



ONCONEPHROLOGY: NEW SUBSPECIALTY, OLD PROBLEMS

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1. INTRODUCTION

Literature data indicates the interdependence between kidney diseases and cancer. Chronic kidney disease (CKD) is a risk factor of cancer development, and cancer or its treatment can lead to kidney damage.^[1] It is important because the occurrence of CKD as well as cancer is growing with age.^[2] In patients with CKD progression, cancer frequency increases with the estimated glomerular filtration rate (eGFR) decline and it is especially high in patients treated with dialysis. Moreover, cancer frequency is higher in patients after kidney transplantation in comparison to the general population.^[3] Cancer diagnosis and treatment in CKD patients can be hampered especially in later CKD stages when eGFR is lower than 30 ml/min.^[4] It concerns the possibility of performing imaging examination with contrast medium, interpreting concentrations of cancer biomarkers in patients' blood, and using specialized oncological treatment, e.g. chemotherapy. These limitations cause that results of cancer treatment in CKD patients are significantly worse in comparison to the general population. On the other hand, cancer and its treatment can cause kidney damage.^[5] It is well known that nephrotoxicity of drugs used in oncology can lead to acute kidney injury (AKI) or CKD progressing with the eGFR decline, which makes treatment continuation impossible.^[6,7] Cessation of oncological treatment or reduction in doses of oncological drugs due to kidney function deterioration is the main reason for worsening of cancer treatment results in these patients. Decline in kidney excretory function is the reason for the limitation of using new oncological therapies, for example molecular ones, in patients with advanced CKD.^[8] Thus cancer diagnosis and treatment in CKD patients are a big challenge for nephrologists and oncologists. The new subspecialty, onconeurology, deals with the described above problems of cancer and kidney diseases.^[9] In this article, the authors discuss only some chosen onconeurology problems such as cancer occurrence in CKD patients and some problems associated with cancer diagnosis and treatment.

1. Cancer occurrence in CKD patients

Literature data shows that the risk of cancer development is higher in CKD patients. Wong E et al. state that the third stage of CKD can already be an independent risk factor for cancer development in older men and increases this risk by about 40%. These authors declare also that the cancer risk in CKD patients begins when eGFR is about 55 ml/min and is growing with the eGFR decline.^[10] A higher cancer risk is observed in patients with end stage renal disease (ESRD) treated with renal replacement therapy (RRT).^[11] A standardized incidence ratio (SIR) of cancer in patients undergoing RRT is from 1.1 to 1.8 in comparison to the general population.^[12,13] The highest risk of cancer development is found in patients after kidney transplantation, being 2-3 times higher than in the general population.^[14,15,16] There are many postulated mechanisms to explain the relationship between the impaired excretory kidney function and an increased risk of cancer development. Uremic toxicity, growing with the eGFR decline can lead to carcinogen accumulation and disturb repair processes of DNA.^[17,18] Chronic inflammation and enhanced oxidative stress

observed in CKD patients and especially in those with ESRD^[19,20] can favor cancer development.^[21] What is more, CKD patients have immune system disturbances with impaired cellular and humoral immunity^[22,23] and endothelial dysfunction^[24], which can play an important role in cancer development.^[25] ESRD patients demonstrate very high levels of comorbidity and are treated with many medicines, for example immunosuppressive, statins and hypotensive which may affect cancer development.^[26,27]

The literature data concerning localization of the most common cancers in CKD patients is not fully consistent. Lowrance WT et al.^[28] conducted retrospective research in the population larger than 1000 000 adults over 40 years of age without cancer, dialysis treatment and kidney transplantation history. Analysis showed a significant relationship between lowered eGFR and kidney cancer. Patients with eGFR lower than 30 ml/min have a more than twice higher kidney cancer incidence rate in comparison to patients with eGFR ranging 60-89 ml/min. These authors demonstrated also a significant

relationship between lower eGFR and urothelial cancer occurrence, whereas they did not find any significant correlation between lower eGFR and prostate, breast, lung and colorectal cancer. This site-specific risk of renal and urothelial cancer in CKD patients may be connected with chronic inflammation, enhanced oxidative stress and immune system disturbances which are present in this group of patients and may play an important role in cancer development.^[29,30]

Xu H *et al.*^[31] analyzed a relationship between eGFR and cancer occurrence in the population of over 700 000 patients in Sweden over 40 years of age without cancer history. Cancer was diagnosed in 9% of analyzed patients and lower eGFR was significantly correlated with a higher occurrence of skin (non-melanoma), urothelial, prostate and hematopoietic cancers. These authors state that the relationship between eGFR and skin and prostate cancer was not observed by other authors. An increased incidence ratio of skin cancer in ESRD may be connected with chronic inflammation, uremic pruritus and the use of immunosuppressive drugs.^[32] The main hematopoietic cancer in this observation was multiple myeloma whose relationship with impaired kidney function is well known.^[33]

