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VIA MEDICA

Nephrotoxicity of immune checkpoint inhibitors in immunotherapy of oncologic patients

Abstract

Immune checkpoint inhibitors (ICIs) are monoclonal antibodies directed at negative regulatory components on T cells, such as cytotoxic T lymphocyte-associated antigen 4, programmed cell death-1 (PD-1), and its ligand, programmed cell death ligand-1 (PD-L1). They stimulate the immune system to destroy the cancer cells, however, may lead to immune-related adverse events (irAEs) that affect a variety of organs including the kidney. Kidney damage is characterized most by acute kidney injury (AKI) as well as a subnephrotic syndrome, pyuria or haematuria mainly due to acute tubulointerstitial nephritis. Depending on the symptom severity, after exclusion of other causes of AKI such as infection, dehydration, kidney obstruction, nephrotoxicity related to other nephrotoxic drugs, the management includes ICIs discontinuation and treatment with or without systemic steroids for longer than 4–6 weeks. Kidney biopsy should be considered to rule out other rare kidney complications such as minimal change disease, immune complex glomerulonephritis or thrombotic microangiopathy. In patients with good response and renal symptoms withdrawal, the immunotherapy can be restarted. There are no studies on the use of these drugs in dialysis and transplant patients, only case reports are available, but it seems that the impaired kidney function should not be a contraindication to use ICIs.

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In cancer treatment, an increase in the frequency of the use of immunotherapy, besides chemo- and radiotherapy is observed. Medication used in this type of therapy belongs to the group of immune checkpoint inhibitors (ICIs). In clinical practice, ICIs are used in melanoma therapy, non-small cell lung cancer, kidney cancer and urothelial cells cancer, etc

INTRODUCTION

In cancer treatment an increased use of immunotherapy, alongside chemo- and radiotherapy is observed. Medication used in immunotherapy belongs to the group of immune checkpoint inhibitors (ICIs). In clinical practice, ICIs are used in melanoma therapy, non-small cell lung cancer, urothelial carcinoma etc. This list is being updated with new cancers, the treatment of which is being still studied, and immunotherapy has shown to be effective. Within the Polish National Health Fund's drug programs, ICIs may be used to treat patients with melanoma, lung carcinoma, kidney cancer, Hodgkin's lymphoma, oral, pharyngial or laryngial (data from 2nd November 2020).

MECHANISM OF ACTION OF ICIS

Neoplasms can weaken the immune system. Cancer cells are not destroyed by the host's immune system. The so-called negative regulatory components participate in this phenomenon. They bind to the appropriate ligand in the cancer cell, which results in constituting a pathway inhibiting the anti-cancer immune response [1]. ICIs inhibit activation of negative regulatory components and so activate the anti-cancer function of the immune system [1].

There are two main pathways that ICIs activate. In the 1st stage, a T-lymphocyte which is latent — in the state of anergy, may be stimulated by the binding of ligand CD80/CD86 on the antigen-presenting cell with CD28 receptors on this lymphocyte. The interaction be-

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The most common symptoms of ICI nephrotoxicity are: subclinical deterioration of kidney function, subnephrotic proteinuria, leukocyturia and microscopic hematuria

tween the CD80/CD86 ligand on a cancerous antigen-presenting cell and CTLA4 (cytotoxic T-lymphocyte-associated protein 4) receptor on T-lymphocytes causes inhibition of the cytotoxic activity of this lymphocyte [1, 2]. The anti-CTLA4 monoclonal antibody (e.g., ipilimumab or tremelimumab) binds to CTLA4 receptor and activated a T cell [1].

The other route takes place on a tissue level in the cancer environment. Active T cells become latent through the activation of programmed cell death-1 (PD-1) receptors on the T cell with its ligand PD-L1 or PD-L2, which occur in cancer cells. T cell enters the state of anergy, so it does not demonstrate cytotoxicity. AntiPD-1 (nivolumab, pembrolizumab, cemiplimab) and antiPD-L1 (atezolizumab, avelumab, durvalumab) antibodies inhibit binding and, by implication, activation of T-lymphocytes which destroy cancer cells [1, 2].

