THE KEY CHALLENGES OF BIDIRECTIONAL MANAGEMENT OF PATIENTS WITH CANCER AND CHRONIC KIDNEY DISEASE

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Abstract
Chronic kidney disease is a significant growing health problem, with prevalence of 9.1%–13.4% of the population worldwide. Cancer is the second leading cause of death in people with chronic kidney disease. The incidence of chronic kidney disease in patients with cancer is higher than in the non-cancer population and is associated with reduced cancer survival.
Chronic kidney disease can complicate cancer treatment due to impaired kidney function, which affects drug metabolism and clearance. Chemotherapy drugs and other medications may need to be adjusted to minimize the risk of toxicity and maintain efficacy. Managing cancer in patients with kidney disease, including those undergoing dialysis, requires a sensitive approach due to the impact of both conditions. In this review, we aim to highlight the crucial role of multidisciplinary approach that requires a strict comprehensive understanding of treatment options to provide optimal care and improve patient outcomes.

Keywords: Cancer, Chronic kidney disease, Anticancer therapy, Management.

SFIDAT KRYESORE TË MENAXHIMIT BIDIREKSIONAL TË PACIENTËVE ME KANCER DHE SËMUNDJE KRONIKE TË VESHKAVE

Abstrakt
Sëmundja kronike e veshkave është një problem i rëndësishëm ne sistemin shëndetësor, me prevalencë prej 9,1%-13,4% të popullsisë në mbarë botën. Kanceri është shkaku i dytë kryesor i vdekjeve tek njerëzit me sëmundje kronike të veshkave. Incidenca e saj në pacientët me kancer është më e lartë se në popullatën normale dhe shoqërohet me ulje të mbijetesës së kancerit.
Sëmundja kronike e veshkave mund të komplikojë trajtimin e kancerit për shkak të funksionit të dëmtuar të veshkave, i cili ndikon në metabolizmin dhe pastrimin e barnave. Barnat e kimioterapisë dhe medikamentet e tjera mund të kenë nevojë të modulohen ne doza për të minimizuar rrezikun e toksicitetit dhe për të ruajtur efikasitetin. Menaxhimi i kancerit në pacientët me sëmundje të veshkave, duke përfshirë ata që i nënshtrohen dializës, kërkon një qasje

të ndjeshme për shkak të ndikimit të të dy kushteve. Si përfundim, në këtë permbledhje, ne synojmë të theksojmë rolin vendimtar të qasjes multidisiplinare që kërkon një kuptim të rreptë gjithëpërfshirës të opsioneve të trajtimit për të ofruar kujdes optimal dhe për të përmirësuar rezultatet e pacientit.

Fjalë kyçe: Kanceri, Sëmundja renale kronike, Terapia kundër kancerit, Menaxhimi.

Introduction

Chronic kidney disease (CKD) affects more than 10% of the general population worldwide, amounting to >800 million individuals (1). Bidirectional relationship between CKD and other conditions is essential to improve the outcomes among these enormous number of patients. Many studies have revealed that the incidence of CKD in cancer patients is higher than in general population. Understanding this crucial relationship can affect in treatment options, quality of life and survival. It's important to underline the potential benefits of recognizing increased risk of cancer in risk prediction mechanisms used for the management of CKD and vice versa.

1.1 CKD and incident cancer

There is an increased risk of cancer incidence and death associated with kidney function (2). In a French observational study The Renal Insufficiency and Cancer Medications (IRMA) of nearly 5000 patients approximately half of participants diagnosed with cancer had mild reduction in kidney function (3), demonstrating the high prevalence of renal impairment.

In a prospective cohort study in Taiwan with 405878 participants, with major chronic diseases, CKD contributed to more than one fifth of the risk for incident cancer and more than one third of the risk for cancer death (4).

The link of low estimated glomerular filtration rate (e-GFR) and albuminuria is well known and are commonly associated with cancer risk. Various studies demonstrate that there is an increased risk of incident cancer in patients with albuminuria (5).

1.2 The role of e-GFR in incident cancer

According to Kidney Disease Improving Global Outcomes (KDIGO), CKD is defined as abnormalities of kidney structure or function present (GFR) < 60 mL/1.73 m2 for 3 months or more, irrespective of cause and is classified based on causes, GFR category (G1–G5), and albuminuria category (A1–A3), abbreviated as CGA. Several studies have shown a potential relationship between markers of CKD (below eGFR 60 ml/min/1.73m2, with or without albuminuria) with higher risk of incidence from overall cancers (6-8). Despite the contradictions of kidney function assessment, e-GFR should be calculated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations using serum creatinine (e-GFRcr), cystatin C (e-GFR-cys) or a combination of creatinine and cystatin C (e-GFRcr-cys) (9). Cancer incidence and mortality may be detectable early in CKD, and is more easily detected using e-GFR-cys (10). The impact of CKD markers is crucial on cancer outcome in particular is concerning and needs special consideration (11).

2. Potential mechanisms of CKD and cancer connections

The potential mechanisms of CKD-associated cancer or anticancer therapy-associated kidney injury remain profoundly in decipherable, although in recent years, the link has been well established and there has been rapid advancement in this interdisciplinary approach.

