Anticancer Induced Nephrotoxicity: A Review

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Received 24-05-2022 Accepted 22-06-2022

ABSTRACT:

Introduction: Drug-induced adverse effects are the major challenging issue in the clinical setting of chemotherapy. Kidneys are responsible for the elimination of many chemotherapeutic agents which makes them a common target for adverse effects. Nephrotoxicity is a deleterious adverse effect carrying a great negative impact on body homeostasis and maintenance of cellular functions.
Aim: The present review aims to focus on anticancer-induced nephrotoxicity including the causes and mechanisms of toxicity.
Methods: Different databases of published materials are recruited mainly from PubMed, Google Scholars, and Iraqi Virtual Science Library.
Results: The review shows that the recurrent use of many anticancer drugs can cause different types of kidney damage via different mechanisms.
Conclusion: Anticancer-induced nephrotoxicity is a crucial problem which needs more research to clarify the mechanisms of kidney damage and the methods to prevent them. Maintaining appropriate and enough hydration, electrolyte replacement, and avoiding concomitant medications are useful steps in overcoming the nephrotoxicity.

Keywords: anticancer drugs, adverse effect, nephrotoxicity

السمية الكلوية الناجمة عن مضادات السرطان

الخلاصة:
المقدمة: الآثار الضارة الناجمة عن استعمال الادوية هي التحدي الرئيسي في استعمال الادوية في معالجة الحالات المرضية. إضافة الى الأعضاء الحيوية الأخرى في الجسم فإن الكلى هي المسؤولة عن تخلص الجسم من ادوية العلاج الكيميائي،وهذا يجعل الكليتين هدفاً شائعا للآثار الضارة. السمية الكلوية هي آثار جانبية ضارة تحمل تأثيرا سلبيا كبيرا على توازن الجسم والحفاظ على وظائف الخلية.
الهدف: الهدف من هذا المقال هو التركيز على السمية الكلوية الناجمة عن مضادات السرطان مع التركيز على أسباب وآلية السمية.
طرق العمل: تم البحث وتوظيف قاعدة بيانات مختلفة لبحوث منشورة ومركزين بشكل أساسي على بنك المعلومات الدولي و متصفح الباحث العلمي ومكتبة العلوم الافتراضية العراقية.
النتائج: أكدت نتائج البحث أن الاستخدام المتكرر للعديد من الأدوية المضادة للسرطان يرتبط بأنواع مختلفة من تلف الكلى وعبر آليات مختلفة.

الاستنتاج: إن السمية الكلوية الناجمة عن مضادات السرطان تشكل مشكلة خطيرة تتطلب اجراء المزيد من البحوث لتوضح آليات الإصابة الكلوية وطرق الوقاية منها. إن الحفاظ على الارواء الكلوي المناسب بالماء وتزويد الايونات وتجنب الأدوية المضرة بالكليتين تعتبر خطوات مفيدة في التغلب على السمية الكلوية.

الكلمات المفتاحية: الأدوية المضادة للسرطان، الاعراض الجانبية، السمية الكلوية.

INTRODUCTION:

The term "nephrotoxicity" refers to a fast decline in kidney function caused by the toxic effects of medicines and substances. There are several types, and some medications may have several effects on renal function. Nephrotoxins are chemicals that cause kidney damage. Renal tubular toxicity, inflammation, glomerular injury, crystal nephropathy, and thrombotic microangiopathy are some of the processes that cause nephrotoxicity. Blood urea and serum creatinine are classic indicators of nephrotoxicity and renal dysfunction, however, these tests are considered poorly sensitive in detecting early renal impairment [1]. Drug-induced nephrotoxicity can be avoided by identifying susceptible patients at risk; via monitoring renal function based on glomerular filtration rate (GFR). Nephrotoxicity can also be avoided by ensuring proper drug dosing and monitoring the patient's renal function [2]. Patients with cancer may develop kidney abnormalities that compromise their immediate survival and make it difficult to treat the underlying malignancy effectively. Both oncologists and nephrologists face significant challenges as a result of these nephrological issues.

