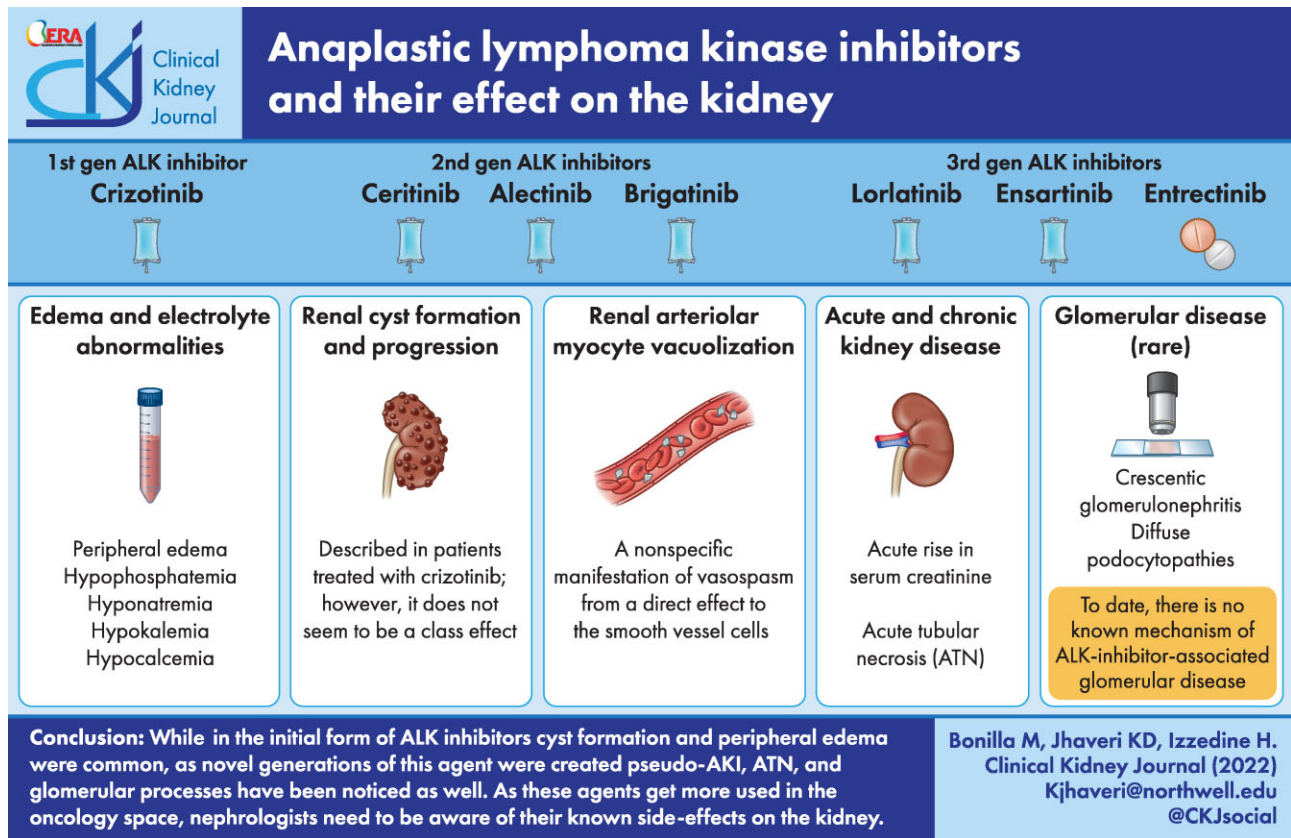
ABSTRACT

Lung cancer is the leading cause of cancer-related mortality and approximately 5% of non-small-cell lung cancer (NSCLC) patients are positive for anaplastic lymphoma kinase (ALK) gene rearrangement or fusion with echinoderm microtubule-associated protein-like 4. ALK inhibitors are the mainstay treatment for patients with NSCLC harboring a rearrangement of the ALK gene or the ROS1 oncogenes. With the recent publication of pivotal trials leading to the approval of these compounds in different indications, their toxicity profile warrants an update. Several ALK-1 inhibitors are used in clinical practice, including crizotinib, ceritinib and alectinib. According to the package insert and published literature, treatment with several ALK-1 inhibitors appears to be associated with the development of peripheral edema and rare electrolyte disorders, kidney failure, proteinuria and an increased risk for the development and progression of renal cysts. This review introduces the different types of ALK inhibitors, focusing on their detailed kidney-related side effects in clinical practice.

