Part 5: Fundamentals of cancer targeted therapies

Rationale

In recent years targeted therapies have been established as a vital cancer treatment modality.

Knowledge and understanding of the molecular and biological processes that transform a normal cell to a malignant cell have advanced. There has also been a corresponding increase in the number of agents used to target these processes and alter the growth and survival of cancer cells.

Specialist Cancer Nurses (SCNs) must keep abreast of this emerging treatment modality and its application in cancer treatment.

You should already have a good understanding of the concepts underpinning targeted therapies. If you would like an update before starting this module, you may wish to review:

- **EdCaN module: The Biology of Cancer**

Key concepts

- Classification of targeted therapies.
- Factors influencing the selection of targeted therapies for cancer.
- Role of targeted agents in the treatment and palliation of cancer.
- Methods for administering targeted therapies.
- Future directions in therapies on various health domains.
- Prevention, detection, and management of common health alterations experienced by people receiving targeted therapies for cancer.

Objectives

On completion of this module you should be able to:

1. Explain the role of targeted therapies in the treatment and palliation of cancer.
2. Outline the classifications of targeted therapies used in the management of cancer.
3. Discuss principles for administering targeted therapies.
4. Discuss the experience and impact of targeted therapies on the various domains of health.
5. Implement interventions to prevent, detect, and manage common health alterations experienced by people receiving targeted therapies for cancer.
6. Discuss the challenges of targeted therapies for cancer treatment now and in the future.

Learning activities

At times, you will have learning activities to complete. Click on the learning activities button and a list of questions will pop up. The questions will relate to the content you've just read or the video you've just watched.

Resource links

Resource links are included throughout the resource. These links lead to interesting articles or websites, and are designed to encourage you to explore other available resources.

Suggested citation:

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Targeted therapies in cancer treatment

The range of targeted therapies has increased exponentially in the last ten years in cancer care and continues to be the focus of much anticancer drug development.[1] Targeted cancer therapies are drugs or other substances that interfere with specific molecules involved in cancer cell growth and survival. Targeted therapies are often cytostatic (they block tumour cell proliferation) whereas standard chemotherapy agents are cytotoxic (they kill tumour cells).[1]

Biological and molecular targeted therapies have therapeutic and supportive roles in cancer control:[1, 2]

- curative when used in the primary or adjuvant setting
- improve treatment response by improving disease free survival when used in conjunction with conventional therapies
- control or stabilise disease in advanced cancers in the palliative care setting
- maintain or enhance quality of life.
- minimise the severity of toxicities associated with other therapeutic treatments.

The mechanism of action underlying biological and molecular targeted therapies vary depending on the agent, and include:[1, 3]

- enhancement of the individual's immune system
- alteration of the environment in which cancer cells grow
- increasing the vulnerability of cancer cells to the body's immune system
- alteration of the pathway by which normal cells transform to malignant cells
- prevention of metastasis of cancer cells
- enhancing the repair of normal cells damaged by treatment
- changing cancer cells so they behave like healthy cells
- facilitating delivery of toxic therapies to cancer cells.

As knowledge develops regarding the hallmarks of cancer and enabling characteristics of cancer development and progression, mechanism based targeted therapies are emerging. Examples of this are provided in Table 1: Therapeutic Targeting of the Hallmarks of Cancer.

Table 1: Therapeutic Targeting of the Hallmarks of Cancer[4]
(Adapted from Hanahan, D. and Robert A. Weinberg, *Hallmarks of Cancer: The Next Generation.* Cell, 2011. **144**(5): p. 646-674.)

Hallmarks of cancer	Examples of therapeutic approaches
Resisting cell death	Proapoptotic BH3 mimetics
Deregulating cellular energetics	Aerobic glycolysis inhibitors
Sustaining proliferative signaling	EGFR inhibitors
Evading growth suppressors	Cyclin-dependent kinase inhibitors
Avoiding immune destruction	Immune activating anti-CTLA4 mAb
Enabling replicative immortality	Telomerase inhibitors
Tumour-promoting inflammation	Selective anti-inflammatory drugs
Activating invasion and metastasis	Inhibitors of HGF/c-Met
Inducing angionesis	Inhibitors of VEGF signaling
Genome instability and mutation	PARP inhibitors

Key resources

Targeted therapies, aspects of pharmaceutical and oncological managment[5] Cancer Forum, 2013
Hallmarks of cancer: The next generation[4] Cell, 2011

Learning Activities	
Completed	Activities
☐	1 Access Targeted therapies, aspects of pharmaceutical and oncological managment[5] and: • develop a definition of targeted therapy • outline how targeted therapy is different to conventional chemotherapy
☐	2 Briefly describe how you would explain the role of targeted therapies to a nurse new to the field of cancer care.
☐	3 Discuss some of the concerns that a person about to undergo targeted therapies may have about these treatments.

