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Common statement of experts of the Polish Oncological Society, Polish Lung Cancer Group, Polish Society of Lung Diseases, Polish Society of Gastroenterology, Polish Society of Endocrinology, and the Polish Society of Cardiology for minimal requirements in diagnosis and monitoring of selected adverse events of immunotherapy in oncological patients

Introduction

The introduction of a new treatment strategy — immunotherapy — based on fighting the neoplasm by activation of the immune system, has contributed to a considerable prolongation of overall survival of cancer patients [1–4]. The drugs which activate the immune system are generally immune checkpoint inhibitors (ICIs,), which include monoclonal anti-CTLA-4 (anti-cytotoxic T lymphocyte antigen-4) and anti-PD-1/L1 (anti-programmed cell death 1/ligand 1) antibodies. Currently, the following ICIs have been registered by the American Food and Drug Administration (FDA) and/or the European Medicines Agency (EMEA):

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anti-CTLA-4 (ipilimumab), anti-PD-1 (nivolumab, pembrolizumab, cemiplimab), and anty-PD-L1 (atezolizumab, avelumab, durvalumab) [4].

There is a problem with the occurrence of specific toxicities associated with the use of immunotherapy — the so-called immune-related adverse events (irAE), which in some cases can be very serious or even lead to death. It should also be pointed out that currently ICIs are more and more frequently used together with other drugs, for example, chemotherapy (lung cancer), targeted therapy (kidney cancer) or as combination therapy (melanoma, lung cancer) [5], which may increase the risk of occurrence and intensification of adverse effects. Therefore appropriate qualification of patients for immunotherapy and appropriate monitoring are of paramount importance. Continuous education of medical personnel and patients and their family (caregivers) is also indicated.

This article presents the joint statement of scientific associations (Polish Oncological Society, Polish Lung Cancer Group, Polish Society of Lung Diseases, Polish Society of Gastroenterology, Polish Society of Endocrinology, and the Polish Society of Cardiology) defining the minimal diagnostic requirements (laboratory and imaging parameters) in diagnosing, monitoring, and treatment of the most common adverse events of immunotherapy in patients with malignant neoplasms.

Recommended procedure before and during immunotherapy with ICIs

A detailed medical history and appropriate additional tests before and during immunotherapy are the most important for patient safety during treatment with immune checkpoint inhibitors. It should be noted that irAEs can affect practically any organ and occur at various stages of treatment (frequently even after immunotherapy is completed) [6–11]. The mechanisms through which immunotherapy exerts its antineoplastic activity are also responsible for irAE development. These are, namely, activated T lymphocytes escaping from central control because of the inhibition of immune checkpoints, which unfortunately may lead to uncontrolled irAE development. It is particularly important to note that initially mild symptoms may in a short time intensify considerably and lead to a severe course of irAEs. Therefore, it is extremely important to perform appropriate analyses before immunotherapy and to monitor patients during treatment. The recommended procedure and analyses before and during immunotherapy are presented in Table 1.

The next aspect is the need for continuous education of patients and their family (caregivers) about the possibility of occurrence and the course of irAEs. A good clinical practice should be providing patients with appropriate materials with information (e.g. informative brochures, reference charts) about irAEs and about procedures in the case of their appearance. Patients should also be informed about using appropriate contraception when ICIs are administered, and the problems of procreation should always be discussed before initiating treatment.

There are few data on the use of ICIs in patients with pre-existing autoimmune diseases, because in most cases they were excluded from clinical trials due to concerns that autoimmune diseases may increase the risk of severe irAEs. However, an analysis of the literature data on the use of ICI in patients with pre-existing disease indicates no increase in the incidence of new irAEs, but unfortunately exacerbation of pre-existing autoimmune disease [12]. Due to the high probability of autoimmune disease exacerbation, clinical decisions regarding the use of ICI in patients with ongoing autoimmune disease should be carefully analyzed and the benefits of ICI therapy should outweigh the possible consequences of autoimmune disease exacerbation.

Immne releted adverse events associated with the gastrointestinal tract

Gastrointestinal irAEs are most common during treatment with immune checkpoint inhibitors (anti-CTLA-4, anti-PD-1, anti-PD-L1) and in some cases can be severe and even fatal. Therefore before startingimmunotherapy, a medical historyshould be collected about diseases of the gastrointestinal tract and also the motor activity of the alimentary canal (frequency of defecation, consistency of stool), to determine if after initiation of treatment an actual change has occurred and the number of defecations has increased [13–19].

