Management of toxicities related to immunotherapies

Immunotherapy agents are being used to treat a growing range of cancers, but emerging evidence from randomised trials and clinical practice shows very different patterns of toxicity compared to chemotherapy. **Jean-Marie Michot** reviews what doctors should look out for when treating patients with immunotherapy, and the action to take.

This grandround was first presented by Jean-Marie Michot, from Gustave Roussy Cancer Campus Grand Paris, Villejuif, France, as a live webcast for the European School of Oncology. Marco Siano, from Cantonal Hospital, St Gallen, Switzerland, posed questions raised during the presentation. It was edited by Susan Mayor. The webcast of this and other e-sessions can be accessed at e-eso.net.

The management of toxicities with immunotherapies used to treat cancer is relatively new, as these therapies have been used in clinical practice for only the last four years. The main classes of immunotherapy are monoclonal antibodies, immuno-conjugated agents, bispecific monoclonal antibody CAR-T cells, and immune checkpoint inhibitors (see table p 42). Each of these classes is associated with different types of toxicity. This article will focus on managing toxicities with immune checkpoint inhibitors, which are mainly auto-immune-like adverse reactions.

How checkpoint inhibitors cause immune-related adverse events

Checkpoint inhibitors enable activation of T cells so they can attack tumours cells, resulting in tumour death. There are essentially two ways to reduce the anti-tumour tolerance of T cells and enhance their capacity to attack tumour cells: first, using agonists to activate T-cell receptors such as CD28 or OX40; and second, using antagonists for inhibitory receptors including CTLA-4 and PD-1. Agents currently available include the anti-PD1 drugs nivolumab and pembrolizumab and the anti-PD-L1 drugs atezolizumab and durvalumab.

Following treatment with checkpoint inhibitors, tumour specific T cells (CD8 cells) increase in number. The numbers of effector T cells increase rapidly after treatment, followed by

Immunotoxicities with different types of immunotherapy

Class of agent	Examples of drugs in this class	Type of toxicity	Mechanism of toxicity
Monocolonal antibody	Obinutuzumab	Infusion-related reaction	Immuno-allergic
Immuno-conjugated	Brentux-imab vedotin, inotuzumab ozogamicin, ibritumomab tiuxetan	Cytotoxicity, direct	Chemotherapy-like
Bispecific monoclonal antibodies CAR-T cells	Blinatumumab	Cytokine release syn-dromes (CRS), neurologic	Cytokines (IL-6 and interferon-gamma), T cell migration to the CNS
Immune check-point blockade	Anti-CTLA4, anti-PD1, anti-PD-L1	Immune-related adverse events	Auto-immune like

Source: J M Michot et al (2016) *Eur J Cancer* 54:139-48; DW Lee et al (2014) *Blood* 124:188-95

an increase in memory T cells after several months (see figure opposite). The effector T cell response can result in very effective tumour control, with responses lasting for many months or even years in some patients treated for metastatic melanoma, although the tumour response depends on the quality of the immune response evoked by checkpoint inhibition.

In addition to an anti-tumour effect, checkpoint inhibitors can cause an auto-immune response by expanding an autoreactive clone of CD8 cells. This can result in a wide spectrum of toxicities that have not been seen with previous types of cancer therapies. These toxicities include skin reactions, such as maculopapular rash and psoriasis, inflammatory colitis, uveitis and pneumonitis, although the pattern of toxicity is quite different with PD-1 inhibitors and with PD-L1 inhibitors.

Toxicity of immunotherapy vs chemotherapy

Overall, immunotherapy is better tolerated than chemotherapy. For example, a study comparing the PD-1 inhibitor nivolumab with docetaxel showed a lower rate of treatment-related adverse events with nivolumab (69%) than with docetaxel (88%) (see table opposite) (*NEJM* 2015, 373:1627–39). The rate of severe adverse events (grade 3–4) was also lower with immunotherapy (10% vs 54%) and, importantly, fewer patients stopped treatment due to adverse events (5% vs 15%). In practice, I explain to patients that immunotherapy is better tolerated than chemotherapy, but it is important to inform them that they may experience adverse events that they have not had with chemotherapy. It is also important to explain that adverse events with immunotherapy are unpredictable and can happen at any time during treatment, and sometimes even afterwards, and that they are reversible by steroids. Adequate patient information about adverse events is one of the crucial points in their management.

