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Review

Nephro-oncology: clinical and biochemical aspects of kidney disease and cancer

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Onco-nephrology is a new field of medicine which combines many aspects of kidney injury in cancer patients and cancers in patients with kidney disease. This connection takes many forms and includes drug-induced nephrotoxicity, electrolyte disorders, numerous paraneoplastic syndromes and an increased rate cancers in dialysis and transplanted patients. The appropriate laboratory assessment of the kidney function allows to optimize chemotherapy and thus minimizes the risk of complications. This article focuses on acute kidney injury (AKI), chronic kidney disease (CKD), various electrolyte and acid-base disorders, the most common cancers after kidney transplantation and the kidney disorders associated with HSCT (hematopoietic stem cell transplantation). The possibility of the application of novel cancer therapy, such as cancer immunotherapy and proton therapy in transplant recipients was also discussed.

Key words: onco-nephrology, cancer, kidney disease, transplantation, HCT, therapy

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Abbreviations: ACKD, acquired cystic kidney disease; ADPKD, autosomal dominant polycystic kidney disease; AKD, Acute kidney disease; AKI, acute kidney injury; AML, acute myeloid leukaemia; ANP, atrial natriuretic peptide; BC, bladder cancer; BCC, basal cell carcinoma; BSA, body surface area; CKD, chronic kidney disease; CNI, calcineurin inhibitors; CTLA4, cytotoxic T-lymphocyte-associated protein 4; EFS, event-free survival; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; FGFR, fibroblast growth factor -23 receptor; FSGS, focal segmental glomerulosclerosis; GvHD, graft versus host disease; HCT, hematopoietic cell transplantation; HCT-CI, specific comorbidity index; HD, hemodialysis; HSCT, hematopoietic stem cell transplantation ; ICIs, immune checkpoint inhibitors; irAEs, immune-related adverse events; KDIGO, Kidney Disease Improving Global Outcomes; KTx, kidney transplantation; MCC, Merkel cell carcinoma; MDRD, Modification of Diet in Renal Disease; MM, malignant melanoma ; mTOR, mammalian target of rapamycin kinase; PC, prostate cancer; PD-1, programmed cell death-1; RCC, renal cell carcinoma; RT, radiotherapy; SCC, squamous cell carcinoma; SCLC, small-cell lung cancer; SIADH, inappropriate secretion of antidiuretic hormone; SOTR, solid organ transplant recipients; TA-TMA, transplant-associated thrombotic microangiopathy; TBI, total body irradiation; TNF, tumor necrosis factor; UTIs, Urinary tract infections; VEGF, vascular endothelial growth factor

INTRODUCTION

There are complex relationships between kidneys and cancer. Many crucial points could be underlined by factors such as acute kidney injury and chronic kidney disease in a cancer patient, the renal effects of anticancer therapy, adverse effects of the tumor itself, management of patients after nephrectomy due to kidney cancer, cancer treatment on dialysis and after kidney transplantation (KT). Another very important issue is oncological treatment in other than kidney solid organ transplant recipients (SOTR) and in hematopoietic cell transplantation (HCT).

A multidisciplinary onco-nephrology team, including not only oncologist and nephrologist, but also other health professionals is crucial to providing care to the aforementioned groups of patients (Cosmai *et al.*, 2016). This was the reason for the creation of a new field of medicine – called onco-nephrology (Bączkowska *et al.*, 2019)

In this paper, we discussed acute and chronic kidney disease in SOTRs with cancer as well as nephrotoxicity associated with existing and novel cancer therapy. We also focused on the most common cancers in SOTRs such as skin cancer and urinary tract cancer. An additional part is dedicated to kidney disease in HCT recipients.

Adequate assessment of kidney function allows for selecting the optimal anticancer therapy in terms of the type of drug and its dose (Malyszko *et al.*, 2020a). Treatment efficacy and outcomes, as well as survival, could be affected by both the overestimation and underestimation of renal function.

Patients with impaired renal function are at a higher risk of developing adverse events and toxicities to an anti-cancer drug. The use of some drugs in patients with renal failure can lead more often to myelotoxicity, hepatotoxicity, and life-threatening electrolyte disorders (e.g., cisplatin, cyclophosphamide, vinblastine, and vincristine).

An equally important issue is the use of new groups of anticancer drugs in patients with kidney damage and kidney transplanted patients (Małyszko *et al.*, 2016; Sprangers *et al.*, 2021). In recent years, novel therapies, including immunotherapy with immune checkpoint inhibitors (ICIs) and proton therapy, have revolutionized cancer treatment and are becoming a new standard of care for many tumor types. Nephrological problems more and more often also affect patients undergoing stem cell transplantation (Kępska-Dzilińska *et al.*, 2022). Kidney damage/deterioration is often found in these patients due to the extension of the eligibility criteria for this procedure and its use in older patients and/or with additional chronic diseases. Kidney injury after high-dose chemotherapy might be due to the direct effect of cytotoxic agents or indirect complications caused by cytotoxic agents such as mucositis and diarrhea, infections, or veno-occlusive disease. On the other hand, HCT is increasingly used in patients with renal failure, including end-stage renal disease undergoing dialysis due to multiple myeloma. The different HCT protocols are required in patients with normal renal function, mild impaired renal function, and dialysis-dependent patients, which is discussed in this article.

Kidney transplantation is the best method of renal replacement therapy, it prolongs the patient's life by decades but the price is much higher than in the general population - the risk of cancer. Cancer is listed as the second, after cardiovascular diseases, cause of death in patients after KT and also causes death in many other SOTRs (Serkies *et al.*, 2022). Treatment of these patients is very complex due to immunosuppression and requires the cooperation of specialists in many fields depending on the transplanted organ and type of neoplastic disease. Skin cancers are the most common tumors in SOTRs. The most prevalent are squamous cell carcinoma (SCC), basal cell carcinoma (BCC), malignant melanoma (MM), and Merkel cell carcinoma (MCC) (Mittal & Colegio, 2017). Appropriate prophylaxis allows for a considerable reduction of the risk of skin cancer, while regular dermatological examination allows for a diagnosis in the early phase of the disease and improves the prognosis. The second most common are cancers of the urinary tract, including the transplanted kidney (Bellini *et al.*, 2022). As these neoplasms occur more often in older age, their detection is growing with time, with the number of recipients followed up. In the case of urinary tract cancers, surgery is recommended. The possibilities and limitations of urological management are presented in our article.

The presented paper summarizes the key information provided in lectures delivered during the 2nd Scientific and Training Conference "Nephro-oncology" in Gdańsk, Poland, on October 2–3, 2020. It is also updated using crucial management issues in nephrology relevant to patients with malignancy, published by KDIGO (Kidney Disease: Improving Global Outcomes) and the current status on malignancies in adult kidney transplant candidates and recipients published most recently in NDT (Porta *et al.*, 2020; Małyszko *et al.*, 2020a; Serkies *et al.*, 2022).

KIDNEY INJURY IN CANCER

Acute and chronic kidney disease definition and classification

The term Acute kidney disease (AKD) was introduced recently to incorporate both acute kidney diseases and disorders. The definition of AKD includes abnormalities of kidney function and/or structure with implications for health lasting ≤3 months. AKD may include AKI (acute kidney injury), but, more importantly, also other abnormalities in kidney function that are not as severe as AKI or that develop over a period of >7 days (Table 1) (Lameire *et al.*, 2021; Levey *et al.*, 2022). The cause(s) of AKD should be sought, and classification includes functional and structural parameters. Minimal dataset for evaluation: history and examination including; past medical history, drug history (in cancer patients particularly important), infectious diseases, full physical examination including blood pressure, assessment of volume, serum creatinine and eGFR (estimated glomerular filtration rate), urea and electrolytes, full blood count, urinary dipstick (qualitative albuminuria/proteinuria), and ultrasound. Management of AKD is currently based on empirical considerations.

Kidney function assessment in oncology

It has been learnt that renal function in patients with malignancy should be estimated to profile the survival risk, assess the appropriate dose of antineoplastic drugs and define the eligibility of these patients for clinical trials with novel therapies (Porta *et al.*, 2020). The problem of drug dosing in oncology was described in detail in two recent reviews (Sprangers *et al.*, 2021; Małyszko *et al.*, 2020a). Treatment efficacy and outcomes as well as survival could be affected by both overestimation and underestimation of renal function. Overestimation of renal function may result in overdose or inappropriate choice of anticancer drugs with their serious adverse

Table 1. Functional and structural criteria for kidney diseases and disorders.