It is extremely important to collect information concerning the following diseases:
— ulcerative colitis
— Leśniowski-Crohn disease,
— autoimmune hepatitis,
— microscopic colitis,
— chronic diarrhea (functional).

In the case of coexistence of ulcerative colitis, Leśniowski-Crohn disease, or autoimmune colitis, the risk of exacerbation of these diseases during immunotherapy should be taken into consideration, as well as the increased risk of irAEs.

Table 1. Recommended procedures and examinations before and during immunotherapy

Examinations before immunotherapy	Frequency of examinations during immunotherapy
Anamnesis for diseases: • autoimmunological (ulcerative colitis, Leśniowski-Crohn's disease, connective tissue diseases, etc.) • endocrinological (thyroid, pancreas diseases, etc.) • other organs (cardiac and vascular diseases, kidney failure, hematological diseases, etc.)	Evaluation of potential adverse effects during each visit and before each immunotherapy administration
Anamnesis for infectious diseases: • as required analyses — HBsAg, HBsAb, HBcAb, hCAb, CMV antibodies, T-spot test, HIV antibodies, HIV antigen (p24)	Tests are important if patients develop irAEs and immunosuppressive treatment is required such as glucocorticosteroids and/or anti-TNFa treatment
Initial evaluation of gastrointestinal tract function: • defecation frequency, stool consistency	Evaluation during each visit and before ICIs administration
Examination of skin: • examination of skin and mucous membranes with evaluation of the extent and type of occurring lesions	Evaluation during each visit and before ICIs administration
Imaging studies: • evaluation of disease stage (CT, MRI, PET-CT) depending on the indications • central nervous system MRI depending on the indications	Periodic imaging studies depending on drug program and indications
Laboratory analyses: • CBC with differential • ALAT, ASPAT, ALP • Bilirubin • Creatinine • Urea • Electrolytes (Na, K, Ca) • Glucose • Total protein • Albumins	Tests every 4–6 weeks during immunotherapy (or before each dose of immunotherapy), depending on the drug program and indications
Thyroid: • TSH • fT4	Tests every 4–6 weeks during immunotherapy (or before each dose of immunotherapy), depending on the drug program and indications
Cardiovascular system: • ECG • Consider laboratory tests for cardiac troponin and NT-proBNP • Cardiological consultation considered individually for patients with increased cardiovascular risk	Consider periodic tests in patients with irregular results or reporting symptoms
Respiratory system: • O_2 saturation level	Consider periodic tests in patients with irregular initial results
Musculoskeletal system: • examination/functional evaluation in patients with preexisting disease	Routine controls not required in asymptomatic patients
Pancreas: • preliminary tests not required	Routine controls not required in asymptomatic patients

ALAT —alanine aminotransferase; ALP — alkaline phosphatase; ASPAT — aspartate aminotransferase; CBC — complete blood count; CMV — cytomegalovirus; CT — computed tomography; fT4 — free thyroxine); HIV — human immunodeficiency virus; irAEs — immune-related adverse events; MRI — magnetic resonance imaging; NT-proBNP — N-terminal pro-B-type natriuretic peptide; PET-CT — positron emission tomography-computed tomography; TNF — tumor necrosis factor alpha; TSH — thyroid stimulating hormone

Diarrhea and colitis

Diarrhea can be an indication of developing colitis or other serious and potentially life-threatening immunological toxicities. Diarrhea requires strict monitoring as it can lead in a very short time to significant dehydration, and as a consequence of water and electrolyteimbalance, to acute renal failure and death.

Diarrhea is among the most frequent immunological toxicities as well as one of the main symptoms of developing immune-mediated colitis. The remaining symptoms indicating colitis are predominantly abdominal pain and the presence of blood in the stool, weight loss, fever, nausea, and/or vomiting. Immune-mediated colitis may lead to many complications, including bowel perforation, anemia, necrosis, bleeding, and *megacolon toxicum*.

