Immune-Related Adverse Events in Metastatic Renal Cell Carcinoma

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Immune checkpoint inhibitors (ICI) are, among other cancers, routinely used for the treatment of advanced or metastatic renal cell carcinoma (mRCC). A profound understanding of immune-related adverse events (irAE) and the differential diagnosis of adverse reactions caused by other therapeutic agents in combination therapies is of paramount importance.

immune-related adverse events | side effects | immune-checkpoint inhibitors | renal cell carcinoma

1. Introduction

Immune checkpoint inhibitors (ICI) have been established as therapies for a growing number of cancer types. These antibodies target programmed cell death protein 1 (PD-1), its ligand (PD-L1), or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) [1]. Originally used as monotherapy, ICI are now frequently combined with tyrosine kinase inhibitors directed against the vascular endothelial growth factor receptor (VEGFR-TKI) or other immunotherapies (dual checkpoint inhibition: anti-PD-(L)1 plus anti-CTLA-4) [2].

ICI are associated with the occurrence of immune-related adverse events (irAE) which markedly differ from adverse reactions caused by VEGFR-TKI regarding the underlying mechanisms [1][3][4], but may cause similar symptoms. Delays in recognition and treatment of irAEs may lead to exacerbation of symptoms and further complications [1].

ICI are used in therapeutic indications often managed by multidisciplinary teams. With regard to genitourinary cancer, ICIs are best established in metastatic renal cell carcinoma (mRCC) and are currently analysed in clinical trials in the (neo-)adjuvant setting [2]. Hence, a thorough understanding of the basics, indications and specific features of ICI is extremely important.

2. Common irAE per Entity

Based on their frequency, adverse reactions (including irAEs and non-irAEs) are classified as "very common / very frequent" (≥10%), "common / frequent" (1-10%), "uncommon / occasional" (0.1-1%), "rare" (0.01-0.1%) and "very rare" (<0.01%). This classification is also used here.

2.1. Skin and Mucosal Toxicity

Pruritus and rash, the clinically most relevant very common dermatological adverse reactions, are reversible and well manageable. VEGFR-TKI-associated palmar–plantar erythrodysesthesia (“hand-foot”) syndrome is also very common in the respective combinations. Prophylactically, skin irritation on hands and feet should be avoided (e.g., by wearing comfortable footwear) and lipophilic urea creams should be applied. The latter may also prevent common erythema, dry skin, urticaria, eczema and dermatitis. Grade 1 immune-related skin reactions are treated with moisturizing creams or lotions, newer generation oral antihistamines, or mild topical corticosteroids; ICI therapy may be continued. However, skin-related events of other aetiologies (e.g., infection, vasculitis, contact dermatitis) should be ruled out by follow-up examinations. For grade 2 irAE, additional moderate to strong topical corticosteroids are indicated whereas, for grade 3, strong topical or systemic corticosteroids (0.5–1 mg/kg) are required. In case of grade 3 and 4 symptoms, therapy should be interrupted and discontinued, respectively. If severe skin reactions occur (Stevens–Johnson syndrome, toxic epidermal necrolysis) 1–2 mg/kg (methyl-) prednisolone i.v. should be applied [5].

2.2. Hepatobiliary Toxicities

Depending on the ICI administered (as monotherapy or combined) elevated laboratory values for transaminases, alkaline phosphatase, gamma-glutamyltransferase and total bilirubin occur frequently to very frequently. All may indicate occasional to frequent hepatitis.

Since immune-related hepatitis usually begins asymptomatically, serum transaminases and bilirubin should be determined before each therapy cycle for early detection. Immune-related hepatitis is primarily associated with increased transaminases as a “transaminitis” while a concomitant increase in bilirubin may indicate another cause. An ultrasound examination of the liver (cholestasis? progression of liver metastases?) and hepatitis serology are recommended for diagnosis by exclusion. In addition, the patient’s medication should be reviewed regarding hepatotoxic drugs. VEGFR-TKI may also cause hepatotoxicity with elevated transaminases which should be taken into account for ICI/VEGFR-TKI combinations. Therefore, the VEGFR-TKI should be primarily discontinued with the laboratory values being closely monitored. The ICI (infusion) therapy may be continued despite the occurrence of grade 1 “transaminitis”, however, this should be weighed thoroughly against a dose delay which may allow for classifying this event as an irAE. In the respective SmPCs, the recommendations for therapy management depend on levels of transaminases and/or bilirubin that may not necessarily correspond to a clear CTCAE grade. In any case, an ICI treatment delay is required for grade 2 laboratory abnormalities [6]; in certain cases also discontinuation may be required. If transaminases and/or bilirubin remain elevated or continue to rise after several days of VEGFR-TKI treatment discontinuation (cabozantinib > 5–7 days, due to the long half-life), treatment with (methyl-)prednisolone should be initiated. For grade 3, interruption or permanent discontinuation may be required, depending on the ICI/VEGFR-TKI combination applied and on the levels of the respective lab values. Grade 4 changes, however, require permanent discontinuation of treatment and initiation of (methyl-) prednisolone therapy.