In another observational study, Wong G *et al.*^[34] evaluated cancer occurrence in different CKD stages and deaths due to cancer in the group of over 32 000 patients. In conclusion they stated that the impaired kidney function is connected with a higher risk of urothelial, digestive tract and thyroid cancers. This risk is the highest in ESRD when patients are treated with dialysis, but the authors observed that the risk of prostate cancer is lower in patients with impaired kidney function. In the discussion concerning death analysis, the authors indicated that CKD patients, especially those with ESRD have a higher death risk from cardiovascular diseases in comparison to the general population and they are also at high risk of death from other diseases.^[35] Cancer is one of the most common causes of death among noncardiovascular diseases. Observational studies reported 1.5 times higher death risk caused by cancer in patients undergoing dialysis treatment.^[12] Other observational studies showed a significant correlation between impaired kidney function and kidney, urothelial, thyroid and digestive tract cancers.^[15,36] Wong G *et al.*^[10] analyzed over 3 600 patients aged 49-97 years and stated that the risk of lung and urothelial cancer but not prostate cancer is higher in CKD men.

Chinnadurai R *et al.*^[37] performed the analysis of almost 3 000 CKD patients. Over 13% of them had earlier cancer history, the annual risk of cancer was 1.6%. Most common cancers were the following: urothelial (kidney and bladder), prostate and testis in men as well as uterus and ovary in women. Then the authors created two observational groups with or without earlier cancer history, each consisted of 337 patients. They observed that mortality was significantly higher in the group with

previous cancer history, however CKD progression to ESRD was similar in both groups.

Numerous publications indicate a high cancer risk in patients after kidney transplantation.^[15,16,38] Many factors are thought to be responsible for very high cancer incidence in this group. Kidney and urothelial cancer occurrence is connected with demographic factors, time of dialysis treatment before transplantation, immunosuppressive treatment and transplanted kidney function.^[39] Immunosuppressive treatment and viral infections are typical factors of cancer occurrence in patients after kidney transplantation.^[14] It is difficult to analyze the influence of every immunosuppressive agent on cancer development because of using multidrug immunosuppressive protocols. Literature data indicates that cancer risk depends on the time and doses of immunosuppressive treatment. Calcineurin inhibitors, cyclosporine and tacrolimus, can promote cancer development due to tumor growth factor beta (TGF- β) stimulation. This action depends on doses of immunosuppressive agents.^[40,41] Prospective studies did not show significant differences between the effect of cyclosporine and tacrolimus on cancer development in patients after kidney transplantation.^[42] Azathioprine, which was used earlier in immunosuppressive protocols, increased the risk of lymphoma and solid tumors.^[40] Recently it has been replaced by mycophenolate mofetil (MMF). Studies showed that immunosuppressive protocols with MMF were associated with a lower cancer risk.^[43] Literature data indicates that the use of mammalian target of rapamycin (mTOR) inhibitors may be connected with a lower cancer risk in comparison to calcineurin inhibitors.^[44] Meta-analysis of 21 randomized trials revealed that sirolimus treatment was related to a 40% decrease in the general cancer risk and a 56% decrease in non-melanoma skin cancer.^[45] Other studies also confirmed a lower cancer risk in patients treated *de novo* with the mTOR inhibitor.^[46] Moreover, there is data in literature which does not provide strong evidence that sirolimus prevents posttransplant cancer, but it may be advantageous among kidney transplant recipients with high cancer risk.^[47]

Patients after kidney transplantation are at risk of frequent primary viral infections and reactivation of latent infections. Viral infections may play a very important role in cancer development in patients after organ transplantation receiving immunosuppressive therapy.^[14] Literature data indicates a relationship between BK polyomavirus (BKV) and urothelial cancer in organ recipients.^[48] Moreover, it is postulated that patients with BKV nephropathy have almost a threefold higher risk of bladder cancer in comparison to patients without BKV nephropathy^[49], which indicates an important role of BKV infection in urothelial carcinogenesis. The relationship between hepatitis virus and hepatocellular cancer, Epstein-Barr virus infection and lymphoma, human papilloma virus and sexual organ cancer or herpesvirus and Kaposi's sarcoma in patients

after kidney transplantation has been well known in literature.^[14]

The discussed above review of available literature indicates a higher cancer risk in CKD patients and after kidney transplantation, which can be a strong motivation for nephrologists and oncologists to prepare standards and recommendations regarding cancer screening in these patients to recognize cancer at an early stage, which is necessary for effective treatment.