The following should be excluded in a differential diagnosis of diarrhea and toxicity:

— infection by Clostridium difficile or other pathogens [in each patient in whom intense diarrhea occurs during treatment with anti-CTLA-4, anti-PD-1, or anti-PD-L1, microbiological/mycological analysis of the stool should be performed as well as checking for infection by cytomegalovirus (CMV); immunoglobulin M (IgM); polymerase chain reaction (PCR)];
— occurrence of metastases to the digestive tract, especially in melanoma patients.

The examination of choice confirming the diagnosis of immunological colitis is colonoscopy with collection of samples for histopathology. The diagnosis of immunological colitis (without diarrhea) is generally based on histopathological analysis.

The differential diagnosis of grade 1 diarrhea or colitis should include complete blood count (CBC) with differential, hepatic and renal tests, electrolytes, and glucose. Additional analyses should be performed in patients with diarrhea and symptoms of colitis if they are ≥ G2 [20] and should comprise stool analysis (*C. difficile*), evaluation of calprotectin in the stool, or other examinations aimed at determining infection, including COVID-19 depending on the clinical indications. Determining thyroid stimulating hormone (TSH) and diagnosis of celiac disease (antibodies against transglutaminase together with total IgA concentration) is recommended if there is a clinical suspicion of celiac disease due to ICIs [13–19]. Disease progression or neoplasm dissemination in the abdominal cavity should also be excluded (in melanoma patients, metastases to the alimentary tract are common).

In cases of pronounced diarrhea or symptoms of colitis of grade ≥ 3 (G3/G4) or their long-term (≥ 5 days) persistence at grade 2 (G2), as well as in the case of doubts about the diagnosis of immunological toxicity, endoscopic analysis of the colon should be performed (sigmoidoscopy and/or colonoscopy), with taking sections for histopathological analysis [13–19]. In cases in which colonoscopy is ruled out, for instance, with suspicion of colon perforation or megacolon toxicum, computed tomography (CT), which is an effective and non-invasive option, should be performed. Irregularities in the CT picture associated with immunotherapy-induced colitis include mesenteric swelling and thickening of the colon wall.

Recommended additional analyses in patients with suspected/diagnosed diarrhea and/or immun-mediated colitis are presented in Table 2.

Table 2. Indicated additional tests in patients with suspected/diagnosed diarrhea and/or immune colitis

Laboratory analyses
CBC with differential
Creatinine, urea
Electrolytes (sodium, potassium, calcium)
ASPAT, ALAT
Bilirubin
Glucose
TSH, fT4
Test for CMV (IgM, PCR)
Imaging examinations
Abdominal USG
Computed tomography of abdominal and pelvis
Stool analysis
Bacteriological test (*C. difficile*)
Mycological test
Calprotectin in stool
Endoscopic examinations
Sigmoidoscopy with samples for histopathology
Colonoscopy with samples for histopathology

ALAT — alanine aminotransferase; ASPAT — aspartate aminotransferase; CBC — complete blood count; fT4 — free thyroxine; CMV — cytomegalovirus; IgM — immunoglobulin M; PCR — polymerase chain reaction; TSH — thyroid stimulating hormone; USG — ultrasonography

Hepatitis

Hepatitis associated with immune checkpoint therapy is generally asymptomatic and diagnosed by elevated serum alanine aminotransferase (ALT) and/or aspartate transaminase (AST). It should be noted that elevated levels of ALT/AST may also be associated with muscle damage, including the cardiac muscle; therefore, an extension of the diagnosis in this direction is recommended (creatine kinase levels, troponin, ECG, etc.).

In a differential diagnosis, the following factors should also be taken into consideration: the appearance or progression of metastases to the liver, cholestatic jaundice, infections [including hepatitis type B or C virus, CMV, Epstein-Barr virus (EBV), sepsis], hepatic vein thrombosis, diet (including alcohol consumption), use of

other drugs, stimulants, or supplements (alternative medicine) by the patient, other autoimmunological diseases, and genetic background or coexisting diseases. Laboratory analyses evaluating hepatic function should be performed before each immunotherapy infusion.