Fluid balance, glucose regulation, and medication excretion are all essential functions of the kidney. Unfortunately, more than 20% of the adult population has lost renal function due to drug-induced nephrotoxicity [3]. The kidney's proximal tubule is a complicated vascular system that is especially susceptible to drug-induced nephrotoxicity. A vascularized human renal spheroid model with tissue-integrated micro sensors for oxygen, glucose, lactate, and glutamine allows real-time cellular metabolic analysis. At sub-toxic doses, both the immunosuppressive medication cyclosporine and the anti-cancer agent cisplatin alter the polarity of the proximal tubule, resulting in glucose buildup and lipotoxicity. According to Sharbaf et al., (2017), using glucose transport inhibitors to prevent glucose reabsorption reduced the toxicity of cyclosporine and cisplatin by 1000 and 3 times, respectively [4].

A retrospective study of 247 patients diagnosed with renal impairment who received cyclosporine or cisplatin in combination with sodium-glucose-2 transporter inhibitor empagliflozin (SGLT2) showed significant improvement ($P < 0.001$) in renal function, as well as decreased markers of kidney damage (creatinine and uric acid) [5].

Nephrotoxic Drugs

Aminoglycoside antibiotics, cyclosporine, cisplatin, indomethacin, beta-lactam antibiotics, and amphotericin B have all been shown to be nephrotoxic. Their nephrotoxicity is induced by a variety of methods. However, there are a few generalizations that can be drawn. Substances that produce tubular damage have a synergistic toxic impact, especially when other nephrotoxic medications are given at the same time, this synergism occurs [6]. Moreover, utilizing a nephrotoxic drug in a patient who has a kidney infection would

cause serious kidney injury. In addition, the drug's serum levels don't relate to the seriousness of nephrotoxicity in individual patients. Third, early indications of renal injury may be simple (e.g., minor changes in electrolyte discharge) or intense (e.g., extreme changes in electrolyte discharge). The little modifications are particularly significant since they can be utilized to true prediction of nephrotoxicity [7].

Risk Factors for Nephrotoxicity of Drugs

The ability of the kidneys to tolerate drug nephrotoxicity is primarily impaired by known chronic kidney disease (GFR <60 ml/min). In addition, when a patient's GFR is reduced, the dosage of many drugs must be adjusted. Otherwise, the risk of toxic effects increases. The risk of nephrotoxicity is also increased by age over 60, diabetes, myeloma, and specific pharmacogenetic polymorphisms. Concomitant use of several toxic drugs and impaired renal circulation also increase the risk [1].

In addition, adequate blood circulation to the kidneys is essential for their function [8]. Renal blood flow may be impaired as the circulating blood volume decreases due to, for example, diarrhea, vomiting, fever, or diuretics. Additionally, reduced blood flow can be associated with other conditions including low blood pressure due to heart failure, swelling associated with severe liver damage, or vasodilation caused by sepsis. The kidneys seek to compensate for the decrease in blood flow via activation of the renin-angiotensin-aldosterone system (RAA) and relaxing the importing arterioles of the glomeruli by prostaglandins. However, medicines can block the RAA system (e.g., angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and mineralocorticoid antagonists) or prostaglandin production (NSAIDs, including COX2-selective "coxibs") [7].

Direct Tubule Toxicity

Some drugs have a direct, dose-dependent nephrotoxic effect such as aminoglycosides, vancomycin, and amphotericin B, specific anti-cancer drugs, calcineurin inhibitors, lithium, and X-ray contrast agents). Therefore, monitoring Aminoglycoside levels in the blood is recommended. In addition, alerts on drug doses and interactions associated with medical record systems are likely to be better utilized in the future [9].

Kidney Damage by Allergic Mechanism

In principle, all drugs can cause kidney damage by an immunological, hypersensitivity-type mechanism. However, it is neither predictable nor dose-dependent. Typical examples are beta-lactam antibiotics, NSAIDs, and proton pump inhibitors. Kidney damage can develop in patients through an allergic mechanism, even if their kidneys are already functioning normally. This can lead often to acute tubulointerstitial nephritis or acute tubular necrosis, but sometimes glomerulonephritis can also develop [10]. Tubulointerstitial nephritis develops variably within days, weeks, or months of drug use. The condition can also progress to chronic kidney damage if not noticed early. The onset of the disease includes mainly a slow rise in creatinine, sometimes rash, and blood eosinophilia. Urinary incontinence is relatively mild, and the presence of white blood cells in urine and hematuria are possible. In addition, there may be varying amounts of protein in the urine. Sometimes a kidney specimen is needed to confirm the diagnosis [11].

