**Management of Immune Checkpoint Blockade Dysimmune Toxicities**

**A Collaborative Position Paper**

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**Abstract and Introduction**

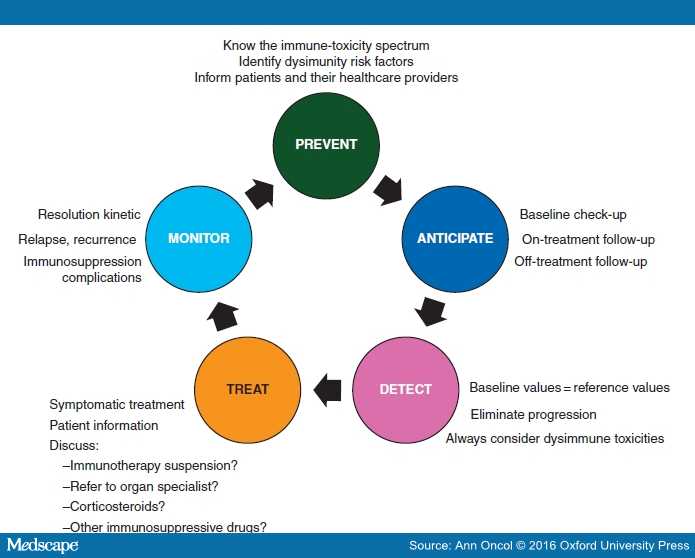
**Abstract**

Monoclonal antibodies targeted against the immune checkpoint molecules CTLA-4 and PD-1 have recently obtained approval for the treatment of metastatic melanoma and advanced/refractory non small-cell lung cancers. Therefore, their use will not be limited anymore to selected hospitals involved in clinical trials. Indeed, they will be routinely prescribed in many cancer centers across the world. Besides their efficacy profile, these immune targeted agents also generate immune-related adverse events (irAEs). This new family of dysimmune toxicities remains largely unknown to the broad oncology community. Although severe irAEs remain rare (~10% of cases under monotherapy), they can become life-threatening if not anticipated and managed appropriately. Over the last 5 years, Gustave Roussy has accumulated a significant experience in the prescription of immune checkpoint blockade (ICB) antibodies and the management of their toxicities. Together with the collaboration of Gustave Roussy's network of organ specialists with expertise in irAEs, we propose here some practical guidelines for the oncologist to help in the clinical care of patients under ICB immunotherapy.

**Introduction**

Thanks to their recent FDA and EMA approval, anti-CTLA-4 and anti-PD-1 immune checkpoint blockade (ICB) monoclonal antibodies are becoming parts of the oncologists' armamentarium against melanoma and non small-cell lung cancer (NSCLC). Beyond melanoma and NSCLC, ICBs are showing promising responses across many different cancer subtypes including small-cell lung cancer [15% objective response rate (ORR)],[1] renal cell carcinoma (25% ORR),[2] urothelial cancer (25% ORR),[3] head and neck squamous cell carcinoma (12%–25% ORR),[4,5] gastric cancer (20% ORR),[6] hepatocellular carcinoma (20% ORR),[7] ovarian cancer (15% ORR),[8–10] triple negative breast cancer (20% ORR),[11] mismatch repair deficient colorectal cancer (60% ORR)[12] and Hodgkin disease (65%–85% ORR).[13,14] Because these responses are durable and eventually impact the overall survival of patients, it can be already anticipated that many other indications will extend the current approvals. Therefore, ICBs have settled in the oncology arena for good and they will be prescribed in a large number and wide variety of cancers in a near future. As a consequence, the number of patients exposed to these new immunotherapies will also dramatically increase. ICBs generate atypical types of tumor responses[15] and have a specific toxicity profile which is challenging the historical oncologists' practices.[16] Indeed, the clinical management of immune-related adverse events (irAEs) is new to many oncologists. Most irAEs remain mild in intensity but ~10% of patients treated with anti-PD-1 ICBs will develop severe, sometimes life-threatening, grade 3–4 dysimmune toxicities.[17]

On the basis of our immunotherapy clinical practice and our experience in irAEs management together with our network of organs' specialists, we have built institutional guidelines for the clinical care of ICB-treated patients. In this manuscript, we aim at sharing with the oncology community the five pillars of Gustave Roussy cancer center immunotherapy toxicity management guidelines (Figure 1).