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GRAPHICAL ABSTRACT



Keywords: ALK-1, anaplastic lymphoma kinase, crizotinib, cyst, onconeurology, serum creatinine

INTRODUCTION

Non-small-cell lung cancer (NSCLC) is the leading cause of cancer-related deaths worldwide and in the United States [1, 2]. Most patients who have NSCLC present with advanced or incurable disease and cytotoxic chemotherapy generally results in low response rates and only modest improvements in overall survival. Early in the 2000s, investigators in Japan identified anaplastic lymphoma kinase (ALK) as another potential target in NSCLC [3, 4]. In a small subset of NSCLC tumors, a chromosomal inversion event leads to the fusion of a portion of the ALK gene with the echinoderm microtubule-associated protein-like 4 (EML4) gene [3, 4]. The resulting EML4-ALK fusion protein is constitutively activated and transforming, leading to a state of oncogene addiction. EML4-ALK fusion and other ALK rearrangements occur in 3–7% of patients with NSCLC (referred to as ‘ALK-positive’ lung cancer) and are associated with younger age, never-smoking or light-smoking history and adenocarcinoma histology. Patients who have advanced ALK-positive NSCLC are highly responsive to ALK inhibitors [5].

Subsequently, ALK gene fusions, predominantly the NPM1-ALK fusion, have been identified in nearly all pediatric and approximately half of the adult cases of anaplastic large cell lymphoma (ALCL), a rare form of non-Hodgkin lymphoma [6]. Other cancer types in which ALK fusions have been identified include renal, pancreatic, colorectal, breast and thyroid cancers [7]. Neuroblastoma, a childhood cancer arising in immature nerve cells

that accounts for ~10% of pediatric cancer deaths, is characterized by a different kind of oncogenic ALK alteration [8]. In addition to fusions and mutations, ALK gene amplification and copy number gain are observed in many tumor types, including neuroblastoma, rhabdomyosarcoma and esophageal cancer. ALK inhibitors have been used in other cancers, including pancreatic cancer, cancers of unknown origin and thyroid cancer. Data on renal effects in those cancers are not available [7, 9–23].

With the increased use of ALK inhibitors, adverse events have been noted [21–26]. In the US Food and Drug Administration Adverse Event Reporting System analysis [27], 88 cases of renal impairment were noted, consistent with published reports. In addition, we found evidence of electrolyte disorders as well (hyponatremia, 24 cases; hypokalemia, 13 cases). There is no evidence of those disorders reported in the existing literature.

This review focuses on the kidney-related side effects associated with ALK inhibitors (Figure 1) [28, 29].

ALK inhibitor molecules

First-generation ALK inhibitors

Crizotinib. Crizotinib (Xalkori) is a first-generation ALK inhibitor approved for ALK-positive NSCLC [30]. It has activity against EML4-ALK, mesenchymal-epithelial transition factor (c-MET)

