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.

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

<table>
<thead>
<tr>
<th>Class of agent</th>
<th>Examples of drugs in this class</th>
<th>Type of toxicity</th>
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<td>Immuno-conjugated</td>
<td>Brentuximab vedotin, inotuzumab ozogamicin, ibritumomab tiuxetan</td>
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<td>Bispecific monoclonal antibodies CAR−T cells</td>
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<td>Immune checkpoint blockade</td>
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<td>Immune-related adverse events</td>
<td>Auto−immune like</td>
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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, myasthenia, 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. 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

<table>
<thead>
<tr>
<th>Nivolumab vs docetaxel toxicity in NSCLC</th>
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<tr>
<td><strong>Nivolumab n = 287</strong></td>
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<tr>
<td>All Grade AEs, any cause</td>
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<tr>
<td>Treatment-related AEs</td>
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<td>Grade 3-4 AEs, any cause</td>
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<tr>
<td>Treatment-related Grade 3-4 AEs</td>
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<tr>
<td>Grade 5 AEs, any cause</td>
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<td>Patients withdrawing from treatment due to AEs</td>
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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*
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


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

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.

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.

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...
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.

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 sulfamethoxazole 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.


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 immunosuppressive 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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