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Authors: Joanna Domagała-Kulawik, Przemysław Leszek, Witold Owczarek, Tomasz Rawa, Maria Stelmachowska-Banaś, Piotr Rutkowski

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Immunotherapy of solid tumors: how safely treat the patients

Joanna Domagała-Kulawik
Department of Internal Medicine, Pulmonary Diseases and Allergy Medical University of Warsaw, Poland
Przemysław Leszek.
1/The National Cardinal Stefan Wyszyński Institute of Cardiology, Warsaw, Poland
2/National Research Institute of Oncology, Warsaw, Poland
Witold Owczarek
Department of Dermatology, Military Institute of Medicine, Warsaw, Poland
Tomasz Rawa
1/Department of Gastroenterology, Hepatology and Clinical Oncology, Centre of Postgraduate Medical Education, Warsaw, Poland
2/Department of Gastroenterology, National Research Institute of Oncology, Warsaw, Poland
Maria Stelmachowska-Banaś
Department of Endocrinology, The Centre of Postgraduate Medical Education, Warsaw, Poland
Piotr Rutkowski
Department of Soft Tissue/Bone Sarcoma and Melanoma, National Research Institute of Oncology, Warsaw, Poland
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Corresponding author:
Joanna Domagała- Kulawik
Department of Internal Medicine, Pulmonary Diseases and Allergy Medical University of Warsaw
ul. Banacha 1a
02 097 Warsaw, Poland
Tel +48 22 599 1351 jdomagala@wum.edu.pl
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Abstract

Immunotherapy with immune checkpoint inhibitors (ICIs) was shown to improve survival of patients with solid tumors like: melanoma, renal carcinoma, non-small cell lung cancer, cutaneous carcinomas or head and neck carcinoma. However, a special type of ICIs toxicity is observed, namely non-infectious inflammation of different organs connected with autoimmunity known as immune related adverse events (irAEs). This non-infectious inflammation may affect different organs and systems as endocrine organs, the gastrointestinal tract, heart, skin and the nervous system. The lungs are also often involved and this condition is referred to as checkpoint inhibitor pneumonitis (CIP). ICIs toxicity is graded from 1 to 5 depending on the clinical course, the 5 grade being a fatal complication. Corticosteroids are the treatment of choice, generally with good efficacy. In some difficult cases, escalation of immunosuppression is required. The knowledge on irAEs should be promoted among clinicians of all specialties, nurses, patients and their families. The aim of this review is to present the wide spectrum of irAEs: clinical signs and symptoms, differential diagnosis, diagnostic procedures and treatment. The data are supported by our own clinical observations.

Key words: immunotherapy, immune checkpoint inhibitors, immune related adverse events

Introductions

Increasing successful use of therapies with immune checkpoint inhibitors (ICIs) in oncology may lead to development of immune related adverse events (irAEs) from all types of body organ systems. The frequency of ir AEs is observed in combination therapies, next anti-CTLA-4, anti-PD-1 and anti-PD-L1 inhibitors with some specificity for individual organs [1; 2]. The mechanisms of occurring irAEs are common and related to hyperactivation of
immune system leading to autoimmunological response to body tissues. Some of these irAEs may have delayed onset even after withdrawal administration of ICI. Infusion-related reactions (IRRs) occur in less than 1% of patients treated with ICI, slightly commonly with anti-PD-L1 drugs with striking exception for avelumab where IRRs were noted in approximately one fourth of patients and premedication is used before the first infusion [3]. Only few studies specifically evaluated ICIs in patients excluded or underrepresented in clinical trials which are usually referred as "special populations", as patients with autoimmunological disorders, with immunosupression, carrying major viral infections, and major organ dysfunctions, so uncertainty remain regarding the use of immunotherapy in this setting [4]. It includes elderly population, however new data indicate that ICI therapy is safe and at least as efficient in older population as compared to younger patients [4;5]. Effective management depends of their early diagnosis and introduction of immunomodulatory therapies (usually starting from corticosteroids) in multidisciplinary way according to existing standardized management algorithms as prepared by European Society of Medical Oncology (ESMO)[1], Society for Immunotherapy of Cancer (SITC) [2], American Society of Clinical Oncology (ASCO) [6], National Comprehensive Cancer Network (NCCN) [7] or Polish authors [8].

**Gastroenterological toxicities induced by immunotherapy**

Diarrhea and liver injury are the most frequent and severe of irAEs leading to discontinuation of immunotherapy [9]. Other gastrointestinal toxicities are mouth ulcers, oesophagitis, gastritis, duodenitis, cholangitis and pancreatitis [10]. Severe constipation related to enteric neuropathy induced by immunotherapy has been recently reported in two cases [11;12].
The frequency of diarrhea ranges from 19% to 54% [13]. Diarrhea usually appeared between 5th and 10th week of treatment initiation but it may occur at any time after the first dose of ICI or even after the four months after the end of therapy [1; 14].

The reason of diarrhea associated with immunotherapy is not clear. Diarrhea may be related to fungal, bacterial (Cl. difficile), viral (CMV) or parasitic infection and these reasons should be considered in differential diagnosis. The potential cause is colitis, which may be a life-threatening complication leading to perforation (0.7-1.5%) [9; 15], megacolon toxicum and even death (0.6-1.0%) [10]. The risk of immune-related colitis (irC) is described in 5 to 22% [1; 14] [16]. Recently, important risk factors for the occurrence of irC have been identified: the dose, concomitant intake of non-steroidal anti-inflammatory drugs, coexistence of inflammatory bowel diseases and intestinal microbiota disturbance [10; 17; 18]. IrC seems to be more frequent in patients treated for melanoma in comparison to nonsmall cell lung cancer (NSCLC) or renal cell cancer [19; 20].