Frequency of immune-related events with immunotherapy

Immunotoxicity differs according to the class of immune checkpoint inhibitor. Immune-related events are much more frequent with CTLA-4 inhibitors than with PD-1 and PD-L1 inhibitors (see figure p 44). Skin reactions can occur with CTLA-4 inhibitors, but grade 3–5 gastrointestinal adverse events, including colitis, are a particular concern with this type of immunotherapy. It is essential to have a gastroenterologist in the cancer network to manage this problem.

The pattern of immunotoxicity is quite different with anti-PD1 agents, with pneumonitis, thyroiditis and arthralgias being the most frequent adverse events, while immune-related adverse events are less frequent with anti-PD-L1 agents (*NEJM* 2018, 378:158–68).

The immunotoxicity occurring with immunotherapy also varies according to the type of tumour being treated. Patients treated for melanoma have higher rates of vitiligo (around 10%), while patients with non-small-cell lung cancer (NSCLC), and those with renal carcinomas, are more likely to experience pneumonitis, and those treated for thymic carcinoma may have myocarditis, which affects less than 0.5% of patients (*NEJM* 2018, 378:158–68).

Combination immunotherapy

Immune-related adverse events are more common when patients are treated with a combination of immunotherapy agents, with a study showing that grade 3–4 immune-related adverse events were additive in patients treated with a combination of nivolumab plus ipilimumab (*NEJM* 2015, 373:23–34). Adverse events with combination immunotherapy can be quite difficult to manage, and combined immunotherapies should be used with caution.

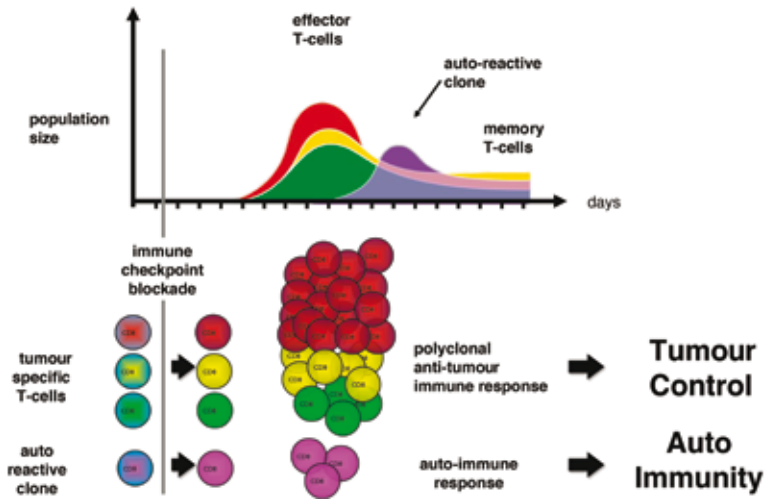
Diversity of adverse events

The diversity of adverse events with immunotherapy is perhaps more important than the frequency when managing toxicity (see figure p 45). Patients treated with immunotherapy agents experience a wide range of adverse events not previously seen with other types of cancer treatments. These include Guillain–Barré syndrome, myasthaenia, gastritis, pancreatitis, adrenal insufficiency, and retinitis, and theoretically any organ could be affected by an immune-related adverse event.

There are three 'red alert' categories of toxicity with immunotherapy: cardiovascular, including myocarditis, pericarditis and vasculitis; neurological, including neuropathy and encephalopathy; and haematological, including haemolytic anaemia, thrombocytopenia and aplastic anaemia. Patients suffering even grade 1 cardiovascular, neurological or haematological adverse events should promptly put treatment on hold and be rapidly and comprehensively investigated for these three organs: heart, brain and nervous system, and the haematopoietic system. Those suffering grade 1 adverse events affecting other organ categories can generally continue immunotherapy while further investigations are carried out.