	AKI	AKD	CKD
Duration	Within 7 days	≤3 months	>3months
Functional criteria	increase Scr by >50% within 7 days or increase SCr by >0,3mg/dL (26.5µmol/L) within 2 days or oliguria for ≥4 hours	AKI or GFR<60 mL/min/1.73m2 or decrease GFR by >35% vs baseline or increase SCr o >50% w vs baseline	GFR <60 ml/min/1.73m^2
And/or		And/or	And/or
Structural criteria	Not defined	Markers of kidney damage (albuminuria, hematuria, or pyuria are most common)	Markers of kidney damage (albuminuria is most common)

Abbreviations: AKD, acute kidney disease; AKI, acute kidney injury; CKD, chronic kidney disease; GFR, glomerular filtration rate; SCr, serum creatinine.

events. On the other hand, underestimation of renal function may cause underdosing or exclusion/withdrawal of an anticancer agent leading to worse outcomes/subsequent treatment failure. The majority of patients with malignancies are treated with several anticancer drugs with renal clearance. Therefore, patients with impaired renal function are at higher risk for developing adverse events and toxicities to these therapeutic protocols. Recently introduced immune checkpoint inhibitors (e.g., ipilimumab, nivolumab, and pembrolizumab) may cause acute interstitial nephritis and podocytopathy. Moreover, anti-VEGF (vascular endothelial growth factor) drugs may cause microvascular injury and DITMA (drug-induced thrombotic microangiopathy) or various glomerulopathies, in particular, minimal change disease and/or collapsing-like FSGS (focal segmental glomerulosclerosis). Therefore, in patients with malignancy, an accurate assessment of kidney function i.e. GFR is critical. To date, creatinine is a nearly ideal filtration marker, despite some limitations. Therefore, several formulae assessing GFR were introduced in healthy subjects as well as in patients with chronic kidney disease, however, the use of these formulae in cancer patients is not established. Sarcopenia is a common finding in patients with advanced malignancy prior therapy, in addition, it develops or worsens during anticancer therapy in the vast majority of patients. As creatinine is produced by muscles, in patients with reduced muscle mass creatinine-based formulae are not appropriate with potentially negative consequences. Recently, Janowitz and others performed an extensive study and showed that the BSA-adjusted CKD-EPI formula appeared to be the most accurate and least biased GFR estimate of those currently used in oncology patients when compared with ^{51}Cr-EDTA (Janowitz *et al.*, 2017). Calculation of GFR based on the Janowitz formula is available online at http://tavarelab.cruk.cam.ac.uk/JanowitzWilliamsGFR/. It appears that the Janowitz formula is the best option for creatinine-based equations in cancer patients. In everyday clinical oncology practice, adjustment of drug dosage is generally based on eGFR. However, The US FDA promotes the usage of Cockcroft-Gault or the MDRD formulae for drug dosage prescriptions (Malyszko *et al.*, 2020a). Despite the fact, that either Janowitz or CKD-EPI formula estimates GFR more precisely, the drug manufactures still refer drug dosage to other eGFR formulae. Therefore, we need to take into account these eGFR formulae when adjusting the drug dose. Kidney function, besides changes in glomerular filtration rate/serum creatinine, also encompasses tubular dysfunction and vascular disorders, more studies including urinalysis and imaging studies such as computed tomography, magnetic resonance imaging, etc are to be considered prior to taking therapeutic decisions (Malyszko *et al.*, 2020a).

Evaluation of renal function in AKI is another challenge for nephro-oncologists, as AKI is common in cancer patients either due to malignancy or its therapy. It is of utmost importance as AKI represent a dynamic state with a fast fall in GFR whereas CKD is a relatively stable state and GFR formulae were developed in stable CKD patients. Therefore, in AKI, estimation of eGFR based on creatinine may lead to serious errors. Moreover, as kidney injury originates in tubules, significant tubulopathy may not result in significant rise in serum creatinine concentration and changes in creatinine/GFR represent relatively late changes. Taking into account these limitations, there is a search for serum and urinary markers. Several biomarkers such as neutrophil gelatinase–associated lipocalin, proinflammatory cytokines (interleukin-6 and interleukin-8), kidney injury molecule-1, netrin, semaphorin, etc and some others were assessed (Malyszko *et al.*, 2020a). However, no data are available on their application in cancer patients. Serum uric acid might reflect a convenient and simple measure of kidney function. Recently, fasting urine osmolarity has been proposed as a simple measure of tubular function (Malyszko *et al.*, 2020a). In the setting of known tubular damage, impaired urine concentration ability precedes a decline in GFR Thus, fasting urine osmolarity determination may be a simple and inexpensive tool to assess renal function and could be done at the bedside.

As kidney function assessment and the problem of the narrow therapeutic range of anticancer drugs is crucial, we should look for the appropriate methods used to assess renal function to avoid either underdosing or overdosing leading to failure/relapse or toxicity, respectively, both resulting in worse outcomes (Sprangers *et al.*, 2021).

Acute kidney injury in patients with cancer

Acute kidney injury is diagnosed frequently in patients with cancer (Porta *et al.*, 2020). The incidence of AKI differs from 12 to more than 20% of these patients. It is significantly higher in patients with multiple myeloma (up to 50%) and those who were treated with cisplatin (20-30%) or were admitted to the Intensive Care Unit (more than 50%) (Salahudeen *et al.*, 2013). Up to 70% of all AKI develop during the first week after admission to the cancer centre. Many patient-specific (age, comorbidity especially diabetes mellitus, nephrotoxic chemotherapy, etc.) and cancer-related risk factors (neutropenia, sepsis, haematological cancers, hypercalcemia, tumour lysis syndrome, and many others) may increase the risk of AKI in patients with cancer (Rosner & Perazella, 2019). In the pathogenesis of AKI in patients with cancer several prerenal (extracellular fluid depletion, cardiac failure), intrarenal (glomerular or tubulointerstitial diseases, sepsis, thrombotic microangiopathy) or postrenal (obstructive uropathy) causes may play an important role. Many of these factors are present in patients with multiple myeloma; therefore, the incidence rate of AKI is high in these patients (Malyszko *et al.*, 2020b). Chemotherapy plays a crucial role in the pathogenesis of AKI in cancer patients, which may affect each of the nephron segments (Malyszko *et al.*, 2016). Mortality related to AKI in patients with cancer is high (25-30%) and up to 60% of these patients will develop end-stage kidney disease in the future, requiring renal replacement therapy (Salahudeen *et al.*, 2013). Therefore all prophylactic maneuvers are very essential, including magnesium supplementation and the algorithms for the prevention of AKI after CT with contrast media frequently performed in patients with cancer (Cosmai *et al.*, 2020).

Electrolyte disorders in cancer patients

Electrolyte disorders are very common conditions in cancer patients, and may significantly worsen the treatment outcome. Malignancy-specific electrolyte disorders can lead to life-threatening complications, particularly in patients with AKI. Hyponatremia, hypokalemia, hypomagnesemia, hypercalcemia and hyperphosphatemia can be disturbances directly related to the tumour or its treatment.

The Chinese population study revealed electrolytes and acid-base balance disturbances in 58% of 25,800 cancer patients (Li *et al.*, 2020). This proportion is significantly higher than in other reported patient populations,

such as elderly people (22%) or patients admitted to the emergency units (14%).

Hyponatremia

Hyponatremia is the most common electrolyte disorder in patients with cancer. The prevalence of hyponatremia ranges from approximately 4% to as high as 44% (Berardi *et al*., 2019). The most common disturbance directly related to malignancy is the inappropriate secretion of antidiuretic hormone (SIADH) from cancer cells (paraneoplastic syndrome). It is most commonly seen in small-cell lung cancer (SCLC) and head/neck cancer because as many as 10% to 15% of patients are hyponatremic from the beginning of the disease. Additionally, up to 70% of patients have significant elevations of plasma arginine vasopressin (AVP) (Rosner & Dalkin, 2014). The drugs most often associated with SIADH are cyclophosphamide, cisplatin, vinblastine, and vincristine (Verzicco *et al*., 2020). For many patients with malignancy-related SIADH, the hyponatremia can be refractory to therapy. Another possible mechanism of hyponatremia in SCLC is the nonphysiological release of atrial natriuretic peptide (ANP) (Berardi *et al*., 2019). Cisplatin can cause not only SIADH but also salt-losing nephropathy.