The occurrence of diarrhea is an indication for differential diagnosis. It should be carried out as soon as possible because early and correct diagnosis allows for effective treatment [21]. The infectious reasons must be excluded- the stool analyses for enteropathogens and Clostridium difficile toxin should be performed [1; 2; 10].

The immunotherapy as a reason must be taken into account when the infectious causes of diarrhea have been excluded [14]. Coexisting symptoms such mouth ulcers, perianal abnormalities, arthritis, skin lesions, liver damage or endocrinopathy suggest relation of diarrhea with side effect of immunotherapy. Blood tests may reveal anaemia, elevated C-reactive protein, hypoalbuminemia, increase of faecal calprotectin [22].

A definitive diagnosis of irC is based on endoscopic and histopathological evaluation. In the majority of patients the rectum or/and the left colon are involved therefore the flexible sigmoidoscopy is sufficient for diagnosis. However some patients need colonoscopy [22–
The endoscopic lesions include erythema, luminal bleeding, erosions and ulcerations [22–24]. The presence of these changes but also a normal appearance of the mucosa are usually not sufficient. The final diagnosis can be made only after histological (immunohistological) evaluation of the biopsy. This examination allows for definitive exclusion the infectious disease and confirm inflammatory bowel disease (if no macroscopic changes and histopathological features of inflammation a microscopic colitis is diagnosed).

Regardless of the cause and severity of the symptoms, the first therapeutic step should be a diet to slow down intestinal peristalsis and reduce intestinal secretion [1;10]. In mild form of diarrhea (National Common Terminology Criteria for Adverse Events- CTAE grade 1) there is no necessity to discontinue immunotherapy. Constipating drugs such loperamide and atropine sulphate may be used only after the exclusion of infection [1;14].

If the above methods are ineffective and there is an ultimately diagnosis or strong suspicion of inflammatory bowel disease, the immunotherapy must be discontinued and corticosteroids should be introduced (Table 1) [14;25;26]. Corticotherapy is highly effective leading to resolution of symptoms in 87.5% [24]. However, in a small group of patients resistant to steroids infusion of single dose of infliximab (IFX) should be used. Response to a single dose is very good, sometimes the dose is repeated [27;28].

Very rarely a severe damage to the large bowel occurs, a colectomy with ileostomy is indicated [22]. In severe colitis a definitive discontinuation of immunotherapy is recommended. In patients with moderate form of colitis it is debatable but immunotherapy should be discontinued at least temporarily. After resolving, a return to immunotherapy with low dose steroids may be considered, alternatively, if occurred after administration of anti-CTLA-4, this may be converted to anti-PD-1/PD-L1 inhibitors [29].
Immune-related hepatitis (irH) is the second frequent gastroenterological complication of immunotherapy. It usually appears between 6th and 14th weeks of treatment \([9; 14; 29]\) and affects 1 to 17% of patients \([30]\).

The clinical signs of irH appear late and are usually associated with severe liver damage. Therefore, liver function tests have to be intensively monitored to recognize IrH early (activity of aminotransferases (AT), \(\gamma\)-glutamyltranspeptidase and alkaline phosphatase).

The results of laboratory indices of liver damage strongly supports its immunological reason. However, the exclusion of other possible causes of liver injury always applies: progression of the neoplasm or its complications (e.g. thromboembolism), which can be determined by imaging examinations: ultrasonography or computed tomography. It is also necessary to perform serological tests to exclude acute viral infection \([31]\) and to perform an anamnesis to eliminate other possible causes such as alcohol, drugs, herbs. Liver biopsy is not necessary but may be useful individually in rare cases of doubt or fulminant course \([9]\).

The initial finding of liver damage is an indication to repeat laboratory tests at least once a week \([1; 31]\). Mild irH usually disappears after 4-6 weeks of appropriate treatment (table 1) and the return to immunotherapy is accepted \([1]\). It has recently been shown that azathioprine at 1-2 mg/kg dose may be effective in patients who have not completely respond to prednisone or who flare during tapering steroid \([26; 31–33]\). The administration of IFX for irH is contraindicated due to possible immune mediated hepatitis \([31]\).

**Endocrine immune-related adverse events**

ICI-induced immune system activation often leads to the endocrine irAEs. Endocrinopathies are usually mild (grade \(\leq 2\)), whereas severe or life-threatening (grade \(\geq 3\)) are very rare. Endocrinopathies generally do not require permanent discontinuation of ICIs (even in grade
≥3 CTCAE) and rarely require high-dose corticosteroids, although lifelong management may be required when persistent [34–36]. The most frequent endocrinopathies include thyroiditis and hypophysitis and the symptoms are rather non-specific. The centers using immunotherapy should have access to appropriate hormonal diagnostics and cooperate with endocrinologists.

ICI-induced hypophysitis (IH) has been described as the most frequent endocrine irAEs associated with anti-CTLA-4 administration with the incidence up to 17% [1], although in recent meta-analyses it is estimated at 3.2-5.6% [35; 36], the lowest with anti-PD-1 /PD-L1 monotherapy (<1%) [34; 36]. Risk factors for IH include male sex and older age. There are observations indicating longer survival of patients who develop IH [37].

Non-specific symptoms include headache, weakness, nausea, loss of appetite and weight, cold intolerance. In sporadic cases, symptoms of the optic chiasm compression are present. The IH diagnosis is based on clinical picture and the results of hormonal tests showing hypopituitarism. MRI indicates pituitary gland abnormalities with enlargement, stalk thickening, and contrast enhancement. However, a normal image of pituitary MRI does not rule out IH. The majority of patients (80%) have multiple hormone deficiencies, usually affecting ACTH, TSH, and FSH/LH secretion, although isolated anterior pituitary hormone deficiency can be present, while diabetes insipidus is extremely rare [38; 39].