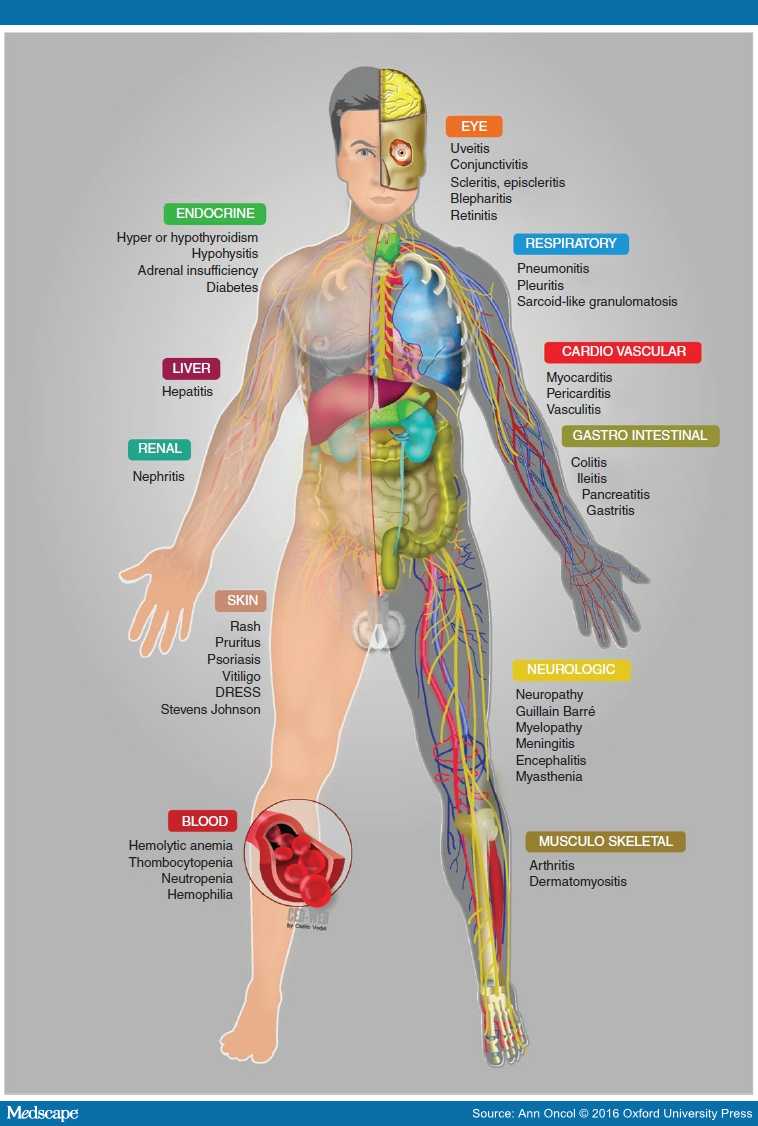
**Figure 1.**

The five pillars of immunotherapy toxicity management.

**Prevent**

**Know the Immune-toxicity Spectrum**

Before prescribing ICBs to their patients, oncologists need to be aware of their spectrum of toxicity. Anti-CTLA4 and anti-PD1/PD-L1 reported studies have mainly drawn attention to colitis or pneumonitis because of their frequency and severity. However, nearly all organs can be affected by immune-related toxicities (Figure 2).[18–20] As reported in the literature, dysimmune toxicities can affect the skin (maculopapular rash, vitiligo, psoriasis, Lyell syndrome, DRESS),[21,22] the gastrointestinal tract (enterocolitis, gastritis, pancreatitis, celiac disease),[23–25] the endocrine glands (dysthyroidism, hypophysitis, adrenal insufficiency, diabetes),[26–28] the lung (pneumonitis, pleural effusion, sarcoidosis),[29,30] the nervous system (peripheral neuropathy, aseptic meningitis, Guillain–Barré syndrome, encephalopathy, myelitis, meningo-radiculo-neuritis, myasthenia),[31–36] the liver (hepatitis),[37,38] the kidney (granulomatous interstitial nephritis, lupus-like glomerulonephritis),[39–43] hematological cells (hemolytic anemia, thrombocytopenia, neutropenia, pancytopenia),[44–52] the musculo-articular system (arthritis, myopathies),[53–55] the heart (pericarditis, cardiomyopathy)[56,57] or the eyes (uveitis, conjunctivitis, blepharitis, retinitis, choroiditis, orbital myositis).[40,53,58–65]



**Figure 2.**

Spectrum of toxicity of immune checkpoint blockade agents.

The low incidence rate of these toxicities in clinical trials will turn into more frequent clinical cases in routine practice as the number of patients treated will not be in hundreds anymore but in thousands. Also, toxicity incidence rates are not helping for clinical practice as a patient has either a toxicity or not (it is a 0% or 100% incidence rate on a per patient basis).

**Identify Dysimmunity Risk Factors**

Before starting an ICB, oncologists must identify potential risk factors that could favor the emergence of irAEs.

**Personal and Family History of Autoimmune Diseases.** Patients should be interrogated for their personal and family history of autoimmune diseases affecting every organ: digestive (Crohn's disease, ulcerative colitis, celiac disease), skin (psoriasis), rheumatic (spondyloarthritis, rheumatoid arthritis, lupus), endocrine (diabetes, thyroiditis), respiratory (interstitial pneumonitis, sarcoidosis), pancreatic (pancreatitis), kidney (nephritis), hematological (hemolytic anemia, immunologic thrombocytopenic purpura), neurological (myasthenia, multiple sclerosis), eye (uveitis, scleritis, retinitis) or cardiovascular (heart failure, left ventricular systolic dysfunction, myocarditis, vasculitis). As patients may be unaware of the exact diagnosis for their close family members, prescribers should look for 'long term follow up for a chronic disease', 'long-term prescription of cortisone', notion of 'chronic rheumatism', 'inflammatory bowel disease', 'cutaneous disease' or 'thyroid disease' running in the family. Medical terms of systemic autoimmune diseases such as 'Sjögren's syndrome' or 'lupus' should be mentioned. Personal history of dysimmune toxicities to a previous line of immunotherapy should be identified as it would at least require specific attention or may contraindicate a second line of immunotherapy. Since the pathophysiology of dysimmune toxicities is not well understood so far, other bystander causes leading to dysimmunity should be identified for specific prospective surveillance such as tumor infiltration, opportunistic pathogens, co-medications, professional toxic exposure.

**Tumoral Infiltration.** As the immune infiltrate induced by ICBs could enhance peritumoral inflammation and be responsible for different patterns of toxicity depending on tumor location, prescribers should identify patients with higher risk of pulmonary lymphangitis or carcinomatous meningitis. Such tumor infiltrates may potentially be revealed by ICBs and become symptomatic with dyspnea or headache and be diagnosed as interstitial pneumonitis or meningitis. Such paradoxical aggravations could be considered as a focal immune reconstitution inflammatory syndrome such as described in human immunodeficiency virus (HIV) patients.[66] Differential diagnosis with tumor progression is often difficult if no other lesions are simultaneously progressing. Only cytological or histological documentation can help out in these situations.

**'Opportunistic' Pathogens.** Because chronic infections are known to induce T-cell exhaustion through the expression of immune checkpoints such as PD1,[67] ICB's administration could be responsible for an inflammatory reaction against such pathogen by reinvigorating the antipathogen immune response. Thus, interstitial lung infiltrates could reveal a pneumocystic pneumonia, acute diarrhea an infectious colitis, a granulomatosis syndrome a tuberculosis infection, elevated liver enzymes a viral chronic hepatitis. Therefore, history of previous infections and risk for viral infections such as HIV or viral hepatitis should be evaluated.

**Co-medications and Professional Exposures.** Some medications are already associated with autoimmune diseases such as antiarrhythmics, antihypertensives, antibiotics, anticonvulsants or antipsychotics.[68] One can hypothesize that ICBs could potentially release drug-associated potential of autoimmunity. Prescribers should therefore be particularly careful with patients' co-medication list as it may modulate the immune system. Other medications could confer a protecting role through immune-suppression mechanisms [steroids, allopurinol, nonsteroidal anti-inflammatory drug (NSAID), salicylates or metformin]. Some professional exposure are associated with an increased risk of autoimmune diseases such as the use of chemical products (silica with lupus or systemic sclerosis) or the exposure to mineral dusts. These factors should not prevent the initiation of an ICB because there are too little data to support any causative interaction and because the risk/benefit balance goes toward the cancer therapy. However, these factors should be recorded in the patients' file.