Diagnostic analyses at the moment of the occurrence of grade ≥ 2 toxicity should include ALT, AST, alkaline phosphatase, clotting estimation — prothrombin time/international normalized ratio (INR), bilirubin levels in serum, iron levels, autoimmunological panel for hepatitis: anti-nuclear antibodies (ANA), anti-neutrophil cytoplasmic antibodies (ANCA), anti-mitochondrial antibodies (AMA), peripheral ANCA (p-ANCA), anti-smooth muscle antibodies (ASMA), and analyses for hepatitis C virus (HCV), hepatitis B virus (HBV), and CMV, EBV [13–19].

In the case of hepatic toxicity of grade ≥ 3, abdominal imaging tests should be considered [e.g. computed tomography, magnetic resonance imaging (MRI), etc.] if the patient had prior liver disease or there is a suspicion of progression of the disease/metastasis to the liver.

A biopsy may be considered to determine the cause of unsuccessful therapy with steroids or suspicion of steroid-resistant immunological hepatitis [13–19].

Laboratory analyses [ALT, ASP, alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGTP), bilirubin, albumins, PT/INR] should be repeated once a week in the case of G1–G2 liver toxicity and every 1–2 days at toxicity ≥ G3.

Indicated additional examinations in patients with suspected/diagnosed autoimmune hepatitis are presented in Table 3.

Table 3. Indicated additional tests in patients with suspected/diagnosed immune hepatitis

Laboratory analyses
CBC with differential
Creatinine, urea
Electrolytes (sodium, potassium, calcium)
ASPAT, ALAT, ALP, GGTP
Bilirubin Glucose
Clotting system (PT/INR)
Albumins
TSH, fT4
Test for CMV (IgM, PCR), EBV
Test for HBV (HBsAg) and HCV (anti-HCV)
Panel for autoimmune hepatitis (ANA, ANCA, ASMA) — in selected cases
Imaging examinations
USG of the abdominal cavity
Liver MRI
Computed tomography of abdominal cavity and pelvis
Histopathological examinations
Liver biopsy (if no reaction to glucocorticoid treatment)

ALP — alkaline phosphatase; ALAT — alanine aminotransferase; ANA — anti-nuclear antibodies; ANCA — anti-neutrophil cytoplasmic antibodies; ASMA — anti-smooth muscle antibodies; ASPAT — aspartate aminotransferase; CBC — complete blood count; CMV — cytomegalovirus; EBV — Epstein-Barr virus; GGTP — gamma glutamyl transpeptidase; fT4 — free thyroxine; IgM — immunoglobin M; INR — international normalized ratio; HBV — hepatitis B virus; HCV – hepatitis C virus; MRI — magnetic resonance imaging; NT-proBNP — N-terminal pro-B-type natriuretic peptide; PCR — polymerase chain reaction; PT — prothrombin time; TSH — thyroid stimulating hormone; USG — ultrasonography

Immune related adverse events associated with the endocrine system

Immune-related adverse events are relatively common in the endocrine system and it is important to note that in many cases they will persist after immunotherapy is completed. Usually it is associated with permanent damage to the endocrine gland or impaired function as a result of autoimmune reactions. The most common endocrinopathies are hypothyroidism or hyperthyroidism and hypophysitis. The damage rarely concerns multiple endocrine organs, however, this may make both the diagnosis and the treatment difficult, as hypophysitis, thyroiditis, or adrenalitis due to immunotherapy often give unspecific symptoms such as, for example, nausea and vomiting, headache, fatigue, or perturbed vision. It is also difficult to estimate the frequency of endocrinopathy occurrence because of different methods of evaluation, diagnosis, and monitoring in clinical trials. Symptoms that may suggest the development of endocrinological immunological toxicities are presented in Table 4.

Table 4. Symptoms suggesting the development of endocrinological immunological toxicities

Symptoms suggesting the development of endocrinological immunological toxicities
Headache
Perturbed vision
Tachycardia
Increased sweating
Fatigue or weakness
Muscle pains
Weight loss or gain
Dizziness or fainting
Changes in appetite (increased appetite or thirst)
Hair loss
Changes in mood or behavior, or amnestic symptoms
Chills
Constipation
Change in voice timbre
Polyuria
Nausea or vomiting
Abdominal pain

Hyperthyroidism/hypothyroidism

Thyroid function perturbations in the course of immunotherapy are the most common immunological complication concerning the endocrine system. They may take the form of hyperthyroidism or hypothyroidism, and in some cases the initial hyperthyroidism transforms into hypothyroidism. In most patients both hypothyroidism and hyperthyroidism are asymptomatic or show equivocal symptoms, requiring routine monitoring of biochemical blood parameters such as TSH, free triiodothyronine (fT3), and free thyroxine (fT4). Thyroid function (TSH, fT4) should be examined every 4–6 weeks during ICI treatment and continued every 6–12 months after termination of treatment.