Other Nephrotoxic Mechanisms

Nephrotoxicity may also be due to drug-induced rhabdomyolysis, vasoconstriction, thrombotic microangiopathy, or nephrocalcinosis. Some

medicines may cause kidney failure when they crystallize in high concentrations in the medication) which can be prevented by increasing the patient's urine output with plenty of hydration. Uterine nephropathy may result from tumor lysis as a desirable effect of anti-cancer drugs [12]. Although trimethoprim slightly increases plasma creatinine as it competes for creatinine tubular secretion, the slight increase in creatinine associated with its use does not reflect a natural deterioration in renal function. Nephrotoxic medicines harm the kidneys by causing intrarenal vasoconstriction, direct tubular toxicity, and intratubular blockage, among other things [13]. The kidney's susceptibility to a variety of potentially nephrotoxic substances can be related to several functional features, including a plentiful supply of blood (cardiac output 25%), which ensures a high tubular reabsorptive capacity and high levels of toxicant delivery (via specific transporters), which gives the ability to concentrate chemicals results and increases intracellular tubular cell concentrations.

Nephrotoxicity of Anti-Cancer Agents

The discovery of new mediators that control cancer cell growth and death has aided the creation of more effective anti-cancer drugs, which have changed cancer therapy choices and clinical results. On the other hand, many novel agents frequently have serious adverse effects that affect a wide range of body systems, including kidney function. In recent years, the development of new anti-cancer drugs with the potential for nephrotoxic kidney damage has heightened the need for attention among all doctors caring for cancer patients [13].

Furthermore, for xenobiotic metabolism, the kidneys are an important location, and they have the potential to convert relatively innocuous parent chemicals into hazardous metabolites. They urinary tract (e.g., specific antiviral and anti-cancer
also have a high metabolic rate, which causes greater susceptibility to toxicants and vasoactive substances due to the increased strain on renal cells [14]. Many antineoplastic drugs are excreted by the kidney. Nephrotoxic drugs may increase the toxicity of these agents by delaying drug elimination [15].

Finally, many anti-neoplastic medicines and their metabolites are eliminated by the kidneys. As a result, renal impairment might cause chemotherapeutic drug excretion and metabolism to be delayed, leading to more significant systemic toxicity. Therefore, when administered in the presence of renal impairment, many medicines need dosage adjustments.

Nephrotoxicity of Anti-Angiogenesis Drugs

Patients with cancer may develop a range of kidney abnormalities that compromise not only their immediate life but also their ability to treat the underlying malignancy effectively. Both oncologists and nephrologists face substantial challenges as a result of these nephrological issues [16]. Several trials using so-called targeted medicines primarily compounds interfering with tumor-associated angiogenesis pathways have been conducted in cancer patients. Tumor cells use diffusible growth factors to interact with vascular endothelial cells in growing neoplasms, resulting in enhanced vascularization and subsequent tumor development. As a result, one of the main goals of new anti-neoplastic therapies is to disrupt pro-angiogenic signalling pathways, with vascular endothelial growth factor (VEGF) as a significant target [17]. Although tumor angiogenesis is essential for tumor development, invasion, and metastasis, as discussed in a recent review published by Conlon and Murray (2019) in most

malignancies [16]. On the one hand, vessel production is hastened, but on the other hand, every element of their structure and function is abnormal. This creates a tumor microenvironment that is hostile to the tumor, with hypoxia, low pH, and high interstitial negative fluid pressure, all of which can change the fundamental characteristics of tumor cells, allowing for the selection of malignant tumor clones and the facilitation of tumor cell escape through leaky vessels. Additionally, aberrant tumor vasculature might obstruct immune cell activity as well as the delivery and distribution of chemotherapeutics and oxygen [18]. As a result, tumor cells may become resistant to radiation treatment and several chemotherapeutics due to aberrant tumor vasculature. Hypoxia also causes cancer and stromal cells to produce more angiogenic factors, aggravating vascular instability and fueling non-productive angiogenesis in a never-ending self-reinforcing cycle.

