Principles of immunotherapy

Classes of immunotherapy drugs and mechanism of action

Clinical management of immunotherapies
Overview of immunotherapy

Immunotherapy, in the cancer setting, is any treatment which increases or restores the immune system’s ability to detect and destroy cancer cells.

Immunotherapies assist the immune system by:

- increasing the amount of tumour antigens available
- increasing the amount of immune effector cells (such as B cells or cytotoxic T cells), or improving their action
- inhibiting actions which lead to an immunosuppressive tumour environment.

Benefits & limitations of immunotherapy

<table>
<thead>
<tr>
<th><strong>Benefits</strong></th>
<th><strong>Limitations</strong></th>
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<tbody>
<tr>
<td>Immunotherapy has the potential to selectively target cancer cells.</td>
<td>It is difficult to predict which patients will benefit from immunotherapy.</td>
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<tr>
<td>Immunotherapies may have an advantage where other therapies have failed in the treatment of refractory disease.</td>
<td>Immunotherapy is not effective in the treatment of all cancer types.</td>
</tr>
<tr>
<td>Immunotherapies may generate an immune memory and contribute to a sustained response.</td>
<td>Some tumours may be resistant or become quickly resistant to immunotherapy.</td>
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The human immune system

The human immune system is a complex network of cells, organs and processes which work together to rid the body of pathogens and damaged cells.

The immune system involves two lines of defence.

- **Innate**: rapid and non-specific response to pathogens.
- **Adaptive**: slower sustained response, antigen specific.

The main cells involved in immunity are leukocytes (commonly referred to as white blood cells).

There are three types of leukocytes.

- **Lymphocytes**: Activate when they recognise their specific antigen.
  - **T cells**: Neutralise antigens and contribute to immune memory and immune regulation.
  - **B cells**: Neutralise antigens and contribute to immune memory. Release antibodies.

- **Monocytes**: Activate the adaptive immune system by presenting antigens to B and T cells.

- **Granulocytes**: Ingest and destroy pathogens and contribute to an inflammatory response. Include neutrophils, eosinophils, basophils and mast cells.

Immunity and cancer

Some mutations allow cancer cells to avoid immune detection and grow uncontrollably into a tumour.

Tumour cells may use the following to assist immune escape:

- reducing their expression of tumour antigens
- reducing the amount of T cell activating molecules on their surface
- increasing the amount of T cell deactivating molecules on their surface
- creating an immunosuppressive tumour environment.
Monoclonal antibodies

Monoclonal antibodies may be used in cancer treatment as a targeted therapy or as an immunotherapy.

When acting as an immunotherapy, monoclonal antibodies rely upon involvement from the immune system in order to damage or destroy tumour cells.

Monoclonal antibodies used as an immunotherapy have various mechanisms of action in treating cancer.

- Flagging tumour cells for destruction by immune cells.
- Activating the complement system, resulting in the release of cytokines which attack cell membranes and cause cell death.
- Interrupting immunosuppressive cell signalling (immune checkpoint inhibition).

Cancer vaccines

There are a variety of cancer vaccines currently in development. Cancer vaccines are not widely approved for use in Australia.

Therapeutic cancer vaccines increase tumour antigen presentation, assisting the immune system to recognise the tumour and activate the adaptive immune system.

Another type of cancer vaccine is called an oncolytic vaccine (OV). OV introduces a virus into the body which is capable of selectively infecting and killing only the cancer cells.

Other non-specific immunotherapies

Non-specific therapies stimulate the immune system by:

- prompting the growth and division of immune cells
- increasing the quantity of immune cells
- drawing immune cells to the tumour environment.

Examples of non-specific immunotherapies include cytokine therapy, such as interferon and interleukin therapy, Adoptive cell transfer, including CAR T cell therapy and BCG therapy.

Immune checkpoint inhibitors

Immune checkpoint inhibitors are a subset of monoclonal antibodies which disrupt the extracellular pathways (immune checkpoints) that tumour cells use to suppress immune activity.

Two common immune checkpoints which play a role in tumour immunity are PD1/PDL1 and CTLA4. When these pathways are activated T cell activity is reduced.

Monoclonal antibodies designed to bind to CTLA4, PD-1 or PD-L1 can prevent these pathways from being completed, improving T cell function.

Examples of immune checkpoint inhibitors include nivolumab, pembrolizumab and ipilimumab to name a few.

Summary

Classes of immunotherapy drugs and mechanism of action

Click here to view the Classes of immunotherapy module
Principles of safe handling and preparation

There is limited information available about the hazardous potential and safe handling and preparation requirements for monoclonal antibodies. The following recommendations apply to currently marketed monoclonal antibodies (MABs) except MABs conjugated to a cytotoxic agent, fusion protein or a radioisotope; these are considered hazardous.