Hypokalemia

Hypokalemia is the second most common electrolyte disorder, with a prevalence of around 15% (Li *et al*., 2020). The reasons for hypokalemia can be related to cancer and/or the used treatment. Cancer-specific causes include tumours that secrete ectopic adrenocorticotropin hormone (ACTH) such as SCLC, carcinoids, neuroendocrine tumours, or thyroid medullary carcinoma. These tumours cause the typical symptoms of hypercortisolemia and stimulate renal potassium wasting by activating the mineralocorticoid pathway. Another cancer-specific etiology for hypokalemia is possible in M4 and M5 subtypes of acute myeloid leukaemia (AML) (Milionis *et al*., 1999). These malignancies increase serum lysozyme and lysozymuria, which leads to tubular injury (Mason *et al*., 1975). Hypokalemia in these patients usually occurs together with other electrolyte and acid-base disorders (hyponatremia, hypokalemia, hypophosphatemia, hypomagnesemia and metabolic acidosis).

Chemotherapeutic agents (such as cisplatin, and ifosfamide) may induce serum potassium derangements mainly by changing renal tubular transport. Platinum-derived agents can also induce hypokalemia due to renal potassium wasting secondary to hypomagnesemia. In this case, potassium supplementation may fail until hypomagnesemia has been corrected. The incidence of cisplatin-related hypokalemia is around 27%. The treatment for hypokalemia often prevents the continuation of anticancer therapy with cisplatin, ifosfamide or/and cyclophosphamide.

Calcium and phosphate disturbances

The most common and relevant mineral disturbances in malignancies include hypercalcemia and hyperphosphatemia in the tumour lysis syndrome, and calcium and phosphate disturbances associated with the use of anticancer drugs and tumor-induced osteomalacia.

The tumour lysis syndrome is a consequence of the massive and acute lysis of the cancer cells caused either by chemotherapy or, rarely, due to their spontaneous rupture (Belay *et al*., 2017). The lysis of the cancer cells leads to the release of large amounts of ions, including potassium and phosphate, that rapidly proliferating neoplastic cells are rich in. Tumour lysis syndrome is mainly diagnosed in hematologic malignancies and is uncommon in solid tumours. The release of phosphate leads to secondary hypocalcemia that may cause muscle cramps and seizures. The most important measures in managing patients with a high risk of tumour lysis syndrome include intensive hydration and monitoring of the serum levels of phosphate and calcium. Only the patients with the highest risk are administered allopurinol for prophylaxis and recombinant enzyme rasburicase for the treatment (Belay *et al*., 2017).

Many drugs used for chemotherapy may cause mineral disturbances. The pathomechanism of these disturbances may vary from the tumour cell lysis, acute tubular necrosis with a secondary tubulopathy resulting in an impaired urine electrolyte excretion, a direct interference of the drug with the tubular transport of water and electrolytes, to thrombotic microangiopathy and thrombosis (Verzicco *et al*., 2020).

The drugs that frequently cause mineral disturbances include cisplatin and carboplatin (hypocalcemia, hypophosphatemia and hypomagnesemia), ifosfamide and bendamustine (hypophosphatemia), sorafenib, nilotinib and erlotinib (hypocalcemia), cetuximab, panitumumab and 5-fluorouracil (hypocalcemia), and anthracyclines (hypophosphatemia) (Verzicco *et al*., 2020).

The new promising class of antineoplastic drugs includes blockers of the fibroblast growth factor-23 receptor (FGFR). These drugs directly interfere with the mechanism of renal phosphate disposal and therefore hyperphosphatemia has been a major concern in clinical trials (Mahipal *et al*., 2020).

Tumour-induced osteomalacia is a rare paraneoplastic syndrome caused by increased production of the fibroblast growth factor-23 by tumour cells (Florenzano *et al*., 2021). It is mainly caused by slow-growing benign mesenchymal tumours and may manifest with muscle weakness, bone pain and bone fractures. The treatment of the condition includes the surgical removal of the tumour, phosphate and vitamin D supplementation.

Other consequences of oncological therapy

Hypertension

Several classes of antineoplastic drugs have hypertensinogenic properties (angiogenesis inhibitors, 17α-hydroxylase CYP17 inhibitor - abiraterone, aromatase inhibitors – anastrozole and letrozole and cisplatin derivatives) (Essa *et al*., 2020). New onset hypertension or aggravation of pre-existing hypertension is predominantly found in patients treated with angiogenesis inhibitors like vascular endothelial growth factor (VEGF) inhibitors and tyrosine kinase inhibitors (Katsi *et al*., 2019). Angiogenesis inhibitors exert their effect through inhibition of the VEGF signalling pathway. Inhibition of this pathway suppresses nitric oxide synthesis, leading to endothelial dysfunction and capillary rarefaction. VEGF signalling inhibitor-induced blood pressure increase appears to be mechanism-dependent on-target toxicity and has been suggested to be a positive biomarker of the clinical efficacy of these drugs. Results of several retrospective studies demonstrated that hypertension caused by angiogenesis inhibitors was associated with improved results of antineoplastic therapy (Liu *et al*., 2019).

In the absence of controlled trials, hypertension in oncology patients should be managed by utilising the same treatment guidelines as for the general population (Tini *et al*., 2019). The only specific recommendation is that

non-dihydropyridine calcium channel blockers, such as verapamil and diltiazem, should be avoided by patients treated with angiogenesis inhibitors. These antihypertensive drugs inhibit cytochrome P450 3A4, leading to the potentially high, toxic plasma concentration of angiogenesis inhibitors (Rizzoni *et al.*, 2017). It should be stressed that, in clinical practice, new onset hypertension or aggravation of pre-existing hypertension due to antineoplastic therapy, should be treated preferably by initiation or intensification of antihypertensive therapy, but not by reduction of dose or by ceasing therapy with antineoplastic agents.

Urinary tract infections

Urinary tract infections (UTIs) represent a severe complication in immunocompromised-neoplastic patients. Predisposing factors include urinary tract obstruction, catheterisation (i.e. with Foley catheter most often), percutaneous nephrostomy (PCN), hemorrhagic cystitis (after chemo- or radiotherapy), neutropenia, bone marrow transplantation, neoplasms (especially of the urinary tract) after transplantation, history of recurrent UTIs and/or kidney stones with prolonged antibiotics treatment, and autosomal dominant polycystic kidney disease (ADPKD). Enterococcus species are the leading cause of UTIs, especially in hospitalized patients, regardless of a cancer diagnosis. Despite the fact that their clinical manifestation is often mild, they can cause serious complications such as bacteraemia or endocarditis. Limited therapeutic options for UTIs due to the emergence of multidrug-resistant enterococci, particularly vancomycin-resistant *E. faecium* and *E. faecalis*, have become a global crisis over the last few years. It became a cause of higher patient mortality as well as increased worldwide healthcare costs (Giannakopoulos *et al.*, 2019). Currently, there is an overall lack of consensus about the optimal approach to catheter-associated urinary tract infections (CAUTIs). One of the strategies is an evidence-based, nurse-driven protocol for discontinuing indwelling urinary catheters (McCoy *et al.*, 2017). To reduce the high rate of recurrent infections and the potential delay of further chemotherapy, when the result of the antimicrobial susceptibility test is available and the patient is under compatible antimicrobial therapy, clinicians should proceed with an immediate Foley catheter or PCN replacement (PCN ideally within the first 4 days of the infection) (Szvalb *et al.*, 2019).

On the other hand, the link between recurrent UTIs and cancer development has been studied for many years, but the results are inconclusive so far. Several of them reported an association between chronic UTIs and prostate or bladder cancer (Giannakopoulos *et al.*; Anderson-Otunu & Akhtar, 2016). There are some prerogatives that ADPKD, besides ascending UTIs, cyst infections and haemorrhage, predispose to renal cell carcinoma, mainly in chronic dialysis patients.