ADVERSE EFFECTS OF ICI TREATMENT

The anti-cancer effect associated with activation of T-lymphocytes may cause adverse effects resulting from excessive stimulation of the immune system (immune-related adverse events, irAEs) — these adverse effects include nephrotoxicity

An imbalance of stimulating and inhibiting immune factors occurs during the use of ICIs. The anti-cancer effect associated with the activation of T-lymphocytes may be the cause of adverse effects resulting from excessive stimulation of the immune system (*immune-related adverse events*, irAEs). They may affect all organs and tissues, skin, central and peripheral nervous system, lungs, heart, digestive system, liver, endocrine glands, and kidneys. It is estimated that irAEs occur in 15% to 90% of patients treated with ICIs [1]. Nephrotoxicity symptoms are reported in around 2% of patients receiving monotherapy and up to 5% of patients receiving combination therapy of antiCTLA4 and antiPD-1/PD-L1. However, with wider use of ICIs, kidney-related complications seem to occur more frequently, even up to 30% of patients treated with this group of drugs [3].

MECHANISMS OF NEPHROTOXICITY ASSOCIATED WITH ICIS

Several hypotheses explain the mechanisms of nephrotoxicity caused by ICIs. The use of ICIs may foster the occurrence of anti-kidney tissue antibodies. It is suspected that some cells have checkpoint receptors on their surfaces which cause an immune reaction directed at these structures by combining anti-CTLA4 and antiPD-1/PD-L1 antibodies. Moreover, new or reactivated T-lymphocytes directed at cancer antigen may cross-react with kidney cells. Therefore, the stimulation of cytokines and chemokines may cause inflammation in the kidneys. It is also possible that ICIs reactivate the latent T-lymphocytes (drug-specific T-lymphocyte), causing the loss of tolerance to the used drugs, such as proton pump inhibitors (PPI) which may cause acute interstitial nephritis (AIN) [2].

SYMPTOMS OF ICI-RELATED NEPHROTOXICITY

The kidney-related adverse effect that occurs most often is silent, clinical deterioration of kidney function, expressed by the increase in the creatinine concentration, which often fulfils the criteria of acute kidney injury (AKI, AKI qualification criteria KDIGO [4]). Second most frequent symptom of kidney damage during ICI treatment is proteinuria, usually subnephrotic [5]. Pyuria and haematuria are also quite frequent [2, 6]. The presence of eosinophilia in urine is not considered a helpful factor due to a large percentage of false-positive and false-negative results. Eosinophilia of peripheral blood occurs in about 10% of patients. Based on serum creatinine and/or the severity of proteinuria, the degree of kidney damage severity is evaluated. The grades are following: 1–2 determined as mild, while 3–4 as severe (Tab. 1) [6].

Risk factors associated with ICI-related acute kidney injury are: initially compromised renal function (eGFR < 30 mL/min/1.73 m^2), simultaneous use of PPI, and the use of combined therapy antiCTLA4 and antiPD-1/anti-PD-L1. There is no evidence that age, sex, or history of autoimmune diseases increase the possibility of renal irEAs [5].

Around 70% of patients with AKI in the course ICI treatment took medication could cause of acute tubulointerstitial nephritis, e.g., non-steroidal anti-inflammatory drugs or PPI (it was taken by over 50% of patients) [5]. Renal irAEs may occur after one dose of medication from around 3 weeks since starting the cancer treatment until even several months after it has been finished. The median time of symptom onset is 3 months following therapy initiation [6]. Therefore, close monitoring of renal parameters before administering the first and next doses of the medication is significant. IrAEs associated with taking antiCTLA4 occur earlier (6–12 weeks since the administering) in comparison to antiPD-1 (3–6 months) [4].

