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independent content

Top tips: cancer immunotherapy

Dr Anna Olsson-Brown (pictured) and **Dr Nicola Harker** offer 10 top tips on the novel use of immunotherapies in cancer treatment

Read this article to learn more about:

- the role of checkpoint inhibitors in cancer treatment and which cancers they are licensed to treat
- detecting and managing immune-related adverse events resulting from oncological immunotherapy
- the impact of oncological immunotherapy on patients and general practice.

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The use of immunotherapies has exploded into mainstream oncological practice because they have shown activity in cancers that previously had limited treatment options and poor prognoses, and they have the potential to induce long-term control.[1,2] Immunotherapies are a set of drugs known as checkpoint inhibitors (CPIs). CPIs have led to a step change in cancer management and have altered the landscape in terms of mechanism of action, day-to-day management, toxicity, patient experience, and prognostic outlook. This article explores the key considerations for GPs and primary care clinicians when managing patients who are undergoing immunotherapy treatment for cancer.

1 Understand how checkpoint inhibitors work

Immune surveillance is the process by which aberrant cells are removed by the immune system and cancer fails to develop.[3] When a person develops cancer, immune surveillance fails; the cancer overexpresses a number of checkpoint proteins such as CTLA-4 and PD-1 to prevent immune destruction. CPIs work by blocking these proteins, allowing the person's own immune system, specifically $CD8^+$ T cells, to be active against cancer once again (Figure 1).[4] It is the $CD8^+$ T cells that then destroy the cancer cells.[5] It is thought that after a period of treatment with CPIs the immune system becomes 're-educated' and the person's tumour-specific T-cell function is altered, meaning the T cells remain active against the cancer without further CPI therapy.[8]

Unlike with chemotherapy and targeted agents, CPIs do not act directly on the tumour; the CPIs act on the patient's T cells to bring about the therapeutic effects.[6] In activating a 'middle man' in the form of the $CD8^+$ T cells, there is no direct external control over the downstream effects, leading to many differences between immunotherapies and other systemic anticancer treatments.[9] CPIs cause an immune chain reaction that each patient will respond to differently.

> … checkpoint inhibitors act on the patient's T cells to bring about the therapeutic effects

The immune system is an effective yet autonomous ally in this type of cancer treatment and so the standard management practices cannot be applied. The process is summarised in Box 1.

2 Recognise which drugs are oncological immunotherapies

The number of oncological therapies in mainstream use is ever increasing, so it is becoming less clear which drug does what. Broadly speaking, systemic anticancer therapies can be broken down into those directly causing cell death (chemotherapy), small molecules (-ibs), and monoclonal antibodies (MABs). Currently all CPIs are MABs; however, not all MABs are CPIs.[11] Immunotherapies are distinct because the MAB blockade enables the activation of T cells instead of a direct reduction in cancer cell burden (Figure 2). CPIs include anti (α)-CTLA-4 (ipilimumab and tremelimumab), α-PD-1 (pembrolizumab and nivolumab), and α-PD-L1 (atezolizumab, durvalumab, and avelumab).[13]