Anti-angiogenic small-molecule multi-target tyrosine kinase inhibitors (MTKIs), anti- vascular endothelial growth factor ligand inhibitors (bevacizumab and aflibercept) (pazopanib, sunitinib, vandetanib, ponatinib, cabozantinib, axitinib, vandetanib, sorafenib) that target the (VEGF) with ongoing clinical trials of novel formulations of these medicines, the usage of these treatments has expanded to many other solid tumors. They are used for metastatic renal cell carcinoma (RCC), which accounts for 2.5 percent of all new cancer diagnoses, they're now the first-line treatment [19]. Through the participation of the von Hippel–Lindau (VHL) gene, receptor tyrosine kinases have a critical role in developing clear-cell carcinoma, the most common form of Renal cell carcinoma (RCC) RRC. By deletion, mutation, or methylation, in up to 80% of sporadic cases of clear-cell carcinoma, VHL is inactivated. This tumor suppressor gene releases a protein that regulates the synthesis of hypoxia-inducible proteins, including VEGF and the platelet-derived growth factor PDGF. The overexpression of these VEGFR and PDGFR agonists is caused by the inactivation of the VHL gene. The sustained stimulation of receptors that results could boost tumor angiogenesis, growth, and metastasis. As a result, the VEGF and PDGF receptors are viable targets, particularly in the treatment of clear-cell RCC, which has a high VEGF expression level [12].

Kumar et al. 2017, found that the anti-VEGF antibody bevacizumab is effective in treating RCC. In recent years, the introduction of MTKIs has improved progression-free survival and quality of life in patients with metastatic RCC. Although the introduction of new molecular-targeted medicines such as sunitinib and sorafenib marks a significant advancement in the treatment of metastatic RCC, the range of side effects may be greater than initially anticipated [11]. As VEGF-targeted therapies became more widely used, it became evident that hypertension and proteinuria were severe side effects of both biologics and small molecules. In recent critical reviews, both the adverse effects of VEGF inhibition, hypertension, and proteinuria, have been examined [10]. Because VEGF is produced by renal visceral epithelial cells and binds to VEGF receptors on glomerular podocytes, endothelium, and mesangium, anti-VEGF inhibition has renal adverse effects, and on peritubular capillaries. Figure 1 represents a model of VEGF signalling in the glomerulus, whereas Figure 1b demonstrates how anti-cancer medications can disrupt the VEGF system on multiple levels [20].