<table>
<thead>
<tr>
<th>Safe handling recommendation</th>
<th>Administration</th>
<th>Dose Preparation</th>
</tr>
</thead>
<tbody>
<tr>
<td>The use of gloves and effective hand hygiene</td>
<td>Recommended</td>
<td>Recommended</td>
</tr>
<tr>
<td>A respirator mask and protective eyewear</td>
<td>Not mandated. May be considered where disconnecting administration lines may present a risk of aerosolisation.</td>
<td>Recommended</td>
</tr>
<tr>
<td>The use of gowns and/or coveralls</td>
<td>Not warranted</td>
<td>Not warranted</td>
</tr>
<tr>
<td>The use of isolator cabinets and cytotoxic drug safety cabinets</td>
<td>Not required</td>
<td>May be considered to reduce operator exposure</td>
</tr>
<tr>
<td>The use of closed systems</td>
<td></td>
<td>The area should be restricted and centralised</td>
</tr>
<tr>
<td>Suitability of work area</td>
<td></td>
<td>In accordance with the disposal of clinical waste, i.e. not as cytotoxic waste</td>
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Hypersensitivity reaction

Hypersensitivity is an adverse reaction to a drug and can occur whilst a drug is being given or within a few hours up until a few days following administration.

Hypersensitivity reactions range in severity. The most severe reaction is anaphylaxis which can be fatal if not treated early.

The signs and symptoms of hypersensitivity reactions include:
- flushing and/or itching of the skin
- skin rash
- tightness in the throat
- alterations of heart rate and blood pressure
- dyspnoea and/or hypoxia
- chest pain/discomfort
- back and/or abdominal pain
- nausea, vomiting, and/or diarrhoea
- dizziness and/or seizures.

During administration it is important to closely monitor the patient for the above signs and symptoms as well as for changes in:
- blood pressure
- temperature
- pulse
- oxygen saturation.

If a hypersensitivity reaction is suspected it is important to:
- stop the infusion
- organise urgent medical review
- continue to monitor vital obs
- manage symptoms
- be prepared to initiate cardiopulmonary resuscitation is required
- call a Medical Emergency per local guidelines.

Immune related adverse events

Treatment with immune checkpoint inhibitors can result in a loss of immune regulation and may result in damage to healthy tissues.

Immune related adverse events (irAEs) are a distinctive range of immune-mediated toxicities.

Immune related adverse events may:
- affect any body system
- present at any time during or after treatment
- be life-threatening.

irAEs may present as a physical symptom or be identified in blood test results. Early identification and swift management are key in avoiding life threatening severity.

See the irAE table here.

Common irAE management techniques

- Treatment of symptoms (some grade 1 toxicities).
- Withholding treatment (grade 1 – 3 toxicities).
- Discontinuation of treatment (grade 3 - 4 toxicities).
- Systemic corticosteroid treatment (grade 2 - 4 toxicities).

Referral to other specialists should be considered as part of the management plan.

Patients experiencing severe grade 3 or 4 toxicities may require hospitalisation.
Nursing assessment and monitoring

The identification of upward or downward trends in blood results and signs of new or worsening of symptoms from baseline may indicate the onset of irAEs. Therefore, it is important to establish a baseline and compare subsequent assessments against baseline to identify trends.

The susceptibility of developing irAEs should be considered in the baseline assessment of patients on immunotherapy. The following may increase susceptibility to irAEs:

- history or current treatment of autoimmune disease
- previous use of immune checkpoint blockade therapy
- other previous therapies e.g. radiation therapy.

In addition to a physical assessment, the European Society for Medical Oncology (ESMO) recommends that the following blood tests are performed at baseline and subsequent assessment.

- Thyroid function tests
- Other endocrine tests (e.g. adrenal and hormone)
- Electrolytes, urea and creatinine (EUC)
- Liver function tests
- Full blood count

A physical assessment should be undertaken at every cycle.

Patient education

The following are education priorities for patients receiving immunotherapy.

- How immunotherapy works
- Patterns of response
- Treatment aim
- Treatment protocol
- Treatment-related procedures and reactions
- Self-care procedures
- Supportive care services
- Identify irAEs

Patients, their families and carers require education on how to identify and respond to irAEs to avoid potentially life threatening consequences.

The following information should be provided to patients, their families and carers in both verbal and written form.

- Signs and symptoms
- How to perform a self-assessment
- When irAEs may arise
- When and how to get help
- What situations require urgent care
- Who to contact