When IH is suspected, the corticotropic axis should be evaluated firstly. Untreated severe adrenal insufficiency (with hypotension, dehydration, hyponatraemia and hyperkalemia) leads to an adrenal crisis which is a life-threatening condition. Diagnosis of secondary adrenal insufficiency is confirmed by low levels of morning cortisol (<5μg / L) with low /normal ACTH levels. In case of IH, it is also advisable to determine other hormones assessing pituitary function (TSH, fT4, FSH, LH, E2/testosterone).
The use of high-doses of corticosteroids is not necessary because it does not reverse hypopituitarism [35]. It is recommended (e.g. prednisone 1 mg / kg/day) when the symptoms of so-called "mass effect" are present, i.e. severe headaches or visual disturbances. In our experience, in adrenal insufficiency the replacement with hydrocortisone (10-30 mg / day p.o.) leads to a rapid clinical improvement. The patient in adrenal crisis requires intravenous administration of high-doses of hydrocortisone, hydration and monitoring. Levothyroxine (LT4) replacement for secondary hypothyroidism should be implemented if fT4 levels are below the normal range. Hydrocortisone replacement is important before starting LT4 to avoid precipitating adrenal crisis. Secondary hypothyroidism may be transient, whereas adrenal insufficiency is permanent requiring lifelong hydrocortisone replacement. Hypogonadism can be corrected if the gonadal axis did not recover after 3 months and no contraindications are present [40].

Thyroid dysfunction is one of the most common organ-specific irAEs. The lower incidence is with anti-CTLA-4 (7%), higher with anti-PD-1 or anti-PD-L1 (19%), and the highest with anti-PD-1/anti-CTLA-4 combination (28-50%) [41; 42]. Thyroid dysfunction is typically abused by a destructive (silent) thyroiditis, which is manifested initially by a transient thyrotoxicosis, appearing in the first weeks after starting immunotherapy [43]. Thyrotoxicosis may be asymptomatic or cause mild symptoms of hyperthyroidism. Extremely rarely, thyroiditis is the cause of life-threatening disorders (0.1%) [38]. The phase of hyperthyroidism resolves spontaneously within 4-6 weeks or in majority (80%) progresses to permanent hypothyroidism. The anti-thyroid antibodies (anti-TPO, anti-Tg) can be detected in some patients. ICI-induced Graves' disease is very rare [38]. The destructive thyroiditis and Graves’ disease may also coexist in some patients.
The acute phase of thyroiditis with asymptomatic and transient thyrotoxicosis does not require treatment, only monitoring of TSH, fT4, fT3 at intervals of 2-3 weeks. In symptomatic patients (with tachycardia) beta-blockers are recommended. In severe hyperthyroidism, corticosteroids should be introduced (e.g., prednisone 1 mg / kg). Antithyroid drugs should be considered in case of Graves’ hyperthyroidism. LT4 replacement for symptomatic hypothyroidism should be started with a dose of 25-50 µg in the morning and adjusted (after 4-6 weeks) to achieve normal TSH level. Immunotherapy may be continued in most cases of thyroid dysfunction. In our opinion TSH level should be also regularly monitored in patients treated for hypothyroidism before using ICIs, as TSH may increase or transient thyrotoxicosis may occur after starting immunotherapy.

**Autoimmune diabetes mellitus (DM)** is a rare complication (<1%) [44] [30]. The time to onset of hyperglycemia varies from the first weeks to 12 months after starting ICIs [45; 46]. A characteristic feature is a very rapid increase in glycemia with complete lack of insulin secretion, confirmed by undetectable C-peptide levels at the time of diagnosis. Patients often present with signs and symptoms of hyperglycemia or ketoacidosis [44]. Glucose levels should be routinely checked during the course of immunotherapy. ICI-induced DM resembles the so-called fulminant DM, a form of type 1 DM first described in Japan [47]. ICI-induced diabetes is a life-threatening condition, patients often require admission to intensive care units. ICI-related DM results in long-term need for insulin; restarting ICIs can be considered when adequate glucose control has been achieved.

**Primary adrenal insufficiency** is a very rare complication of immunotherapy [38; 48] but can lead to life-threatening adrenal crisis. Laboratory tests show hyponatraemia with hyperkalaemia, and may include hypoglycaemia and hypercalcaemia. Elevated ACTH in the presence of low morning cortisol levels indicate primary adrenal insufficiency.
**Skin toxicity**