Given the potential risk of encephalitis with immunotherapy, patients experiencing neurological symptoms should stop immunotherapy immediately and be further investigated by brain MRI, and be tested for specific antibodies against central nervous system compounds in the context of cancer, i.e paraneoplastic antibodies. Patients with any respiratory symptoms, including shortness of breath, should be discussed with a specialist, recognising the risk of pneumonitis and myocarditis. The risk of these serious adverse events underline why it is

Kinetics of T cell response: tumour control and auto-immunity



Different types of T cell responses kick in at different time points

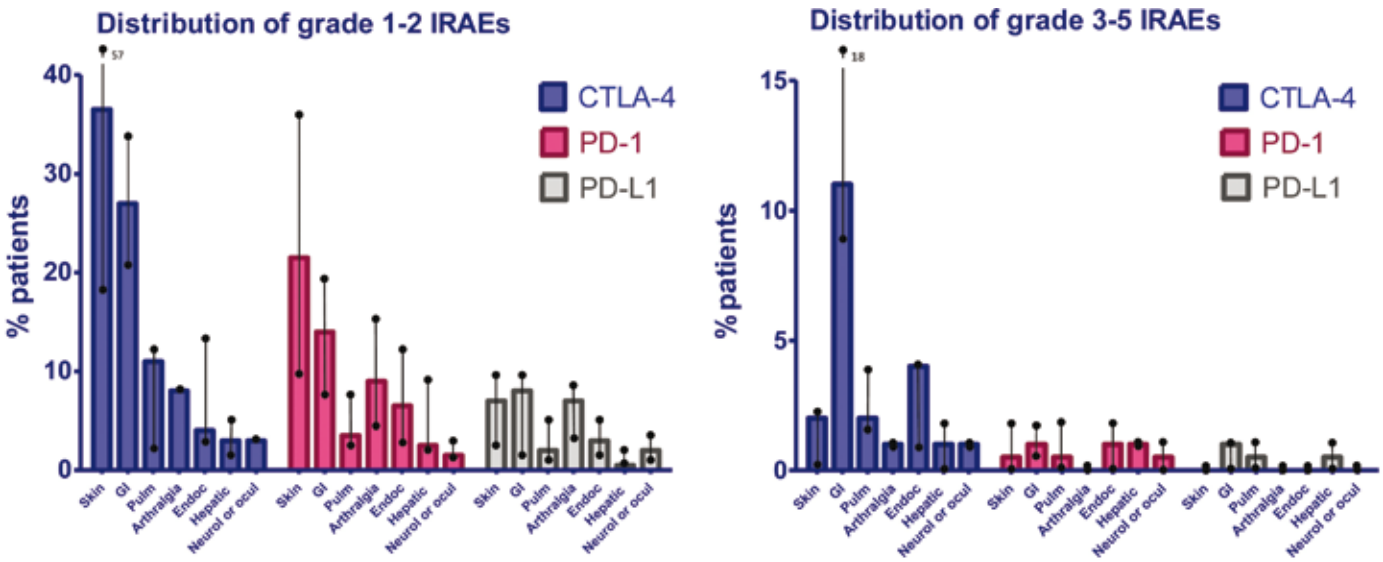
Nivolumab vs docetaxel toxicity in NSCLC

	Nivolumab n = 287	Docetaxel n = 268
All Grade AEs, any cause	98%	99%
Treatment-related AEs	69%	88%
Grade 3-4 AEs, any cause	46%	67%
Treatment-related Grade 3-4 AEs	10%	54%
Grade 5 AEs, any cause	8%	5%
Patients withdrawing from treatment due to AEs	5%	15%

Overall, immunotherapy is better tolerated than chemotherapy, as shown here with the adverse event (AE) rates for nivolumab versus docetaxel in patients with non-small-cell lung cancer (NSCLC)

