MINI REVIEW

New Medication Toxicities in The Field of Onco-Nephrology

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Brown S. New medication toxicities in the field of Onco-Nephrology. Clin Nephrol Res. 2022; 6(1):7-9.

ABSTRACT

New anticancer drugs are fast entering the clinical arena, promising patients with previously resistant tumors more effective therapies that will allow them to live longer. However, adverse renal effects can occur in treated individuals with underlying risk factors, necessitating a familiarity with nephrotoxic effects among the nephrology community. Acute kidney injury, variable levels of proteinuria, hypertension, electrolyte abnormalities, and chronic kidney disease are the most prevalent clinical nephrotoxic symptoms of these medicines. Thus, nephrologists will benefit from an update on older medications with newly known nephrotoxic potential as well as newer substances that may be associated with kidney injury in order to practice successfully in the 'onco-nephrology' arena. With that in mind, the purpose of this brief update is to present doctors with the most up-to-date information on the nephrotoxicity of a class of anticancer drugs.

Key Words: *Acute Kidney Injury; Chemotherapy; Chronic Kidney Disease; Onco-Nephrology*

INTRODUCTION

Several viable medicines for previously untreatable malignancies are rapidly becoming available in clinical trials. This is unquestionably a significant step forward and welcome news for many individuals suffering from life-threatening cancers. As a result, cancer patients are living longer lives. They do, however, acquire drug-related toxicities, which have an impact on their quality of life and overall longevity [1,2]. Adverse renal consequences are among them. Providing care for patients who are exposed to newly released anticancer medicines with unknown and/or poorly understood nephrotoxicities is a challenging task for many clinical nephrologists today. Indeed, some have claimed that the increasing complexity of kidney disease in patients with cancer-related renal illness and drug-induced kidney injury necessitates additional 'Onco-Nephrology' training, if not a new specialist [3]. At the very least, nephrologists who provide consultation treatment to these patients should be kept up to date on novel medicines and those that have recently been identified as having nephrotoxic potential. Despite the fact that many of the drug-associated nephrotoxicities documented are rare, have few data, and lack definite mechanisms of harm or established histology, we evaluated them to increase awareness among clinical nephrologists who encounter patients on these drugs. With these restrictions in mind, the purpose of this study is to offer a quick update on a set of anticancer drugs that have been linked to prostate cancer.

Anti-angiogenesis medications

Renal cell carcinoma, gastrointestinal tumors, breast cancer, non–small-cell lung cancer, and a variety of other cancers are treated with this family of medicines as a main or supplementary therapy. These medicines, while clearly efficacious, have well-documented dose-dependent adverse renal consequences [4]. The most common symptoms are hypertension and mild proteinuria, but nephrotic-range proteinuria and/or Acute Kidney Damage (AKI) can occasionally occur [5-8]. The underlying pathophysiological alterations that result in the various kidney diseases are unknown, but they are obviously linked to Anti Vascular Endothelial Growth Factor (VEGF) downstream consequences. A meta-analysis found that bevacizumab medication caused overt proteinuria (>0.5 g/day) in 21–41% of low-dose (5–7.5 mg/kg) patients (related risk for proteinuria, 1.4) and up to 64% (relative risk for proteinuria, 2.2) of high-dose (15 mg/kg) individuals [9-10]. With this medicine, hypertension developed in a dose-dependent manner: at low doses, the ratio risk of hypertension was 3.0, and at large doses, the relative risk was 7.5.

Hypertension and proteinuria are two side effects of modest tyrosine kinase inhibitors. Cediranib, which is now in clinical trials, caused proteinuria in 27/40 (68%) and hypertension in 32/40 (80%) of patients in a phase I study in Japanese patients.