Skin toxicity is among the most prevalent irAEs reported with ICIs. It occurs in 30–40% of patients receiving PD-1 / PD-L1 inhibitors and in approximately 50% of patients treated with ipilimumab [2]. The mechanism of formation of dermatological irAEs is not fully understood. However, their close association with T-cell activation bound by checkpoint blockers is noteworthy. Dermal toxicity is the first to occur during treatment with ICIs and it appears to be independent of the dose of drug used [49]. In addition, some of the irAEs like maculopapular rash and vitiligo may be correlated with a better therapeutic response [50–52]. The overall incidence of dermatological irAEs is higher with ipilimumab compared to anti-PD-1 or anti-PD-L1 agents and occur more frequently, appear earlier, last longer and are more severe when anti-CTLA-4 and anti-PD-1 antibodies are used in combination [49; 53]. Most of irAEs are mild (grade 1-2) and their nature is very similar. The most common is nonspecific maculopapular rash and pruritus. A pruritic maculopapular rash is the most common irAEs (Fig.1A-C) (with incidence 24.3% for ipilimumab, 16.7% pembrolizumab and 14.3% for nivolumab [49; 54; 55]). Rash occurs mainly on the trunk, less frequently on the upper limbs, next it spreads peripherally to the extremities. Most often it appears after a couple of treatment cycles, and the severity of the changes may increase during subsequent cycles. The average time to onset of maculopapular rash is 3-4 weeks from start of anti-CTLA-4, 5 weeks- anti-PD-1, and 2 weeks - combination of ipilimumab and nivolumab [49]. Changes may also appear many months after the introduce of treatment [53]. In assessing the severity of lesions (CTCAE), the extent of the lesions and the negative impact on health-related quality of life is taking into account. Grade 1 includes lesions occupying less than 10% of the skin's surface, grade 2 - 10-30% and grade 3 more than 30% of the surface. Grade 4/5 is rare. In patients treated for advanced melanoma, changes ≥grade 3 were observed in ≤2% in monotherapy and 3-5% in combination [2; 49]. The rash may also be the first clinical manifestation of a severe cutaneous drug reaction. During ICIs therapies, the occurrence of Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis acute generalized
exanthematous pustulosis or drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported \[49; 56\]. Itching is a common and troublesome symptom. It typically develops concomitantly with maculopapular rash, albeit it can also be associated with a normal-appearing skin. The frequency in patients during treatment for advanced melanoma ranges between 14-47% and is the lowest in the case of anti-PD-1 therapies and the highest in the combination anti-CTLA-4 / anti-PD-1. Pruritus with severity \(\geq\) grade 3 occurred in \(\leq\) 2% of treated patients \[2; 49; 53\]. Vitiligo-induced ICIs occurs during melanoma therapy (7.5-11%) (Fig.1.D). The mechanism of its formation is probably related to a cross-reaction against antigens shared by melanoma cells and normal melanocytes \[49\]. PD-1 / PD-L1 blockers can activate pre-existing immune disorders or/also induce the development of de novo autoimmune skin diseases. The occurrence of bullous pemphigoid (Fig.1.E.F), dermatitis herpetiformis, psoriasis, vasculitis, Sjogren’s syndrome, dermatomyositis have been found. These immune disorders may overlap in some patients. Individual cases of Grover’s disease, sarcoidosis, Sweet’s syndrome, and pyoderma gangrenosum have also been reported. In addition, hair and nail changes were found: most often is alopecia (1-2% of the patients), also changes in the texture of the hair and nail dystrophy with an onychomadesis or a proximal onychoschizia. Diffuse onycholysis and paronychia involving whole finger or toenails can develop. The other are oral symptoms- xerostomy and oral lichenoid reactions \[2; 49\]. Treatment of skin complications of ICIs therapy depends on the severity of the symptoms. It should be remembered that symptoms, which are initially mild might suddenly become much worse and severe. Therefore is very important to diagnose irAEs correctly, define their severity and introduce an appropriate treatment as soon as possible. In the case of mild changes, the procedure includes proper skin care and protection against UV radiation. In more severe changes topical corticosteroids are recommended. If the changes improve, systemic corticosteroids are used. For Grade 4 cutaneous toxicity, immunological therapy should be strongly discontinued \[2; 53\]. Algorithms for the prevention and treatment of skin toxicity are useful in the management. In some cases, dermatological consultation and skin biopsy should be
considered for histopathological and immunopathological evaluation [2;53;57]. If autoimmune skin disorders are found, treatment should be adequate to the diagnosed disease. Thus, early recognition and management of the lesions are critical in controlling their severity.

**Pulmonary toxicity**

Pulmonary complications of immunotherapy belong to the frequently observed IrAEs, but are not restricted to the treatment of lung cancer. IrAEs of the respiratory system are referred to as checkpoint inhibitors pneumonitis (CIP) [58]. The term “pneumonitis” shows the importance of involvement of lung parenchyma rather than of airways. The definition of CIP includes the new respiratory symptoms: dyspnoea, cough, fever, chest pains with desaturation in effort in the presence of new infiltrations visible on chest imaging. The recognition of ICIs pneumonitis needs the confirmation of ICIs use and the exclusion of other complications, especially infections [58;59]. Grading the severity of this complication is similar to other irAEs and depends on the development of respiratory failure (Table 2) [1;2;6].

The incidence of CIP in clinical trials was as follows: 0.5-10% for all grades, 0.5-3% in grades>=3 and was higher when ICIs were combined with chemotherapy up to 6.5% and with anti-CTLA-4 agents - up to 7%. CIP is the leading cause of death by irAEs: 35-42% of all fatal irAEs. The mean time from ICIs introduction to CIP was 7 to 15 weeks. The data of case reports present 3.5-19% of CIP, also the prevalence in NSCLC with the onset shorter in NSCLC than in other malignancies [60;61].

To date there are no defined risk factors for the development of CIP. The influence of smoking is uncertain, histological type of NSCLC, PD-L1 expression does not predict CIP. Also, the pre-existing autoimmune diseases seem not to predict complications [62;63]. The analysis of observations shows that lung fibrosis does not exclude immunotherapy [60] however the course of pulmonary complications may be accomplished by comorbidities.
Many patients suffer from chronic obstructive lung disease (COPD) and interstitial lung diseases. The recognition of CIP is complicated by the similarity of symptoms, on the other hand, the course is unfavourable, especially in the elderly [58-60;64]. Among pulmonary complications, tuberculosis and opportunistic infections need to be considered. Thus, the knowledge of patient’s history is essential for a differential diagnosis. Furthermore, the signs in patient examination are also unspecific and these are mainly crackles in auscultation. The analysis of blood gases and pulmonary function tests with the diffusion capacity is necessary to assess the severity of restriction or hyperinflation as well as gas exchange disturbances.