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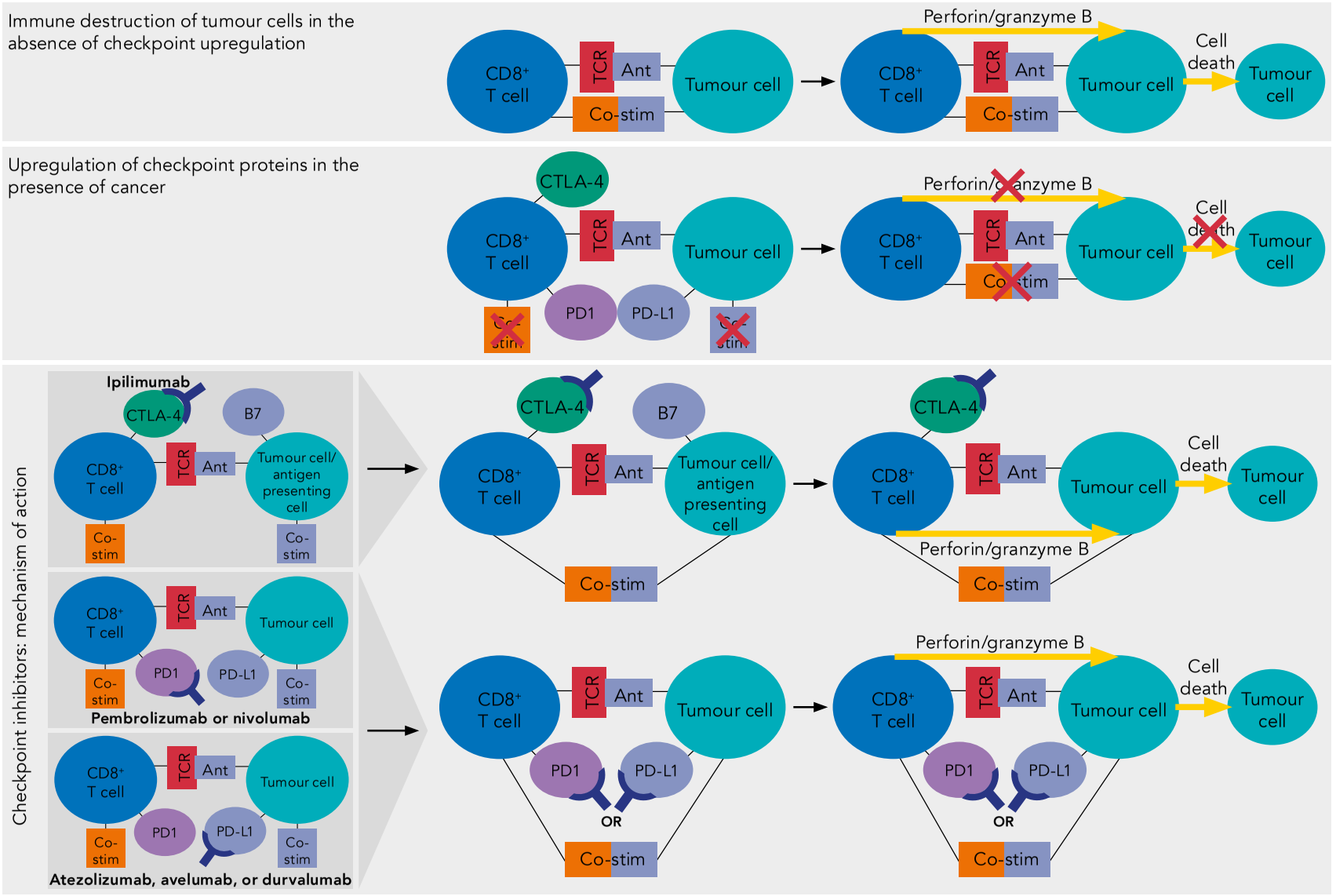
Figure 1: The effects of checkpoint inhibitors in cancer treatment



TCR=T-cell receptor; Ant=antigen protein; Co-stim=co-stimulatory signal; CTLA-4=cytotoxic T-lymphocyte-associated protein 4; PD-1=programmed cell death protein 1; PD-L1=programmed death-ligand 1

Normally, the T-cell receptor of the T cell binds to the antigen protein in the tumour. This leads to a secondary co-stimulatory signal (Co-stim), after which the T cell destroys the tumour cell via the release of perforin and granzyme B. When a tumour upregulates checkpoint proteins, this process cannot happen as it prevents the co-stimulatory mechanism. When checkpoint inhibitors are used the co-stimulatory signal is once again active and the T cell can be active against the tumour cells.[4,5,6,7]