Categories of targeted therapies

Current broad groups of targeted therapies include:[1]

- *Hormone therapies* slow or stop the growth of hormone-sensitive tumours, which require certain hormones to grow. For example, Anastrazole targets amomatase and is indicated for hormone dependent postmenopausal breast cancer.[5]
- *Signal transduction inhibitors* block the activities of molecules that participate in signal transduction, the process by which a cell responds to signals from its environment. For example, Gleevec / imatinib / STI571 is used in early chronic myeloid leukaemia which is driven by one oncoprotein, Brc-Abl. [6]
- *Apoptosis inducers* cause cancer cells to undergo a process of controlled cell death called apoptosis. For example, Temsirolimus is an mTOR inhibitor used in advanced renal cell carcinoma.[5]
- *Angiogenesis inhibitors* block the growth of new blood vessels to tumours (a process called tumour angiogenesis). For example, bevacizumab is a monoclonal antibody that recognizes and binds to vascular endothelial growth factor. [5]
- *Immunotherapies* trigger the immune system to destroy cancer cells. Some immunotherapies are *monoclonal antibodies* that recognize specific molecules on the surface of cancer cells. These antibodies are produced by recombinant DNA technology and may consist of human and non-human protein, or be partially or fully humanised. Chimeric antibodies are more likely to elicit hypersensitivity reactions due to pre-existing immunity to foreign animal protein.[7] Monoclonal antibodies that deliver toxic molecules can cause the death of cancer cells specifically. For example, trastuzumab targets HER2 and is indicated for HER2-positive for breast cancer. [5]
- *Cancer treatment vaccines* are designed to treat cancers that have already developed by strengthening the body's natural defences against the cancer. For example, sipuleucel-T (Provenge®) is designed to stimulate an immune response to prostatic acid phosphatase (PAP), an antigen that is found on most prostate cancer cells.[8]

Certain agents may fall under more than one category. For example:[9]

- trastuzumab is a monoclonal antibody and also falls under the EGFR targeted therapy category
- gefitinib is an EGFR tyrosine kinase inhibitor and also has action as an angiogenesis inhibitor.

The SCN needs to keep abreast of current and investigational biological and molecular targeted agents and their application in clinical practice. As knowledge of molecular processes improves, the categories and application of biotherapeutic agents will evolve. The large number of agents currently under investigation may be approved for clinical practice. Existing agents may also have application in the treatment of new diagnostic groups and in combination with antineoplastic agents.

Resource

A list of approved targeted therapies in Australia was published in Cancer Forum in 2013.

Brown, M.P. & Burdett, N. (2013) Targeted therapies, aspects of pharmaceutical and oncological management. Cancer Forum, 37 (1)

Learning Activities		
Completed	Activities	
☐	1	Identify an example where a targeted therapy is being used in combination with antineoplastic agents.
☐	2	Explain the rationale for combining this biological agent with antineoplastic agents.
☐	3	Describe one targeted therapy that has application in more than one cancer.
☐	4	Explain the mechanism of action of the targeted therapy identified in response to learning activity 3.

Cytokines

Cytokines such as interleukin-2 (IL-2), interferon (IFN), and tumour necrosis factor (TNF) have been used with varying success in the treatment of cancer, due to their immunostimulatory effect.

Interferons were the first cytokine to be studied.[9] The interferons have a number of activities such as:[10]

- antiviral
- anti-proliferative
- immunomodulation
- inhibition of angiogenesis
- regulation of differentiation
- anti-tumour effects.

They have been used in cancer therapy in a variety of doses and schedules. Interferons can be divided into two types:[11]

- Type I (IFN-α and IFN-β) binds to the cell surface receptor of effector cells
- Type II (IFN-γ) binds to different cell surface receptors.