Source: H Borghaei et al. (2015) *NEJM* 373:1627–39

Frequency of immune-related adverse events with immunotherapy



Immunotoxicity differs according to the class of immune checkpoint inhibitor

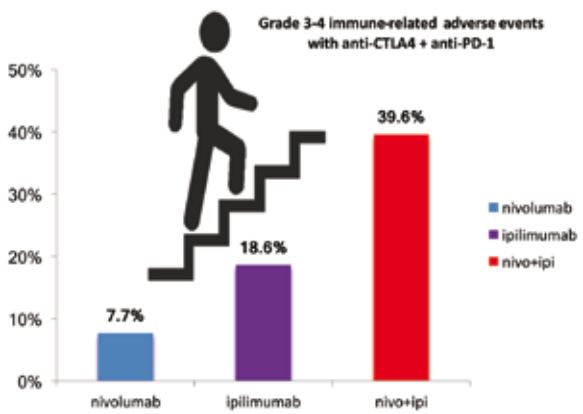
IRAEs – immune-related adverse events, GI – gastrointestinal, Pulm – pulmonary, Endoc – endocrine, Neurol – neurologic, Ocul – ocular

Source: J M Michot et al (2016) *Eur J Cancer* 54:139–48, reproduced with permission from Elsevier

essential to work closely with specialists in internal medicine to investigate and manage the range of toxicities that can occur in cancer patients treated with immunotherapy.

Our understanding of the immunotoxicity that can occur with immunotherapy is growing over time. For example, fulminant myocarditis was reported with combination immune checkpoint blockade in a report in 2016 (*NEJM* vol 375, pp 1749–55) and a case of paraneoplastic acral vascular syndrome has been documented in a patient with metastatic melanoma treated with immune checkpoint blockade (*BMC Cancer* 2017, 17:327). In some hard-to-manage cases, advice from a specialist in general internal medicine could be useful and add value.

Toxicity increases with combination immunotherapy



Immune-related adverse events are not so rare when used in combination, as shown by these data for patients treated with a combination of the CTLA4 blocker ipilimumab and the PD-1 blocker nivolumab

Source: Courtesy of S Champiat and J-M Michot, Gustave Roussy Institute, Paris

Kinetics of onset and resolution of adverse events

It is important to be aware of the likely timing of the onset and potential resolution of immune-related adverse events with immunotherapy agents. A pooled analysis of patients with advanced melanoma treated with nivolumab showed that most adverse events occurred at around 10 weeks (*JCO* 2017, 35:785–92). However,

adverse events can occur at any time during treatment with immunotherapy (*Lancet Haematol* 2019, 6:e48–e57). There are two key messages: 10 weeks is the 'warning zone' when it is essential to check patients for possible immune-related adverse events, but clinicians should monitor patients for adverse events very regularly during their therapy.

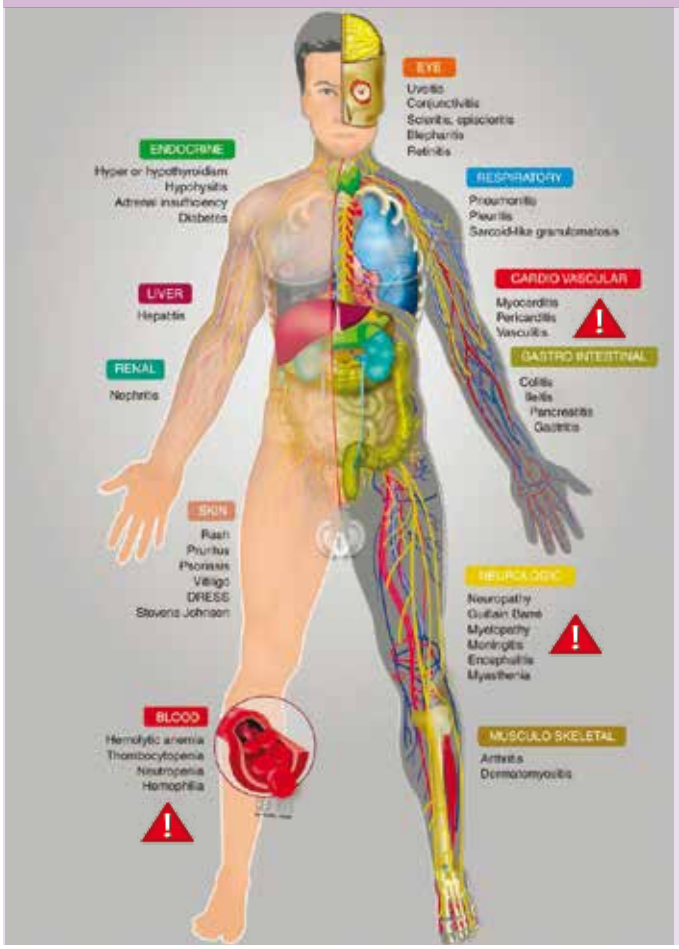
Relationship between immunotoxicity and dose