The key method of CIP recognition is chest imaging with high resolution computed tomography (HRCT) as superior. Different patterns in HRCT could be visible and the most frequent ones are: ground glass opacities, consolidations, reticular opacities and micronodules [60;64]. The overlap of changes is frequently observed [58]. The interstitial inflammation process is dynamic and the HRCT pattern may show more or less active or more or less irreversible (fibrotic) changes. There are some attempts to incorporate the classification of interstitial lung diseases (ILD) to the CIP classification and the nonspecific interstitial pneumonia (NSIP) pattern seems to be leading followed by organising pneumonia (OP) - like a pattern [60;64]. Bilateral distribution and localisation away from lung tumor are often observed [58]. Pleural effusion and mediastinal lymph nodes involvement are rare.

The issue of CIP is non-infectious parenchymal inflammation and the COP, AIP or NSIP pattern was confirmed by histological examination, however the data are scanty [59]. Sarcoid granulomatosis is a special kind of possible toxicity, however rare, it may involve extrapulmonary organs though [60]. The differential diagnosis of new lung infiltrations in ICIs treated patients include tumor progression or pseudoprogression, pneumonia or pneumonitis. Thus, the full microbiological tests and histopathological examination of sputum/material from bronchoscopy is often needed and decisive. The course of CIP is often
rapid and the decision of therapy is urgent, hence the application of bronchoalveolar lavage (BAL) fluid examination might be suggested [60;65] (evidently, acute pneumonitis may be a contraindication to bronchoscopy with BAL). BAL fluid analysis allows the recognition of infection (also opportunistic), the presence of malignant cells and, by total and differential immune cell count, the character of interstitial lung disorder [66]. The predominance of lymphocytes is suggestive for active non-infectious inflammation [65]. According to our experience the considerable BALf evaluation could be ensured by microscopic examination of slides stained with haematological and histological methods, combined with flow cytometry analysis for immune cell subtyping [66;67].

The treatment and management of CIP include the modification of ICIs therapy with or not immunosuppression and depends on the clinical course [68]. The resume of current recommendations is shown in table 2 [1;2;6]. In general, in the stages 1 and 2 improvement is possible. However, a relapse could incidence and if corticosteroids are ineffective, another immunosuppressant is indicated: mycophenolate mofetil, infliximab, cyclophosphamide. The prognosis is worse in patients with symptomatic pneumonitis, coexisting other lung diseases, combined therapies, previous chemo- radiotherapy [69]. Interestingly the better efficacy of ICIs was reported in patients with associated irAEs [70;71].

**Immune checkpoint inhibitors – associated cardiotoxicity.**

In real practice true incidence of ICIs cardiotoxicity is unknown and it seems that the problem is underestimated. This is particularly important as not only the range of ICIs sensitive cancers but also treatment strategies that include ICIs are increasing rapidly. Clinical observations show that immune involvement of the cardiovascular system, particularly of the heart, lead to the highest case fatality rate among the IrAEs [72].
The ICIs block inhibitory molecules expressed on T lymphocytes what cause activation of systemic T-cell response as well as those in the cardiovascular system, especially myocardium. In the experimental autoimmune myocarditis T lymphocytes contribute not only to the induction but also myocardial damage. In experimental studies eg. CTLA-4/PD-1 deficient animals displayed increased inflammation and myocardial damage \[73, 74\]. PD-L1 is also expressed on cardiomyocytes. It is postulated that PD-L1 exerts dual cardio-protective function by transmit direct cardioprotective signaling. This seems particularly important in patients with pre-existing cardiovascular dysfunction as the cardiac stress / ischemia / hypertrophy upregulated PD-L1 expression \[75\]. Thus, in cardiovascular system, ICIs can results not only in autoimmune T-cell related injury, but also PD-L1 inhibition which might accelerate pre-existing heart disease.

The cardiac antigens being tumor related factors stimulate tumor/cardiac T-cell clones and are capable of increase ICIs toxicity. The concurrent ICIs related toxic effects, e.g. myositis is common in patients with myocarditis and may reflect a shared antigen profile between cardiac and skeletal muscle. Pre-existing cardiovascular diseases as well as autoimmune diseases are potential risk factor for irAEs.

The risk factors of cardiotoxicity are not the same among patients and due to diverse presentation the strategy for personalizing surveillance should be incorporated based on initial assessment \[76, 77\].

The incidence of myocarditis is higher during ICIs combination therapy, and usually occurs early after exposure. Of concern, around 50% cases are fatal. Myocarditis may occur with acute manifestation as acute heart failure with cardiogenic shock, multiorgan failure, pulmonary oedema (mimicking pneumonitis), new event of left ventricle impairment, malignant ventricular arrhythmia or advanced conduction disease \[78\]. ICIs associated
cardiotoxic effects can extend beyond myocarditis; however the first approach is to exclude myocarditis; if confirmed it is crucial to urgently follow myocarditis management protocol.

Cardiotoxicity is also manifested as arrhythmias included atrial fibrillation, atrio-ventricular conduction diseases, pericarditis with or without pericardial effusion [76; 79]. Possible complication is myocardial infarction related to coronary vasculitis or vasospasm. Different forms of left ventricular dysfunction without evidence of myocarditis are observed including new episode of ventricular impairment or Takotsubo syndrome.

Diagnostic tests including ECG, Holter ECG, cardiac biomarkers and different cardiac imagining (eg. ECHO, MRI, CT, angiography) are appropriate. Optimal diagnostics tools should be selected depending on the kind of ICI related toxicity and its clinical manifestation [79]. (Figure 2, Table 3).

The first and most urgent step is to consider ICI discontinuation. The final decision should be taken jointly by oncologist and cardio-oncologist. The second approach is the implementation of typical conventional cardiac treatment to alleviate complications. In the most severe cases, intensive monitoring and adequate invasive management is recommended. The third approach is the introduction of immunosuppression. In the most serious events eg. myocarditis, severe heart failure, effusion pericarditis, advanced conduction disturbance, serious arrhythmia with confirmed (or highly probable relationship) ICIs relation, high – intensity immunosuppression followed by oral corticosteroids is recommended.