If an irAE is suspected and blood values do not improve after 2–3 days, additional mycophenolate mofetil treatment (2 × 1000 mg/day) should be considered and a hepatologist should be consulted. As a third-line therapy with, however, very limited data available, anti-thymocyte globulin or tacrolimus may be used. Provided an adequate treatment, hepatitis improves within 4–6 weeks. If this is not the case, the causal relationship or other co-factors must be re-considered [5].

2.3. Gastrointestinal Toxicities

Very common ICI-related gastrointestinal toxicities include diarrhoea, nausea, vomiting, constipation, and abdominal pain, as well as increases in lipase and amylase.

Diarrhoea (all grades) is observed in more than 50% of patients undergoing ICI/VEGFR-TKI combination therapy, most frequently caused by the VEGRF-TKI. In contrast to immune-related diarrhoea or colitis, which are usually characterised by an acute onset of pronounced symptoms, TKI-associated diarrhoea usually has an insidious onset. In addition to prophylactic measures such as the intake of frequent small meals and a bland diet, treatment with antidiarrheal drugs may be necessary and compensation for electrolyte or fluid losses should be considered.

Especially in cases of acute or pronounced diarrhoea and/or abdominal discomfort or pain, irAE should be ruled out or, if in doubt, assumed and treated. Enterocolitis may result in anaemia, elevated C-reactive protein (CRP), and decreased serum albumin [7]. In order to rule out causative infection, a stool culture should be examined for bacterial pathogens and clostridioides difficile toxins. If diarrhoea reaches grades 2–3, therapy should be delayed. In case of recurrent or persistent symptoms of grade 3 and for grade 4 events permanent discontinuation is indicated. For nivolumab+ipilimumab therapy should already be discontinued at grade 3. This is due to the significantly increased incidence of (severe) diarrhoea with anti-CTLA-4 therapy (ipilimumab) as compared with anti-PD-(L)1-ICI, as well as its earlier onset in time [8]. Systemic corticosteroids (1–2 mg/kg/day, i.v.) should be considered from grade 2 onwards depending on the severity of symptoms (diarrhoea, abdominal pain, deterioration of general condition) and if symptoms persist despite treatment delay, at the latest in the case of deterioration to grade 3. If there is no response after 3–5 days, infliximab can be added [5]. Due to the risk of recurrence of immune-related colitis, slow tapering of corticosteroids over 4 weeks starting from improvement to grade 1 is strongly recommended.

An increase in amylase and lipase may indicate immune-related pancreatitis. However, frequently these laboratory changes are not accompanied by clinical symptoms (e.g., abdominal pain, vomiting) and therapy can be continued despite grade 3, or possibly even grade 4, with close monitoring. In case of doubt or if the laboratory values continue to rise, it is recommended to interrupt the therapy and sequentially resume it after improvement. Regardless of this, clear manufacturer recommendations for pancreatitis exist for atezolizumab and avelumab+axitinib: For atezolizumab, therapy interruption is recommended in cases of confirmed grade 2–3 pancreatitis, and therapy discontinuation is recommended in cases of grade 4 or repeated occurrence of grade 2–3. In contrast, for avelumab+axitinib, regardless of CTCAE grade, therapy is interrupted if pancreatitis is suspected and discontinued if the diagnosis is confirmed.

2.4. Endocrinological and Metabolic Toxicity

The onset of immune-related endocrinopathies is slow. Additionally, their resolution can take several weeks and these irAE are—in contrast to most others—frequently not reversible. Appropriate patient education including information on the possible need for long-term hormone replacement therapy is recommended.