Chronic kidney disease

According to registries and population studies, as many as 16–25% of cancer patients present with eGFR<60 ml/min (de Francisco *et al.*, 2019). Considering that every fifth cancer patient developed CKD, the mutual relationship between malignancy and CKD seems obvious. It was demonstrated that in the Chinese population 32.4% of patients with newly diagnosed cancer exhibited CKD. In addition, renal function was inversely related to all-cause mortality. Moreover, eGFR below 60 mL/min/1.73m^2 was an independent predictor of mortality relative to eGFR ≥60 mL/min/1.73 m^2, and it was dependent upon the cancer site (Yang *et al.*, 2016)

On the one hand, CKD progression and accumulation of uremic toxins cause multiple quantitative and functional changes in the immune system, resulting in reduced malignancy surveillance and aberrant responses to cancer (Corredor *et al.*, 2020). On the other hand, cancer may induce CKD in numerous, largely unknown mechanisms. Circulating factors produced by the tumour cells may be suspected. For example, IL6 and TNF concentrations were reported to be significantly higher in cervical cancer patients than in the controls (Vitkauskaite *et al.*, 2020). Also, other tumours including lung cancer and renal cell carcinoma were found to produce excess amounts of IL6. Another factor derived from the tumour mass, and able to stimulate autoimmune reactions, is circulating free DNA (cfDNA). After release from cancer cells, the cfDNA circulates and can be detected in serum. Several types of cancer are currently diagnosed using specific cfDNA analysis. The potential of cfDNA to stimulate dendritic cells via toll-like receptor 9 could explain glomerular immune activation, inflammation and damage. Increased incidences of CKD, particularly, in the elderly, are of clinical importance and relevance. Many cancer drugs are cleared primarily by the kidneys as unchanged drugs or active metabolites. Therefore, any impairment in kidney function can potentially lead to alterations in pharmacokinetics, elevated blood levels of the drugs, and the increased toxicity discussed in the first parts of the paper (Janus *et al.*, 2010)

THE MOST OFTEN CANCERS IN SOLID ORGAN TRANSPLANT RECIPIENTS

Skin cancers

Skin cancers are the most common tumours in SOTRs. The most often are squamous cell carcinoma (SCC), basal cell carcinoma (BCC), malignant melanoma (MM) and Merkel cell carcinoma (MCC) (Euvrard *et al.*, 2003; Mittal & Colegio, 2017) Common risk factors include: chronic exposure to ultraviolet (UV) radiation, HPV infection, pretransplant skin cancer, older age at transplantation, white race, male sex and immunosuppression (being those with a higher risk azathioprine and cyclosporine) (Al-Adra *et al.*, 2022). The mean interval between transplantation and skin tumour diagnosis is 3 to 5 years (Euvrard *et al.*, 2003). Skin tumours in SOTRs are also more likely to be multiple and more aggressive with a higher risk of relapse, metastasis and death due to tumour progression.

The risk of developing BCC in patients after solid organ transplantation (SOT) is about 10 times higher than in the general population (GP). BCC is the most common skin cancer in the GP, while in SOTRs the SCC/BCC ratio changes in favour of SCC. BCC may develop at the site of precancerous conditions or previously unchanged skin. BCC occurs in younger patients than in the GP and grows more often multifocally and more extensively. The prognosis for early diagnosis and appropriate treatment of BCC is good, and the risk of recurrence is 5–10% (Euvrard *et al.*, 2003).

Squamous-cell carcinoma is the most common skin cancer in SOTRs, occurring 65 to 250 times as frequently as in the GP (Euvrard *et al.*, 2003; Mittal & Colegio, 2017). The majority of cancers arise from precancerous lesions including actinic keratosis, Bowen's disease, and Queyrat erythroplasia. Patients who develop their first

focus SCC have an over 60% risk of developing more SCC in the next 5 years. According to Lindelöf *et al*., 25% of patients with a first SCC will have a second lesion within 13 months, and 50% will have a second lesion within 3.5 years (Lindelöf *et al*., 2000). SCC develops in younger patients and has a rapid growth rate. In 50% of cases it develops multifocally, more often presents deep tissue invasion and metastasizes (8–12%) (Liddington *et al*., 1989; Berg *et al*., 2002). As in the GP, recipients with a fair skin phototype and high cumulative dose of UV radiation are associated with a higher risk of SCC. The main location of the SCC is the face, backs of the hands, forearms and mucous membranes, mainly the lower lip. Tumours appearing on the skin usually are asymptomatic, but 1/3 of patients experience tenderness, pain or itching. These symptoms constitute an unfavourable prognostic factor that may indicate a perineural invasion. The risk of metastases in the course of SCC in GP is 3.6% within 3 years, whereas for immunocompromised such as SOTRs the risk reaches 7%–12%. In SOTRs SCC may cause distant metastases. Patients who suffer from metastatic SCC have a bad prognosis (3-year survival is 56%, and 5-year survival is 34%) (Haug *et al*., 2020; Imko-Walczuk *et al*., 2015). SOTRs have a 2 to 8-fold increased risk of developing MM in the posttransplant period (Mittal & Colegio, 2017). Melanoma in SOTRs can arise in three principal scenarios; an existing MM prior to transplantation, an MM arising *de novo* after transplantation and MM derived from an organ donor (Imko-Walczuk *et al*., 2009; Matin *et al*., 2008). Melanoma results from the malignant transformation of melanocytes, representing the skin tumour with the highest mortality rate. This tumour has high immunogenicity and changes its behaviour in the field of immunosuppression. The incidence of MM in SOTRs is increased to a smaller degree as compared to SCC and BCC, although its potential morbidity and mortality have to be considered in post-transplant care. In candidates for SOT with MM in medical history, such factors as: tumour stage, disease control, and the period from diagnosis to transplantation are the most relevant factors to consider. In a study conducted by Penn and others the risk of MM recurrence in SOTRs was 19% which was similar to the GP subjects, whereas mortality was 30% (50% higher than in the GP) (Penn, 1996). Waiting time for transplantation depends on the MM stage and is as follows: MM in situ has 100% survival therefore no waiting time is required (Imko-Walczuk *et al*., 2015); MM of <1 mm depth and without surface ulceration (stage I) have a good prognosis (85% 5-year survival), however, due to a risk of metastasis, the waiting time should be two years; MM with a 4-mm-depth, has a high potential of metastasis, and bad prognosis (5-year survival is 45–67%), it is, therefore, necessary to postpone SOT for 5 to 10 years (Penn, 1996; Imko-Walczuk *et al*., 2015).

The risk of MM transmission from the donor through circulating cells localized in the graft is very high. To prevent this transmission, the donor's medical history and physical examination are essential, and the history of MM in a donor candidate is an absolute exclusion criterion for donating organs (Penn, 1996). Initial treatment of melanoma appearing in the posttransplant period does not differ from the standard approach in the GP. In addition to that, reduction or change of immunosuppression is suggested to be a reasonable and effective adjuvant strategy. A balance must be struck between a strength of immunosuppression that does not favour tumour spread and that, at the same time, avoids rejection of the transplanted organ. Therapeutic management is particularly challenging in advanced MM stages as the use of immune checkpoint inhibitors confers a high risk of organ rejection.

Merkel cell carcinoma (MCC) is a rare neuroendocrine neoplasm that typically appears in the elderly in sun-exposed areas. SOTRs have a 24-fold higher risk of MCC. This tumour presents at a younger age than in immunocompetent individuals (the mean age at diagnosis is 50 years) (Goedert, 2009). Most cases result from malignant transformation secondary to the Merkel cell polyomavirus infection, which may be relevant in SOTRs. It was confirmed that immunosuppression is an established risk factor for MCC (Hernandez *et al*., 2022; Penn & First, 1999). Just as with other skin cancer, the highest incidence of MCC was observed in patients receiving a combined regimen of azathioprine and cyclosporine (Hernandez *et al*., 2022). The key role of immunosuppressants on MCC development is also confirmed by the fact of temporary regression of the tumour upon reduction or withdrawal of the immunosuppressive treatment. MCC typically presents as a painless, rapidly expanding cutaneous nodule or plaque. Lesions are often erythematous or violaceous with a smooth and shiny appearance and generally arise on sun-exposed areas, notably the head and neck, and limbs (Euvrard *et al*., 2003; Kanitakis Jean, 2009). SOTRs with MCC should be treated with similar modalities as patients without immunosuppression i.e. wide local excision, radical node dissection, radiation therapy, and chemotherapy. The prognosis is serious because 31% of patients develop tumour recurrence with a mean interval of 58 months after excision of the primary foci. Two-thirds of SOTRs MCC develop rapid lymphatic metastases to the regional lymph nodes and systemic metastases to the liver, bones, and lung with a high 1-, 3-, and 5-year mortality rate (20%, 51%, and 54%, respectively) (Greenberg & Zwald, 2011; Goedert, 2009; Lewis *et al*., 2020).