Finally the restart of ICI after the interruption is very difficult to make. It is crucial to define the clinical certainty that event is ICIs-related cardiac complication. The restart in myocarditis is not recommended because of the potential risk for fatal relapse. In cases of less severe cardiotoxic ICIs related complications (eg. subclinical myocardial dysfunction or pericarditis) it may be possible to restart immunotherapy with close surveillance for
recurrence. The close cooperation between oncologist and cardiologist is crucial for appropriate decision [76–79].

**Other rare immune-related toxicities**

Rheumatologic (musculoskeletal), renal, neurologic, ophthalmologic and hematologic belong to relatively less frequent IrAEs. The most of these irAEs are rather mild in severity, but occasionally may be life-threatening.

*Rheumatological irAEs* occur the most commonly among rare toxicities of ICIs (in 2-15% of all patients on immunotherapy, more frequently anti-PD-1 based). The most challenging is differential diagnosis of myalgia and arthralgia [1; 2; 80]. Generally rheumatic/musculoskeletal adverse events are mild in severity, reversible, varying in the timing of presentation and usually treated with non-steroidal anti-inflammatory drugs (NSAID). Inflammatory oligo or polyarthritis is rarely the sole irAEs with three phenotypes: a) large joint reactive arthritis (the most frequent), sometimes developing in association with uveitis and conjunctivitis; b) polyarthritis similar to rheumatoid-like arthritis, affecting the small joints of the hand, very rarely seropositive, potentially erosive; c) seronegative, oligo and polyarthritis, which typically starts in the medium/large joints and is characterized by synovitis/ involvement of tendons and entheses, with/without joint erosions [2]. When limited joints are affected intraarticular steroids injections may be considered. Management of more severe symptoms (at least grade 2) requires corticosteroids, sometimes in conjunction with immunomodulators and disease-modifying antirheumatic drugs (DMARDs) including anti-tumor necrosis factor (TNF) drugs, methotrexate, sulfasalazine, leflunomide and hydroxychloroquine [2; 81].
The prevalence of other manifestations of rheumatic irAEs like inflammatory myositis, vasculitis, and sicca syndrome (with severe eye and mouth syndrome, parotitis), polymyalgia rheumatica or systemic lupus erythematosus is less clear.

Current CTCAE terms for musculoskeletal symptoms (e.g. arthritis and myositis) are not easily converted to clinically relevant descriptors [1]. All patients with CTCAE grade ≥2 should be referred to rheumatologist, discontinuation of ICIs may be required. Persistence of rheumatic AEs may occur after stopping immunotherapy [1; 6]. ICIs use may induce exacerbation of the disease in those patients which are affected by rheumatological disorders.

Nephrotoxicity is considered as rare adverse event. In large meta-analysis on 3695 patients ICIs-related acute kidney injury was estimated to occur in approximately 2.2% of patients [82], higher in other studies [83] or isolated cases of interstitial nephritis [2], granulomatous nephritis, thrombotic microangiopathy or lupus nephritis [82–84]. Renal involvement is usually asymptomatic. Serum sodium, potassium, creatinine and urea should be measured before every infusion of ICIs. When renal dysfunction is suspected it is necessary initially to stop nephrotoxic drugs, to perform differential diagnostics to rule out other reasons for renal insufficiency. ICIs therapy should be withheld the administration of systemic corticosteroids considered. Close monitoring of serum creatinine should accompany the treatment.

Nephrotoxicity typically resolves, and ICIs treatment can resume if grade 2–3 adverse events resolve promptly, but therapy should be permanently discontinued in case of persistent or recurrent grade 2–3 adverse events or grade 4 toxicity with a help of nephrologist [2].

Incidence of neurotoxicity related to ICI is low but probably underreported, on the other hand its incidence is related to the terminology and reporting common symptoms as headache or dysgeusia [1; 85; 86]. The time for onset of neurologic irAEs is usually early
within first two weeks, nevertheless there were some reports of neuro-related toxic events late after stopping ICIs. The most common are encephalitis and myopathies, however there is a diversity of reported events (Table 4) [87; 88]. Although rare, neurological toxicities may be fatal complication of immunotherapy [89]. It is always very important to rule out the progression of cancer in central nervous system, infection, depression and metabolic/hormonal disturbances [1; 8]. In rare clinical situation neurotoxicity may be related to concomitant use of radiation therapy on central nervous system. According to clinical presentation diagnostic investigations should include imaging of the central nervous system, nerve conduction studies and/or lumbar puncture (characteristic feature is lymphocytic pleiocytosis in cerebrospinal fluid) [90–92]. Early consultation with a neurologist should be considered. For all but mild neurological symptoms (grade 1), ICI therapy should be held until the AE nature is diagnosed. In the case of moderate/severe symptoms i.v. steroids should be immediately administered since neurotoxicities may be life-threatening. Additionally, aggressive approach with plasmapheresis or i.v. immunoglobulins may be required in the treatment of myasthenia, Guillain Barre´ syndrome and Acute/Chronic Demyelinating Polyradiculoneuropathy. Moreover, upfront readiness for intensive care support of ventilator functions should be taken into account [92]. In case of neurotoxicity early detection and multidisciplinary treatment is critical for reducing the risk of morbidity and mortality.

Ocular irAEs are rare, occurring in <1% of patients. These AEs are heterogeneous (Table 4) [1; 2; 8; 91; 93]. Patients treated with ICIs should be warned to inform the clinician about the onset of any eye symptoms. The counseling of patient is basis for early recognition of eye toxicity as uveitis may lead to decrease of clearness of sight and potentially brings about loss of visual function (in this event permanent stop of ICI administration is required). Early referral of patient to ophthalmologist is crucial and treatment of these rare ICIs adverse
events depends on their severity with use of topical corticosteroids in cases of episcleritis and anterior uveitis as well as administration of systemic corticosteroids in the cases of severe ocular and orbital inflammation. Intravitreal anti-vascular endothelial growth factor (VEGF) is usually indicated for choroidal neovascularization [93].