**Inform Patients and Their Health Care Providers**

Patients and their health care providers should be informed of the specific risks of ICB toxicities ( ). Indeed, these side-effects are usually not managed like other chemo or targeted treatments' toxicities. Therefore, patients should avoid self-management of their symptoms without coordination with their oncologists or general practitioner. Occurrence or worsening of new symptom should be rapidly reported without delay. Patients must also be informed that immune-adverse reactions may occur at any time: at the beginning, during or after treatment discontinuation. It is currently admitted that the identification and early treatment of dysimmune side-effects are essential to limit the duration and severity of irAEs.

**Table 1.  Immune checkpoint blockade (ICB) toxicities**

|  |
| --- |
| Frequent (>10%) ICB toxicities |
| Ipilimumab (anti-CTLA4): diarrhea, rash, pruritus, fatigue, nausea, vomiting, decreased appetite and abdominal pain    Nivolumab (anti-PD1): fatigue, rash, pruritus, diarrhea and nausea    Pembrolizumab (anti-PD1): diarrhea, nausea, pruritus, rash, arthralgia and fatigue |
| Rare (<10%) life-threatening ICB toxicities |
| Colitis and risk of gastrointestinal perforation    Pneumonitis including acute interstitial pneumonia/acute respiratory distress syndrome    Infusion reaction and anaphylactic shock    Type 1 diabetes and risk of diabetic ketoacidosis    Severe skin reactions, DRESS, Stevens Johnson syndrome    Hemolytic anemia or immune thrombocytopenia and hemorrhagic risk    Neutropenia and sepsis risk    Encephalopathy and neurological sequelae    Guillain–Barré syndrome and respiratory risk    Myelitis and motor sequelae    Myocarditis and cardiac insufficiency    Acute adrenal insufficiency and hypovolemic shock    Pleural and pericardial effusion    Nephritis |

Patients should be informed that most of these irAEs are mild and reversible if detected early and specifically addressed. Therefore, patients should be educated about signs of organ inflammation that would require prompt referral:

* Digestive: diarrhea, blood or mucus in the stool, severe abdominal pain
* Endocrine: fatigue, weight loss, nausea, vomiting, thirst or appetite increase, polyuria
* Skin: extensive rash, severe pruritus
* Respiratory: shortness of breath, coughing
* Neurological: headache, confusion, muscle weakness, numbness
* Arthralgia or swelling joints
* Myalgia
* Unexplained fever
* Hemorrhagic syndrome
* Severe loss of vision in one or both eyes

To facilitate patients' education and health care partners' information, we recommend at our institution the use of an 'Immunotherapy Patient Card' (supplementary Material 1, available at [*Annals of Oncology* online](http://annonc.oxfordjournals.org/content/27/4/559/suppl/DC1)) and to send a letter of information to all the patients' health care providers (supplementary Material 2, available at [*Annals of Oncology* online](http://annonc.oxfordjournals.org/content/27/4/559/suppl/DC1)). This should help patients to properly inform their other health care providers (including physicians, house nurses and physiotherapists) about the management and monitoring requirements for dysimmune toxicities associated with immunotherapy. The management of these dysimmune toxicities is specific and can sometimes be urgent. It absolutely requires coordination with the prescribers' healthcare team. Any new symptom or deterioration of pre-existing symptoms must at least be monitored attentively and if necessary be explored to determine its etiology and rule out any dysimmune cause that could be worsened by immunotherapy continuation. Early identification and treatment of dysimmune adverse events are essential to limit their duration and severity. Since toxicity sequelae from previous treatments can affect cancer patients, any worsening of these sequelae should also be considered as suspect. Physical examination, laboratory tests and imaging carried out at baseline (before starting immunotherapy) will therefore be used as a reference for any clinical, biological or imaging abnormality occurring under treatment. On the basis of the adverse event severity, the immunotherapy treatment may be suspended and/or corticosteroids administered. Life-threatening or recurrent serious adverse events can lead to immunotherapy termination. If prolonged immunosuppression with corticosteroids is necessary to treat a severe adverse event, patients can be eligible to receive antibiotic prophylaxis to prevent opportunistic infections. When corticosteroids are stopped, a gradual decrease of doses must be initiated over a period of at least 1 month from the improvement. A too rapid decrease in dose may cause a relapse or worsening of adverse effects. The scheme of corticosteroids tapering shall be planned with the organ specialist referral. Patients should be under close monitoring as an irAE may occur at any time: at the beginning, during or even after treatment discontinuation. We recommend that this surveillance continues for 1 year after immunotherapy discontinuation.

**Patients With Specific Conditions**

**Elderly.** Across the different approved ICBs, no overall differences in safety were reported in elderly patients (≥65 years old). No dose adjustment is recommended.[18–20]

**Renal and Hepatic Impairment.** Currently approved ICBs have not been evaluated in patients with severe renal or hepatic impairment.[18–20] Nevertheless, no dose adjustment is recommended for patients with mild or moderate renal impairment (i.e. ≥30 ml/min creatinine clearance) or mild hepatic impairment (i.e. total bilirubin > ULN to 1.5 N). Risk/benefit ratio and dose/frequency of injections should be evaluated and adapted on a per patient basis.

**Pregnancy and Breast-feeding.** There are no data on the use of ICBs in pregnant and breast-feeding women. Since IgG can cross the placental barrier, ICBs have the potential to be transmitted from the mother to the developing fetus. Animal studies indicate that ICBs could cause fetal harm including abortion, stillbirth or premature delivery. Therefore, ICBs should not be used during pregnancy unless the clinical benefit outweighs the potential risk.[18–20] Women of childbearing potential should use effective contraception during treatment and for at least 6 months after the last dose.