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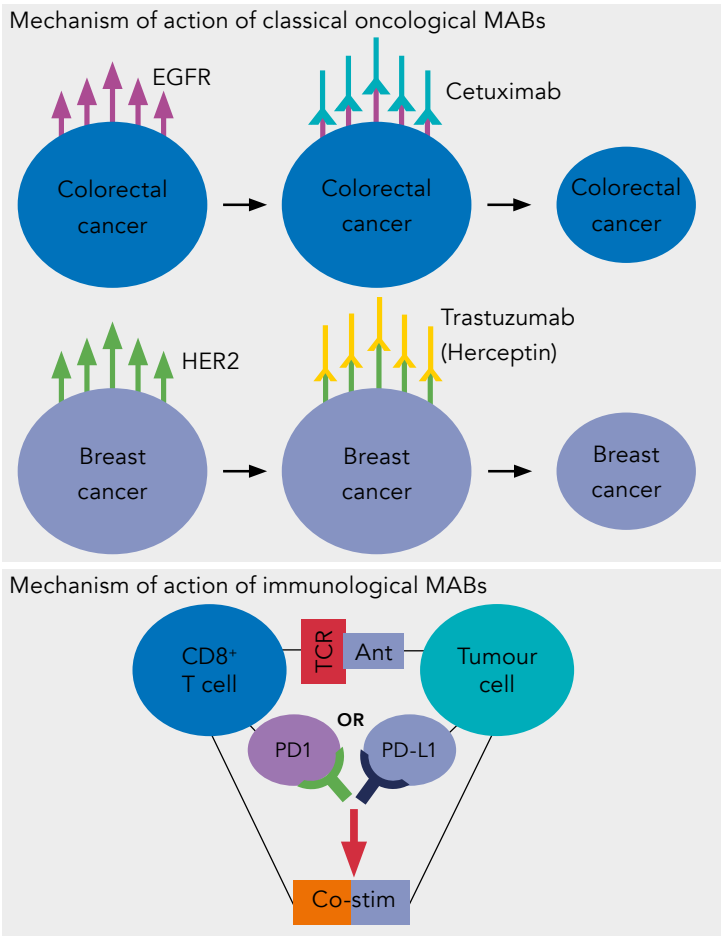
Box 1: Cancer immunotherapy treatment with checkpoint inhibitors[10]

- Cancer causes overexpression of checkpoint proteins (e.g. CTLA-4, PD-1) to prevent immune destruction
- CPIs block checkpoint proteins and stimulate cytotoxic T cells to be active against cancer
- Measurable effects may be delayed as it is the T cells that affect the cancer, not the drug
- Treatment can cause toxicities such as irAEs
- The effects on the immune system by CPIs become self-perpetuating after the drug has been given, meaning that toxicities may continue after the drug has been stopped and are rarely self-terminating
- Drug holidays/dose reductions do not lead to improvement in toxicity
- irAEs need to be managed with drug treatment, e.g. steroids.

CTLA-4=cytotoxic T-lymphocyte-associated protein 4; PD-1=programmed cell death protein 1; CPIs=checkpoint inhibitors; irAEs=immune-related adverse events

Figure 2: Comparing the mechanism of action of classical oncological MABs and the newer immunomodulatory MABs[5,7,12]



MABs=monoclonal antibodies; EGFR=epidermal growth factor receptor; HER2=human epidermal growth factor receptor 2; TCR=T-cell receptor; Ant=antigen protein; PD-1=programmed cell death protein 1; PD-L1=programmed death-ligand 1; Co-stim=co-stimulatory signal

While the names of CPIs are all complex they share one thing in common, which is the presence of the letter 'l' (el) in the middle of their name. This is because the nomenclature stem for an immunomodulatory is the letter 'l'. Thus if a patient is receiving a MAB for cancer and the name contains an 'l' centrally (for example, nivolumab) it is worth considering that they may be receiving an oncological immunotherapy.[14]

3 Know which cancers CPIs can treat

The number of cancer sites for which CPIs are used is increasing. The current NICE-approved indications are listed in Table 1.[15–34]

Most indications are in the palliative, metastatic setting, although other indications are evolving, such as maintenance therapy and use in combination with other CPIs, chemotherapy, or radiotherapy. CPIs are being used in the adjuvant setting, with nivolumab now holding a European Medicines Agency (EMA) licence (NB not yet approved by NICE) as adjuvant therapy for metastatic melanoma.[35,36] This is under NICE review with other adjuvant indications in trial.[37]

