Immunotherapy

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Immunotherapy, also known as *immune checkpoint inhibition,* has revolutionized oncology care. Many metastatic malignancies, such as melanoma and lung, bladder, and kidney cancer, that were previously fatal within months of diagnosis can now be treated with therapies that result in long-term survival.

How does immunotherapy work?

Immune checkpoint proteins such as programmed cell death 1 ligand 1 (PD-L1) and CTLA-4 (cytotoxic T lymphocyte–associated protein 4) are normally expressed by tissues to prevent autoimmune attack by T cells (**Figure 1**).[1] Many cancers, especially those that are highly mutated, are able to hijack these immune checkpoint proteins to escape immune attack.

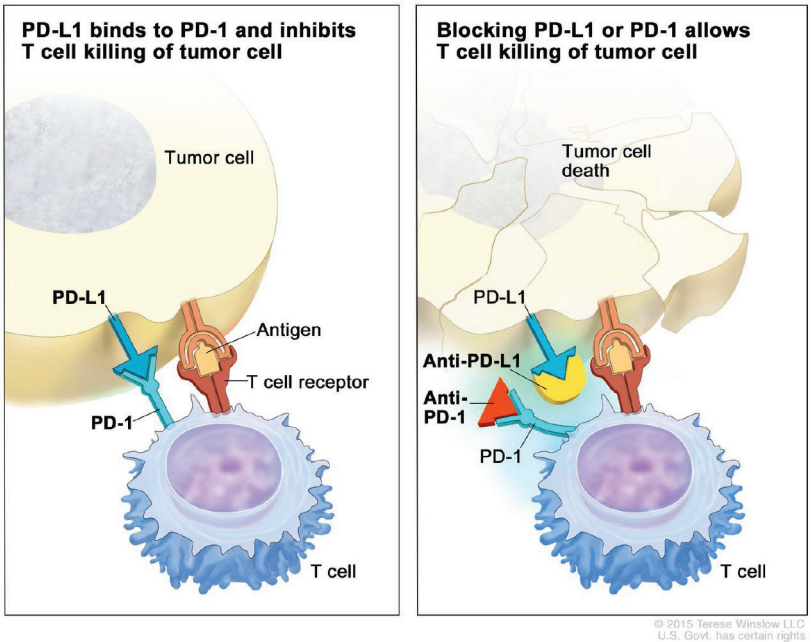
Immune checkpoint inhibitors block PD-L1, programmed cell death 1, CTLA-4, or any combination of these receptors with monoclonal antibodies, thereby activating the body's T cells to recognize and destroy cancer cells.[2] Expression of PD-L1 by tumour cells can be measured during pathologic analysis of tumours, but levels of expression of this biomarker do not always correlate with immunotherapeutic response.[3]

Does it really work?

Statistically significantly increased survival has been seen in many immunotherapy trials, with the alluring potential of long-term disease-free survival. Pooled data from 4 studies of patients with metastatic non–small cell lung cancer (NSCLC) for whom first-line chemotherapy had failed and who were given second-line immunotherapy (nivolumab), versus standard-of-care chemotherapy (docetaxel), showed a 4-year survival rate of 16% compared with 4% in those who did not receive immunotherapy.[4] Overall survival was higher (19%) for those with PD-L1 expression greater than 1% compared with those with PD-L1 expression less than 1% (11%). Results for melanoma were even more astounding, with a 52% 5-year survival in patients with stage 4 melanoma in the CheckMate 067 trial, when a traditional 1-year survival benchmark for these patients would be 25% to 35%.[5]

After immunotherapy was shown to be effective in treating metastatic disease, it was then tested in the adjuvant setting in the PACIFIC trial. Patients with stage 3 unresectable NSCLC and a high risk of recurrence received immunotherapy (durvalumab) after completion of standard radiotherapy and chemotherapy. A statistically significant improvement in time to progression

Figure 1. Mechanism of action of immunotherapy



PD-1—programmed cell death 1, PD-L1—programmed cell death 1 ligand 1.