**Patients With a History of Autoimmune Diseases.** Patients with a history of autoimmune diseases, in particular those requiring systemic immunosuppressive treatment for pre-existing active autoimmune disease, were not evaluated in clinical trials. ICBs may interfere with immunosuppressive therapy and/or result in an exacerbation of the underlying disease. The experience of ICBs treatment in patients with a history of autoimmune disease is relatively limited and only based on case reports.[69–71] Thus, a fewer number of patients affected by ulcerative colitis, multiple sclerosis or rheumatoid arthritis have been treated with the anti-CTLA-4 ipilimumab. Some cases have been reported where disease activity remains stable and occasionally, signs of improvement have been unexpectedly observed. Patients with a history of an organ-specific autoimmunity could also present additional irAEs. ICBs can be prescribed in patients with vitiligo or endocrine deficiencies adequately controlled with substitutive treatment. Treatment decision should be based on individual potential benefits and expected risks. If treated, patients should be monitored closely in partnership with the physician in charge of the autoimmune disease.

**Patients With a History of Chronic Infection.** Inhibitory immune checkpoints have been described as immune exhaustion markers which are upregulated during chronic viral infections or acute bacterial sepsis to avoid an excessive deleterious immune response.[72,73] Therefore, patients with a history of chronic viral infection such as HBV, HCV or HIV were excluded from clinical trials. Nevertheless, administration of anti-CTLA4 or anti-PD1 in HBV or HCV patients in the context of hepatocellular carcinoma seems to have a good safety profile with no occurrence of immune-mediated fulminant hepatitis.[7,74–77] However, hepatic toxicity with transient transaminase elevation seems to be more frequent.

**Drug Interactions**

Monoclonal antibodies are not metabolized by cytochrome P450 enzymes; therefore, enzymatic competition is not expected. A hypothetical interference may exist with the use of corticosteroids explaining why it is recommended to avoid its use at baseline. However, systemic corticosteroids or other immunosuppressants can be used to treat dysimmune toxicities. Other agents such as anticoagulants or anti-aggregants must be carefully used in case of colitis symptoms (risk of gastrointestinal hemorrhage) or dysimmune thrombopenia.

Finally, a specific attention may be needed to evaluate whether dysimmune adverse reactions would occur more frequently in patients treated by pharmaceutical agents implicated in the development of autoimmune diseases such as antihistamines, NSAIDs, antibiotics (quinolone, β-lactam, cyclin), antimalarials (quinine), antiarrhythmics, antihypertensives (β-blockers), statins, anticonvulsants or antipsychotics.[78]

**Anticipate**

**Before Immunotherapy Initiation**

Since cancer patients can present with toxicity sequelae from previous treatments, physical examination, laboratory tests and imaging performed at baseline will be used as a reference for any new abnormality occurring during immunotherapy. To help with the patients follow-up, we have defined an 'Immunotherapy baseline checklist' that can be used to follow patients prior receiving an ICB ().

**Table 2.  Immunotherapy baseline checklist**

|  |
| --- |
| Physical examination |
| Performance status    Weight, size, body mass index    Heart rate and blood pressure    General symptoms such as asthenia or appetite should be evaluated as they are frequently affected    Particularly pay attention to pre-existing symptoms regarding: intestinal transit, dyspnea and coughing, rash, nausea, headaches, signs of motor or sensory neuropathy and arthralgia    History of fever or recent infection must be checked and investigated appropriately Baseline electrocardiogram    Ongoing treatment |
| Laboratory test |
| Complete CBC    Serum electrolytes: Na, K, alkaline reserve, calcium, phosphorus, uric acid, urea, creatinine with estimated GFR (MDRD or CKD EPI)    Glycemia    Total bilirubin, AST, ALT, GGT, PAL    Albuminemia, CRP    TSH, T4    Cortisol and ACTH at 8 am    LH FSH estradiol testosterone    Proteinuria: morning sample, fasting if possible (g/l with concomitant dosing creatinine in mmol/l)—better than an urine dipstick to detect low levels of proteinuria and tubular proteinuria    Urinary sediment    Quantiferon tuberculosis or TST in case of anterior exposure    Virology: HIV, HCV and HBV serology    Antibody: ANA, TPO Ab, Tg Ab    If doable, we recommend a plasma/serum biobanking before the beginning of immunotherapy to retrospectively titrate at baseline any other factor of interest in case of development of toxicity with biological marker. |
| Imaging |
| X-ray chest imaging reference is recommended at baseline    The conventional pretherapeutic thoracic CT scan should be performed with thin sections with and without injection to have a baseline reference in case a pulmonary toxicity occurs. |

Any other evaluation may also be necessary before starting immunotherapy depending on patient's history, symptoms or diseases detected at baseline.

**During Treatment**

New symptoms or increase of pre-existing symptoms should be checked and appropriately investigated. Before immunotherapy administration, prescribers should check routine laboratory tests including CBC, renal function, serum electrolytes, glycemia, CRP, coagulation and liver function. Patients' values should always be compared with baseline values to detect a gradual modification of these values over time. TSH should be evaluated every 2 months. Proteinuria with morning sample should be controlled every 2 months. Besides the regular tumor assessments, no toxicity related imaging is routinely recommended in the absence of symptoms.

**After Treatment Termination**

Patients should be clinically and biologically evaluated on a 3-month basis during first year and then every 6 months. Oncologists should seek occurrence or worsening of any symptoms that may be related to dysimmune toxicities since they can develop even after therapy cessation. Laboratory tests can include CBC, renal function, serum electrolytes, glycemia, coagulation, liver function and TSH. No imaging is routinely recommended in the absence of symptoms. Any suspicious symptoms should lead to proper investigation.

**Overdose**

As reported in phase I clinical trials of ipilimumab, nivolumab and pembrolizumab, no maximum tolerated dose hase been reached with these drugs. In clinical trials, patients received up to 20 mk/kg of ipilimumab or 10 mg/kg of nivolumab or 10 mg/kg of pembrolizumab without apparent dose limiting toxicity.[18–20,79–84] In the case of immunotherapy overdose, patients must be closely monitored for signs or symptoms of dysimmune toxicities.

**Detect**

When an adverse event occurs during ICB therapy, consider three potential etiologies: a disease progression, a fortuitous event or a treatment-related dysimmune toxicity (). Compared with conventional anticancer drug toxicities, oncologists are less familiar with dysimmune toxicities that may lead to misdiagnoses and therefore inadequate treatments. Moreover, the diversity and the relatively low frequency of most irAEs reduce the ability for clinicians to gain sufficient experience in this field. Neglecting immune-related toxicities could be potentially fatal; it also seems that delaying adequate care of dysimmune disease could lead to a worse prognosis. Conversely, focusing predominantly on irAEs and ignoring potential fortuitous events (such as infection and thrombosis) may also be deleterious. Therefore, oncologists should have a global, non-biased view of potential etiologies and properly explore each.