Glomerular endotheliosis, focal segmental glomerulosclerosis (sometimes collapsing), different glomerulopathies, and most commonly thrombotic microangiopathy with a few cases of acute

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Received: 10-January-2022, Manuscript No. PULCNR-22-4126; Editor assigned: 12-January-2022, PreQC No. PULCNR-22-4126(PQ); Reviewed: 16-January-2022, QC No. PULCNR-22-4126(Q); Revised: 17-January-2022, Manuscript No. PULCNR-22-4126(R); Published: 27-January-2022, DOI: 10.37532/pulcnr.22.6.(1).7-9

interstitial nephritis, are among the kidney diseases seen with these medicines. Furthermore, kidney function was sustained once blood pressure was controlled and the anti-VEGF medicine was stopped. These findings help to distinguish TMA caused by VEGF/VEGF receptor inhibitors from TMA caused by other iatrogenic causes. TMA caused by gemcitabine and/or mitomycin is more severe, with more hematologic abnormalities, glomerular and arteriolar renal localisation, and poorer renal survival despite medication withdrawal. Proteinuria, hypertension, and thrombotic microangiopathy are all linked to the anti-VEGF impact of the medications and are linked to the therapy's anti-tumor effect. When nephrologists are called to advise on these patients, they should be aware of these clinical symptoms. Hypertension and proteinuria should induce blood pressure medication, not drug cessation, in most cases. AKI with thrombotic microangiopathy, on the other hand, is a sign that pharmacological therapy should be stopped. Despite the lack of published guidelines, patients taking these drugs should be monitored with blood pressure monitoring, as well as intermittent kidney function and proteinuria monitoring, in order to detect these complications early.

The therapy of androgen deprivation

Androgen Deprivation Therapy (ADT) is a well-accepted treatment for advanced prostate cancer that slows the disease's growth. Despite the fact that this therapeutic technique is not new to the clinical arena, current observational evidence suggests that it is linked to AKI in patients with prostate cancer. ADT is linked to AKI in males with newly diagnosed non-metastatic prostate cancer, according to a nested case–control research conducted in an observational cohort from 1997 to 2008. Patients who developed AKI on their own were compared to matched controls (20:1 controls: cases). The average time of follow-up was 4.1 years. There were 232 incident cases of AKI out of 10,250 patients, or 5.5 per 100 person-years. Intriguingly, current ADT usage was linked to a higher risk of AKI than never use (odds ratio: 2.48), resulting in a rate difference of 4.43/1000 person-years. The risk of AKI in treated patients was predominantly driven by combined anti-androgen therapy.

Crizotinib

Crizotinib, a small molecule inhibitor of anaplastic lymphoma kinase, has been linked to AKI. Crizotinib is a targeted medication used to treat anaplastic lymphoma kinase fusion oncogene-positive non–small-cell lung tumours. It's an FDA-approved oral medication with a 43 percent bioavailability and high protein binding that's processed in the liver and eliminated in the stools and urine (22%). During the first 12 weeks of therapy and on the last day of crizotinib exposure, a large retrospective study of 38 patients with non–small-cell lung malignancies treated with crizotinib found a rise in serum creatinine or a reduction in estimated glomerular filtration rate (eGFR). Volume depletion, tumour lysis syndrome, contrast exposure, and other potential nephrotoxins were all ruled out as alternative possible causes of AKI.

Based on the limited information available, crizotinib appears to cause AKI either through direct tubular injury consistent with a 'toxic nephropathy,' as demonstrated in two kidney biopsies, or maybe through glomerular injury (mesangiolysis noted on one biopsy). Acute interstitial nephritis or prerenal AKI are additional possible. Because the rise and fall of serum creatinine were rather rapid, it has been proposed that the increase in serum creatinine is due to suppression of tubular creatinine secretion rather than genuine renal injury.

Clofarabine

Clofarabine is a purine nucleoside analogue that inhibits DNA synthesis and ribonucleoside reductase, according to the FDA. This medicine is effective in treating relapsed or refractory acute lymphoblastic leukaemia in children and adults, as well as acute myelogenous leukaemia in adults. It is given intravenously for 5 days (30–40 mg/m2) at a dose of 30–40 mg/m2. The drug is somewhat protein bound (47%) and is eliminated largely through organic cation tubular transit in the kidney. Case reports, clinical trials, and the FDA Adverse Event Reporting System have all revealed reports of renal toxicity.

