Creating guidelines for managing the side-effects of immunotherapy

Immunotherapy is a relatively new type of treatment in cancer services and its side-effects are still unfamiliar to staff. This article describes a nurse-led project that consisted of developing bespoke management guidelines covering the main immune-related adverse events (irAEs) seen in patients treated with immunotherapy.

Rise of immunotherapy
William Coley, known as the ‘father of immunotherapy’, first attempted to harness the power of the immune system to treat cancer over a century ago (Sell, 2017), but the presence of immunotherapy in the oncology arsenal is still relatively new. In recent years, however, its use has taken root in mainstream cancer care.

T cells (or T lymphocytes) are a subtype of white blood cells. Developed in the thymus gland, they play a central role in cell-mediated immunity and are responsible for a variety of immune responses. T cells not only help activate B cells, but they also help activate cytotoxic T cells to kill infected target cells (Alberts, 2008).

Immune checkpoint inhibitors (ICIs) activate T cells to recognise cancer cells by blocking inhibitory signals (Spain et al, 2016). The most common ICIs act on cytotoxic T lymphocyte antigen 4 (CTLA-4), programmed cell death-1 (PD-1) and its ligand (PD-L1), disrupting the inhibitory signals to activate the immune response against malignant cells (Sell, 2017).

With ICIs, long-term stability of disease and even complete response to therapy have been seen in cancers that had a poor prognosis, such as metastatic melanoma, non-small cell lung cancer and renal cancer (Spain et al, 2016).

Immune-related adverse events
Although ICIs have a more favourable toxicity profile than chemotherapy and improve overall survival, they are not without challenges. These challenges are related to their mechanism of action: by eliminating T cell co-inhibition through the blocking of inhibitory signals, they enable the immune system to detect and attack tumour cells; however, in doing so, they also potentially cause irAEs.

The most common irAEs are skin rashes, diarrhoea, hepatitis, endocrinopathies and pneumonitis. Less common ones
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include uveitis (inflammation of the middle layer of the eye), nephritis (inflammation of the kidneys), neuropathies, diabetes and immunotherapy-related neutropenia (abnormally low level of neutrophils) (Weber et al, 2012). Any of these irAEs can be severe or even life-threatening; however, with early recognition and prompt initiation of immunosuppressive therapy, they are usually reversible.

Traditional anticancer agents such as chemotherapy suppress the immune system, increasing the risk of infections, clotting problems and anaemia; in contrast, immunotherapy agents activate the immune system, which can lead to irAEs due to the T cell response. This different side-effect profile poses significant challenges, not least because this is a new class of drugs – so staff need to learn how to recognise, assess and treat their side-effects.

How the project started

The Clatterbridge Cancer Centre is one of the UK’s leading cancer centres. From 10 operating sites across Merseyside and Cheshire, it treats over 27,000 patients with solid tumours and blood cancers annually, offering pioneering chemotherapy, radiotherapy, proton therapy and immunotherapy.

Since 2014, The Clatterbridge Cancer Centre has had a nurse-led immunotherapy service (Upton, 2016). Being in charge of that service, I developed specialist knowledge and skills in the management of irAEs. However, when assessing patients, I found that I lacked practical guidance that was quick to access. Immunotherapy is increasingly used in disease areas other than cancer, so I was also aware that, beyond my own setting, acute care services generally were struggling to manage irAEs.

I decided to amalgamate the outcomes of clinical trials and information from pharmaceutical companies to produce a bespoke set of management algorithms, or guidelines, for the most common irAEs. The idea was to standardise the management of the immune-mediated side-effects of cancer treatment to:

- Prevent unnecessary hospital admissions;
- Reduce the costs incurred through unnecessary admissions;
- Reduce the length of stay in hospital;
- Improve the consistency of management;
- Improve staff’s knowledge;
- Improve patient safety, experience and quality of life.

Developing the guidelines

In 2015, I started developing the guidelines, for which I adopted the ‘red, amber, green’ (RAG) colour coding widely used within and outside healthcare. This means staff are able to quickly differentiate between the different grades of toxicity (grade 1 = mild, grade 2 = moderate, grade 3 and 4 = severe or life-threatening) and determine what type of management is required. The RAG coding makes the guidelines easy to interpret and potentially gives them a broad reach. The guidelines also use the same layout and visual triggers as the management guidelines of the UK Oncology Nursing Society (UKONS, 2013).

An expert body, the Immuno-Oncology Working Group, was set up at The Clatterbridge Cancer Centre to review, correct and approve the drafts. The group worked with a number of clinical experts in medicine and surgery with site-specific expertise, to ensure the guidelines followed best practice.

“I truly amazing nurse-led service that has nationwide applicability” (Judges’ feedback)

Second version

Now in their second version, the guidelines have been ratified by the Immuno-Oncology Working Group for use throughout the Merseyside and Cheshire Clinical Network. They are available on our website (www.clatterbridgecc.nhs.uk), where any health professional who needs guidance on the appropriate and timely management of immune-related toxicities can access them. Box 1 summarises their benefits for patients and staff.

The guidelines currently cover the management of seven immune-mediated irAEs: diarrhoea; endocrinopathies (divided into two different guidelines, one for thyroid dysfunction, the other for adrenal dysfunction); hepatotoxicity; neurological toxicities; pneumonitis; renal toxicities; and skin toxicities.

Patients starting immunotherapy at The Clatterbridge Cancer Centre receive an alert card that gives them direct access to the guidelines via a QR code (Upton et al, 2017).

What comes next?

I have been working closely with the UKONS to include the management of irAEs in its revised guidelines (due for publication in April 2018), which will promote the standardisation of care at a national level. I have also been involved in the second version of the UKONS triage tool (UKONS, 2016), which has been updated to help staff recognise and grade irAEs. Since its introduction in 2016, the revised triage tool has improved patients’ access to steroid treatment and prevented unnecessary hospital admissions.

Guidelines to manage hyperglycaemia, hypophysitis (adverse events affecting the endocrine system) and arthralgia (adverse events affecting the musculoskeletal system) are currently in development. I am also working on an e-learning module and on a quick-reference trouble-shooting guide for staff. I hope that The Clatterbridge Cancer Centre guidelines will help frontline staff working in acute cancer care and emergency departments deal with irAEs, at the centre and beyond.

References

Sell S (2017) Cancer immunotherapy: breakthrough or ‘deja vu, all over again’? Tumour Biology, 39; 6, 10104283/7701776.

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Box 1. Benefits of the guidelines

- Give staff quick and easy access to best practice guidance
- Contain specialist advice developed in collaboration with experts
- Standardise patient management
- Are user-friendly thanks to the ‘red, amber, green’ (RAG) colour coding
- Developed in parallel with guidelines of the UK Oncology Nursing Society
- Are readily available online for any health professional
- Can be used to educate patients on immunotherapy