**Table 3.  Symptoms and laboratory abnormalities associated with immune-related toxicities**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Symptoms** | **Frequently associated diagnosis in oncology** | **Immune-related adverse events to be suspected** |
| General | Headache | Intracranial hypertension Leptomeningeal metastasis Cerebral hemorrhage Meningitis due to carcinomatous meningitis or opportunistic infection Other drug-related | Febrile headache: dysimmune meningitis Non-febrile headache: dysimmune hypothyroidism Progressive: hypophysitis Acute/subacute: stroke due to vasculitis |
|  | Acute confusion | Metastatic brain evolution, carcinomatous meningitis Sepsis Metabolic: hypercalcemia, dysnatremia Encephalopathy: hypoxic/hypercapnic/liver/uremic Iatrogeny: new drug, pain Urinary globe, fecal impaction Toxic | Febrile confusion: dysimmune meningoencephalitis Afebrile confusion: encephalitis, hypophysitis Acute/subacute: stroke due to vasculitis Hyperosmolar coma linked to dysimmune diabetes |
|  | Chest pain | Pulmonary embolism Pneumonia/pleurisy infectious Tumor pleurisy Parietal tumor invasion Rib fractures Pneumothorax Shingles Anxiety | Dysimmune pericarditis Dysimmune myocarditis Dysimmune pleurisy Dysimmune gastritis |
|  | Asthenia | Brain tumor progression Sepsis Chronic pain Iatrogenic: opiates, psychotropic, antiepileptics, … Metabolic: dysnatremia, anemia, hypercalcemia (paraneoplastic, bone metastases … ) Iatrogenic: corticosteroids: steroid myopathy or adrenal insufficiency id steroids stopped Toxicities of previous treatments: surgery, radiotherapy and cerebral postradiation encephalopathy, … Depression Decompensation of chronic organ failure: renal, cardiac, respiratory, liver | Endocrine: dysimmune hypothyroidism, dysimmune hypophysitis with antipituitary insufficiency, adrenal acute failure, dysimmune diabetes Metabolic: renal failure on dysimmune nephropathy, Neurological and muscular: dysimmune encephalitis, acute polyradiculoneuropathy, dysimmune myositis, dysimmune myasthenia Blood: dysimmune hemolytic anemia Induced connective tissue disease |
|  | Peripheral edema | Vein thrombosis Compression venous or lymphatic tumor Sodium retention with corticosteroids Malnutrition Venous stasis-related movement disorders or sensory (brain tumor, spinal cord compression, neuropathy) | Nephro: dysimmune nephropathy with glomerulonephritis Cardio: dysimmune pericarditis, dysimmune myocarditis Endoc: dysimmune hypothyroidism Systemic: dysimmune vasculitis, APLS with thrombosis Neuro: dysimmune neuropathy |
|  | Weight loss | Tumor progression Mechanical obstruction digestive tumor/ENT Oral thrush, bad dental status Digestive surgery: derivation/short bowel syndrome Radiation-induced esophagitis Mucositis in chemotherapy Long-term corticosteroid Toxic: nausea/vomiting in opiates Pain Depression Hypercatabolism related to inflammatory syndrome Loss of autonomy for food | Dysimmune gastritis Dysimmune enterocolitis Celiac disease Dysimmune hyperthyroidism Dysimmune hypophysitis Dysimmune adrenal insufficiency Dysimmune diabetes Induced systemic diseases |
|  | Influenza syndrome, fever | Sepsis: infection of the catheter, pneumonia, urinary tract infection, cholangitis, erysipelas, deep infection Thrombosis phlebitis Tumor-specific inflammation (elimination diagnosis) Paraneoplastic | ILI reaction to immunotherapy Dysimmune colitis Hyperthyroidism Thrombosis Vasculitis |
| Neurologic | Sensory loss | Medullary compression/metastatic evolution Carcinomatous meningitis Neurotoxicity previous treatments Paraneoplastic | Dysimmune mononeuritis Dysimmune Polyradiculoneuritis/Guillain–Barré Encephalitis Myelitis Vasculitis |
|  | Motor deficit | Medullary compression/metastatic evolution Carcinomatous meningitis Neurotoxicity previous treatments Paraneoplastic | Dysimmune mononeuritis Dysimmune polyradiculoneuritis/Guillain–Barré Encephalitis Myelitis Vasculitis Myasthenia Myositis |
|  | Seizure | Brain metastasis and carcinomatous meningitis Infectious encephalitis Neurotoxicity previous treatment Paraneoplastic | Dysimmune encephalitis |
| Cutaneous | Rash | Anaphylactic or anaphylactoid urticarial (off target effects of conventional drugs) | Immune-related hives, eczema (on-target off tumor effects of immune-targeted drugs) Pemphigus |
|  | Pruritus | Cholestasis secondary to liver/pancreatic metastasis | Dysimmune hypo/hyperthyroidism Immune-related hives, eczema |
| Respiratory | Acute dyspnea/desaturation | Pneumonia/pleurisy infectious, aspiration pneumonia Thoracic tumor invasion Bronchial tumor compression/ specific pleurisy/lymphangitis carcinomatosis Rib fractures on bone metastases Tumoral hemoptysis Pneumothorax Anemia Overdose of morphine, benzodiazepines Anxiety | Dysimmune interstitial lung disease Hydrops, pleurisy autoimmune Dysimmune pericarditis Dysimmune myocarditis Dysimmune myasthenia Acute autoimmune polyradiculoneuropathy |
| Rheumatic | Arthralgia | Bone metastasis Referred pain of visceral metastasis Thrombosis pathological fracture | Dysimmune arthritis |
| Digestive | Abdominal pain | Tumor compression of the biliary tract, urinary tract, pancreatic ducts Peritoneal tumor invasion Tumor or iatrogenic bowel obstruction Intra-abdominal infection (cholecystis … ) Hypercalcemia Pancreatitis (lithiasis, alcohol … ) Thrombosis | Dysimmune enterocolitis Dysimmune pancreatitis Dysimmune gastritis Dysimmune pericarditis Dysimmune myocarditis Dysimmune pleurisy Occlusive syndrome of enteric neuropathy Occlusive syndrome in dysimmune hypothyroidism Acute adrenal insufficiency Ketoacidosis due to dysimmune diabetes |