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or death (hazard ratio of 0.52) was noted for these patients.[6] In resected stage 3 melanoma, 1 year of adjuvant immunotherapy (pembrolizumab) increased recurrence-free survival (hazard ratio of 0.57).[7]

The role of neoadjuvant (pre-definitive treatment) immunotherapy is now a focus of investigation[8] in high-risk NSCLC, where it has increased overall survival,[9] and in melanoma, where substantial pathologic responses have been seen with 2 cycles of immunotherapy before surgery.[10]

Which cancers can immunotherapy treat?

As a result of these trials and the hundreds of others that are ongoing, immunotherapy is now standard of care for many cancers (**Box 1**).[11] Of interest, immunotherapy does not seem to be effective in treating pancreatic and colon cancers, perhaps owing to lower tumour mutational burden, which renders these tumours less antigenic.[3] Breast cancer also has a low mutational load; however, there might be a role for immunotherapy in the treatment of metastatic triple-negative breast cancer.[12]

How is immunotherapy administered?

Immunotherapy drugs are generally intravenous infusions given in 2- to 6-week cycles for up to 2 years in the metastatic setting, and for shorter durations (1 month to 1 year) for adjuvant and neoadjuvant indications. Response to immune checkpoint inhibitors might be delayed by as much as 6 months after therapy and can last long after therapy is discontinued.[2] Radiation given before immunotherapy might boost the efficacy of immune response, perhaps owing to increased release of tumour antigens.[13] Caution should be used in reassessing cancer response to treatment in patients too early after initiation of immunotherapy, as "pseudoprogression" can be seen, whereby tumours initially look worse on imaging before they begin to shrink, owing to intense tumour necrosis and inflammation.[14] Patients with pre-existing autoimmune disorders might be able to undergo immunotherapy, but these patients have not been studied in clinical trials and should be intensively monitored.[3]

Box 1. Cancers commonly treated with immunotherapy

Immunotherapy is the standard of care for the following cancers:

- Head and neck squamous cell carcinoma
- Melanoma
- Renal cell cancer
- Urothelial cancer
- Non–small cell lung cancer
- Hepatocellular cancer
- Esophageal cancer
- Microsatellite instability–high colon cancer
- Hodgkin lymphoma

What are the side effects of immunotherapy?