4 Know how effective these treatments are

CPIs do not work for every patient or every type of cancer. However, they have an increasing role in cancer therapy because of their short-term and long-term benefits, and enduring effects even after the drug has been stopped.[2] In terms of long-term benefit, remission lasting for years is increasingly seen with a not insignificant number of patients with advanced melanoma benefiting from treatment 3, 5, and 10 years after therapy, even after discontinuation of treatment.[38,39] With other systemic anticancer treatments the effects

are generally limited after a patient stops treatment, with progression seen in a few months. This does not appear to be the case for CPIs, where the response is enduring.[38,39] The optimal duration of therapy is still to be determined; however, 2 years of treatment is currently standard practice in all tumour groups except melanoma,[21–34] which is under consideration.[40]

The main toxicities associated with CPIs are immune-related adverse events

5 Be aware of toxicities

On balance, CPIs are significantly better tolerated than other systemic anticancer therapies. Fatigue is common but tends to be experienced after a patient has been on treatment for a number of months. The main toxicities associated with CPIs are immune-related adverse events (irAEs). These occur as a result of off-target effects of the reactivated immune system and essentially mimic endogenous autoimmune diseases (Figure 3).[10]

Immune-related adverse events are often graded by severity:[42]
- grade 1—mild
- grade 2—moderate
- grade 3—severe
- grade 4—life-threatening.

Data from clinical trials show that grade 3–4 reactions occur in up to 27% of patients treated with CPIs that target CTLA-4; up to 19% for CPIs that target PD-1/PDL-1; and up to 58% for CPI combination treatment (CTLA-4 and PD-1/PDL-1).[1,2,13,41]

The most common irAEs include skin toxicities, colitis, hepatitis, and endocrinopathies, but any organ/system may be affected.[10,41]

Table 1: Checkpoint inhibitor agents in mainstream use approved by NICE[15–34]

Metastatic malignancy	Line of therapy	Checkpoint inhibitor
Malignant melanoma	First line	Ipilimumab and nivolumab[15] Nivolumab[16] Ipilimumab[17] Pembrolizumab[18]
	Second line and beyond	Ipilimumab[19] Nivolumab[16] Pembrolizumab[20]
Non-small-cell lung cancer	First line	Pembrolizumab[21]
	Second line and beyond	Pembrolizumab[22] Nivolumab[23,24] Atezolizumab[25]
Renal cell cancer	Second line and beyond	Nivolumab[26]
Urothelial cancer	First line (cisplatin ineligible)	Atezolizumab[27] Pembrolizumab[28]
	Second line and beyond	Atezolizumab[29] Pembrolizumab[30]
Head and neck cancer	Second line and beyond	Nivolumab[31]
Merkel cell cancer	Second line and beyond	Avelumab[32]
Classical Hodgkin lymphoma	Relapsed or refractory	Nivolumab[33] Pembrolizumab[34]

6 Understand how immune-related adverse events may present

Toxicities are generally episodic with patients having periods when they are well and others when they experience toxicity. IrAEs can occur months or years after finishing treatment; therefore, they are worth considering if a patient is unwell even if the patient is not currently receiving treatment.[41,43]

IrAEs can be grouped into symptomatic and asymptomatic toxicities (Table 2). Patients generally feel well even in the presence of symptoms, which can be falsely reassuring. Those presenting with symptoms should be treated with a high index of suspicion for an irAE and this should be discussed with oncology services.[41,45] For example, if a patient has diarrhoea on a CPI it is highly likely to be an irAE and not due to other causes such as infective diarrhoea, and the patient should be reviewed.