Hypophysitis

Hypophysitis is a serious AE associated with immunotherapy as it may lead to considerable hormonal perturbations, including: secondary adrenal insufficiency caused by ACTH (adrenocorticotropic hormone) deficiency (adrenocortical insufficiency may require immediate medical attention), secondary hypothyroidism due to TSH deficiency or disorders due to follicle-stimulating hormone (FSH) and luteinizing hormone (LH) deficiency.

The most common hypophysitis symptoms are fatigue, nausea, vomiting, weakness, headaches, blurred vision, and perturbations of sexual functions (including loss of libido or menstrual disorders, or erection perturbations). Hypophysitis is diagnosed by analyzing concentrations of hormones produced by the hypophysis: low concentrations of ACTH, TSH, FSH, LH, growth hormone (GH), and prolactin, and by imaging studies, including MRI. MRI (preferably performed according to the pituitary protocol) may confirm immunological hypophysitis and exclude other causes of perturbations of the hypophysis, including metastases. Moreover, it should be noted that the results of assaying cortisol and ACTH may be perturbed if patients receive steroids at the beginning of treatment, for example, patients with lung cancer simultaneously receiving chemotherapy and checkpoint inhibitors with dexamethasone premedication.

Primary adrenal insufficiency

Adrenal insufficiency is rare during ICIs treatment. However, this is an emergency that requires prompt intervention. It may cause dehydration, hypotension and electrolyte imbalance (hyperkalaemia, hyponatraemia) up to an adrenal crisis. Intravenous corticosteroids and immediate hospitalization are recommended when an adrenal crisis is suspected.

Type I diabetes

Checkpoint inhibitor treatment is associated with an acute start of type I diabetes in about 0.2–0.9% of cases. Unfortunately, in many cases, patients have severe hyperglycemia or even ketoacidosis. However, some patients are asymptomatic, and some have symptoms such as fatigue, nausea, weight loss, polyuria, or polydipsia. All cases require insulin treatment from the moment of diagnosis and in general permanent insulin supplementation. Diabetes associated with ICI treatment may develop immediately after its initiation but also even a year later. Thus it is extremely important to monitor glucose concentrations at each dose of immunotherapy.

Indicated additional tests in patients diagnosed with/suspected of immunological complications associated with the endocrine system are presented in Table 5.

Immune related advers events associated with the respiratory system

Diagnosis of immune related pneumonitis (IP) is not easy. Both clinical and radiological symptoms are not characteristic and require differentiation from infectious pneumonia, progression of neoplastic disease, or pneumonitis due to radiotherapy. During periods of increased infections with the SARS-CoV-2 virus, differentiation between IP and COVID-19 with pneumonia may be problematic because of the similarity of clinical and radiological symptoms [21].

Table 5. Indicated additional tests in patients with suspected/diagnosed immunological complications of the endocrine system

Laboratory tests
Complete peripheral blood count with differential white blood count
Creatinine, urea
ASPAT, ALAT
Bilirubin
Electrolytes (sodium, potassium, chlorine, calcium, magnesium)
Glucose
TSH, fT3, fT4
Laboratory tests for suspected hypophysitis or adrenal dysfunction
ACTH, FSH, LH, GH, prolactin, cortisol, IGF-1, testosterone (men), estradiol (women)
Test of adrenal reserve (test with Synacthen)
Imaging studies for suspected hypophysitis
Brain MRI according to pituitary protocol

ACTH — adrenocorticotropic hormone; ALAT — alanine aminotransferase; ASPAT — aspartate aminotransferase; GH - growth hormone; FSH — follicle-stimulating hormone; fT3 — free triiodothyronine; fT4 — free thyroxine; LH — luteinizing hormone; MRI — magnetic resonance imaging; TSH — thyroid stimulating hormone

The symptom most commonly reported by the patients is dyspnea and coughing, less commonly other symptoms such as fever, pain, discomfort in the chest, tachycardia, a sensation of cardiac palpitations, or fatigue [22].