Pemetrexed

Pemetrexed disodium is an FDA-approved folate analogue metabolic inhibitor for advanced or metastatic nonsquamous non–small-cell lung cancer and malignant pleural mesothelioma. Purine and thymidine nucleotide and protein synthesis are inhibited by pemetrexed, which inhibits three enzymes involved in folate metabolism and DNA synthesis. This injectable medication is strongly protein bound, barely digested, and eliminated unchanged predominantly by the organic anion tubular transport system by the kidneys (70–90 percent). Because of the high protein binding, dialysis is unlikely to remove the medication.

As a result, pemetrexed should be regarded a major source of toxic nephropathy in cancer patients, and renal function as well as serum electrolytes should be evaluated to detect nephrotoxicity early in treatment.

Carfilzomib

This FDA-approved next-generation proteasome inhibitor, which is used to treat relapsed/refractory multiple myeloma, has the potential to cause AKI. Extra-hepatic metabolism clears carfilzomib via peptidase cleavage and epoxide hydrolysis after it is injected. Because of its better specificity for the chymotrypsin-like function of the 20 S proteosome, the medicine is thought to have less toxicity than bortezomib. With only one case report and six reports in the FDA Adverse Event Reporting System over a 12-month period, the existing evidence to establish nephrotoxicity is insufficient.

Ipilimumab: anti-cytotoxic t-lymphocyte–associated antibody

Ipilimumab is an FDA-approved monoclonal human cytotoxic T-lymphocyte antigen-4–blocking antibody used to treat unresectable or metastatic melanoma. Because cytotoxic T-lymphocyte antigen-4 also promotes regulatory function through regulatory T cells, ipilimumab is likely to generate immune-mediated adverse responses such as dermatitis, colitis, thyroiditis, hypophysitis, and hepatitis by interfering with this function. This medicine is given intravenously, is broken down into small peptides, and has a long half-life (15 days) with no hepatic or renal side effects. Adverse renal events are currently uncommon. Out of 120 patients exposed to ipilimumab, two occurrences of AKI were identified in a retrospective investigation of unexpected and unusual ipilimumab-induced adverse effects. Ipilimumab-induced renal impairment has been reported mostly in individuals with underlying malignancy who developed lupus-like nephritis. Ipilimumab-induced kidney injury appears to be

a rare but potentially serious side effect, highlighting the value of kidney biopsy in assessing individuals with renal symptoms during ipilimumab treatment. The mechanism of ipilimumab-induced kidney damage is currently uncertain and poorly understood. Cell-mediated immunity and/or a potential autoimmune mechanism are both conceivable mechanisms. Early detection of kidney impairment is critical, as is early steroid therapy to avoid serious consequences and biopsy to learn more about the condition.

Directions for the future

As new drugs are introduced into clinical practise to save and extend the lives of cancer patients, it is evident that adverse effects must be recognised. When these agents are introduced into clinical practise and detailed in case reports and series, the majority of medication-related adverse renal effects are recognised. As a result, it is important to the nephrology community to be aware of and attentive about the nephrotoxic consequences of medications used to treat various types of cancers. Clinicians and researchers, academics and private practitioners, nephrologists and oncologists, urologists and pharmacologists, and everyone else involved in the care of cancer patients must work together to discover adverse drug effects that affect the kidneys. This article focuses on a class of medications that have the potential to cause nephrotoxicity. We can precisely catalogue the nephrotoxic potential of antitumor drugs by reporting adverse renal events, collecting clinical, laboratory, and pathologic data, and maintaining a registry by reporting adverse renal events, collecting clinical, laboratory, and pathologic data, and maintaining a registry.

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