|  | Diarrhea | Secondary to antibiotic use Enteropathy due to cancer Clostridium difficile Exocrine pancreatic insufficiency on tumor compression | Dysimmune enterocolitis Celiac disease Dysimmune hyperthyroidism |
|  | Nausea vomiting | Bowel obstruction by the tumor Carcinomatous peritonitis Carcinomatous meningitis Intracranial hypertension Hypercalcemia Hyponatremia | Dysimmune meningitis Dysimmune enterocolitis Ketoacidosis due to dysimmune diabetes Dysimmune adrenal insufficiency Dysimmune nephropathy Dysimmune pancreatitis Dysimmune hepatitis |
| Hepatic | Liver Enzymes Elevation | Hepatic cancer progression Sepsis Concurrent medication | Dysimmune hepatitis Dysimmune myocarditis (AST) Dysimmune myositis (AST) Dysimmune hemolytic anemia (AST) |
|  | Jaundice, bilirubin elevation GGT and ALP elevation | Intrinsic liver cancer progression, gall, locoregional tumor or extrinsic compression Sepsis Medication, parenteral nutrition | Dysimmune hepatitis Sclerosing cholangitis Primary biliary cirrhosis Dysimmune granulomatosis Dysimmune hemolytic anemia (unconjugated bilirubin) |
| Hematologic | Anemia | Prior chemotherapy toxicity Tumor bleeding Marrow involvement Deficiency Vitamin B9, B12 or martial inflammatory anemia false anemia: hemodilution, splenomegaly, monoclonal peak | Dysimmune hemolytic anemia Dysimmune hypothyroidism Dysimmune pancytopenia Immune thrombocytopenic purpura Thrombotic microangiopathy: TTP, HUS Evans syndrome |
|  | Thrombocytopenia | Marrow involvement Prior chemotherapy toxicity Disseminated intravascular coagulation due to tumor progression Myelodysplasia Heparin-induced thrombocytopenia Vitamin B12 or folate deficiency | Immune thrombocytopenic purpura (ITP) Evans syndrome Autoimmune pancytopenia Thrombotic microangiopathy: Thrombotic thrombocytopenic purpura (TTP) Hemolytic uremic syndrome (HUS) |
|  | Abnormal hemostasis | Hepatocellular insufficiency: decreased PT, aPTT, decreased factors II, VII, X and factor V, fibrinogen decreased. Vitamin K deficiency: decreased PT, aPTT, factors of the vitamin K-dependent consumption: II, VII, IX, X, proteins C and S; Factor V is normal DIC: decreased PT, APTT prolongation, thrombocytopenia, hypofibrinogenemia, reduction of factors V, PDF and increased D-dimer. | Immune thrombocytopenic purpura (ITP) Evans syndrome Dysimmune pancytopenia Thrombotic microangiopathy (MAT): Thrombotic thrombocytopenic purpura (TTP) Hemolytic uremic syndrome (HUS) Acquired hemophilia A |
|  | Thrombosis | Local tumor compression Cancer relapse Endovascular Tumor progression Heparin-induced thrombocytopenia Iatrogeny due to other drugs (revlimid, bortezomib) | Antiphospholipids antibody syndrome (APLS) |
| Renal | Elevated serum creatinine | Tumor obstruction Renal toxicity related to intercurrent medicines, an iodinated contrast agent injection Tumor lysis syndrome | Dysimmune nephropathy Thrombotic thrombocytopenic purpura (TTP) Hemolytic uremic syndrome (HUS) |
|  | Hypokalemia | Deficiency of potassium intake: anorexia, vomiting, taking laxatives, diuretics, exclusive artificial nutrition Excess extrarenal losses: Acute diarrhea, digestive fistulas | Dysimmune nephropathy Colitis, autoimmune enterocolitis |
|  | Hyponatremia | SiADH due to tumor in lung, brain … Iatrogenic: diuretics, potomania Excess of hypotonic perfusions False hyponatremia: hyperglycemia … | Dysimmune nephropathy Dysimmune colitis, dysimmune enterocolitis Dysimmune hypothyroidism Dysimmune adrenal failure (central or peripheral) Dysimmune diabetes |
|  | Abnormality of the urinary sediment | Tumoral infiltration of the urinary tract Urinary sepsis Sequelae of surgery or radiotherapy | Dysimmune nephropathy |
| Cardiovascular | Hypertension | Corticosteroid Erythropoietin treatment Anxiety Brainstem infiltration | Dysimmune vasculitis Dysimmune glomerulonephritis Dysimmune hyperthyroidism |
|  | Arrhythmia | Infections Hypo/hypercalcemia Hypo/hyperkalemia Corticosteroids, digoxin, psychoactive drugs Ischemic cardiopathy | Dysimmune myocarditis Dysimmune pericarditis Dysimmune hyperthyroidism |
|  | Deep venous thrombosis/pulmonary embolism | Local tumor compression Cancer disease relapse or progression in Thrombosis venous access Prolonged bed rest Heparin-induced thrombocytopenia | Lupus Antiphospholipids antibodies syndrome (APS) Dysimmune vasculitis |
| Endocrine | Adrenal failure | Peripheral: adrenal bilateral metastases Central: corticosteroids withdrawal, brain radiation | Peripheral: adrenal dysimmune granulomatosis, dysimmune vasculitis with bilateral adrenal vein thrombosis Central: dysimmune hypophysitis |
|  | TSH, T3, T4 | Iatrogenic (radiotherapy …) | Dysimmune thyroiditis |
| Eye | Red or painful eye | Tumor infiltration Local sepsis Allergic conjunctivitis Dry eye syndrome | Dysimmune conjunctivitis Dysimmune scleritis Dysimmune episcleritis Dysimmune uveitis Dysimmune blepharitis |
|  | Visual impairment | Brain tumor location Radiation therapy sequelae on optic nerves or lenses Ischemic ocular neuritis | Dysimmune uveitis Dysimmune retinitis Dysimmune optic neuritis Dysimmune encephalitis |
|  | Diplopia | Cranial base tumor location Infectious rhombencephalitis | Dysimmune vasculitis Dysimmune thyroiditis Myasthenia gravis Dysimmune neuritis |