Over one-half of IP patients also have toxicity symptoms from other organs [23]. Importantly, IP is asymptomatic in one-third of the patients [23].

A preliminary imaging study is a chest X-ray that shows new pathological changes in the pulmonary parenchyma but does not allow the determination of their exact character. Radiological monitoring of the response to treatment using chest radiograms seems justified, especially in patients with a good general status or achieving a rapid clinical improvement, as it is an easily accessible analysis, it is cheap and is not a burden for the patient.

The basic radiological analysis in diagnosing IP is spiral chest CT with contrast. This allows evaluation of the character of the changes in lung parenchyma and the lymph node appearance and, therefore, is useful for differential diagnosis between IP and other possible causes of pathology mentioned above. IP appearance in a chest CT is not characteristic and most commonly has the form of consolidation and frosted glass but also it can look like organizing pneumonia, different interstitial lesions (thickening of interlobular septa, infiltration around bronchovascular bundles, subpleural reticular, and honeycomb lesions), pneumonitis with hypersensitivity with intralobular tumors, peribronchiolar infiltration, a tree with buds, or a combination of the above-mentioned images [22, 23]. If CT is the selected method of monitoring the response to treatment, a complementary method may be the use of high-resolution computed tomography, enabling a better, as compared to standard CT, evaluation of the character and intensity of interstitial lesions in patients with persistent radiological changes [24].

Laboratory analyses are helpful in differential diagnosis of other coexisting organ toxicities of immunotherapy. Immunological pneumonitis is associated with a moderate increase in C-reactive protein (CRP) concentration, and a decrease in CRP concentration correlates with response to treatment [25]. Therefore, additional laboratory tests (e.g., determining procalcitonin concentrations in serum) or bacteriological and virological analyses may be necessary to differentiate IP and pneumonia caused by an infectious agent.

In selected situations, bronchofiberoscopy with collection of biological material and/or bronchoalveolar lavage (BAL) are indicated. The BAL results from patients with IP are characterized by a higher percentage of lymphocytes [26]. Bronchoalveolar lavage may be used for bacteriological and mycological cultures and to check for infection with Pneumocystis jiroveci. An alternative material from the lower respiratory tract which is easier to obtain is sputum — a positive culture result indicates an infectious etiology.

In particular cases, bronchofiberoscopy also allows collection of tissue material through transbronchial biopsy of suspicious radiological lesions. Histopathological analysis will allow the diagnosis of the type of pneumonitis (organizing pneumonia, granulomatous pneumonia, diffuse vesicular damage, or eosinophilic pneumonia) [27].

Functional lung tests, i.e., spirometry with evaluation of forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (DLco), should be performed in patients with established changes in the lung parenchyma. In patients with suspected perturbations of a restrictive type evidenced by spirometry, body plethysmography should be performed to detect lung parenchyma restrictions. Additional tests in patients with suspected/diagnosed immunological pneumonitis are presented in Table 6.

Table 6. Additional tests in patients with suspected/diagnosed immune pneumonitis

Laboratory tests
CBC with differential
Creatinine, urea
ASPAT, ALAT
Bilirubin
CRP
Procalcitonin
TSH, fT3, fT4
Arterial blood gas analysis (alternatively arterialized capillary blood if artery cannot be punctured)
Imaging studies
Chest X-ray
Chest CT
Lung function tests
Spirometry
DLco
Body plethysmography
Bacteriological tests
Sputum culture
Culture of bronchoalveolar lavage
Blood culture
Assay for *Legionella* antigen in urine
Assay for *Streptococcus* antigen in urine
CR/antigen test for SARS-CoV-2 and influenza
Bronchofiberoscopy
Culture of bronchoalveolar lavage
Analysis of cellular content of bronchoalveolar lavage
Transbronchial lung biopsy

Necessary tests are bolded; ALAT — alaninę aminotransferase; ASPAT — aspartate aminotransferase; CBC — complete blood count; CT — computed tomography; CRP – C-reactive protein; DLco – diffusing capacity of the lung for carbon monoxide; fT3 — free triiodothyronine; fT4 — free thyroxine; RTG — X-ray; PCR — polymerase chain reaction; TSH — thyroid stimulating hormone

Immunological complications related to the cardiovascular system

Immunological complications associated with the cardiovascular system are observed relatively rarely in the course of immunotherapy, but their consequences can be very serious, and in some cases, they may even lead to death. However, due to the high effectiveness of immunotherapy in treating patients with neoplasms, treatment should not be stopped without clear clinical evidence of the possibility of developing cardiac toxicity during immunotherapy as this could considerably worsen the patient's prognosis. Therefore, patients treated by immunotherapy should be under special cardiological supervision [28, 29].