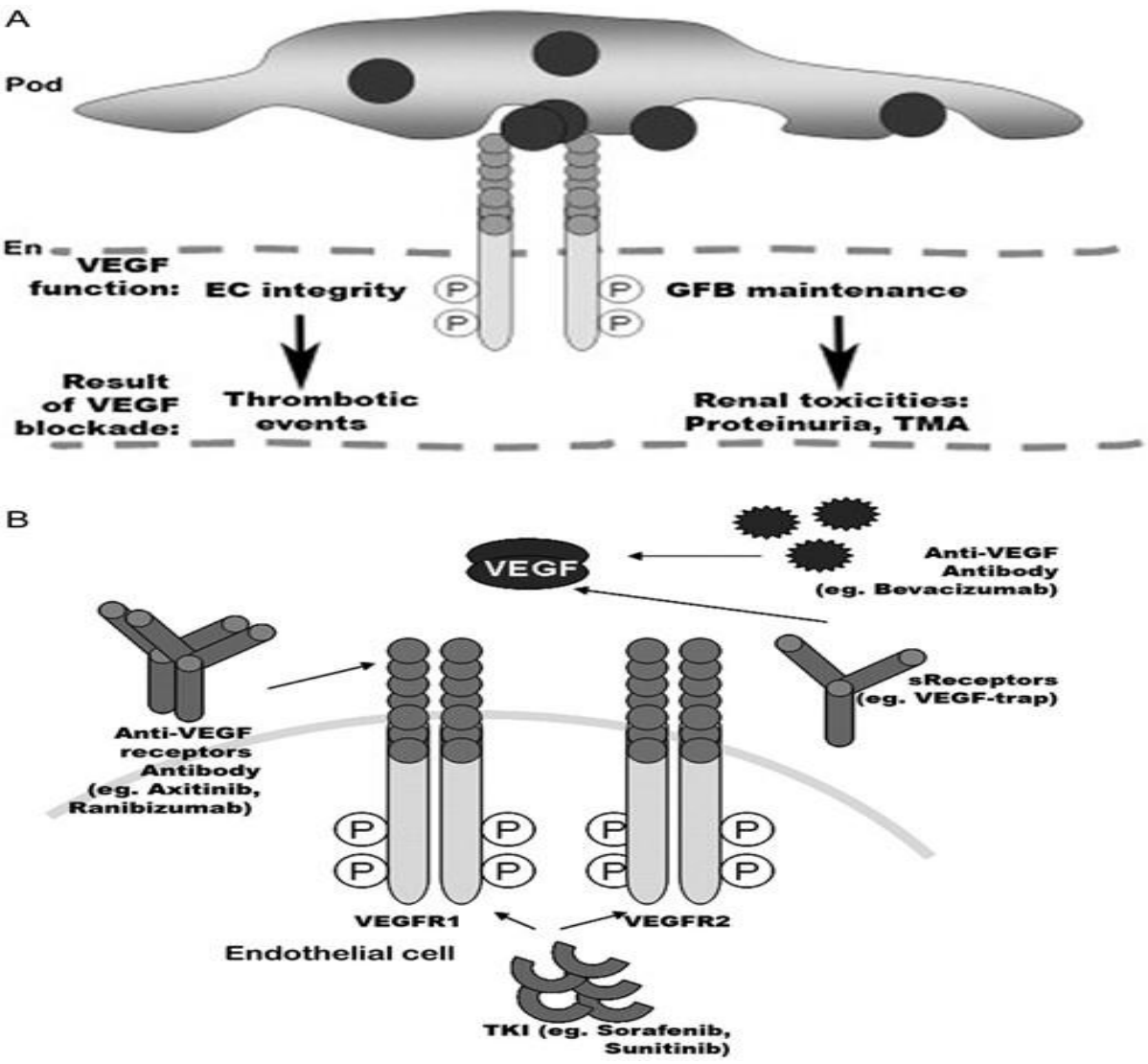

Figure (1). Endothelial cell integrity in glomerular filtration barrier maintained through VEGF which could be disturbed by anticancer. VEGF=vascular endothelial growth factor, TKI= tyrosine kinase inhibitors [20].

Central to preventing nephrotoxicity of drugs is identifying drugs susceptible to kidney damage, identifying patients at risk, and ensuring the proper use of medicines at risk, especially if the patient's renal function is already impaired. In addition, correcting dehydration and low blood pressure is essential. Drug-induced kidney damage can develop with minor symptoms and therefore must be suspected. When high-risk medications are used, the patient's creatinine should be monitored routinely. If drug-induced renal damage is detected, the nephrotoxic drug should be discontinued immediately [4]. In most cases, the drug-induced kidney damage is repaired, but chronic damage is also possible. In tubulointerstitial nephritis, a course of corticosteroids may accelerate recovery. However, the underlying drug should not be used in the future [8]. The main categories of anticancer drugs with their specific mechanism of nephrotoxicity is mentioned in Table 1. Its noteworthy to mention that some

of these anticancer drugs could induce nephrotoxicity in more than one mechanism.

Table 1. Mechanisms of Nephrotoxicity with examples of commonly used anticancer drugs.

Type of Nephrotoxicity	Examples
Prerenal azotemia	Cyclosporine Mitomycin C Tacrolimus
Glomerular injury And Glomerular dysfunction	Carboplatin Cisplatin Cyclosporine Interferon-alpha Methotrexate Mitramycin Tacrolimus Actinomycin D Melphalan
Tubulo-interstitial disease	Carboplatin Cetuximab Cisplatin Ifosfamide Methotrexate
Fanconi syndrome	Azacitidine Ifosfamide Streptozocin
Hemolytic uremic syndrome	Cisplatin Cyclosporine Gemcitabine Mitomycin C

CONCLUSION:

Nephrotoxicity caused by chemotherapy is a leading cause of morbidity and mortality in people with cancer. In cancer patients, monitoring the baseline renal function, modifying drug dosages, avoiding nephrotoxic drug combinations, and correcting extracellular fluid volume deficits are all critical. In the recent years, research have been performed to minimize the anticancer side nephrotoxic effects including the use of reno-protective agents such as antioxidants as well as the effective use of saline-based hydration. Furthermore, urinary alkalization is an additional significant

strategy in the treatment of the anticancer-induced nephrotoxicity.

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