Oncologists should keep in mind that the most frequent adverse events are related to disease progression. On the basis of clinical studies, treatment-related adverse events leading to treatment discontinuation are relatively low compared with those related to tumor progression. Therefore, any new symptoms should prompt us to a tumor evaluation to seek disease progression. However, a dysimmune disorder should always be considered particularly when work-up suggests an underlying disease stability ().

**Table 1.  Immune checkpoint blockade (ICB) toxicities**

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| --- |
| Frequent (>10%) ICB toxicities |
| Ipilimumab (anti-CTLA4): diarrhea, rash, pruritus, fatigue, nausea, vomiting, decreased appetite and abdominal pain    Nivolumab (anti-PD1): fatigue, rash, pruritus, diarrhea and nausea    Pembrolizumab (anti-PD1): diarrhea, nausea, pruritus, rash, arthralgia and fatigue |
| Rare (<10%) life-threatening ICB toxicities |
| Colitis and risk of gastrointestinal perforation    Pneumonitis including acute interstitial pneumonia/acute respiratory distress syndrome    Infusion reaction and anaphylactic shock    Type 1 diabetes and risk of diabetic ketoacidosis    Severe skin reactions, DRESS, Stevens Johnson syndrome    Hemolytic anemia or immune thrombocytopenia and hemorrhagic risk    Neutropenia and sepsis risk    Encephalopathy and neurological sequelae    Guillain–Barré syndrome and respiratory risk    Myelitis and motor sequelae    Myocarditis and cardiac insufficiency    Acute adrenal insufficiency and hypovolemic shock    Pleural and pericardial effusion    Nephritis |

Dysimmune toxicities can develop at any time: at the beginning, under treatment and after immunotherapy termination. As shown with nivolumab, the majority of dysimmune toxicities occur within the first 4 months.[17,85] Median time to onset of treatment-related adverse events can vary depending on the type of toxicity: from 5 weeks for skin adverse events to 15.1 weeks for renal adverse events. On the basis of this median time to onset, dysimmune toxicities could be classified as early (median time to onset <2 months) and late toxicities (median time to onset >2 months). Early toxicities include skin (5 weeks), gastrointestinal (7.3 weeks) and hepatic (7.7 weeks), whereas late toxicities include pulmonary (8.9 weeks), endocrine (10.4 weeks) and renal (15.1 weeks). However, clinicians should keep in mind that all toxicities can develop at any time since confidence interval may vary widely among organs: 0.1–57 weeks for skin; 0.1–37.6 weeks for gastrointestinal.

Any new symptom or laboratory abnormality should be attentively monitored and appropriately explored when not improving. While oncologists usually deal with conventional chemotherapy toxicities according to standards of care, it is important to note that each abnormalities induced by anti-CTLA4 or anti-PD1 should be specifically addressed. For example, a decrease of hemoglobin value below laboratory normal values (13 and 12 g/l for men and women, respectively) is often minimized until it falls below 10 g/dl because oncologists usually reason according to classic transfusion threshold. In the case of patients treated by immunotherapies, oncologists should always consider patients on a case-by-case basis: patient's values at baseline are each patient's reference values. Alert for monitoring or exploration should be triggered according to baseline variations. Also physicians should be aware that irAE can slowly alter biological parameters over time and a decrease or increase of such parameters should be envisioned over multiple time points. In case of a nonsevere and nonspecific symptom, close monitoring should be conducted to evaluate its evolution and easily repeat proper laboratory or imaging tests.

**Treat**

**Key Points of Immune-related Adverse Events Management**

Here are the key points to be handled when a patient is developing an irAE:

* close monitoring
* ambulatory versus inpatient care
* symptomatic treatment
* immunotherapy suspension or termination
* corticotherapy and associated measures
* other immunosuppressive drugs
* patient information on how to self-monitor clinical elements

The typical clinical management of irAEs is described in .

**Table 4.  Typical management of irAEs**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Severity—CTCAE grade** | **Ambulatory versus inpatient care** | **Corticosteroids** | **Other immunosuppressive drugs** | **Immunotherapy** |
| 1 | Ambulatory | Not recommended | Not recommended | Continue |
| 2 | Ambulatory | Topical steroids or Systemic steroids oral 0.5–1 mg/kg/day | Not recommended | Suspend temporarilya |
| 3 | Hospitalization | Systemic steroids Oral or i.v. 1–2 mg/kg/day for 3 days then reduce to 1 mg/kg/day | To be considered for patients with unresolved symptoms after 3–5 days of steroid course Organ Specialist referral advised | Suspend and discuss resumption based on risk/benefit ratio with patient |
| 4 | Hospitalization consider intensive care unit | Systemic steroids i.v. methylprednisolone 1–2 mg/kg/day for 3 days then reduce to 1 mg/kg/day | To be considered for patients with unresolved symptoms after 3–5 days of steroid course Organ specialist referral advised | Discontinue permanently |

Some dysimmune toxicities may follow a specific management: this has to be discussed with the organ specialist.  
aOutside skin or endocrine disorders where immunotherapy can be maintained.

**Corticosteroids Modality**

Before the initiation of corticosteroids or other immunosuppressive drugs, it is necessary to rule out any associated infection. Antibiotic prophylaxis should be envisioned to prevent opportunistic infections in patients under long-term exposure to immunosuppressive drugs with oral trimethoprim/sulfamethoxazole (400 mg qd). Corticosteroid termination should follow a gradual decrease of doses over a period of at least 1 month. Of note, tapering should not be too rapid to avoid recurrence or worsening of the irAE. Whether irAEs are worsening or insufficiently improving despite the use of adequate corticosteroids treatment, the opportunity of additional immunosuppressive regimens should be discussed by prescribers with the referring specialist on a case-by-case basis. In case of severe toxicity requiring the addition of another immunosuppressive drug, patients should be tested for tuberculosis by quantiferon or TST without delaying treatment.