Interleukins are cytokines that send signals primarily between lymphocytes. They have also been found to have broader activities such as coordinating various immune cell activities and other organ systems to mount a multi-level defense.[9] They do not act independently but are messengers to initiate, coordinate, and sometimes augment potent immune defense activities.[9]

There are several interleukins that have been discovered and they are identified by a number. Currently there is only one interleukin, IL-2, that has been used as an anticancer therapy at varying doses and schedules.

There are two types of TNF:[12]

- TNF-α (cachectin) actions include increased catabolism, enhanced phagocytosis, and tumour destruction
- TNF-β (lymphotoxin) actions include cell killing and direct tumouricidal capability.

Colony stimulating factors (CSF) or haematopoietic growth factors (HGF) are naturally occurring proteins or cytokines that regulate proliferation, differentiation, and maturation of all blood cell lines.[13] Recombinant DNA technology has permitted the manufacture of large quantities of these substances.

Some HGF stimulate the growth of multiple blood cell lines such as granulocyte-macrophage CSF (GM-CSF). Others stimulate production of a single cell line.[13]

Single cell line CSF includes:

- granulocyte-CSF (G-CSF)
- macrophage-CSF
- erythropoietin (EPO)
- thrombopoietin (TPO).

Recombinant versions are used as supportive therapy and can prevent or minimise the myelosuppressive effects of cancer control efforts.[13]

Learning Activities	
Completed	Activities
☐	1 Identify a cytokine used in cancer control and describe the: • mechanism of action • indications for its use in clinical practice • nursing care considerations associated with use of this agent.

Monoclonal antibodies

Monoclonal antibody therapy includes some of the first agents that were used in the modern era of targeted therapies. Antibodies are glycoproteins produced in response to a specific antigen found in the body. Monoclonal antibodies are artificially produced proteins, from a single clone of cells sensitised to a specific antigenic protein present on the surface of a target tumour.[10]

There are four distinct types of monoclonal antibodies:

- murine
- chimeric
- humanised
- human.

Hybridoma technology was first used to produce large quantities of specific antibodies using mouse models.[14] Early challenges of this model were the immunogenic reactions involving murine antibodies. Further progress in this area with genetic engineering techniques produces monoclonal antibodies with components from both mouse and human which improves therapeutic applications.[14, 15]

In order for monoclonal antibodies to be successful in cancer therapy, a number of key characteristics must be met:[14]

- specificity - the target antigen must be present on malignant cells only
- density - the quantity of target antigen expression directly relates to tumour response
- function - the role of target antigen in cell survival and proliferation is instrumental in cell destruction
- modulation - modulating antigens internalise the antibody / antigen complex once binding has taken place. This is required for toxin conjugated monoclonal antibodies and is less desirable when it occurs rapidly for unconjugated monoclonal antibodies.

Both unconjugated and conjugated monoclonal antibodies are approved for clinical use in cancer therapy:[9]

Unconjugated monoclonal antibodies target a specific anti-tumour antigen initiating an immunologic response reliant on the host immune mechanisms to destroy the target cell. Unconjugated monoclonal antibodies include:

- rituximab
- trastuzumab
- alemtuzumab.

Conjugated monoclonal antibodies carry radioimmunoconjugates, chemoimmunoconjugates or immunotoxins to a specific target antigen. They are capable of killing cells and do not require any host immune mechanisms. Conjugated monoclonal antibodies include:

- gemtuzumab ozogamicin
- Y^{90} ibritumomab tiuxetan
- I^{131} tositimomab.

- Several other monoclonal antibodies have been developed that target specific molecular events and will be discussed later:

- bevacizumab
- cetuximab
- panitumumab.

Learning Activities		
Completed	Activities	
☐	1	For the monoclonal antibody rituximab, identify the following: • the antigen targeted • its mechanism of action • indications for its use in clinical practice • nursing care considerations.
☐	2	You are asked by a woman who has T-cell lymphoma why she is not receiving rituximab as part of her treatment. Outline your response and identify information resources you may provide her.

Cellular therapies

Tyrosine kinase inhibitors (TKIs) are small molecule compounds that block the ATP binding site of the TK enzyme.[16] Imatinib was the first TKI to be used in humans and inhibits the protein tyrosine kinases - BCR-ABL, PDGFR, and KIT.[10, 11]

Imatinib was developed to target the fusion protein BCR-ABL present on the Philadelphia chromosome in chronic myeloid leukaemia (CML). It acts by blocking the binding site of BCR-ABL thus preventing cell proliferation. Imatinib has been found to have application in the management of other malignancies as it also inhibits two other tyrosine kinases - PDGFR and KIT. This has led to the approval of imatinib in: [5]

- gastrointestinal stromal tumours
- chronic myelomonocytic leukaemia
- aggressive systemic mastocytosis
- hypereosinophilic syndrome / chronic eosinophilic leukaemia
- dermatofibrosarcoma protuberans.