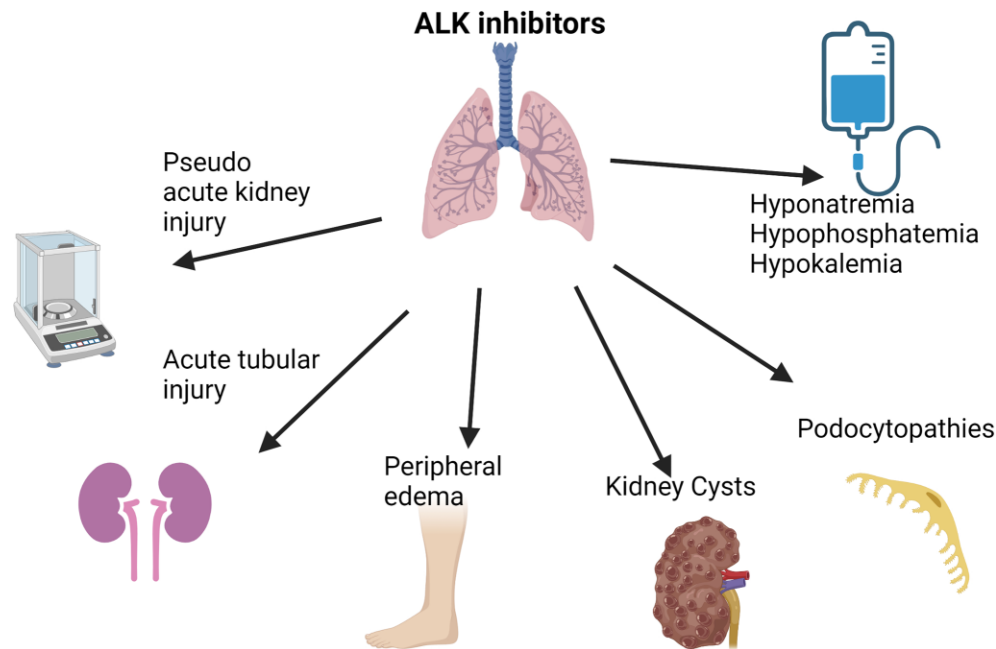


FIGURE 1: Summary of the various renal effects of ALK inhibitors. Figure was created using biorender.com.

and ROS1 tyrosine kinases [31–34]. It is approved for ALK-positive, locally advanced and metastatic NSCLC [35].

Second-generation ALK inhibitors

Ceritinib. Ceritinib (Zykadia) is a potent ALK inhibitor compared with crizotinib [36–38]. Ceritinib was approved for the treatment of relapsed or refractory NSCLC after crizotinib [39].

Alectinib. Alectinib (Alecensa) is a potent and highly selective inhibitor of ALK tyrosine kinase and has activity against L1196M, one of the commonly seen secondary mutations in the ALK gene leading to resistance to crizotinib. Grade 3 adverse events were reported in 26% of patients ($n = 12$) and included elevated creatinine phosphokinase and neutropenia [40].

Brigatinib (AP26113). Brigatinib is another second-generation ALK inhibitor. It is a potent dual inhibitor of ALK and epidermal growth factor receptor (EGFR), including ALK L1196M and EGFR T790M mutants, shown in preclinical and first-in-human studies [41–43]. The most common treatment-emergent adverse events included nausea, diarrhea, fatigue, cough and headache. Early-onset pulmonary events were observed less frequently with the 90 mg starting dose compared with higher doses.

Third-generation ALK inhibitors

Lorlatinib. Lorlatinib (PF-06463922) is a novel, reversible, potent adenosine triphosphate (ATP)-competitive small-molecule inhibitor of ALK and ROS1. This third-generation inhibitor is effective against all known resistant mutants [44–46]. Lorlatinib combined with PI3K pathway inhibitors, such as PF-05212384 (PI3K/mTOR), GDC0941 (pan-PI3K) or GDC0032 (beta-sparing), is used to overcome ALK mutations and ALK inhibitor resistance [47].

Ensartinib. Ensartinib (X-396) is an aminopyridazine-based potent ALK-tyrosine kinase inhibitor with high activity against

both wild-type ALK and all evaluated ALK variants (F1174, C1156Y, L1196M, S1206R, T1151 and G1202R mutants) and brain metastases; it also potently inhibits TPM3-TRKA, TRKC, ROS1, EphA2, EphA1, EphB1 and c-MET [48].

Preclinical data demonstrated increased potency of the drug compared with crizotinib and other second-generation tyrosine kinase inhibitors [49]. The most common treatment-related adverse events were rash [89 (56%)], increased alanine aminotransferase concentrations [74 (46%)] and increased aspartate aminotransferase concentrations [65 (41%)].

Entrectinib (RXDX-101). Entrectinib is a potent, orally available ATP-competitive inhibitor of the ALK, ROS1 and tropomyosin receptor kinase (TRK) family rearrangements. *In vitro* and *in vivo* models of entrectinib showed activity against ALK-rearranged NSCLC with strong intracranial activity. It showed good antiproliferative activity with high activity against the G1269A mutation, slight loss of potency in the presence of C1156Y and L1196M ALK-resistance mutations and minimal activity on G1202R mutation [50].

In two phase I/II trials (Alka-372-001 trial and the STARTRK-1), no significant safety issues were reported, with majority of the adverse events being of grade 1 or 2 [51–53].

Kidney effects of ALK inhibitors

Edema and electrolyte abnormalities. Peripheral edema appears to be the most common side effect from ALK-inhibitor therapy, with up to 50% of patients affected when treated with the first-generation crizotinib and the third-generation lorlatinib [54]. The exact mechanism is unknown, but a postulated explanation is inhibition of the c-MET pathway. This adverse event is generally graded 1 or 2 (Table 1). Compression stockings are used for the management of these patients. For more resistant cases, diuretic use might be appropriate. Peripheral edema appears late in the treatment with ALK inhibitors and seems to be a cumulative effect of these drugs.