In summary, it should be underlined that the risk of all skin cancers in SOTRs is much higher than in the GP. They appear at a younger age, the clinical course is much more serious, and they are more likely to relapse, metastasize and appear de novo in another location. Survival of patients is worse than in the GP.

Urinary tract cancers

The second most common cancers in SOTRs particularly in kidney transplant recipients are urinary tract cancers (Bellini *et al*., 2022). They are common, and as these neoplasms occur more often in older age, their detection is growing with time, with the number of recipients followed-up (Karami *et al*., 2016).

Renal cell carcinoma

The most frequent urological neoplasm encountered after kidney transplantation is renal cell carcinoma (RCC). It may appear in the native kidneys or the transplanted ones. It may arise de novo or be transmitted with the kidney graft and also recur after treatment of the recipient in the past (Porta *et al*., 2020; Serkies *et al*., 2022). The literature shows that the risk of RCC in the native kidneys of dialyzed patients due to end-stage kidney disease (ESKD) is increased by 10–15 times. The incidence grows with the dialysis time along with the development of acquired cystic kidney disease (ACKD). Some authors claim that transplantation, by improving kidney function may reduce ACKD and its oncological potential, but this effect is probably decreased by immunosuppression (Yanik *et al*., 2016). Interestingly, the

longer the dialysis lasts the percentage of a less aggressive papillary RCC in relation to clear cell RCC grows. Nowadays, diseased kidneys are most often left in place after their failure, so the risk of RCC in them has to be addressed and they should be observed by at least an annual ultrasound (Dahle *et al.*, 2022). Nevertheless, the risk of cancer and mortality rate in patients with functioning kidneys or already on dialysis are similar. They are also better compared to the general population as RCC in ESKD tends to present lower malignant potential. It has been generally accepted that in the case of RCC in the native diseased kidneys total nephrectomy is the most appropriate strategy (Yanik *et al.*, 2016).

Noteworthy, nowadays according to Kidney Disease Improving Global Outcomes (KDIGO) in 2020, after radical removal of small <3 cm low-grade T1NOMO RCC the patient can be qualified for the KTx with no waiting period (Karami *et al.*, 2016).

Another issue is de novo cancers in the transplanted kidney. Overall, the risk of it stays within 0.2–0.7% with the observation of 5 years (Hevia *et al.*, 2019). It may be caused by a tumour transmission with unintentional kidney transplantation with an undetected small or even microscopic RCC or by the origination of the tumour in the kidney afterwards (Boissier *et al.*, 2018). It is difficult to distinguish these two scenarios with the time between KTx and diagnosis being the most logical parameter. Its incidence is lower with living donors, who are generally healthy, their kidneys are better examined, and the history of the donor and his family may be well-known, especially as we now are aware of a possible inherited RCC in 5–8%. The transmission may be higher if the donors are older than 50, which is currently accepted more freely because the RCC develop more frequently in older age (Boissier *et al.*, 2018). As far as the treatment of RCC in the graft is concerned, the European Urological Association recommends its surgical removal with the increasing role of the nephron-sparing approach as an alternative to graftectomy, which was the gold standard in the past. Tumours are usually discovered in the early stage without symptoms. The disease staging may be tricky due to the changed tissue layers after implantation (Rodríguez Faba *et al.*, 2018; Tillou *et al.*, 2012).

Nowadays, data shows that total nephrectomy should be restricted to high-grade, high-stage tumours or tumours in the irreversible dysfunctional kidney. It is also known that these high-risk RCCs have a poor prognosis, so many authors recommend biopsy before treatment method selection. Nephron-sparing procedures should be preferred if possible because they give a chance of up to 95% of 5 years survival time in $T_1N_0M_0$. On the other hand, graftectomy with a return to dialysis results in only 34% of 5-year survival, although the patient groups studied usually are different (Boissier *et al.*, 2018).

The nephron-sparing surgery which is limited to the tumour less than 4 cm may be challenging with more complications in about 20% of cases. The open approach is usually used, but recently robot-assisted laparoscopy has also been reported. In some series, a minimally invasive approach using Radio Frequency Ablation or Cryoablation is also described as promising in very small exophytic tumors (Dhakal *et al.*, 2017). The surgery should be used together with a modification of the immunosuppression regimen. In this case, the use of mammalian target of rapamycin (mTOR) inhibitors seems to be the most interesting drug, because of their anti- neoplastic properties(Boissier *et al.*, 2018).

There are interesting considerations about the origin of cancer occurring in the allograft kidney. We used to assume that it arises from the donor cell. Still, some reports suggest that a significant percentage (up to 40 %) may be of recipient origin proved by DNA analysis, with some having mixed DNA being a form of chimerism. Whether it has any clinical importance for example on the choice of immunosuppression, is not known yet (Dhakal *et al.*, 2017).

Having in mind that there is a global lack of kidney donors, there has appeared to be a little controversial concept of using kidneys removed for small, low-risk RCC as a possible so-called "restored" donor of kidneys. The tumour is biopsied and removed outside the body, then prepared and implanted. The published result shows more than 90% of 5-years graft survival and a low cancer recurrence rate of about 2% (Xiao *et al.*, 2013)

Prostate cancer

Generally, the significance of prostate cancer (PC) has been growing as the population of kidney recipients gets more extensive and older. The data about the increased incidence of PC after KTx are unclear, though recent studies suggest that it is higher. However, one has also to remember that any data about this group of patients must consider the estimated life expectancy independent of malignant disease before making any therapeutic decision (Sherer *et al.*, 2017).

Especially interesting is an issue of low-risk PC, which occurs very often and often is managed by active surveillance meaning repeated exams (DRE, PSA, MRI) and biopsies and postponing of the intervention until the proven progression. In the GP it leads to sparing of the treatment in a significant part of patients. Recent studies have shown that active surveillance can be possible also in KTx candidates, where we must assume that undetected small focuses of PC already exist. The same strategy is acceptable in patients on dialysis. The survival in both groups should not differ from the GP (Stöckle *et al.*, 2018).

The situation changes if a medium-risk or a high-risk PC is diagnosed. Then active treatment ought to be implemented with radical prostatectomy being the most popular solution, as it leads to the elimination of the cancer cells, with PSA becoming a perfect cancer marker to follow-up. In KTx candidates, the 2-year waiting time after renal surgery is recommended (Bratt *et al.*, 2020a; Bratt *et al.*, 2020b).

A urologist must regard anatomical relations between the graft and the prostate when the clinically significant PC is discovered after KT. The diagnosis usually is early because the patients are closely controlled. The staging is similar to that of the GP. Surgery can be challenging and this side's lymphadenectomy has very often been skipped. Nonetheless, the results are promising with a 14-years survival time reaching 65% (Carvalho *et al.*, 2017). Modern series recommend using the robot-assisted technique for this situation with a result similar to GP.

Radiation therapy is also a feasible option with some limitations in planning to avoid ureteral stricture or post-radiation nephritis. However, there are a few papers recommending brachytherapy as the better solution (Bratt *et al.*, 2020a).

Bladder cancer

The incidence of bladder cancer (BC) in KTx is reported to be 2–4 times higher than in the GP with the age of presentation being lower and the malignant po-

tential much higher. The non-urothelial histology is also found more often. The upper urinary tract of native kidneys is also involved more frequently. Some authors suggest the BK or HPV viral infection is responsible (Leon *et al.*, 2020). The diagnosis is usually made after hematuria. The medium time after KT is 4 to 5 years. The more aggressive course of the disease caused the waiting time for kidney candidates to be usually preserved with the only exception of very low-risk superficial tumours (Chadban *et al.*, 2020). The staging is based on imaging and transurethral resection with microscopic invasion analysis. The role of surgery is crucial. Superficial tumours in the bladder should be endoscopically resected with adjuvant intravesical chemotherapy. The BCG installation is viewed to be possible, but some authors underline a risk that immunosuppression can provoke Mycobacterium sepsis. In the case of upper tract involvement radical nephroureterectomy is recommended. When there is a high-risk bladder tumour most authors favour early cystectomy with some form of urinary diversion. It can be bowel neobladder of uretero-ileocutaneostomy according to Bricker. During surgery, the lymphadenectomy can be difficult as well as anastomosing of the short transplanted ureter to the bowel without kinking. The same problem exists when a kidney is transplanted into the patient with urinary diversion due to a previous cystectomy due to bladder cancer. Then, it can be solved by implanting the kidney upside down. The treatment results of superficial bladder tumours are similar between kidney recipients and the GP with more local recurrences in the former group.