An emerging problem of imatinib therapy is the development of resistance. Imatinib failure results when there is reactivation of BCR-ABL mutations diminishing the binding of the drug.[12] Second generation tyrosine kinases (such as dasatinib and nilotinib) have different binding characteristics. They have been found to be more potent and highly effective in the setting of imatinib failure.[12]

EGFR tyrosine kinase inhibitors

The epidermal growth factor (EGF) family of receptors comprises four closely related but distinct receptors:[10, 17]

- HER1/EGFR/ErbB-1
- HER2/ErbB-2
- HER3/ErbB-3
- HER4/ErbB-4.

The EGF family receptors are transmembrane glycoproteins that regulate cell growth, differentiation, and survival. [10, 12, 17] The EGFR-tyrosine kinase signal is strictly regulated in normal processes such as embryogenesis, organogenesis, and epithelial tissue repair. Events that can switch on EGFR-tyrosine kinase signaling extracellularly include ligand binding of EGFR and over expression of EGFR.[10]

Intracellular events can include:[10]

- over expression of EGFR
- cross communication between other receptors
- loss of regulatory mechanisms
- mutations of EGFR.

Several cancers have been identified that over express this receptor, resulting in more aggressive tumours with an increased tendency for invasion, metastases, and shortened survival.[10, 12] These cancers include:

- breast
- lung

- head and neck
- pancreatic
- colorectal
- kidney
- ovarian.

A number of monoclonal antibodies have been developed to block the extracellular domain:[9]
- EGFR-1 includes cetuximab and panitumumab in colorectal cancer
- EGFR-2 includes trastuzumab and was the first successful HER-2 targeted therapy in breast cancer.

Small molecule compounds have been developed that target the intracellular domain of EGFR. They inhibit phosphorylation of tyrosine kinase, preventing the message for cell division being sent to the nucleus.[9]
- Erlotinib inhibits EGFR-1 in lung and pancreatic cancer.
- Gefitinib inhibits a number of tyrosine kinases in lung cancer.
- Lapatinib blocks both EGFR-1 and 2 receptor kinases in breast cancer.

Learning Activities	
Completed	Activities
☐	1 Identify a molecular targeted therapy used in cancer treatment, and describe the: • mechanism of action • indications for its use in clinical practice • nursing care considerations.

Cancer vaccines

Cancer vaccines are a type of active specific immunotherapy. Antigens are administered and then presented to the immune system in a way that will activate or enhance a cell mediated anti-tumour response, attacking existing cancer cells.[10, 18] They are intended to delay or stop cancer cell growth; to cause tumour shrinkage; to prevent cancer from coming back; or to eliminate cancer cells that have not been killed by other forms of treatment.[8] Different approaches are being used to develop cancer vaccines and most vaccines remain in clinical trial settings.

Cancer preventive vaccines target infectious agents that cause or contribute to the development of cancer.[8] Australia implemented a national, publicly-funded vaccination program against human papillomavirus (HPV) in 2007.[19] The quadrivalent HPV vaccine (Gardasil) is delivered over a three-dose course, and provides protection against two oncogenic types (HPV 16/18), which are estimated to be associated with approximately 78% of cervical cancer in Australia.[19]

Learning Activities	
Completed	Activities
☐	1 Access current guidelines and Update on HPV vaccination in Australia[19] (Cancer Forum, 2014) • discuss your response to a woman who is concerned about the potential effects of the Gardasil vaccine on her 12 year old daughter

Angiogenesis inhibitors

Anti-angiogenic agents work by targeting the neovasculature of tumours, halting their growth, preventing tumour invasion, and precluding metastatic diffusion.[20] Anti-angiogenic agents ideally should be used with other cancer therapies. More than one agent may be required to target different steps in the angiogenesis process.[21]

Angiogenesis inhibitors can have either a direct or indirect effect.[10]

- *Direct* anti-angiogenesis agents prevent vascular endothelial cells from proliferating, migrating, or avoiding cell death. They are not as likely to induce drug resistance.
- *Indirect* anti-angiogenesis agents prevent the expression of a tumour protein that activates angiogenesis or blocks the expression of its endothelial cell receptor.