Patients are highly likely to present to primary care with irAEs that cause biochemical-only disturbances. This

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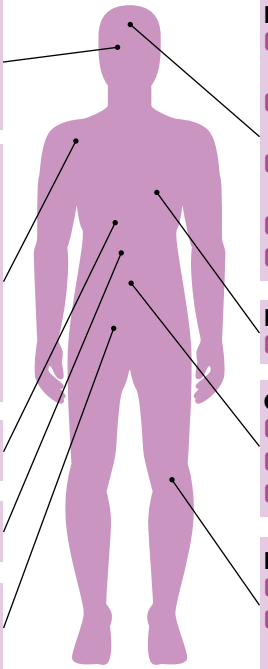
Figure 3: Common immune-related adverse events[1,2,10,13,41]



Eye
- Uveitis
- Iritis
- Optic myositis

Skin
- Maculopapular rash
- Erythema multiforme
- Psoriasis
- Stevens-Johnson syndrome
- Vitiligo
- Alopecia

Liver
- Hepatitis

Pancreas
- Pancreatitis

Renal
- Nephritis (including ATN and GN)

Neurological
- Peripheral neuropathy
- Guillain-Barré-like syndrome
- Myasthenia gravis-like syndrome
- Hyperaesthesia
- Headache

Lungs
- Pneumonitis

Gastrointestinal
- Colitis
- Enterocolitis
- Perforation

Musculoskeletal
- Arthritis
- Myopathies (including PMR)

Endocrinopathies
- Pituitary
  - hypophysitis
  - corticotropin (ACTH) decrease
  - secondary adrenal insufficiency
- Thyroid
  - hyperthyroidism
  - hypothyroidism
- Pancreas
  - diabetes mellitus
- Adrenal
  - primary adrenal insufficiency
- Gonads
  - secondary hypogonadism (primary gonadism is also a possibility)

Rare
- Myocarditis
- Epididymitis
- Cytokine release
- Haematological e.g. neutropenia

ATN=acute tubular necrosis; GN=glomerulonephritis; PMR=polymyalgia rheumatica; ACTH=adrenocorticotropic hormone

is because they are generally relatively asymptomatic with nebulous, non-specific symptoms. They are often clinically well which is an unhelpful marker so a blood test should be done (Table 3), even when suspicion is low.

7 Know how to manage toxicities

Generally, toxicities do not resolve spontaneously and intervention is usually needed even when the drug is withheld. There are several regional and national irAE management guidelines available.[41,44,45] These guidelines follow a general approach and where they differ, they align in the management of counterpart autoimmune disease, for example, CPI-induced colitis is managed as acute inflammatory bowel disease.

A general approach to treatment should be followed:[41,44,45]
- give high-dose corticosteroids (oral prednisolone or intravenous methylprednisolone)
- if the patient is improving, then wean off corticosteroids rapidly (but do not stop suddenly as this can be associated with a flare)
- if the patient is deteriorating, add in additional immunosuppression such as infliximab, mycophenolate mofetil, tacrolimus, or methotrexate
- if a patient has an endocrinopathy then lifelong hormone replacement with hydrocortisone, levothyroxine, or testosterone will be required in almost all cases.

> Generally, toxicities do not resolve spontaneously and intervention is usually needed even when the drug is withheld

Management of irAEs with immunosuppressive agents is not thought to decrease the anti-tumour effects of the CPIs.[47] Most irAEs (except endocrinopathies) are reversible and treatment can be re-started in most cases irrespective of toxicity type.

8 Be aware of the challenges these toxicities may present

Toxicities are hard to recognise, given the minimal symptoms they exhibit, which can be falsely reassuring.[10,41] Symptoms and biochemical disturbances can evolve quickly. The duration of toxicity and therefore immunosuppression often spans weeks to months.[48] Patients require robust follow up when recovering from toxicity. The side-effects of immunosuppression may be significant and include insomnia, oral candidiasis, hypertension, and weight gain.[49] IrAEs can be highly distressing for patients at a vulnerable point in their lives.