The analysis of available trials indicates that the potentially increased risk of complications during immunotherapy is associated with the neoplasm, its prior or concomitant treatment, the status of the immune and cardiovascular systems, and most probably with genetic factors. Potential risk factors promoting higher frequency of adverse events during immunotherapy are presented in Table 7.

For cardiological supervision during immunotherapy, a preliminary evaluation is important which should include a detailed cardiological interview, measurement of basic heart functions (echocardiography — ECG), determination of basic biochemical parameters including cardiac troponins and N-terminal pro-B-type natriuretic peptide (NT-proBNP). The cardiac irregularities/diseases observed during the primary check-up should be clinically corrected or stabilized before initiating immunotherapy [30].

In supervising patients who are receiving immunotherapy, ECG, NT-proBNP, and cardiac troponin assays appear to be broadly accessible, most useful, and at the same time easy and least cumbersome. These are preliminary assays; if irregularities are observed in their values or clinical doubts arise, their broadening is indicated. It is very important to not only diagnose irregularities but also to compare them with the initial results (dynamics of changes), which facilitates therapeutic decisions. Determining cardiac troponin seems to be of particular importance, as it is a simple and specific marker of cardiac muscle [30–35]. Additional analyses in patients with suspected/diagnosed immunological toxicities concerning the cardiovascular system are presented in Table 8.

Table 7. Potential risk factors for the occurrence of cardiac toxicities in patients treated with immunotherapy [30]

Groups of risk factors	Risk factors
Factors directly associated with the type of treatment	• Combined immunotherapy: anti-PD-1 with anti-CTLA-4 (e.g. nivolumab with ipilimumab) • Immunotherapy combined with other cardiotoxic drugs (e.g. molecularly targeted treatment — VEGF tyrosine kinase inhibitors)
Current/prior cardiovascular system diseases	• Ischemic heart disease • Heart failure • Myocarditis • Status after myocardial infraction • Cardiac damage due to prior oncological therapy (e.g. chemotherapy with anthracyclines)
Autoimmunological disease (current and/or in history)	• Systemic lupus erythematosus • Rheumatoid arthritis • Sarcoidosis • Dressler syndrome
Immunological toxicities in other systems	• Immunotherapy-associated skeletal muscle inflammation
Neoplasm associated factors	• Cardiac antigens present in the tumor • Cardiac T-cell clones
Genetic factors	• Unknown

anti-CTLA-4 — anti-cytotoxic T lymphocyte antigen-4; anti-PD-1 — anti--programmed cell death1; VEGF — vascular endothelial growth factor

Table 8. Additional tests in patients with suspected/diagnosed immunological toxicities concerning the cardiovascular system [30]

Cardiological evaluation of patients before initiating immunotherapy
History of prior diseases and evaluation of classical risk factors
ECG
Cardiac biomarkers (cardiac troponin and NT-proBNP) (to be considered)
Echocardiogram (to be considered)
Cardiological evaluation of patients from the high-risk group before and during immunotherapy
ECG
Cardiac biomarkers (cardiac troponin and NT-proBNP) before initiating immunotherapy and before the 2nd and 4th dose; then before the 6th and 12th, then every 3 administrations until completion of treatment
Consider echocardiography after 2nd or before 2nd dose and every 3–6 months in patients with initial damage to the left/right ventricle
Tests if new symptoms associated with the cardiovascular system appear e.g. chest pain, dyspnea, palpitations, fainting, loss of consciousness
ECG
Cardiac biomarkers (cardiac troponin and NT-proBNP)
Echocardiography
Cardiological consultation — always in the case of appearance of a new pathology in ECG, cardiac enzymes, echocardiogram

ECG — electrocardiography; NT-proBNP — N-terminal pro-B-type natriuretic peptide

Conflict of interest

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