Anti-angiogenesis agents that target the extracellular domain include bevacizumab. This therapy potently neutralises the biologic activities of human vascular endothelial growth factor (VEGF), preventing it from binding to VEGF receptor-2.

Anti-angiogenic agents that target the intracellular domain include sunitinib and sorafinib. These multi targeted tyrosine kinase inhibitors block the message in the endothelial cell that has been initiated by VEGFR-2. They have applications in renal cell carcinoma and GIST. Anti-angiogenic and immunomodulatory properties have also been identified in thalidomide. This drug is hypothesised to modulate VEGF inhibiting neovasculature. Another example of these agents is lenalidomide, although its exact mechanism is unknown.[10]

Learning Activities	
Completed	Activities
☐	1 Identify an anti-angiogenic agent used in cancer treatment, and describe the: • mechanism of action • indications for its use in clinical practice • nursing care considerations.
☐	2 Discuss your response to a person who is concerned about being treated with thalidomide due to the drug's historical association with infant deformities.

Miscellaneous agents

Bortezomib is an inhibitor of the 26S proteasome. This proteasome normally regulates the intracellular concentration of specific proteins that are required for controlling homeostasis. Disruption to this pathway results in disruption to multiple signaling pathways encouraging cell death. Its current application is in multiple myeloma.[22]

Denileukin difitox is a fusion protein that contains diphtheria toxin fragments fused to IL-2. It targets cells that have IL-2 receptors containing the CD25 component. The IL-2 portion of the protein binds to IL-2 receptors, the diphtheria toxin fragments are transferred into the cell and ultimately inhibit protein synthesis, resulting in cell death. Its application has been in individuals with:[10]

- cutaneous T-cell lymphoma
- CLL
- Hodgkin and non-Hodgkin's lymphoma.

Temsirolimus is an inhibitor of the mammalian target of rapamycin (mTOR). mTOR is a kinase enzyme inside the cell. When activated it is involved in the control of cell proliferation and angiogenesis.[23, 24] Temsirolimus interferes with the synthesis of proteins that regulate proliferation, growth, and survival, leading to cell cycle arrest in G1. It also inhibits angiogenesis by reducing synthesis of VEGF.[12]

Tretinoin or all-*trans*-retinoic acid (ATRA) is a vitamin A derivative used to treat acute promyelocytic leukaemia (APML). The chromosomal abnormality in APML produces an oncogenic protein that blocks cellular differentiation and maturation of promyelocytes. Tretinoin functions as a differentiating agent allowing the leukemic cells to grow into mature granulocytes.[25]

Learning Activities	
Completed	Activities
☐	1 Identify a miscellaneous agent used in cancer treatment, and describe the: • mechanism of action • indications for its use in clinical practice • nursing care considerations.
☐	2 Define 'ATRA Syndrome' and discuss the nursing and medical approaches to its prevention and management.

Principles of administering targeted therapies

Targeted therapies represent emerging and evolving classes of drugs. There is limited data on the effects of these agents and their potential occupational health risks, so further hazard assessments are required.[9, 12] Most biological agents do not affect DNA and therefore do not cause genetic changes. One agent that is considered a hazardous agent is interferon.[26]

Australian consensus guidelines were developed in 2014 to address uncertainty and variation of practice relating to the handling of monoclonal antibodies for cancer. Recommendations have been made for the minimum safe handling requirements to protect all health care personnel. Safe handling recommendations are based on risk assessment of individual agents. The use of interventions / safeguards to minimise occupational exposure should be risk stratified according to risk of internal exposure and toxicity.[27]

SCNs involved in administering these agents need to ensure local policy and procedures relevant to these agents are updated in light of current evidence, and promote safe practice.

Key resource:

Australian consensus guidelines for the safe handling of monoclonal antibodies for cancer treatment by healthcare personnel. 2014

Biopharmaceuticals are inherently different to other drugs and the following principles guiding their storage, preparation, and handling should be followed:[9, 10]

- biopharmaceuticals are protein-based agents and refrigeration is often required
- biopharmaceuticals cannot tolerate extremes in temperature when transported such as car boots and aeroplane baggage holds
- use safe handling precautions for biopharmaceuticals that are considered hazardous (e.g. IFN)
- wear gloves when biopharmaceuticals are irritating to the skin (e.g. rituximab)
- when lyophilised product is reconstituted the vial should not be shaken, and the solution should be directed down the side of the vial and not onto powder
- do not shake as this may cause foaming and can denature the protein
- not all biopharmaceuticals are compatible with all plastic syringes and intravenous tubing.