In 43% of cases, non-renal adverse effects preceded the onset of kidney damage symptoms

Table 1. Classification of renal immune adverse events and management depending on their intensity [6, 12], modified by the authors of the paper

Grade	1	2	3	4
Creatinine concentration	Increase > 0.3mg/dL or 1.5–1.9 × the initial value	2.0–3.0 × the initial value	> 3 × the initial value or > 3–6 × upper limit of the norm	> 6 × upper limit of the norm or RRT
Proteinuria	1+, DPL < 1 g	2+, 3+, DPL 1.0–3.5 g	4+, DPL < 3.5 g	
Management	• Monitoring of sCr and increase of proteinuria • The consideration of temporary ICIs suspension • Providing sufficient hydration • Discontinuation of other nephrotoxic medication • Exclusion of causes of AKI which are not related to the immune system	• Consideration of hospitalization and starting IV fluids • Temporary discontinuation of ICIs • Consultation with a nephrologist • Exclusion of causes of AKI other than irAEs, marking of antibodies to exclude autoimmune diseases • Discontinuation of nephrotoxic medication • Consideration of kidney biopsy or empirical administration of steroids: prednisone 1 mg/mg body weight	• Hospitalization and the administration of IV fluid therapy • ICIs discontinuation • Discontinuation of nephrotoxic medication • Marking of antibodies for autoimmune diseases • Considering the performance of kidney biopsy or empirical administration of steroids: prednisone 1g/kg of body weight	• As in grade 3 • Consideration of administration of IV MP for 3 days, then prednisone 1 mg/kg of body weight

AKI — acute kidney injury; DPL — daily protein loss; ICIs — immune checkpoint inhibitor; irAEs — immune-related adverse events; MP — methylprednisolone; RRT — renal replacement therapy; sCr – serum creatinine

or accompanied them [5]. Simultaneous presence on non-renal irAEs worsened the odds concerning the recovery of renal function. This may be the result of excessive immune activity or disorders secondary to other irAEs [5, 8].

The most frequent diagnosis (93% of cases) of kidney biopsy of patients with ICI-related nephrotoxicity was AIN with concurrent lymphocytic infiltration and features of *tubulitis* [5, 9]. In solitary cases, the following were also diagnosed: glomerulonephritis (GN): minimal change disease, membranous nephropathy, as well as focal and segmental glomerulosclerosis, IgA nephropathy, C3 nephropathy, but also thrombotic microangiopathy [1, 5, 8–11]. Some of these pathologies occurred as a single cause for deterioration of kidney function, but there were diagnoses of concurrent AIN and other alterations mentioned above.

Kidney biopsy and histopathologic diagnosis are recommended for investigating kidney damage during ICI treatment [6]. Nevertheless, performing a kidey biopsy is dangerous and impossible in some cases. ICIs are used most often in patients in advanced stages of the neoplastic process, with numerous complications and who take anticoagulative medication. Therefore, treatment often must be administered without the histopathologic diagnosis. It should be underlined that there may be many reasons for deterioration of kidney function in advanced cancer patients, and profound differential diagnosis excluding other causes of AKI should be carried out before the decision about kidney biopsy is made.

MANAGEMENT OF PATIENTS WITH ICI-RELATED NEPHROTOXICITY SYMPTOMS

Firstly, a basic differential diagnosis of AKI should be conducted in patients in which deterioration of kidney function is observed during treatment using ICIs. Taking into consideration that patients usually have advanced neoplastic process, the most common causes of AKI should be excluded [9]. They include dehydration due to lack of sufficient fluid intake, as well as vomiting and diarrhoea, for example, during ICI-related enteritis or excessive use of diuretics. These patients may also experience intensification or onset of cardiac insufficiency. Every infection, including urinary tract infection, pneumonia, septic state, especially with the concurrence of hypotension, may cause AKI. The concurrence of obstructive uropathy caused by tumour pressure and/or enlarged lymph nodes should be excluded, especially the prostate gland. It should be remembered that adding opioids to analgesic therapy may be a cause of sudden prostate enlargement and urinary retention. Metabolic disorders (e.g., tumour lysis syndrome), contrast nephropathy or the use of other nephrotoxic medication (e.g., present

In patients with symptoms of ICI nephrotoxicity performing a kidney biopsy ought to be considered following routine differential diagnosis of AKI; the most common cause of AKI in this population is acute tubulointerstitial nephritis

chemotherapy, NSAID, PPI, antibiotics), especially NSAID used with diuretics and ACE inhibitors/sartans, may be the cause of kidney damage [6, 9, 10]. In 2018, the American Society of Clinical Oncology (ASCO) published guidelines concerning management in case of diagnosis of ICIs-related nephrotoxicity. They included 4 grades of acute kidney damage: grades 1–2 were treated as mild, while 3–4 as serious. The 5th grade is the death of the patient (Tab. 1) [6, 12].