2. Some problems of cancer diagnosis and treatment in CKD patients

Detection of cancer at its early stage increases cancer successful treatment and decreases cancer dependent mortality.^[50] Therefore screening to diagnose cancer at its early stage appears to be the most important diagnostic problem in CKD patients. Effective screening depends on good standards and recommendations prepared for given group of patients. Some reports present recommendations concerning cancer screening in the general population^[51,52], but unfortunately there are not good enough for CKD patients. These patients are different in comparison to the general population because of high comorbidity, shorter survival time, higher mortality, worse quality of life and some limitations of cancer diagnosis and treatment. This lack of recommendations can result in a different approach adopted by nephrologists to perform the evaluation of cancer screening in CKD patients, especially in later stages of CKD including patients on dialysis.

James *et al.*^[50] investigated this problem among a group of nephrologists and presented their opinion that making decisions and recommendations for cancer screening in CKD patients is a complex and multifactorial process. Nephrologists have to take many factors into consideration in CKD patients before performing cancer evaluation, such as individual cancer risk, life expectancy, benefits and dangers of screening, comorbidities, possible complications, and patients' preferences. They usually oscillate between advantages and possible complications associated with cancer diagnosis and treatment. Moreover, nephrologists' approach to cancer screening depends on CKD stage. For patients who do not need RRT yet, nephrologists usually perform cancer screening and use recommendations prepared for the general population, however for CKD patients receiving RRT, they make individual decisions about cancer screening for every patient considering the above mentioned factors.

The evaluated group of nephrologists agree that CKD patients prepared for kidney transplantation and after transplantation require complete cancer screening as in the general population. There are many clinical practice guidelines for organ recipients to be used in these patients: Kidney Disease: Improving Global Outcomes (KDIGO, 2009)^[53], European Best Practice Guidelines (ERBP, 2002)^[54], Canadian Society of Transplantation

and Canadian Society of Nephrology (CST&CSN, 2010)^[55], National Kidney Foundation 2 (NKF2, 2009)^[56], Kidney Health Australia – Caring for Australasians with Renal Impairment (KHA-CARI, 2012)^[57], American Society of Transplantation – Kidney (AST-Kidney, 2000)^[58], and Renal Association Clinical Practice Guidelines (RA, 2011, United Kingdom).^[59] The above mentioned recommendations concerned screening of skin, lips, cervical, breast, prostate, kidney, urothelial, colorectal and hepatic cancer.

Acuna SA *et al.*^[60] assessed these guidelines and stated that there is consensus on the recommendations for annual screening of skin cancer with clinical skin examination performed by a trained physician or dermatologist. Recommendations for breast, colorectal, cervical and prostate cancer screening are almost the same as in the general population but screening for lung and kidney cancer is generally not recommended among kidney recipients. In conclusion, the authors indicated that these recommendations varied among organizations and consensus was only for skin cancer screening. New clinical practice guideline for cancer screening is needed for this high risk population of organ recipients and should incorporate consensus of experts such as nephrologists, oncologists, and public health specialists.^[60]

Imaging examinations with the use of contrast medium can pose another diagnostic problem in CKD patients and cancer. This group is at higher risk of contrast-induced acute kidney injury (CI-AKI) in comparison to the general population^[61,62], which is connected with the presence of many risk factors of CI-AKI such as numerous comorbidities, older age, water-electrolyte disturbances, CKD and necessity of using nephrotoxic drugs, e.g. oncological treatment. Performance of contrast imaging examination in advanced CKD with very low eGFR or AKI is usually limited, which considerably hampers monitoring of treatment efficiency and may often cause the withdrawal of cancer treatment.^[63] Therefore, it is very important to prevent CI-AKI in CKD patients with cancer. It is suggested in the literature to use preventive procedures in accordance with KDIGO recommendations.^[64]

The interpretation of cancer marker concentrations in CKD patients' blood used in cancer screening can be another important diagnostic problem. These markers have usually impaired kidney clearance in CKD patients what may overvalue their results and disturb their interpretation.^[65] Serum concentration of CEA, PSA, chromogranin A and Ca125 (in males) seems to be elevated in CKD patients^[66] but AFP, Ca125 (in females) serum concentrations seem to be independent of renal function.^[67] The data on Ca19-9 serum concentration in CKD patients is not consistent, some authors note an increase in Ca19-9^[66], others observe no differences in Ca19-9 serum concentrations between CKD patients and healthy subjects.^[68] There is data in the literature

regarding the importance of neutrophil gelatinase-associated lipocalin (NGAL) which can be used as a marker connecting kidney function and cancer. NGAL is a possible predictor of acute kidney injury^[69] and it is also a marker of CKD progression because serum and urinary levels of NGAL are inversely related to kidney function.^[70] NGAL seems to be responsible for non-specific immune response and may play a role in the regulation of proliferation, differentiation and development of some cancers.^[71,72] Further research including more CKD patients and cancer is needed to establish clinical importance of the above discussed markers in these patients.