Increased cancer incidence rate in CKD might be due to chronic inflammation, accumulation of carcinogenic compounds, oxidative stress, impairment of DNA repair, excessive parathyroid hormone and changes in intestinal microbiota (12-15). Persistent low-grade inflammation had been identified as an important pathological trait of CKD. The inflammatory condition of CKD is multifactorial, including increased sensitivity to infection, acidosis and oxidative stress, metabolic changes of adipose tissue and intestinal conditions (12, 13). Biomarkers of inflammation (IL-1β, IL-6, and TNF-α) are inversely associated with measures of kidney function. It is well established that chronic inflammation is one of the common peculiarity of infections. Analogously, inflammation has long been considered as one of the important participants in the process of cancer formation leading to tumor growth, invasion and metastasis. Radical oxygen scavengers (ROS) is constantly generated by aerobic metabolism mitochondria (15), during oxidative stress, this causes serious damage to cell structure and function and induce mutations and cancer cells transformations.

In CKD patients, low DNA damage repair capacity may lead to mutable genes and aberrations in the chromosome, which might be responsible for pathological transformations of cells (16, 17).

Many studies approve that end stage kidney disease patients have uremic environment and are exposed to high levels of carcinogenic compounds due to reduction of excretion and accumulation of such substances in plasma. Progression of CKD causes decline of renal function and this leads to hypocalcemia and hyperphosphatemia and is the main cause of hyperparathyroidism. It has been reported that this condition might be pro-carcinogenic (18, 19).

3. **Anticancer treatments and acute kidney injury / chronic kidney disease**

Many studies confirm that anticancer therapy, including chemotherapy, radiotherapy, nephrectomy, molecular targeted therapy and immune checkpoint inhibitor cause acute kidney injury (AKI)/proteinuria and hypertension (20, 21).

Some of these treatments are cleared by the kidney or may have nephrotoxicity (22). Limiting patient access to best treatment options solely because of the presence of kidney disease is a form of renalism. The renalism was first used almost two decades ago by Chertow et al., to depict the systematic withholding of indicated, potentially beneficial studies and interventions from patients on the basis of coexisting kidney disease (23).

Platinum, crizotinib, ifosfamide typically cause tubular disfunction, the risk of renal side effects increases with higher doses and cumulative exposure, co-administration with other therapies and in patients with pre-existing kidney disease (24, 25). Thrombotic microangiopathy is a common side effect of gemcitabine and antiangiogenetic drugs and BRAF inhibitors/tyrosine kinase inhibitors are well known for the tubulointerstitial injury (26).

Studies estimate that approximately 50% of patients with cancer have decreased kidney function and receive at least one anticancer drug that requires dose adjustment, which may influence treatment decisions and overall management.

3.1 Medications use in the treatment of CKD may cause cancer

Erythropoiesis-stimulating agents, used in the treatment of renal anaemia, may exacerbate pre-existing cancers (27). Glomerulonephritis treatments algorithm include some medications (such as cyclophosphamide) and it is proved that can increase the risk of certain cancer (24).

4**. Cancer in dialysis and kidney transplanted patients**

Cancers occurring after dialysis or transplantion have long been described, but risk assessment by cancer site has been available only recently. Cancers most strongly associated with dialysis include tumors of the oral cavity (Kaposi sarcoma), kidney, bladder, thyroid, lung, liver and cervix (28-30). Dialysis patients are at risk of fluid and electrolyte imbalances, which can be exacerbated during cancer treatment. Careful observation of fluid status, electrolyte levels, and kidney function is mandatory to prevent complications such as hyperkalemia, fluid overload, and electrolyte disturbances (31). Kidney transplant patients are excluded in most clinical trials but few randomized controlled trials oriented for skin or other conditions due to the nature of being on immunosuppressive agents and the resulting complexities of treatment protocol. Kidney transplant recipients are at very high risk of cancers (32-34), most, but not all, of which with likely viral (Epstein–Barr virus, cytomegalovirus, human papillomavirus, human T-cell lymphotropic virus and hepatitis B and C) etiology (35).

Conclusion

CKD is common in cancer and it is related with high incidence and mortality rate among these patients. The risk is under-recognized due to the fact that most clinical trials exclude these subgroups and kidney function markers such as e-GFR and albuminuria are not acknowledged in cancer risk calculators. Kidney markers of glomerular filtration like cystatin C reveal an association with increased risk of cancer incidence and mortality at an earlier stage.

Accurate measurement or estimation of kidney function is vital to appropriate anticancer therapy dosing. A limpid understanding of the mechanisms will aid in devising strategies to reduce cancer risk among people with CKD. Identifying the causative drug and stopping exposure in acute toxic injury or detecting and treating chronic kidney injury as early as possible it is now considered the best way in managing CKD-Cancer patients. Multidisciplinary approach is mandatory to fill the knowledge gap and improve the outcome of cancer patients with kidney dysfunction.

Conflicts of Interest: No conflict of interest.

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