According to these guidelines, if the alterations are not significant (proteinuria < 1.0 g/d, creatinine concentration less than 1.5 of the initial value), after excluding other causes of AKI, a waiting attitude may be assumed. Other nephrotoxic medication, including PPI, may be discontinued (in Polish conditions, famotidine may be used, an exchange of PPI to H2 blockers may be considered), the patient should be sufficiently hydrated, and the kidney function and intensity of proteinuria should be monitored. Whereas in more intensive kidney damage (creatinine concentration > 2 times the initial value, proteinuria > 1 g/d), using ICIs should be stopped, and a nephrological consultation should be conducted. Admitting the patient to a hospital for intravenous fluid administration, excluding secondary causes of AKI, and considering kidney biopsy should be inspected as soon as grade 2 of the damage. These procedures should also be considered in grade 3, in which hospitalization is recommended. The 4 grade of kidney damage is diagnosed when kidney function worsens to the stage in which dialysis is required (or increase of creatinine concentration > 6 times the initial value). Adding steroids in the form of oral prednisone in the dose of 1 mg/kg body weight/day may be considered from grade 2. In more advanced grades, intravenous methylprednisolone in the dose 500 mg for three days with later conversion to oral prednisone should be considered. Treatment should be continued with dose reduction for around 2 months. Detailed recommendations are presented in Table 1 [6, 12].

Control evaluation of renal parameters is recommended twice a week until grade 1 is reached, then once a week during steroids' doses reduction. Adding calcium, vitamin D supplements, gastroprotection (H2-blockers are recommended), and *Pneumocystis jiroveci* prophylaxis (remembering that trimethoprim sulfamethoxazole may also cause AIN and can be exchanged for atovaquone) should be taken into account considering steroid-related adverse effects. Discontinuation of ICI treatment is recommended from grade 2. Discontinuation of ICIs should be recommended cautiously, considering that the medication is used in patients with the advanced neoplastic process and constitutes a chance to inhibit the disease progression. Therefore, there are cases that after the recovery kidney function, ICIs were readministered, and no nephrotoxicity symptoms recurred [5, 10]. Such management may be considered in patients in which kidney damage symptoms withdrawal occurred shortly after the administration of steroids. ICIs should not be readministered if kidney parameters normalized after 30 days from the administration of steroids or worsened kidney function remained despite therapy, also in patients whose initial kidney functions were impaired [6]. There are single cases of effective chronic use of prednisone (around 10 mg/d) with ICIs to enable the use of immunotherapy and prevent kidney damage. Empirical inclusion of steroids in the case of lack of possibility to perform kidney biopsy after performing laboratory diagnosis, e.g., lack of anti-nuclear antibodies, ant-neutrophil cytoplasmic antibodies, anti-phospholipase A2 receptor antibodies seems to be justified. Yet, it should be remembered that steroids may facilitate cancer progression. The concurrence of GN or thrombotic microangiopathy, which needs special treatment, should also be considered. It is recommended to analyse the risks and benefits resulting from their inclusion individually for every case. Above all, a kidney biopsy should be performed if possible. Single cases of the use of immunosuppressants: mycophenolate mofetil, cyclophosphamide, rituximab, or even eculizumab for the treatment of ICI-related renal toxicity symptoms [3, 6].

THE USE OF ICIS IN DIALYSIS PATIENTS

Data concerning the use of ICIs medication in dialysis patients are limited. Even though HD removes the need for adjusting drug doses to eGFR, this group of patients is not included in clinical studies, and the available data are based on experiences with their use in small groups of patients, often based on case studies or series of clinical cases.

Out of 19 patients to whom ICIs was administered, 6 (32%) developed irAEs. Thyroiditis, myocarditis, and pneumonia were the most often diagnosed conditions. 42% of patients from the studied group sur-

vived > 12 months. Three out of four patients were treated for the disseminated neoplastic process during melanoma [13]. Based on the available literature and considering the pharmacokinetic properties, it seems that ICIs, as a new and promising anti-cancer therapy, may also be recommended for dialysis patients. However, further research concerning adverse effects and their appropriate management is crucial.