9 Understand the patient's experience of receiving CPIs

Most patients are well while receiving CPIs and remain well throughout treatment. Only around 20% of patients on monotherapy will experience significant (≥grade 3) toxicity.[1,49–52] However, the percentage of patients on combination CPI therapy who experience significant toxicity is much higher (approximately 60%).[2]

Immunotherapy treatment is not associated with all the negative connotations of chemotherapy. The CheckMate 025 trial examined quality of life alongside efficacy in patients receiving CPIs or tyrosine kinase inhibitors (TKIs). It found that patients receiving CPIs had a significantly improved quality of life compared with those on targeted agents.[48]

> Most patients are well while receiving checkpoint inhibitors and remain well throughout treatment

Patients generally feel well while receiving treatment. If patients are working when starting treatment they are often able to continue to work. Most patients report no ill-effects from the drug infusion[1,2,49–52] and continue their activities of daily living.[49] Although toxicity can have a significant impact while treatment is ongoing, it tends to be episodic with periods (often long periods) of wellness in between. Patients with endocrinopathies often feel well and have baseline level of function once hormonal replacement is optimised.[53]

The uncertainty of outcomes with these therapies is a significant issue. It can be challenging for patients who do not know if they will respond to treatment, if they will get a toxicity and how severe the toxicity will be, and if they will be able to continue therapy with CPIs.

Because of the potential for long-term response, CPIs bring uncertainty in the presence of a palliative diagnosis.[45] While the potential benefit is significant, those who do not respond to therapy or have a limited response may experience overwhelming disappointment. Tempering this appropriately is a challenge for healthcare professionals and patients alike. Conversely, for patients who do respond to CPI treatment, learning to live with the diagnosis, the tentative response, the scan anxiety every 3 months, the ever-present potential for progression, and the logistics of receiving treatment every 3–4 weeks for 2 years all provide significant challenges.

Table 2: Categorising irAEs as either symptomatic or asymptomatic[41,43,44]

Symptomatic irAEs	Relatively asymptomatic irAEs
Colitis	Hepatitis
Arthritis	Nephritis
Dermatitis	Endocrinopathies
Neuropathies	Thyroid dysfunction
Myopathies	Adrenal dysfunction (may be symptomatic if severe)
Ocular inflammation	Pituitary dysfunction (may be symptomatic if severe)
Pedal oedema	
Epididymitis	

irAEs=immune-related adverse events

Table 3: Recommended blood tests for a patient presenting to primary care[41,44,46]

Patient group	Blood tests
All patients	Full blood count Urea and electrolytes Liver blood tests (including alanine aminotransferase and aspartate transaminase) Thyroid function tests Cortisol Random glucose
Male patients	Testosterone

10 Be aware of the impact of CPIs on general practice

Previous estimations of prognosis in metastatic disease need to be revised in light of these new therapies. GPs and practice nurses need to be aware that patients may be offered these treatments, where previously there were no appropriate treatment options available. Patients may gain a complete response to their disease, which may be long and durable. Not all patients in all tumour groups will respond but an increasing number in an increasing selection of

site-specific tumours are receiving immunotherapies. Immunotherapies work in a novel way, resulting in different and challenging toxicities.

It is important to be aware of these toxicities. If a patient is exhibiting symptoms of toxicity such as diarrhoea, then it is highly likely that it is a CPI-induced irAE. It is necessary to rule out other causes but this should not delay referral/treatment. Patients often present with nebulous and vague symptoms so a blood test is needed for complete assessment. Patients can look well while their inflammation is deteriorating. The oncology team on call should be contacted for clarification.

The long-term effects of CPIs are yet to be fully realised but our knowledge of them is improving as their use increases. This is likely to require a seamless interface between primary, secondary, and tertiary care to ensure that patients are effectively supported in the long term. Provision and management, particularly of endocrinopathies, is likely to require cross-sectional partnership where patients can be assessed, monitored, and managed in the community with specialist input as needed.[41]

Conclusion

The introduction of CPI therapies for patients with cancer has revolutionised therapy and is likely to continue to change the landscape over the coming years. CPIs have great potential for improved outcomes, particularly in malignancies with previously limited therapeutic benefit. However, they present challenges in the short term and long term that have far-reaching impacts for patients and healthcare services. This will require increased working partnerships across primary, secondary, and tertiary services to ensure that all involved are informed and supported in the provision of care to this group of patients.

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