Urothelial cancer in the native kidney upper tract has a worse prognosis than matched ESKD patients, underlining the role of immunosuppression (Chadban *et al.*, 2020). Data about the results of invasive bladder cancer treatment after KTx are limited, but generally high-risk urothelial cancers have a poor prognosis even with an aggressive protocol including early cystectomy and chemotherapy.

Penile Cancer and Testicular Neoplasm

These urological malignancies are so rare that there is no robust data about their association with KTx. Penile cancer occurs in 10 per 1 million a year and testicular neoplasms in 50 per 1mln per year. Both treatments after KTx should not differ from the GP, with the need to modify immunosuppression in more advanced cases. In both, chemotherapy plays an essential role, so the renal function is important. Results of both depend strongly also on lymphadenectomy so it is vital that surgically there may be some difficulties when dealing with the patient after KTx (Besarani & Cranston, 2007).

KIDNEY IN BONE MARROW TRANSPLANTATION

Bone marrow transplantation is a common name for hematopoietic cell transplantation (HCT) in which the most important for hematopoietic system recovery are stem cells present among the CD34+ cell population. The stem cell source might be autologous or allogeneic determining the type of HCT (autologous or allogeneic; auto-HCT, allo-HCT). These two types of transplantation have different spectra of complications. In fact, the synonym of auto-HCT is high-dose chemotherapy with the support of the hematopoietic cells; therefore, the complications including those related to kidneys are limited to high-dose chemo/radiotherapy administered as a conditioning regimen before cell infusion. In allo-HCT, in addition to the conditioning regimen that might be myeloablative, reduced, or even non-myeloablative, two other important factors contribute to kidney injury: post-transplant immunosuppression and immune-related complications such as graft versus host disease (GvHD) or transplant-associated thrombotic microangiopathy (TA-TMA). Hence, the greatest risk of acute kidney injury (AKI) carries myeloablative allo-HCT (21–73%), followed by nonmyeloablative allo-HCT (29–56%), and then autologous HCT (10.4–19%) (Miyata *et al.*, 2022).

Chronic kidney disease is a risk factor for transplant-related complications. In the HCT-specific comorbidity index (HCT-CI) the presence either of serum creatinine concentration above 2 mg/dL (177 umol/L), being on dialysis or prior renal transplant increases 1-year non-relapse mortality (NRM) to 21% in allo-HCT and 3% in auto-HCT recipients, respectively. Chronic kidney disease present after HCT also indicates poor survival both after auto-HCT and allo-HCT. A recently published study on a large cohort of allo-HCT recipients showed the impact of different degrees of renal dysfunction on HCT outcomes using growing grades of renal dysfunction based on estimated glomerular filtration rate (eGFR) (<45; 45-59; 60–90; and >90 mL/min); Increased risk for NRM and the requirement for dialysis post-HCT were associated with an eGFR <60 mL/min (Gutiérrez-García *et al.*, 2020; Farhadfar *et al.*, 2021).

Kidney injury related to high-dose chemotherapy

Kidney injury after high-dose chemotherapy might be due to the direct effect of cytotoxic agents or indirect complications caused by cytotoxic agents such as mucositis and diarrhoea, infections or veno-occlusive disease. The most common cytotoxic agents used as a part of the conditioning regimen before auto- and allo-HCT are alkylating agents such as melphalan, cyclophosphamide, busulfan, carmustine, bendamustine; antimetabolites: fludarabine, and much less common cladribine and clofarabine and most recently bcl-2 inhibitors such as venetoclax. Most of the aforementioned agents do not induce nephrotoxicity directly despite some of them (e.g. busulfan, cyclophosphamide) being used in much higher doses compared to standard chemotherapy regimens. A few exceptions include bendamustine (used in the BeEAM protocol: bendamustine, etoposide, cytarabine, melphalan) that have been reported in three cases to induce nephrogenic diabetes insipidus (Desjardins *et al.*, 2022).

High-dose chemotherapy adjustment in patients with chronic kidney disease

HCT recipients suffering from CKD have a substantial risk of unintended overdosing or underdosing due to variable pharmacokinetics in this patient population. Overdosing may lead to multiorgan toxicity and/or graft failure whereas underdosing may result in graft rejection or inadequate disease control (Bodge *et al.*, 2014). Therefore, the dose adjustment of some agents used in the conditioning regimens in patients with CKD is recommended to avoid excessive toxicity, particularly to hematopoietic cells usually infused 24 hours after the end of the conditioning regimen.

The best example is melphalan commonly used as a single agent dosed on body surface area (BSA) at day-1 (200 mg/m^2) of the conditioning regimen before auto-HCT for patients with multiple myeloma (MM). Patients with CKD and eGFR <50 ml/min/1.73 m^2 or older than 70 years with additional co-morbidities or frailty

Table 2. The different auto-HCT protocols applied in patients with: a) normal renal function, b) impaired renal function and c) patients on haemodialysis.

Autologous High-Dose Melphalan (HDM) transplant protocol			
Day	Normal Renal Function	Impaired Renal Function	Haemodialysis
-5			Admission
-4			Dialysis
-3		Admission	Melphalan 140 or 100 mg/m^2 [a]
-2	Admission	*Melphalan 140 or 100 mg/m^2	Rest day: dialysis
-1	Melphalan 200 mg/m^2	Rest day	Rest day
0 [b]	Cell return 24 hrs after Melphalan infusion	Cell return 48 hrs after Melphalan infusion	Cell return 72 hrs after Melphalan infusion
			Return units and dialysis Ensure 2 hrs gap if dialysis post-re-infusion[c]
+5	GCSF	GCSF	GCSF

Abbreviations: GCSF granulocyte colony-stimulating factor. [a]Patients on dialysis require a 72-hour (hr) gap after the Melphalan infusion and prior to stem cell infusion, whereas patients with renal impairment require a 48 hr gap. [b]The Melphalan dose can be further reduced to 100 mg/m^2, depending on the presence of co-existent comorbidities. [c] For patients on hemodialysis, a repeat dialysis session is scheduled after the return of the fourth stem cell unit, with a 2hr gap between the stem cell infusion and the dialysis.

usually receive a lower dose of melphalan of 100 or 140 mg/m^2. Recently, CKD was reported as an independent risk factor for AKI after HCT for MM, with a significantly higher mortality rate in this subgroup of patients (Andronesi *et al.*, 2019). Surprisingly some centers do not reduce melphalan dose in patients with moderate CKD since despite higher toxicity improved outcomes were reported in patients with moderate CKD receiving melphalan at a high dose of 200 mg/m^2 (Sweiss *et al.*, 2016). Of note, melphalan is not removed by dialysis (Bodge *et al.*, 2014).

However, recently published data on 370 MM patients who underwent the first auto-HCT without CKD or with mild, moderate, and severe CKD showed no significant difference in NRM, progression-free (PFS), or overall survival (OS) regardless of renal function. The results of this study indicate that auto-HCT is an effective and rather safe option for MM patients with CKD, including those on dialysis, allowing some of them to permanently discontinue dialysis. Specific protocols applied in this population are presented in Table 2.