Among the “common” to “very common” ICI-related immunoendocrinopathies are diseases of the thyroid gland (hypothyroidism, less frequently hyperthyroidism or thyroiditis). Their high incidence with nonspecific symptoms necessitates close monitoring of TSH (also fT3, and fT4 if TSH is repeatedly elevated or depressed). If hypothyroidism has been diagnosed, thyroid hormone substitution (L-thyroxine, initial dose 50 µg) should be initiated depending on clinical symptoms. Mild and asymptomatic hyperthyroidism may be initially observed and convert to hypothyroidism as it progresses. In symptomatic patients, beta-blockers might be useful and, in case of doubt, thyroid sonography and/or determination of thyroid autoantibodies (MAK, TAK, TRAK) may be useful (differential diagnosis: thyroiditis, Basedow’s disease) [5]. Delay of ICI therapy until improvement of symptoms is recommended in CTCAE grade 3 according to the SmPC. Treatment may frequently be resumed after initiation of a hormone replacement therapy.

Immune-related adrenal insufficiency or hypophysitis occurs occasionally with ICI monotherapy and frequently with combination therapies. Adrenal insufficiency may manifest with various nonspecific symptoms (signs of dehydration, hyperkalemia, hyponatremia, hypotension, dizziness, possibly shock); occasionally, acute adrenal insufficiency may occur [9]. Whether the adrenal insufficiency is secondary to (sometimes partial) pituitary insufficiency, is determined by the constellation of laboratory values (see below).

Immune-related hypophysitis can lead to local swelling and hormonal dysfunction, most commonly presenting as central adrenal insufficiency (see above). Therefore, hypophysitis is diagnosed by the detection of decreased ACTH, LH, FSH, TSH, and prolactin, and corresponding decreased cortisol and estradiol/testosterone. Magnetic resonance imaging (MRI) of the brain may confirm an enlarged pituitary gland. If cortisol is decreased and ACTH is increased, primary adrenal insufficiency is present.

Symptoms of pituitary inflammation are nonspecific and include those of adrenal insufficiency (see above) as well as headache, visual disturbances, and dizziness. In moderate symptoms (grade 2) of adrenal insufficiency or hypophysitis, corticosteroid replacement may be sufficient; in more severe cases (grades 3–4), initial high-dose steroids are required to treat the “-itis” or central symptoms.

Immune-related endocrine adverse reactions are often accompanied by irreversible destruction of the glands, thus leading to insufficiency. Then, a permanent substitution of thyroid hormones or cortisone becomes necessary. For the latter, if tapering of corticosteroids has been attempted without success, the use of hydrocortisone is recommended to avoid the additional use of the mineral corticosteroid substitute fludrocortisone [10][11].

For type I diabetes mellitus as an occasional irAE it is recommended to regularly monitor blood glucose levels, especially in cases of polydipsia or -uria. In severe cases ketoacidosis is possible [12] and should be treated

according to established guidelines. Insulin substitution and treatment delay may be required for severe symptoms (grade 3–4); resumption of therapy is possible in metabolically stable patients.

2.5. Pulmonary Toxicity

Pneumonitis occurs frequently, dyspnoea and cough frequently to very frequently depending on the ICI administered. Among all irAE, pneumonitis shows the highest mortality rate. Therefore, early diagnosis or differential diagnosis from frequent upper respiratory tract infections and pneumonia is important. The “very common” dysphonia is mainly VEGFR-TKI related and relatively less common under cabozantinib.

Pulmonary symptoms are frequently related to pulmonary metastases including disease progression. However, new or changing respiratory symptoms should always be thoroughly evaluated to exclude pulmonary toxicity. Symptomatic patients (e.g., upper respiratory tract infection, cough, shortness of breath, hypoxia) are evaluated by CT; high-resolution CT of the chest is favoured for differential diagnosis between pneumonia and immune-related pneumonitis. If pneumonitis is present, high-dose corticosteroid therapy should be initiated immediately. Pulmonary function and blood gases should be closely monitored. A chest X-ray should be performed at frequent intervals and, if necessary, infection excluded by bronchoscopy. This also allows safer initiation of immunosuppressive therapy, which in turn increases the risk of opportunistic infections [13]. If the differential diagnosis is uncertain, immunosuppressants and antibiotics should be administered simultaneously at an early stage. If pneumonitis is diagnosed as an (asymptomatic) incidental finding from imaging (grade 1), therapy can be continued but close monitoring is required. However, at the latest at grade 2 therapy must be delayed and in the case of recurrence permanently discontinued depending on the antibody or combination administered. The latter also applies to grade ≥ 3 irrespective of the ICI administered.