Table 1. Incidence of common renal adverse effects of ALK inhibitors based on Kassem et al. and Costa et al. [28, 29]

Author/study	Study type	Patients, n	Edema, grade 1–2/≥3, n (%)	Electrolyte abnormalities and/or HT, grade 1–2/≥3, n (%)	Increased SCr, grade 1–2/≥3, n (%)
ALK inhibitor, first generation					
Crizotinib					
PROFILE 1001	IB	149	44 (39)/0	Hypophosphatemia 2 (4)/5 (10)	
PROFILE 1007	III	343	54 (31)/0		
PROFILE 1014	III	172	83 (49)/1(1)		
J-Alec 2017	III	104	NR		9 (9)/0
Alex trial	III	151	42 (28)/1 (1)		
Camidge 2018	III	138 (Crizo arm)	6 (4)/1 (1)	HT 31 (23)/13 (10)	3 (2)/0
Shaw 2020	III	142 (Crizo arm)	54 (38)/18 (12)	HT 3 (2)/0	
ALK inhibitor, second generation					
Alectinib					
AF-001JP	I/II	46	NR		12 (26)/0
AF-001JP, third year	I/II	58	NR		19 (32.8)/0
NP28673, Global	II	138	34 (25)/0		
NP28761, North America	II	87	20 (23)/0	Hypophosphatemia 2 (2.3)/2 (2.3) Hypocalcemia 2 (2.3)/1 (1.1) Hyponatremia 2 (2.3)/1 (1.1) Hypokalemia 6 (6.9)/2 (2.3)	
J-Alec 2017	I/II	103	NR		11 (11)/0
J-Alec 2017	III	103	9 (9)/0		
Alex trial	III	152	26 (17)/0		
Ceritinib					
ASCEND-1 2627	IB	246	NR	Hypophosphatemia 8 (3.3)/8 (3.3) Hyponatremia 8 (3.3)/11 (4.5) Hypokalemia 17 (6.9)/11 (4.5)	42 (17.1)/0
ASCEND-2	II	140	NR	Hypophosphatemia 7 (5.0)/3 (2.1) Hypokalemia 8 (5.7)/4 (4.9)	
ASCEND-4	III	189	NR		44 (22)/4 (2)
ASCEND-5	III	115	NR		22 (19)/0
ASCEND-6	I/II	103	NR	Hypokalemia 11 (10.7)/8 (7.8)	34 (33)/0
Real life		208	NR		14 (6.7)/8 (3.8)
Brigatinib					
Camidge 2018	III	137 (Briga arm)	53 (39)/1(1)	HT 10 (7)/4 (3)	19 (14)/1 (1)
Gettinger 2016	I/II	137	Dose independent (33%)	HT dose dependent: 6–27% and 0–7%	
Kim 2017	II	222	NR	HT dose dependent: 11–21% and 6%	
ALK inhibitor, third generation					
Lorlatinib					
Bauer	I	295	151 (51.2)/7(2.4)		
Shaw 2017	I	54	21 (39)/0		
Solomon 2018	II	276	113 (41)/6 (2)	Hypophosphatemia 2 (1)/2 (1) Hyponatremia 1 (<1)/1 (<1) HT 4(1)/4(1)	
Shaw 2019	I/II	346	27 (39)/1(1)	Hypophosphatemia 2 (3)/4 (6) Hyponatremia 0/1 (1)	
Shaw 2020	I	149 (Lorla arm)	76 (51)/6 (4)	HT 12 (8)/15 (10)	
Ensartinib					
Horn 2018	I/II	97	15 (15)/1 (1)		
Yang 2019	II	156	14 (9)/2 (1)		30 (19)/0
Entrectinib					
Drillon 2019	I/II	53	22 (16)/0	Hypophosphatemia 2 (1)/1 (<1) Hyperuricemia 11 (8)/1 (<1) HT 0/1 (<1)	17 (13)/1(<1)
Doebele 2019	I/II	355	49 (14)/1 (<1)	Hypophosphatemia 6 (2)/4 (1) Hyperuricemia 13 (4)/5 (1) Hyponatremia 3 (1)/2 (1) HT 0/1 (<1)	52 (15)/2 (1)

NR, not reported; HT, hypertension; SCr, serum creatinine.