The second most common agent used agent for HCT and the most common for allo-HCT is fludarabine (Flu). The dose of Flu is calculated using BSA. The drug is administered IV as a monophosphate prodrug (F-ara-AMP) that is converted to the circulating metabolite F-ara-A, which is mainly excreted by the kidney. Recently published data indicated a substantial variability (more than sixfold) in F-ara-A plasma exposure using standard BSA-based dosing. Extended but still retrospective analysis in 192 allo-HCT recipients showed that Flu exposure is a strong predictor of event-free survival (EFS) (events: relapse, NRM, and graft failure) with two-fold higher HR for EFS in overexposed patients. This translates to the lowest overall mortality in the optimally exposed group (31%), compared to the under- (43%) and overexposed groups (64%). This increase in overall mortality was mainly caused by infections (over- and underexposure), multiorgan failure (overexposure), and GVHD (overexposure). Of note, overall GVHD (grade 2–4 or 3–4) incidence was similar among groups with different exposures (Langenhorst *et al.*, 2019). The data presented above suggest that the current dosing method based on BSA is not optimal and should include not only weight but also kidney function based on eGFR using the Cockcroft–Gault equation. Flu is adequately removed during dialysis, therefore, the dose should be adjusted after dialysis (van Besien *et al.*, 2012; Shadman *et al.*, 2017). Cyclophosphamide may increase myocardial toxicity in CKD patients. Pharmacokinetic studies have demonstrated decreased clearance with renal insufficiency, therefore dosage reduction in the setting of moderate to severe renal impairment should be considered. Cyclophosphamide is moderately dialyzable (20–50%); for dialysis-dependent patients, cyclophosphamide should be administered after hemodialysis (Bodge *et al.*, 2014). The cyclophosphamide doses should be reduced by 25–50% in patients with severe renal impairment (GFR <10 mL/min) and a supplemental dose after dialysis should be considered (Shadman *et al.*, 2017). Clofarabine should be avoided in adults >60 years with creatinine clearance <60 mL/min (NCCN AML guidelines), and a 50% dosage adjustment should be made for patients with eGFR 30 to 60 mL/min. Busulfan and thiotepa dosing does not require modification in patients with CKD (Bodge *et al.*, 2014).

Kidney injury in recipients of allogeneic HCT

Acute kidney injury is a common and important complication after allo-HCT since it increases the risk of both early and late NRM (Malyszko *et al.*, 2020a). The recently published meta-analysis based on reports from 1995–2019 indicates AKI occurrence in about half (55.1%) of allo-HCT recipients, with the most severe form (stage 3) in 8.3% of patients (Kanduri *et al.*, 2020). AKI leading to CKD increases mortality about three times at 1-year post-allo-HCT (HR: 3.54; $p<0.001$). In most allo-HCT recipients the development of AKI is multifactorial. Conditioning with total body irradiation (TBI) and using calcineurin inhibitors for GVHD prevention contribute to the risk of AKI development with a little lower likelihood of AKI induced by tacrolimus relative to cyclosporine (Malyszko *et al.*, 2020b). Other patient-related factors contributing to the risk of AKI after HCT include female sex, older age (>55 years), and comorbidities such as diabetes, hypertension, and pretransplant CKD that are also associated with early mortality (Miyata *et al.*, 2022; Gutiérrez-García *et al.*, 2020). Additionally, other transplant-related complications such as veno-occlusive disease, also known as sinusoidal ob-

struction syndrome, cytomegalovirus reactivation, and bacterial infections (sepsis) increase the risk of AKI (Gutiérrez-García *et al.*, 2020). Finally, in allo-HCT recipients, acute GvHD and TA-TMA often induced by calcineurin inhibitors, especially tacrolimus, make the aetiology of AKI multifactorial and sometimes difficult to determine the leading cause. All attempts should be therefore made to decrease the risk of AKI development including a proper choice of conditioning regimen (myeloablative *versus* reduced intensity or non-myeloablative) regular blood levels measurement of calcineurin inhibitors and other nephrotoxic agents (such as vancomycin, and amikacin), proper hydration, careful dose adjustment for drug interactions – for example, reduction of 90% dose of calcineurin inhibitors in the case of concomitant anti-fungal treatment with voriconazole. Cases with hypertension, refractoriness to platelet transfusions, and increased lactate dehydrogenase activity should prompt suspicion of TA-TMA and a fast decision regarding the continuation of calcineurin inhibitors.

Hemodialyzed patient as a bone marrow transplant recipient

Almost all patients on dialysis are referred for HCT because of MM. Indeed, dialysis-dependent patients with MM should not be excluded from high-dose melphalan and auto-HCT since some of them may even recover renal function on top of other benefits related to auto-HCT. The shorter the hemodialysis period prior to transplantation, the higher the probability of renal function recovery in patients with MM. Improvement of kidney function following auto-HCT can also be observed later after transplants in patients with severe kidney failure. However, only a few cases have been reported so far who became dialysis-independent after a high-dose melphalan autograft (Waszczuk-Gajda *et al.*, 2018). Recent data suggest that auto-HCT can be performed safely in MM patients on dialysis using a specific adjustment to the routine protocol (Table 2). Prior experience including the experience of the Polish centers (24 cases) indicates higher toxicity in hemodialyzed patients compared to non-dialysis matched cases in the following endpoints: mucositis (88% *vs* 55%), infection (79% *vs* 51%), parenteral nutrition (50% *vs* 24%), diarrhea (71% *vs* 38%), prolonged duration of hospitalization (medians: 30 *vs* 21 days), the requirement for red blood cell transfusion (83% *vs* 36%) while no significant differences were found in post-transplant response (ORR; 75% *vs* 87%), 5-year PFS (36% *vs* 20%) and OS (39% *vs* 50%) (Waszczuk-Gajda *et al.*, 2018).

Research conducted by Chapchap and others indicates that HD was associated with decreased survival in allo-HSCT (Chapchap *et al.*, 2022) The HD group (34 HD cases versus 151 controls) had a higher mortality rate (HR:6.68; 95% CI: 4.1–10.9; $p<0.001$). At the Fred Hutchinson Cancer Research Center between 1997 and 2014, only six patients on hemodialysis received allo-HCT. Recently reported the largest group of patients on dialysis at the time of alloHCT (46 patients) had a 1-year probability of OS of 20%, and NRM of 67% (Farhadfar *et al.*, 2021).

The data on patients after kidney transplantation is very limited, and in most institutions, these patients are not referred for allogeneic HCT. Even in very big transplant centres, these patients are exceptional.

CKD in patients after HCT

In most auto-HCT recipients CKD after HCT results from precedent CKD before transplant. A minority experience *de novo* CKD related to sepsis or drug toxicity. The need for hemodialysis after HCT increases late NRM. In allo-HCT recipients, renal dysfunction is a common complication. The cumulative incidence of CKD after allo-HCT varies from 13~60% in adult studies to as high as 62% in children (Chen *et al.*). Causes of CKD are multifactorial and usually overlapping. The result of an interesting paper in which 24 allo-HCT recipients underwent kidney biopsy for either proteinuria or deterioration of kidney function confirms the great diversity of putative causes of kidney damage. The most common pathological findings were GVHD (n=8), membranous nephropathy (MN, n=5), TA-TMA, (n=4), BK virus nephropathy (n=2), and single cases with ischemic nephropathy, chronic interstitial nephritis, minimal change disease (MCD), GVHD with TMA, MN with focal segmental glomerular sclerosis (FSGS), MCD with acute tubular injury, BK virus nephropathy combined with calcineurin inhibitor nephrotoxicity (Chen *et al.*, 2019). Clearly, a kidney biopsy with an expert histopathology examination might be necessary to establish the proper cause of kidney injury after all-HCT.

NOVEL CANCER THERAPY

The use of cancer immunotherapy and proton therapy in transplant recipients (IK)

The standard of care in different cancers includes surgery, chemo- and radiotherapy. In recent years, novel therapy, including immunotherapy with immune checkpoint inhibitors (ICIs) and proton therapy, has revolutionized cancer treatment and is becoming a new standard of care for many tumour types.

ICIs in transplant patients

Mechanism of ICIs action

Cancers can weaken the immune system, and the host's immune system does not destroy cancer cells. The so-called negative regulatory components participate in this phenomenon (Szychowska, 2021). ICIs are monoclonal antibodies capable of blocking negative signals for T-cell activation or T-cell effector activity and represent an essential therapeutic option in the case of many tumours, including melanoma, non-small cell lung cancer, kidney cancer, urothelial cells cancer, Hodgkin's lymphoma, oral, throat or larynx squamous cell carcinoma etc. It seems that about 44% of newly diagnosed cancer can be qualified for ICIs (Haslam & Prasad, 2019).

The anti-CTLA4 (cytotoxic T-lymphocyte-associated protein 4) monoclonal antibody (e.g., ipilimumab or tremelimumab) binds to the CTLA4 receptor and activates a T cell (Perazella & Shirali, 2020). AntiPD-1 (nivolumab, pembrolizumab, cemiplimab) and antiPD-L1 (atezolizumab, avelumab, durvalumab) antibodies act through the activation of programmed cell death-1 (PD-1) receptors on the T cell with its ligand PD-L1 or PD-L2 (Perazella & Shirali, 2018; Perazella & Shirali, 2020).