**Hematological irAEs** occur not commonly but they represent a heterogenous group of events as autoimmune hemolytic anemia, red cell aplasia, neutropenia, thrombocytopenia, hemophilia A, myelodysplastic syndrome, lethal aplastic anaemia, immune thrombocytopenic purpura [1; 2; 61; 94; 95]. They should be distinguished from transient changes in laboratory blood tests at the initiation of immunotherapy as well as other etiologies as hemorrhage, cancer progression in blood marrow [8; 96]. When diagnosed high-dose corticosteroids and other immunosuppressive drugs are usually required after consultation with hematologist.
Table 1

The rules of treatment of gastrointestinal adverse events of immunotherapy depending on the severity of symptoms according to National Common Terminology Criteria for Adverse Events (CTAE)

Table 2

Management and treatment of pulmonary adverse events of immunotherapy with check point inhibitors according to severity.

Table 3

Immune checkpoint inhibitors – proposed management of the associated cardiotoxicity (modified and based on [76])

Table 4

The most common symptoms associated with immune related adverse events of rheumatic, kidney, neurologic, eye or hematologic origin / according to [7]

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Table 1

The rules of treatment of gastrointestinal adverse events of immunotherapy depending on the severity of symptoms according to National Common Terminology Criteria for Adverse Events (CTAE)

| Immune related colitis (IrC)                                               |
|---------------------------------------------------------------------------|
| Grade 1 (G1)                                                               |
| Increase of <4 stools per day over baseline - continue treatment - diet, antidiarrheals |
| Grade 2 (G2)                                                               |
| Increase 4-6 stools per day over baseline, abdominal pain, blood in stool, general symptoms – stop immunotherapy – budesonid 9mg/day 8 weeks, if symptoms aggravate – prednisone 0.5-1mg/kg 7 days |
| Grade 3/4 (G3/G4)                                                         |
| Increase of ≥7 stools per day over baseline, severe or persistent abdominal pain, fever, peritoneal signs, blood in stool, deficiencies in blood tests, severe lesions in colon – stop treatment – i.v. methylprednisolone 1-2mg/kg 5 days followed by oral steroids or IFX 5mg/kg one dose |

| Immune related hepatitis (IrH)                                             |
|---------------------------------------------------------------------------|
| Grade 1 (G1)                                                               |
| AT - <3x ULN – continue immunotherapy – diet plus AT observation once a week |
| Grade 2 (G2)                                                               |
| AT - 3-5x ULN – stop immunotherapy – diet plus AT observation twice a week – no improvement – oral prednisone 0.5-2 mg/kg |
| Grade 3 (G3)                                                               |
| AT - 5-20x ULN and/or symptoms of liver failure – discontinuation of immunotherapy – diet plus i.v. methylprednisolone 1-2mg/kg and 1200 acetylocysteine – no improvement - mycophenolate mofetil 500-1000mg or tacrolimus |
| Grade 4 (G4)                                                               |
| AT - > 20x ULN- stop immunotherapy forever – diet plus i.v. steroid – no improvement - mycophenolate mofetil |

AT - aminotransferases

ULN – upper limit of normal

i.v. – intravenous
Table 2
Management and treatment of pulmonary adverse events of immunotherapy with check point inhibitors according to severity.

| Grade | Description                                  | Investigation, monitoring | ICI administration | Treatment |
|-------|---------------------------------------------|---------------------------|---------------------|-----------|
|       |                                             |                           | drug re-challenge   |           |
| G1    | Asymptomatic, Radiological abnormalities    | Monitor clinically        | Hold therapy        | Yes if resolve radiological abnormalities | Nonspecific |
|       |                                             | HRCT                      |                     |           |
|       |                                             | Pulse oximetry            |                     |           |
|       |                                             | Microbial assessment      |                     |           |
|       |                                             | Bronchoscopy & BAL        |                     |           |
|       |                                             | Hospitalization           |                     |           |
| G2    | Mild symptoms, Medical intervention indicated |                           | Hold therapy        | Yes if resolution to G1 | Prednisone 1-2mg/kg |
|       |                                             |                           |                     |           |
|       |                                             |                           |                     | Taper over 4-6 weeks |
| G3    | Severe symptoms interfering with ADL        |                           | Discontinuation     | No        | Empirical antibiotics, prophylactic antimicrobials |
|       | Supplementation of oxygen required          |                           |                     |           |
|       |                                             |                           |                     | Methylprednisolone i.v. 1-2mg/kg |
|       |                                             |                           |                     | Taper corticosteroids 6-8 weeks |
|       |                                             |                           |                     | If no improvement after 48h- infliximab or mycophenolate mofetil |
| G4    | Life-threatening respiratory failure         |                           |                     |           | |
|       | Invasive support required                   |                           |                     |           | |
| G5    | Death                                       |                           |                     |           | |

ADL activities on daily living, BAL- bronchoalveolar lavage, HRCT high resolution computed tomography
## Table 3