Table 2. Clinical approach to renal adverse effects of ALK inhibitors

Adverse event	Mechanism	Management
Renal cyst	Unknown	Self-limiting, not to be confused with tumor progression
Peripheral edema	Inhibition of c-MET	Diuretics only to be used if severe edema. Be mindful of electrolyte imbalances
Elevated serum creatinine	Pseudo AKI, ATN	Check Cystatin C based glomerular filtration rate to rule out pseudo-AKI. If ATN, drug needs to be withheld
Proteinuria	Likely podocytopathies	Consider holding or decreasing dose

Electrolyte abnormalities have been described with the use of ALK inhibitors, and though uncommon, hypophosphatemia has been most recognized. Hypophosphatemia during the treatment with crizotinib was reported in ~15% of subjects as a severe adverse event [31]. With the second-generation ALK inhibitors alectinib and ceritinib, hypophosphatemia was reported as a severe event (grade 3–4) in ~2–4% of subjects [55, 56], and with the third-generation ALK inhibitors, hypophosphatemia as a severe adverse event was reported in 1% of patients. In a review by Adhikari *et al.* [57], the authors attributed hypophosphatemia in patients treated with crizotinib to inhibition of the insulin (IGF-1) receptor located in the proximal tubules blocking the reabsorption of phosphate and thus producing phosphaturia.

Hyponatremia as a grade ≥ 3 event was reported in up to 5% of patients treated with ceritinib (second-generation ALK inhibitor), a tyrosine kinase inhibitor that selectively and potently inhibits ALK. Several reports have associated hyponatremia in patients treated with tyrosine kinase inhibitors with inadequate secretion of antidiuretic hormone [58]. Fewer adverse events associated with hyponatremia were reported with alectinib (1.1%) and third-generation ALK inhibitors ($\leq 1\%$). Hypokalemia and a few cases of hypocalcemia have also been reported (Table 1) [28, 29]. Currently, no specific etiology has been described with ALK inhibitors.

Acute and chronic kidney disease. ALK inhibitors have been associated with acute and chronic kidney disease. Initially described with the first-generation crizotinib, an acute increase in serum creatinine might not be a reflection of a true kidney injury but a pseudo kidney injury from inhibition of a creatinine transporter, thus interfering with the secretion of creatinine in the proximal tubule [59]. Second-generation ALK inhibitors are more frequently associated with elevated serum creatinine after starting treatment. Alectinib is associated with increased serum creatinine in up to 26% of patients [40], whereas ceritinib is associated in up to 33% of patients [60]. Multiple case reports have described the association of starting alectinib with an increase in serum creatinine and improvement in creatinine level upon withdrawal of alectinib [61, 62], but the exact underlying mechanism is yet to be discovered. Management of an acute increase in serum creatinine levels has been managed with withdrawal of the offending drug, but this becomes challenging in patients with a reduction in the progression of cancer with these therapies; possibly changing to a third-generation ALK inhibitor like lorlatinib may be beneficial. Regardless, any patient treated with ALK inhibitors who develops creatinine elevation should have a cystatin C level and/or iothalamate study to assess for an actual kidney injury. Patients with underlying chronic kidney disease, previous chemotherapy treatments and volume depletion could be predisposed to true kidney injury [63].

In addition, it is essential to keep in mind that diarrhea and vomiting are highly prevalent with this class of medications [29] and can lead to prerenal azotemia.

Gastaud *et al.* [64] described a case of kidney biopsy-proven acute tubular necrosis (ATN) in a patient with locally advanced NSCLC treated with crizotinib for targeted therapy of EML4–ALK. Another case reported an acute kidney injury (AKI) with the second-generation ALK inhibitor alectinib; the authors described a euvolemic patient with no previous exposure to nephrotoxic agents who developed AKI within 6 weeks of treatment with alectinib, requiring emergent hemodialysis. Due to the temporal association between initiation of ALK inhibitor and the absence of other causes of AKI, the authors hypothesized that AKI was likely secondary to ATN, even though no kidney biopsy was performed in this patient. Kidney recovery was achieved after discontinuation of alectinib [61].

Renal arteriolar myocyte vacuolization. Mainly described as vascular toxicity from calcineurin inhibitors (CNIs), arteriolar myocyte vacuolization is a nonspecific manifestation of vasospasm from a direct effect of CNI on smooth vessels cells [65]. It has been described as well with amphotericin B [66].