**When to Resume or Terminate Immunotherapy?**

Oncologists should keep in mind that there are no clear correlations between dose, duration of treatment and efficacy of ICBs. Indeed, anti-CTLA-4 antibodies have been tested between 1 and 10 mg/kg every 3 weeks or every 3 months and anti-PD-1 antibodies have been tested between 1 and 10 mg/kg every 2 or 3 weeks.[79–84] All these regimens showed equivalent efficacy profiles respectively. Also, patients have shown durable tumor responses even upon treatment termination due to toxicity.

Therefore, when a dysimmune toxicity is suspected, prescribers should always consider delaying immunotherapy injection to better monitor symptom evolution and allow sufficient time for proper diagnosis without the fear of losing some dose-intensity of immunotherapy. If a dysimmune toxicity is confirmed, clinician should decide temporary suspension or definitive termination based on the nature and severity of the irAE.

**Immunotherapy Permanent Discontinuation**

Apart from certain exceptions, the causing immunotherapy should be definitively discontinued in case of adverse immune dysfunction:

* life-threatening (grade 4)
* severe (grade 3) and recurring
* moderate (grade 2) but not resolutive in 3 months despite appropriate treatment

Endocrinopathies that are controlled by hormone replacement therapy, even grade 4, do not require the termination of immunotherapy.

**Temporary Suspension**

After suspension, resumption of immunotherapy can only be envisaged:

* if the side-effect is stabilized ≤ grade 1 (returned to baseline) and
* if the steroid dose is reduced to ≤10 mg/day prednisone or equivalent and
* in the absence of other immunosuppressive drugs.

Immunotherapy dose reduction is currently not recommended for the three EMA approved ICBs.[18–20] Phase I studies have indeed shown not dose/toxicity correlation for anti-PD1 or PD-L1. However, anti-CTLA4 trials have revealed that the 10 mg/kg regimen has a higher rate of toxicity.

**Organ Specialist Referral: Why, When and How?**

The current experience of managing immunotherapy toxicities is low and requires expertise. Organ specialist or internist referral is needed for mainly two reasons: for oncologists to learn proper management of specific dysimmune toxicities but also for organ specialists to increase their knowledge about these new drug-mediated toxicities and therefore creating a virtuous circle for patients management. For this purpose, oncologists should define their local organ specialist team based on their interest and expertise on the topic but also availability and responsiveness to sollicitation.

Oncologists should seek for organ specialist support as soon as the diagnosis and treatment of dysimmune toxicities become difficult. Some toxicities such as asymptomatic hypothyroidism or grade 1–2 rash can be easily managed but for most other toxicities, especially if grade >1, specialist expertise is often needed for proper monitoring over time.

**Monitor**

**Resolution Kinetics of Dysimmune Toxicities**

Studies have shown that most dysimmune toxicities, even severe ones, can resolve due to temporary or definitive immunotherapy discontinuation and temporary immunosuppression. Prescribers should be aware that the time needed for irAE resolution can highly vary across the various types of toxicities.[16,17,85–87] Gastrointestinal, hepatic and renal toxicities usually rapidly improve when immunosuppressive measures are taken. On the other hand, skin and endocrine toxicities take more time to resolve and endocrine insufficiency sequelae are common. They might therefore require long-term hormonal substitution. The lower rate of immunosuppressant efficacy is observed in skin, endocrine and gastrointestinal severe (grade 3–4) dysimmune toxicities.

**Impact of Immunosuppressants on Response Rate**

Due to their immunosuppressive role, corticosteroids are suspected to lower the immunotherapy efficacy. Even if prospective studies are still lacking prospective studies to conclude, preliminary data seem to show that systemic immunosuppressants used for irAEs might not have such a negative impact on efficacy.[17] As observed in melanoma with nivolumab, patients who received systemic immunosuppressive therapy show a similar time to response and ORR compared with those who have not.[17]

**Complications Following Immune-suppressive Drugs**

Refractory or severe dysimmune toxicities often require prolonged immunosuppressive treatments with corticosteroids and sometimes with additional immunosuppressants such as antitumor necrosis factor alpha (anti-TNF) in severe and/or corticosteroid-refractory colitis. Of note, as a result of this necessary immunosuppression, cases have confirmed the risk of severe opportunistic infections including pulmonary aspergillus infections, tuberculosis resurgence, CMV viremia or Fournier's gangrene.[88] The need of slow tapering of immunosuppressive drugs (to limit the toxicity relapse) also worsens infectious risks.

Clinicians must be very careful regarding the development of opportunistic infections during immunosuppressive therapy since early detection, diagnosis and treatment remain critical for favorable outcome.

We currently recommend using antibiotic prophylaxis with oral trimethoprim/sulfamethoxazole (400 mg qd) if corticosteroids ≥1 mg/kg are used. Prophylaxis should be pursued until steroid dose is below 10 mg per day.

We also recommend to test patients for tuberculosis (quantiferon or TST) in case of severe toxicity requiring additional immunosuppressive drugs and introduce anti-tuberculosis prophylaxis if positive.

Future experience in managing dysimmune toxicities will help us to define optimal immunosuppressive regimen to maximize dysimmunity control and minimize opportunistic infection risk.

**Conclusion**

Although immunotherapy is spreading across oncological indications and is now available in routine practice for melanoma and squamous NSCLC, the expertise in the management of ICB dysimmune toxicities is currently limited to sites that have been involved in their use in clinical trials. The management of frequent and mild toxicities such as thyroid dysfunction or skin rash will easily be standardized in the near future. However, the important diversity of less frequent dysimmune toxicities requires that oncologists identify a local network of organ specialists to help them in the management of these new types of adverse events.

The current report is summarizing the fruit of such collaborative initiative with our institution's network of organ specialists. The objective is to standardize and facilitate the management of irAEs at Gustave Roussy cancer center. Thus, this comprehensive work has led to the conception of a mobile phone application to make dysimmune toxicity diagnosis and management easily accessible to all immunotherapy prescribers. Such application should help organ specialists and oncologists to exchange about toxicities and share experiences. Moreover, we have established a national pharmacovigilance registry called REISAMIC (Registre des Effets Indésirables Sévères des Anticorps Monoclonaux Immunomodulateurs en Cancérologie) which is dedicated to the collection of immunotherapy severe adverse events (CTCAE Grade 3–4). This registry will be directly accessible via the above-mentioned application to collect more efficiently these irAEs and improve our knowledge in their incidence and their clinical management.

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