Immune checkpoint inhibitors – proposed management of the associated cardiotoxicity (modified and based on A. R. Lyon et. all )

| Event description | Immunosuppression | Cardiac management |
|-------------------|-------------------|--------------------|
| **STOP ICI** | | |
| **Confirmed myocarditis** | First line: iv. Methylprednisolone 500–1000 mg daily until clinically stable, followed by oral prednisolone 1 mg/kg once Second line: mycophenolate mofetil or infliximab Third line: anti-thymocyte globulin or iv immunoglobulin | Follow ESC/PTK guidelines for HF management |
| **New severe conduction disease** | If evidence of myocarditis – iv. intravenous methylprednisolone | Emergency pacing |
| **Ventricular tachycardia / fibrillation** | If myocarditis confirmed: as above | Emergency cardioversion / defibrillation; followed by adequate anti arrhythmic management |
| **Acute myocardial infarction** | If coronary vasculitis on angiography Consider iv. Methylprednisolone Rechallenge only when clinically stable and >30 days post myocardial if on initial angiography no evidence of vasculitis | Follow ESC/PTK guidelines for STEMI / NSTEMI If at coronary angiography atherosclerosis is absent consider vasculitis |
| **Pericarditis with cardiac tamponade** | First line: as above | Urgent pericardiocentesis; followed by colchicine and / or NSAID |
| **Interrupt ICI** | | |
| **New left ventricular systolic dysfunction without inflammation** | Exclude myocarditis Follow myocarditis protocol if myocarditis confirmed Rechallenge only after myocarditis excluded; once left ventricular function stabilized or recovered, with surveillance | Follow ESC/PTK guidelines for HF management |
| **Takotsubo syndrome** | | Follow ESC/PTK guidelines for HF management and avoid QT-prolonging drugs |
| **Frequent ventricular ectopics (>1% of heart beats)** | | adequate anti arrhythmic management |
| **New atrial fibrillation** | | Follow ESC/PTK guidelines for atrial fibrillation; |
| **New asymptomatic increase in cardiac troponin** | | Check baseline (before ICI introduction – if available) and repeat measurements |
| **Acute pericarditis without cardiac tamponade (with /** | Interrupt ICI exclude myocarditis Consider prednisolone 1 mg/kg | Consider oral colchicine and / or NSAID |
| Event Description                          | Action 1                                      | Action 2                                      |
|------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| without effusion)                        | Continue ICI                                  | Assess Holter ECG for advanced conducted disease; if absent, continue ICI increase surveillance with ECG before each cycle |
| New early conduction abnormality on ECG  | Continue ICI once Holter ECG excludes advanced heart block |                                             |
| New asymptomatic increase in BNP / NT- proBNP | Continue ICI - unless myocarditis / new left ventricular systolic dysfunction is detected | Check baseline (before ICI introduction – if available) and repeat measurements: |
Table 4

The most common symptoms associated with irAE of rheumatic, kidney, neurologic, eye or hematologic origin [according to Champiat S. et. Management of immune checkpoint blockade dysimmune toxicities: a collaborative position paper. Annals of Oncology 2016; 27: 559–574.

| Symptoms/laboratory abnormalities | IrAE suspected |
|-----------------------------------|----------------|
| Rheumatological                   |                |
| Arthralgia                        | Dysimmune arthritis |
| Renal                             |                |
| Elevated serum creatinine         | Dysimmune nephritis
Thrombotic thrombocytopenic purpura (TTP)
Hemolytic uremic syndrome (HUS) |
| Hypokalemia                       | Dysimmune nephritis |
| Hyponatremia                      |                |
| Abnormality of the urinary Sediment Oliguria |            |
| Ocular                            |                |
| Red or painful eye                | Dysimmune conjunctivitis
Dysimmune scleritis
Dysimmune episcleritis
Dysimmune uveitis
Dysimmune blepharitis |
| Visual impairment                 | Dysimmune uveitis
Dysimmune retinitis
Dysimmune optic neuritis
Dysimmune encephalitis
Dysimmune vasculitis
Dysimmune thyroiditis
Myasthenia gravis
Dysimmune neuritis |
| Diplopia                          |                |
| Neurologic                        |                |
| Motor deficit                     | Dysimmune mononeuritis
Dysimmune polyradiculoneuritis/Guillain–Barré
Encephalitis
Myelitis
Vasculitis
Myasthenia
Myositis |
| Sensory loss                      | Dysimmune mononeuritis
Dysimmune Polyradiculoneuritis/Guillain–Barré
Encephalitis
Myelitis |
| Seizure          | Vasculitis                                      |
|------------------|------------------------------------------------|
| Dysimmune encephalitis |

| Hematological | Anemia                                               |
|---------------|------------------------------------------------------|
| Dysimmune hemolytic anemia |                |
| Dysimmune hypothyroidism |                |
| Dysimmune pancytopenia |                |
| Immune thrombocytopenic purpura |            |
| Thrombotic microangiopathy: TTP, HUS |  |
| Evans syndrome |            |

| Thrombocytopenia | Immune thrombocytopenic purpura (ITP) |
|-----------------|---------------------------------------|
| Evans syndrome  |                                       |
| Autoimmune pancytopenia |    |
| Thrombotic microangiopathy: Thrombotic thrombocytopenic purpura (TTP) |  |
| Hemolytic uremic syndrome (HUS) |        |

| Abnormal hemostasis | Immune thrombocytopenic purpura (ITP) |
|---------------------|---------------------------------------|
| Evans syndrome      |                                       |
| Dysimmune pancytopenia |                                |
| Thrombotic microangiopathy (MAT): Thrombotic thrombocytopenic purpura (TTP) | |
| Hemolytic uremic syndrome (HUS) |  |
| Acquired hemophilia A |        |

| Thrombosis | Antiphospholipids antibody syndrome (APLS) |
Figure 1

Clinical images of skin toxicity in a patients treated immune checkpoint inhibitors. A-C. Maculopapular rash (A. grade 4, B. grade 3, C. grade 1), D. Vitiligo, E-F bullous pemphigoid.

Author confirms that patients have agreed to use their skin lesion images in a scientific publication.
Figure 2
Management in the case of myocardial infarction related to immune check inhibitors (ICIs).

TnI – troponin level, CKMB-creatine kinase myocardial band), Echo- echocardiography,
MRI- magnetic resonance imaging