Immunotoxicity is related to dose for anti-CTLA4 agents. However, there is no dose relationship for anti-PD1 and anti-PD-L1 agents, although it may be helpful to reduce the frequency of dosing in patients experiencing immune-related adverse events (*NEJM* 2018, 378:158–68). Nevertheless this correlation is tricky, as the general outcome of patients by progression free survival and overall survival is not modified in prospective studies.

What is the significance of immunotoxicity for tumour control?

There have been suggestions that immunotoxicity may be associated with improved tumour control. A pooled analysis of studies in patients with advanced melanoma treated with nivolumab showed that the occurrence of immune-related adverse events was associated with a higher overall response rate (48.6% in patients experiencing any immune-related adverse events vs 17.8% in those experiencing none, $P<0.001$) (*JCO* 2016, 35:785–92). This suggests that patients showing immunotoxicity will also show response to immunotherapy.

Three red alerts among a wide range of toxicities



A wide range of toxicities are associated with immunotherapy. Those in the cardiovascular, neurological and haematological categories should trigger a red alert even when the severity of the adverse event is assessed as grade 1

Source: S Champiat et al (2016) *Ann Oncol* 27: 559–74, republished by permission of Oxford University Press

What is the mechanism for immunotoxicity?

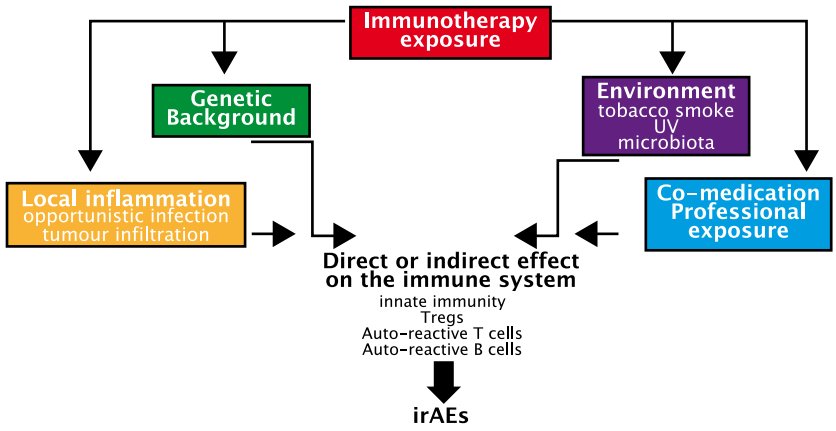
The immunopathogenesis hypothetical model for immunotherapy immune-related adverse events implicates several factors, including local inflammation, genetic background, immunotherapy exposure, environment and co-medication, which have direct or indirect effects on the immune system (see figure p 46). It is important to check a patient's medical history for these factors. Patients at particular risk for immunotoxicity include those with:

- Underlying autoimmune disease
- Chronic organ dysfunction: renal failure/dialysis, respiratory failure, COPD, heart failure
- Chronic viral infection: HIV, viral hepatitis
- Organ transplant.

These are not contraindications for immunotherapy, but it is important to check with the specialist managing these pre-existing conditions that they are well controlled.