To our knowledge, there is one case reporting renal arteriolar myocyte vacuolization associated with the first-generation ALK inhibitor crizotinib [67]. Nephrologists should be aware of these effects from ALK inhibitors; however, it should only be attributed to ALK inhibitors after excluding other causes of vascular injury.

Renal cyst formation and progression. The development of renal cysts has been described in patients treated with crizotinib; however, it does not seem to be a class effect (Table 1). In a study by Lin *et al.* [68], investigators enrolled patients who participated and received crizotinib in three prospective clinical trials. They found that 23 patients had renal cysts before initiation of crizotinib treatment. Seven patients demonstrated a change in their previous renal cysts during treatment with crizotinib. New complex cysts were identified in four patients. After discontinuation of crizotinib, complex renal cysts regressed [68]. A blinded, retrospective independent radiologic review performed by Schnell *et al.* [69] reviewed scans from patients in three clinical trials (PROFILE 1001, PROFILE 1005 and PROFILE 1007). They describe that of 255 patients treated with crizotinib, 22% had a pre-existing simple cyst, 3% had a complex cyst and 2% had both. Patients were assessed at 6 months and 9% of all patients had acquired new cysts. Two percent of patients with preexisting cysts had developed new cysts and enlargements of simple cysts [69]. Close monitoring of patients on treatment with crizotinib who have preexisting cysts is recommended.

Glomerular disease. ALK inhibitor is rarely associated with glomerular diseases. To our knowledge, there are two case reports of minimal change disease or diffuse podocytopathies and one case of crescentic glomerulonephritis associated with ALK inhibitor treatment. Betton *et al.* [70] described a case of an elderly woman who developed nephrotic syndrome 1 month after initiation of lorlatinib for lung adenocarcinoma.

A kidney biopsy showed normal cortical structures under light microscopy and diffuse podocyte foot process effacement under electron microscopy. Lorlatinib was discontinued and within 2 weeks the edema resolved, proteinuria decreased to 0.2 g/g and the level of serum albumin increased. The patient was rechallenged with lorlatinib due to disease progression and subsequent proteinuria quantification increased to 3.6 g/g within 3 days of drug initiation [70]. McGee et al. [71] reported a female patient who developed hyperlipidemia while on lorlatinib and was found to have minimal change disease on kidney biopsy. Another case by Lee et al. [72] reported lorlatinib-induced proteinuria in NSCLC. This was not biopsy-proven but was presumed to be podocytopathy. A dose reduction by 50% led to improvement of the proteinuria [72].

A case of rapid progressive glomerulonephritis was described by Nagai et al. [73], associated with alectinib (second-generation ALK inhibitor). They reported a 68-year-old woman with advanced NSCLC on alectinib who developed rapidly progressive glomerulonephritis within 1 year of starting therapy. Kidney biopsy demonstrated light microscopy, interstitial nephritis with tubular vacuolization and fibrocellular crescent formations in several glomeruli. The immunofluorescence study was negative and electron microscopy showed diffuse foot process effacement. The patient was treated with pulse corticosteroids and corticosteroid taper. The ALK inhibitor was discontinued and kidney function remained stable [73]. To date, there is no known mechanism of ALK inhibitor-associated glomerular disease. Physicians should be aware of this association and monitor kidney function closely while patients receive therapy with these medications. However, it appears that the second-generation ALK inhibitors may lead to podocytopathies. Table 2 summarizes the clinical approach to the kidney adverse events associated with ALK inhibitors.

CONCLUSION

ALK inhibitors have now been approved and are being used for not just NSCLC, but other hematologic and solid tumors. We reviewed the several renal effects of these agents. While in the initial form of ALK inhibitors, cyst formation and peripheral edema were common, as novel generations of these agents have been created, we are noticing pseudo-AKI, ATN and glomerular processes as well. As these agents are used more often in oncology, nephrologists need to be aware of their known side effects on the kidney.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no relevant financial interests. K.D.J. is a consultant for Astex Pharmaceuticals, Natera, GlaxoSmithKline, ChemoCentryx and Chinook and George Clinicals. He is a paid contributor to Uptodate.com and receives honorarium from the International Society of Nephrology and American Society of Nephrology. K.D.J. serves as co-president of the American Society of Onconephrology. M.B. and H.I. have nothing to disclose.

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