Other diagnostic problems are paraneoplastic syndromes, where cancer or its antigens or toxins can cause kidney injury. The most common examples are glomerulonephritis (membranous, minimal change, focal segmental glomerulosclerosis), thrombotic microangiopathy, water-electrolyte and acid-base balance disturbances.^[73] Coincidence of glomerulonephritis and early-stage cancer is frequent and poses a challenge for nephrologists, because glomerulonephritis is usually diagnosed first. Therefore these patients require cancer screening after a glomerulonephritis diagnosis. Standards and recommendations regarding the type of medical tests and their frequency are needed in these patients to avoid missed opportunities to diagnose cancer at its early stages.^[74]

Very important problem in CKD patients and cancer is oncological treatment. Impaired excretory kidney function while beginning oncological treatment may disturb bioavailability and safety profile of oncological medicine which may lead to suboptimal concentrations of oncological drugs and furthermore to nephrotoxic actions with CKD progression or AKI occurrence.^[75] Therefore, some effective oncological medicines cannot be used in CKD patients due to the lack of research regarding their pharmacokinetics in these patients. Anticancer drugs can directly and indirectly injure kidney. Direct nephrotoxic action of traditional cytostatics (f.e. cisplatin) is well known^[76], but fast progress in cancer treatment and introduction of many new drugs, especially with molecular action (f.e. sorafenib, sunitinib) result in side effects afflicting kidney, such as acute interstitial nephritis, thrombotic microangiopathy, hypertension, water-electrolyte and acid-base balance disturbances.^[77,78] Monitoring blood concentrations of oncological drugs in CKD patients, especially in later stages of CKD, and the cooperation between a nephrologist, oncologist and clinical pharmacologist are recommended to obtain a good knowledge of oncological drug pharmacokinetics in CKD patients and to perform effective cancer treatment, avoiding nephrotoxic side effects.^[79] Cancer treatment in ESRD or AKI patients receiving RRT appears to be a therapeutic challenge due to low survival rate of these patients and the limited pharmacokinetic and

pharmacodynamic data on cancer medicines in RRT patients.^[80] To choose oncological medicine, it is necessary to take into consideration an impact of using RRT method (hemodialysis, peritoneal dialysis, hemodiafiltration) on anticancer drug clearance to make treatment effective but not nephrotoxic.

Another therapeutic problem concerns cancer treatment in patients after kidney transplantation, when the balance between effective cancer treatment and the maintenance of transplanted kidney function is required. There is a lack of prospective and randomized trials on this problem, only small reports can be found in the available literature. Therapeutic strategy in kidney recipients who develop cancer includes careful immunosuppression reduction and the use of standard oncological treatment with the adjustment of oncological drug doses to the actual transplanted kidney function, as well as possible interaction of drugs and their effect on the transplanted kidney function.^[81]

The present review of available literature indicates many diagnostic and therapeutic problems in CKD patients and those after kidney transplantation who develop cancer. These problems pose a challenge for nephrologists and oncologists to prepare diagnostic and therapeutic standards helping them in detection of early-stage cancers and their effective treatment.

3. SUMMARY

Dynamic development of a new subspecialty onconephrology has been observed. In the literature, there are more and more publications and congress abstracts related to cancer and kidney diseases.^[82] Nevertheless, onconephrology is still more experience-based than evidence-based medicine. It is a consequence of a fact that cancer patients with kidney diseases, especially with advanced CKD, are usually not included into clinical trials which are stones of evidence-based medicine.

Furthermore, there are no diagnostic and therapeutic standards/recommendations for this special group of patients which differs from the general population. An exception from these standards is the recommendation regarding erythropoietin treatment in CKD patients and those with cancer.^[83] Moreover, single case reports or small retrospective studies dominate in the literature as compared to prospective clinical trials. New onconephrology area needs the integrated diagnostic-therapeutic standards covering the complex care for patients with cancer and kidney diseases. An appropriate solution may be the formation of an onconephrology outpatient clinic, where a multidisciplinary onconephrology team can realize the best diagnostic-therapeutic process for these patients. Recommendations and basic requirements regarding the onconephrology clinic are discussed by Cosmai L *et al.*^[84] Organization of specific training programs in onconephrology, symposiums, and congresses, the exchange of experience

between onconeurology centers and close cooperation between oncologists, nephrologists, pharmacologists and other members of treatment teams may result in a better medical care, diagnosis and treatment outcomes in patients with cancer and kidney diseases comparable to the general population.

Compliance with Ethical Standards

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