2.6. Renal Toxicity

Against first assumptions, “true” renal irAE are not common. Nevertheless, renal dysfunction (creatinine↑) has been observed frequently to very frequently with ICI therapy. Especially with combination therapies, also renal failure was frequently described. Occasionally nephritis occurs.

In the case of increased creatinine, other causes of renal insufficiency need to be ruled out (e.g., exsiccosis). For nephritis, proteinuria (urinalysis) may be indicative [14]. In case of doubt, a renal biopsy should be performed, which occasionally yields surprising findings. For grade 2 nephritis, therapy should be interrupted and discontinued for grade 4. For grade 3, the recommended procedure depends on the ICI administered.

2.7. Cardiac Toxicity

Arterial hypertension is a “very common” VEGFR-TKI-associated adverse reaction and occurs in more than 50% of patients using VEGFR-TKI/ICI combinations. Depending on the administered medication, it is of higher grade (grade 3–4) in 12–25%. “Strict” blood pressure adjustment prior to therapy initiation, regular controls and, if necessary, adjustments of the antihypertensive therapy are mandatory (prescribe blood pressure monitor!).

Arrhythmias have been described frequently, especially with pembrolizumab ± axitinib. Nivolumab “occasionally” leads to tachycardia, in combination with ipilimumab frequently. Rarely to occasionally, potentially life-threatening myocarditis has been reported [15].

Cardiotoxicity may occur early after initiation of therapy. It may manifest nonspecifically (fatigue, hypotension) or directly as acute heart failure. Clinical symptoms as well as an increase in creatinine kinase require further evaluation (echocardiography, cardiac MRI, biopsy). Some patients could be successfully treated with high doses of corticosteroids, in other cases the outcome was fatal.

Treatment delay is recommended for grade 2. Treatment discontinuation is recommended for myocarditis ≥grade 3 or, for avelumab+axitinib for ≥grade 1 and confirmed diagnosis.

2.8. Neurological Toxicity

Frequently to very frequently, patients complain of headache, dizziness, peripheral neuropathies, lethargy and taste disturbances during ICI therapy. Differential diagnosis is sometimes difficult. In one patient population, a facial nerve palsy was observed and classification as either irAE or “idiopathic” was hardly possible. Severe neurological toxicities are rare. These include encephalitis, myasthenia gravis and Guillain-Barré syndrome [16].

Brain metastases should be ruled out as the cause of symptoms by MRI and a neurologist should be involved early. Neurological irAE are treated with high-dose corticosteroids (prednisolone 1–2 mg/kg, p.o. or i.v.) and, if necessary, additional immunosuppressive measures. Permanent discontinuation of therapy is recommended from grade 3 at the latest.

3. Summary and Conclusion

Immunotherapy with ICI plays an important role in the treatment of patients with advanced or metastatic RCC. ICI frequently cause irAE which markedly differ from adverse reactions of other cancer drugs including VEGFR-TKIs and chemotherapeutics. Most frequently irAE involve the skin (rash, pruritus), gastrointestinal tract (colitis/diarrhoea), liver (hepatitis), endocrine system (thyroid disease), and lung (pneumonitis). However, any organ system can be affected. With the new VEGFR-TKI/ICI combination therapies in mRCC the adverse reactions of both drugs appear to numerically add up. Common TKI-associated adverse reactions include diarrhea, hypertension, fatigue, hypothyroidism, hand-foot syndrome, and gastrointestinal symptoms. These are managed by dose modification. In contrast irAE lead to treatment delay or discontinuation and administration of corticosteroids or even more potent immunosuppressants. Differential diagnosis between irAE and TKI toxicity is sometimes difficult but crucial. When in doubt TKI should be discontinued and ICI infusion therapy delayed to safely establish a differential diagnosis. If both ICI and VEGFR-TKI have been interrupted, sequential restart is recommended usually with the TKI being resumed first. Close multidisciplinary collaboration is essential for the safe use of ICI and early detection and management of toxicity.

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