Patients with pre-existing autoimmune diseases raise a particular challenge when treating cancer with immunotherapy. The problem is quite common, with a study in patients with lung cancer showing that 13.5% had autoimmune disease of any kind, including rheumatoid arthritis and

Immunopathogenesis hypothetical model for immunotherapy immune-related adverse events



Several factors are implicated in the pathogenesis of immune-related adverse events in patients treated with immunotherapy

IrAEs – immune-related adverse events

Source: Courtesy of S Champiat, Gustave Roussy Institute, Paris

ulcerative colitis (*JAMA Oncol* 2016, 2:1507–8). These patients are at risk of a flare-up of their autoimmune disease if treated with immunotherapy. Studies show a risk of 30–40% (*JAMA* 2016, 2:234–40; *Ann Oncol* 2017, 28:368–76; *EJC* 2017, 75:24–32). It is essential to check that their autoimmune disease is well controlled before starting immunotherapy and to inform and discuss with their specialist.

A study in patients with pre-existing autoimmune or inflammatory disease whose cancers were treated with anti-PD1 antibodies showed significantly increased risk of immune-related adverse events but similar overall survival to patients without autoimmune disease (*EJC* 2018, 91:21–9). This underlines that autoimmune disease is not a contraindication to immunotherapy for cancer treatment.

Considering patients with underlying infections, there have been a few cases of tuberculosis related to immune checkpoint inhibitors, and the reported cases have been close to immune reconstitution syndrome.

Another issue to be aware of with immunotherapy is hyperprogressive disease. It is defined as a more than two-fold increase in tumour growth rate while on treatment compared to a reference period, and represents a new pattern of progression seen in patients treated by anti-PD1 or anti-PD-L1 agents.

A study indicated that 9% of patients treated with these immunotherapy agents had hyperprogressive disease in the first few weeks of treatment (*Clin Cancer Res* 2017, 23:1920–8).

This phenomenon was seen across all tumour types; it was more common with older age and was associated with worse overall survival. It is important to detect hyperprogressive disease and treat promptly with chemotherapy.

Summing up

A recent position paper on managing toxicities associated with immunotherapy for cancer recommends that the first step is prevention, informed by awareness of the spectrum of toxicities that can occur, and education of the patient and their carers (*Ann Oncol* 2016, 27:559–74).

Potential immune-related adverse events should be anticipated, and patients monitored with a baseline examination and regular follow-up during and after stopping treatment.

Laboratory tests should include: complete blood count, serum electrolytes and liver enzyme tests, endocrine tests for thyroid stimulating hormone (TSH), thyroxine (T4) and triiodothyronine (T3), urine dipstick test and virology tests for HIV, hepatitis B and C, plus tuberculosis or tuberculin skin test when clinically indicated. Patients should also have a CT scan of the lung and an electrocardiogram.

Any immune-related adverse event should be detected early, and progression of toxicity prevented. Patients should be examined and asked about symptoms that may be associated with immunotoxicity at the same time as evaluating possible association with tumour progression or concurrent events such as infection.

Adverse events should be treated symptomatically, and patients provided with information on what has happened.

Treating clinicians should consider suspending immunotherapy, referring to a specialist in the organ affected by the adverse event, and treating with corticosteroids or other immunosuppressants.

Before starting corticosteroids it is essential to check that patients do not have an infection. Also, a patient starting steroids will switch to an immunocompromised status, and should be given antibiotic and antiviral prophylaxis (usually trimethoprim sulfametoxazole and aciclovir). Steroids should be tapered progressively over a

period of at least one month. Patients should then continue to be monitored with resolution of the adverse event and for any recurrence or complications of immunosuppression.

Given the diversity and complexity of immune-related adverse events, multidisciplinary networks are essential for effective management of immunotoxicity.

Guidelines from the European Society for Medical Oncology (*Ann Oncol* 2017, 28:iv119–iv142), the American Society of Clinical Oncology (*JCO* 2018, 36:1714–68) and the Society for Immunotherapy of Cancer (*J Immunother Cancer* 2017, 5:95) set out recommendations on general management of immune-related toxicity.