Considering the mechanism of action of ICIs which is based on the stimulation of the immune system, their use in transplant patients may raise doubts. These drugs have the effect opposite to what is anticipated in the organs of recipients as they stimulate the immune system and, therefore, may facilitate the occurrence of acute or chronic rejection. In the group of 119 KTx recipients to whom ICIs were administered due to other tu-

mours: cutaneous melanoma, hepatocellular carcinoma and cutaneous squamous cell carcinoma, 41.2% patients experienced acute rejection, 23.5% graft failure and immune-related adverse events (irAEs) developed in 18.5%. The overall objective response rate was 34.5%, with a median duration of response of 8.0 months (Portuguese *et al*., 2022). The symptoms of acute rejection, which is the most frequent cellular rejection, were observed on average around three weeks after ICIs administration (Portuguese *et al*., 2022; Manohar *et al*., 2020). Moreover, the activation of T-lymphocytes may cause adverse effects resulting from excessive immune system stimulation (immune-related adverse events, irAEs). They may affect different organs and tissues: skin, lungs, heart, digestive system, liver, endocrine glands, central and peripheral nervous system and also the kidney (Perazella & Shirali, 2020). The kidney-related adverse effect that occurs most often, is deterioration of kidney function, and another one is proteinuria, usually non-nephrotic. Pyuria and haematuria are also quite frequent (Szychowska, 2021). The distinction between irAEs and rejection may be difficult in kidney recipients due to the fact that the symptoms may be similar. The treatment of irAEs depends on symptom severity and includes drug discontinuation and steroid administration (Sise *et al*., 2019; Brahmer *et al*., 2018).

One problem is the implementation of treatment with ICIs to the SOTRs with tumours, but another is the lack of recommendations for immunosuppression management. There are challenges concerning the continuation of immunosuppressive treatment or its minimization. The most frequently described alteration to the immunosuppression plan is the discontinuation of calcineurin inhibitors (CNI) or conversion to mTOR inhibitors (everolimus, sirolimus), the suspension of mycophenolate mofetil/sodium as well as the use of steroids in monotherapy. The minimization of immunosuppression which is frequently recommended in SOTRs with a cancer diagnosis may be one of the causes of such a frequent rejection noted in patients treated with ICIs. As the recent analysis showed, the maintenance of treatment with tacrolimus was associated with a reduction in post-ICI rejection without compromising the effectiveness of cancer response (Portuguese *et al*., 2022). In another study, in the group of patients who were treated with the continuous dose of <10 mg/d of prednisone, there was a higher percentage of acute rejection of the kidney graft, but anticancer effectiveness was better: in 63% of patients' disease remission or stabilization were observed. In patients who continued CNI, acute graft rejection occurred less often, but the anti-cancer therapy was also less effective (Manohar *et al*., 2020). In the Australian, phase 1 study, 17 kidney transplant recipients with low or intermediate immunological risk with various solid tumours were treated with nivolumab and baseline immunosuppression was left unchanged. Complete responses were observed in four of 17 patients, including one patient with microsatellite instability-high colorectal cancer, and three with squamous cell carcinoma of the head and neck. Partial responses were observed in five patients (with squamous cell carcinoma of the head and neck), one with bladder cancer, and one with hepatocellular carcinoma. Only two patients developed acute rejection (T-cell mediated) with a good response to antithymocyte globulin and plasmapheresis in one case, the other patient commenced hemodialysis. There were no treatment-related deaths or treatment-related serious adverse events. The most common adverse events were decreased lymphocyte count, fever or infection, decreased haemoglobin, and increased creatinine in three patients. Based on their observations, the authors concluded that maintaining baseline immunosuppression before treatment with ICIs in kidney transplant recipients might not affect expected efficacy and might reduce the risk of allograft rejection mediated by immune checkpoint inhibitors (Carroll *et al*., 2022). In the management of acute graft rejection during oncologic ICIs therapy, it is considered reasonable to discontinue ICIs and use steroid pulse therapy (Venkatachalam *et al*., 2020; Perazella & Shirali, 2020). As shown in Carroll RP *et al* study the antithymocyte globulin and plasmapheresis may also be a treatment option (Carroll *et al*., 2022).

Some observations indicated that complications occur more often in patients treated with the anti-PD-1 group. The PD-1/PD-L1 pathway plays a significant role in the preservation of immunotolerance. PD-L1 present in the epithelium of renal tubules represses cytokines' production by T-lymphocytes, regulating T-lymphocytes' activation and anergy, and providing the immune balance. In view of the foregoing, blocking the PD-1: PD-L1 pathway may increase the risk of transplant rejection (Perazella & Shirali, 2020; Perazella & Shirali, 2018; Kumar *et al*., 2020).

In conclusion, ICIs are a feasible option for transplant recipients with advanced malignancies but doctors and patients should be aware of the increased risk of acute rejection. Close monitoring and tailoring of immunosuppression are critical. Maintaining an appropriate balance between immunosuppressive treatment, the preservation of the graft function and anti-cancer management requires collaboration between oncologists and transplant physicians as well as the patients and their families.

Radiotherapy and proton therapy in transplant recipients

The kidneys are the dose-limiting organs for radiotherapy (RT) in case of gastrointestinal and gynecologic cancers, lymphomas and sarcomas of the upper abdomen as well as during total body irradiation (TBI). The cause of RT-induced kidney injury is poorly understood but the incidence of this complication largely depends on the use of whole-volume or partial-volume RT to one or both kidneys (Dawson *et al*., 2010).

Even if short-term kidney function is preserved, radiation-induced kidney injury is subclinical and frequently presents during the subacute (3–18 months) and chronic (>18 months) periods and may have a negative consequence on patients' health in the future (Dawson *et al*., 2010).

The KTx patients requiring RT treatment find themselves in a special situation: they have one kidney often with initial kidney impairment; moreover, the presence of a transplanted kidney in the pelvis can be a therapeutic challenge in patients who require pelvis radiation as management. The inferior border of KTx located at the iliac fossa usually lies at the bottom of S2 or S3. Therefore, radiotherapy that includes pelvic lymph nodes will need further evaluation to determine the benefits and the risks. Treatment of pelvic tumours with definitive or neoadjuvant radiotherapy usually includes iliac lymph nodes in the nodal target volume. This nodal target is also included in some cases of adjuvant radiotherapy. The location of the graft in relation to radiation therapy fields increases the risk of damage to the transplanted organ. In the presence of a transplanted kidney, the dose required for the region at risk must be balanced against the potential risk of graft injury (Detti *et al*., 2011). Furthermore, during RT, the increased risk of urethral/ureteral stricture KTx dysfunction should be taken into consideration.

In proton therapy (PT) due to a phenomenon known as the Bragg peak, protons deposit their maximum energy at a specific depth with no exit. This allows for the delivery of a high therapeutic dose of radiation to tumours in challenging anatomic locations, close to critical organs and within damaged organs with a reduced risk of late toxicities in the surrounding tissues and a lower incidence of secondary malignancies (LaRiviere *et al.*, 2019). PT is being investigated as an alternative to intensity-modulated radiation therapy because of its potential to minimize radiation exposure to the transplanted kidney and other organs at risk. Dosimetric studies have demonstrated that PT improves organ-at-risk sparing compared with intensity-modulated radiation therapy, and it does not sacrifice the coverage of the target. There are only some papers based on clinical cases describing the utility of PT in KTx recipients, mainly as a treatment in the case of pelvic tumours (Buchberger *et al.*, 2019; Ileana *et al.*, 2020). Given the relative radiosensitivity of native kidneys, the tissue-sparing effects of proton therapy are of utmost importance in the treatment of patients with pelvic kidneys and pelvic malignancies.

SUMMARY

To identify key management issues in nephrology relevant to patients with malignancy, the panel of multidisciplinary specialists organized the conference on Nephro-oncology in Gdańsk (October 2020). The conference participants emphasized the importance of collaboration among nephrology, haematology/oncology, dermatology, urology and transplant specialists to improve medical care for cancer and kidney disease patients. The four main parts of the paper present the most current diagnostic and therapeutic approaches to cancer and kidney disease patients. This study is based on the authors' expertise and the most recently published relevant literature with their participation.

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