The SCN needs to be familiar with the agents being administered and provide information to individuals on drug interactions.The oral TKI imatinib and the second generation agents dasatinib and nilotinib are all metabolised via the P450 microenzyme CYP3A4.[25, 28] Co-administration of certain drugs may increase or decrease the metabolism of these agents. Individuals taking imatinib should be informed of the need to avoid grapefruit products and alcohol due to the increased risk of liver toxicity and P450 interactions.[28]

Learning Activities		
Completed		Activities
		Access the following resources: • Local policy, procedures and/or clinical guidelines related to safe handling • Australian consensus guidelines for the safe handling of monoclonal antibodies for cancer treatment by healthcare personnel. 2014[27] • Preventing occupational exposure to antineoplastic and other hazardous drugs in health care settings. National Institute for Occupational Safety and Health. (2004).[26]
☐	1	Discuss the major considerations that designate a drug as hazardous.
☐	2	Access the web resources listed and identify those targeted therapies currently classified as hazardous drugs.
☐	3	Discuss the extent to which current local policies and procedures are consistent with the principles of safe handling and administration of targeted therapies.
☐	4	Identify strategies you would use in an oncology setting to ensure practice is consistent with the principles of safe handling and administration of targeted therapies.
☐	5	Access Herb-Drug Interactions in Oncology: Focus on Mechanisms of Induction [29]and Drug Interactions with Newer Oral Chemotherapy Agents[30] , and discuss the implications of herb / drug interactions identified in five agents used in your health care setting.

Management of people receiving targeted therapies

The SCN is at the forefront of monitoring and identifying common effects, and pivotal in ensuring adherence to therapies and effective symptom management for the person affected by cancer.

For the SCN, education of the person affected by cancer presents a new challenge to ensure adherence with therapy. The SCN will need to acquire the necessary knowledge to understand the complex processes underlying targeted therapies. Developing an education plan, communicating it effectively, and evaluating an individual's comprehension of this topic is essential. Many of these agents are oral, making them a convenient long term therapy that can be administered in the home setting when supported by effective education and information provision.[10, 16]

The SCN needs to recognise the unique side effect profiles that targeted therapies present from traditional antineoplastic agents. Adverse effects are usually mild to moderate, and with astute assessment can be controlled through prompt intervention and management. Some agents have effects similar to antineoplastic agents, such as nausea and vomiting, myelosuppression, and diarrhoea. More unique effects are emerging such as:[9, 10]

- cytokine release syndrome with monoclonal antibodies
- dermatological changes with EGFR inhibitors
- hypertension from VEGF inhibitors
- thromboembolic events with anti-angiogenesis inhibitors.

Specific agents are being identified with rare but serious complications when used alone or in combination with other antineoplastic agents, such as:[9]

- profound lymphopaenia with alemtuzumab
- cardiovascular toxicity with trastuzumab, bevacizumab, and sunitinib
- haemorrhage and gastrointestinal perforations with bevacizumab.

To effectively manage individuals receiving targeted therapies the SCN needs to: [9, 10]

- promote participation of individuals in clinical trials to identify the benefits and risks of a specific agent
- review knowledge, adverse effect profile, and risk factors of the agent to be administered
- educate individuals and their carers on how agents work, what effects they may have, how to manage these at home, and when to report effects to health care professionals
- initiate measures such as premedications to prevent infusion related side effects
- monitor and document effects following administration of biological and molecular targeted agents.

Learning Activities	
Completed	Activities
☐	1 Summarise the information and resources an SCN may provide to a person affected by cancer who is receiving a targeted therapy, as an inpatient and upon discharge.
☐	2 Many targeted therapies are administered orally requiring increased participation of the individual in their care. Discuss: • factors that promote adherence to treatment • factors that may contribute to non-adherence
☐	3 Discuss processes the SCN may use to ensure up to date knowledge, resources, and practices associated with use of new agents.
☐	4 Discuss your responsibilities as an SCN with respect to the process of reporting adverse effects of biological and molecular targeted agents.