These include symptomatic treatment for grade 1 adverse events, suspending immunotherapy and oral corticosteroids for grade 2 adverse events, and intravenous corticosteroids for grade 3 or more severe adverse events, in addition to consulting a specialist in the organ affected, and considering an alternative immunosupressive therapy if clinically indicated, generally when steroids are not sufficient to control some severe and persistent immune-related adverse events.

However, there are exceptions to these recommendations, such as endocrine toxicities, where steroids are not generally required, and management is based on adequate hormonal replacement, and where treatment can be continued even at grade 2.

In contrast, cardiac, neurological and haematological toxicities indicate that immunotherapy should be stopped immediately and specialist advice requested urgently.

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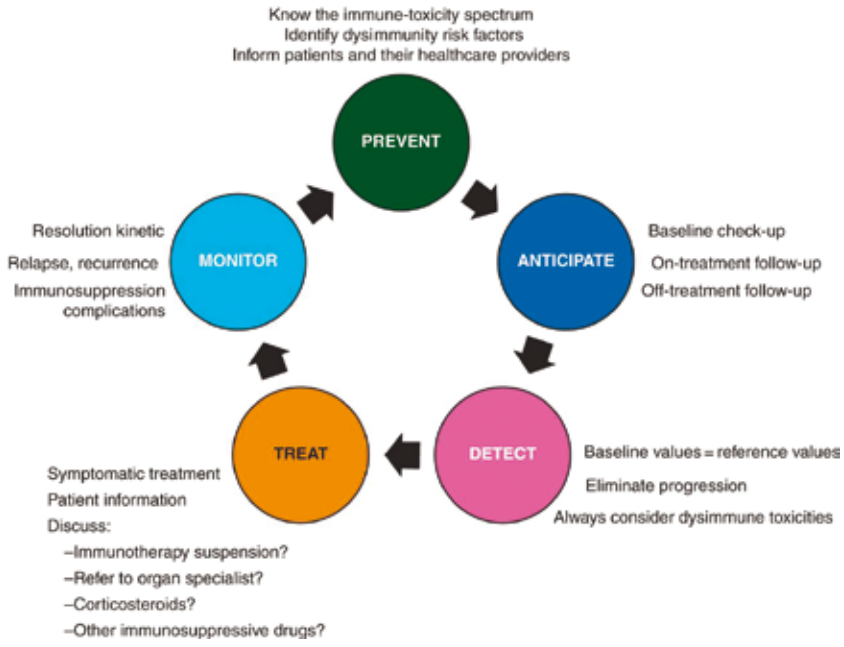
Managing toxicity associated with anti-PD1 therapy



The five pillars of immunotherapy toxicity management

Source: S Champiat et al (2016) *Ann Oncol* 27:559–74, republished by permission of Oxford University Press

Question & Answer session with Jean-Marie Michot

Marco Siano, Cantonal Hospital, St Gallen, Switzerland, posed questions.

Q: Centres in Switzerland just give TNF-alpha immediately when a patient is hospitalised with colitis associated with immunotherapy. Do you agree with this approach or do you consider diagnostics including colonoscopy before deciding on treatment? Steroids are often not sufficient for patients who are hospitalised with colitis, and concern about the risk of perforation makes clinicians afraid to lose time before treating.

A: If a patient needs to be hospitalised with colitis, the severity will be at least grade 3. I carry out clinical examination and investigations including colonoscopy, in close collaboration with a gastroenterologist. I treat with intravenous steroids (2 mg/kg,) and if a patient does not respond satisfactorily after five days then I start anti-TNF-alpha. My experience is that 80% of patients respond well to adequately given steroids, so the anti-TNF alfa may be reserved for patients with severe, resistant, or reccurrent colitis.

Q: How do you taper steroids in a patient with colitis treated with mycophenolate mofetil or other agents, who remains on steroids?

A: Generally at our hospital we treat with three weeks of steroids full dose, and then reduce the dose by 10 mg each week until stopping. Be also aware that some immunosupressive therapies such as mycophenolate mofetil begin to be clinically active only after three weeks of continuous use.