THE USE OF ICIs IN PATIENTS AFTER KIDNEY TRANSPLANT

Immunosuppressive treatment is pivotal in transplant patients. On the one hand, weakening the immune response prevents the transplanted organ from being rejected, but, on the other hand, facilitates the occurrence of cancer. The risk of developing cancer is higher in transplant patients in comparison to the general population. According to various sources, cancer constitutes the second or third most common reason for death in this population [14, 15]. The use of ICIs is associated with the occurrence of irAEs and, considering the mechanism of action of this group of medication which is based on the stimulation of the immune system, it may raise doubts in transplant patients. These drugs have the opposite effect to what is anticipated in transplant patients as they stimulate the immune system and, therefore, may facilitate the occurrence of acute or intensification of chronic rejection. In the described group of 44 kidney transplant patients to whom ICIs was administered, 41% experienced acute rejection; in 33% of cases, it was cellular rejection. The symptoms were observed on average after around three weeks after the treatment administration [16].

Despite the increasing frequency of the use of immunotherapy in cancer patients, including organ transplant recipients, there is still insufficient data and guidelines concerning the management of this special group of patients. The majority of transplant centres collaborating with oncology centres operate based on their knowledge and experience. Given the lack of recommendations determining the management in the case of cancer diagnosis and introducing ICIs therapy in the treatment, there are challenges concerning the continuation of immunosuppressive treatment or its possible modification. The most frequently described adjustment of the immunosuppression regimen is the discontinuation of calcineurin inhibitors (CNI) or exchange for mTOR inhibitors (everolimus, sirolimus), the suspension of mycophenolate mofetil/sodium as well as the use of steroids in monotherapy. It is observed that in the group of patients who were treated with a continuous dose of < 10 mg/d of prednisone, a larger percentage of acute rejection of the transplanted kidney occurred. Simultaneously, the response to cancer treatment was better: 63% of patients obtained remission or stabilization of the disease. Whereas in patients who continued CNI, the percentage of acute rejection was lower, but the response to anti-cancer treatment was also worse [16].

Data showing that medication from the ICI treatment group is associated with a higher risk of transplant rejection are also limited. Yet, it seems that this complication occurs more often in patients treated with medication from the antiPD-1 group [1, 2, 15], which is possible if the above-mentioned mechanisms describing the preservation of the immune tolerance on tissue level utilizing PD-1 are considered. 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 cytokine production by T-lymphocytes, regulating T-lymphocytes' activation and anergy and providing immune balance. In view of the foregoing, blocking the PD-1: PD-L1 pathway may increase the risk of transplant rejection.

Acute kidney graft rejection during oncologic immunotherapy is also not determined. It is considered reasonable to discontinue ICIs and use steroid pulse therapy, but there is no solid evidence for the effectiveness of this management and preserving the functions of the transplanted organ [1, 17]. Maintaining an appropriate balance between immunosuppressive treatment, maintaining of the functions of the transplanted organ and the anti-cancer management requires collaboration between oncologists and transplantologists as well as the patients and their family. The analysis of the benefits and risks associated with administering the suggested anti-cancer treatment is crucial.

SUMMARY

Immune checkpoint inhibitors constitute a new way of treating cancer, using immune mechanisms. These medications lead to adverse effects depending on the excessive im-

▶▶Considering the mechanism of action and pharmacokinetics of ICIs they appear safe for administration in HD patients◀◀

▶▶Using ICIs in transplant recipients may raise concern as ICIs stimulate the immune system, and thus could potentially cause acute and chronic graft rejection◀◀

▶▶Maintaining the balance between immunosuppression, which preserves graft function, and the anti-cancer treatment requires collaboration from oncologists, transplantologists, the patient and their family ◀◀

mune reaction, which include kidney damage that usually appears as deterioration of kidney function in the course of acute interstitial nephritis. A close collaboration between oncologists and nephrologists is very important in the management, as these drugs often constitute deterioration of kidney function in the course of acute interstitial nephritis for cancer patients, and their discontinuation may cause the deterioration of the course of the underlying disease, similarly to unfounded steroid use. Despite its growing frequency of use in oncology, there is still not enough reports concerning the use of immune checkpoint inhibitors in patients undergoing renal replacement therapy, including kidney transplant recipients.

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