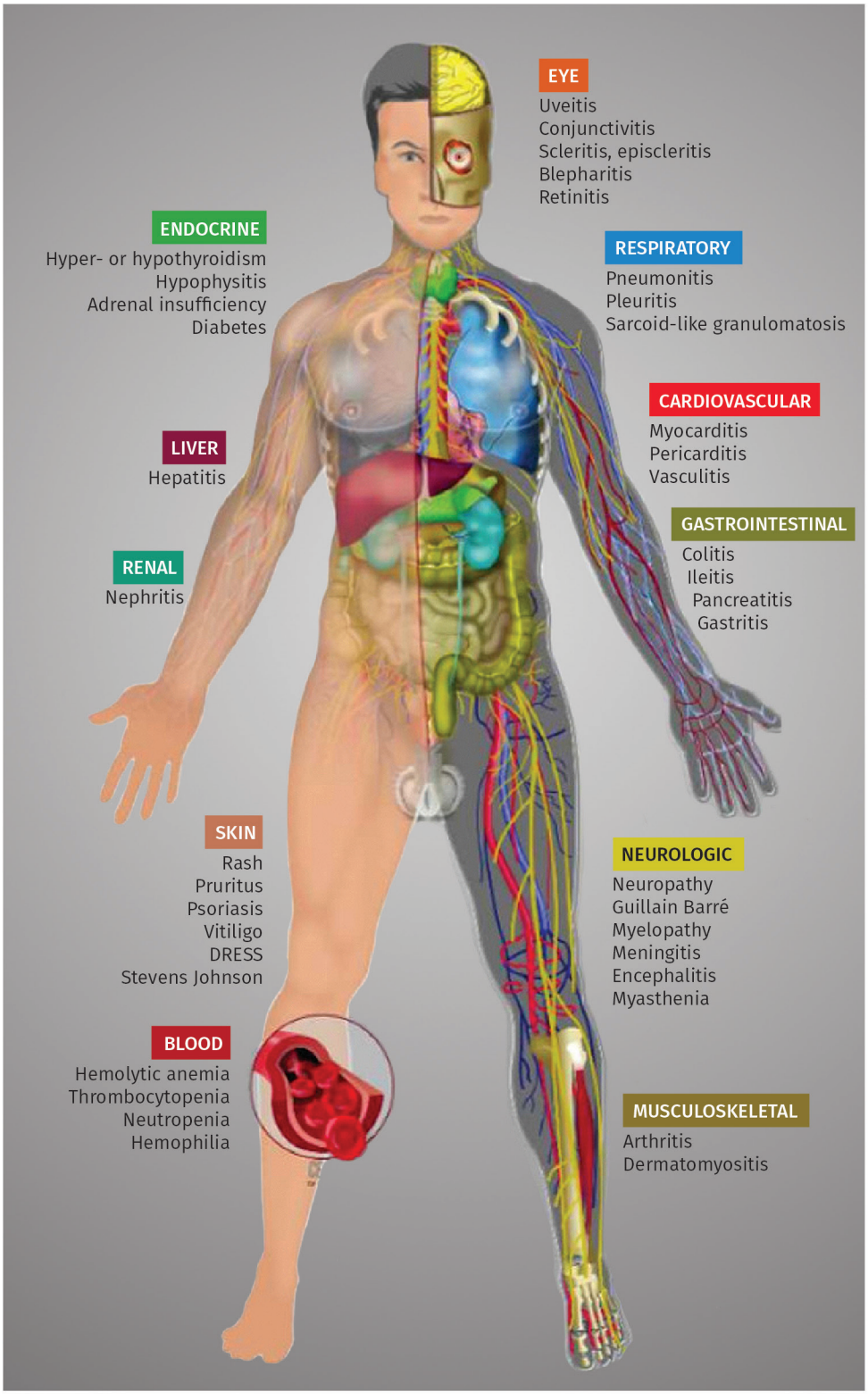
The downside of immunotherapy is the risk of immune-related adverse events (irAEs). Starting weeks after initiation of therapy and potentially presenting months after treatment completion, the escalated immune response primed by immunotherapy might cause the body to attack its own healthy tissue. Such "off-target" immune responses can lead to irAEs such as hepatitis, pneumonitis, colitis, hypophysitis, dermatitis, nephritis, pancreatitis, or any tissue inflammation (**Figure 2**).[15,16] The occurrence of irAEs might indicate improved cancer outcomes. As the range of irAEs is broad, the timing of onset is variable, and the presenting symptoms are nonspecific, clinicians must have a high index of suspicion to recognize irAEs in patients undergoing immunotherapy.

Severe irAEs necessitate cessation of therapy, and steroids are used to treat them, generally with 1 to 2 mg/kg of prednisone or 2 mg/kg of methylprednisolone, tapering gradually over at least 6 weeks.[17] Patients presenting with profound fatigue should have a morning cortisol level checked to ensure there is no hypophysitis. Immune-related adverse event colitis can be life threatening and so must be recognized as a complication of therapy, as treatment with bowel motility agents alone can lead to bowel perforation and death. If colitis does not respond to steroids, escalation of therapy to infliximab must be considered. Given the immunosuppressive effect of steroids, pre-existing steroid use should be minimized where possible in patients receiving immunotherapy; however, irAEs are potentially life threatening and steroid use must not be delayed in this setting.[18]

Conclusion

While immunotherapy has irrevocably changed the field of oncology, there remains much to be learned about the optimal use of these agents. Clinical trials are being conducted to evaluate the suitable dose and duration of therapy. Much needs to be learned about toxicity identification, management, and prevention. Given the expanding indications for immunotherapy and the potential for irAEs to develop months after treatment, family physicians increasingly need to be aware of these agents and the range of potential irAEs so that they can effectively co-manage their cancer patients with oncologists.

Figure 2. Immune-related adverse events



DRESS—drug reaction with eosinophilia and systemic symptoms.

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Competing interests
None declared

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