Adverse effects of targeted therapies

Significant toxicities and effects have been identified for specific agents. These require effective management.

Flu like symptoms

Flu like symptoms are commonly associated with the anti-cytokine therapies such as the interleukins and interferons. Symptoms can be more severe when higher doses are administered.[9, 10] Flu like symptoms have also been associated with monoclonal antibodies.

A phenomenon of tachyphylaxis can develop where the body adapts to certain flu like symptoms (fever, chills, and rigors) and the severity and occurrence decreases with repeated doses of the agent. Other symptoms such as malaise and fatigue are cumulative and dose limiting.

Flu like symptoms include:[9]

- fever
  - rapid onset for interferons and monoclonal antibodies
  - delayed onset in IL-2
  - low grade fevers may occur with colony stimulating factors such as G-CSF
- chills and rigors
  - occur prior to temperature spikes with interferons, interleukins, and monoclonal antibodies
- myalgia or arthralgia, headache, malaise, and fatigue
  - occur commonly with the interferons and interleukins
  - monoclonal antibodies commonly cause arthralgia and malaise, while headache is uncommon and fatigue is rare.

Learning Activities	
Completed	Activities
☐	1 Describe the interventions to prevent, minimise, and/or manage flu like symptoms associated with monoclonal antibody administration.

Infusion related effects

A potentially serious cluster of symptoms known as cytokine release syndrome has been observed as an effect of monoclonal antibodies.[31]

Cytokines, which are naturally occurring proteins, are produced and secreted by most cells of the human body. They include interleukin, interferons, and tumour necrosis factor.[31] Cytokines are essentially chemical messengers. Cells targeted by the monoclonal antibody, along with immune effector cells that have been recruited, release cytokines. This results in the occurrence of the following symptoms, which are usually mild to moderate in severity:[31]

- fever, nausea, chills,
- hypotension, tachycardia
- asthenia, headache, rash
- scratchy throat, tongue and throat swelling, dyspnoea.

Cytokine release syndrome is usually related to the first infusion. Effects appear more severe in those individuals who have not received prior antineoplastic agents. Symptoms subside with subsequent infusions as target cells have been rapidly cleared with the first infusion, resulting in decreased tumour burden and therefore decreased cytokine release.[31]

Cytokine release syndrome is more commonly seen in individuals with haematologic malignancies. It also can occur in individuals with solid tumours.

Management principles include:[31]

- assess need for premedication and administer as required
- always administer via an infusion pump
- the first infusion should be administered slowly and subsequent infusions may be administered more rapidly
- intravenous access should be maintained with normal saline in the event of a reaction
- monitor vital signs frequently and observe individuals closely for reactions
- individuals at high risk may require additional precautions such as:
- inpatient monitoring and frequent assessment of renal function
- allopurinol and hydration to prevent renal damage
- individuals experiencing severe reactions require additional precautions such as:
- supplemental oxygen, bronchodilators, and emergency medications
- monitor for thrombocytopenia and electrolyte abnormalities and replace as required.

Learning Activities		
Completed	Activities	
☐	1	Outline the information and supportive care that may be provided to a person who is to receive rituximab for the first time.
☐	2	List nursing observations that would be undertaken for a person receiving a monoclonal antibody infusion.
☐	3	Discuss immediate nursing responses for a person who is experiencing a severe reaction to monoclonal therapies

Dermatologic effects

EGFR inhibitors bind to receptors on normal epidermal cells found in human skin and the gastrointestinal lining.[10, 32, 33] Although the exact biology is not fully understood it is thought that different mechanisms occur to interfere with keratinocyte growth and survival, cell differentiation and attachment, and migration from basal to stratum corneum.[32, 33]The results are inflammation and dryness of the skin, leading to hyperkeratosis, folliculitis, and finally a papulopustular rash that usually occurs within the first three weeks of treatment.[32, 33]

The spectrum of skin toxicities can vary in severity. Most commonly reported reactions include a mild to moderate skin rash that occurs on the face, upper chest, back, and dorsal arms (sun exposed areas).[32, 33]There can be an increased incidence of the inflammatory reactions and sensitivity to sun exposure. Other changes can include xerosis / pruritus, periungual or nail alterations, hair loss, and eye or eyelash abnormalities. [21] The effects appear to be specific to the EGFR targeted therapies.

How the SCN responds providing education and support measures to the individual experiencing this toxicity will impact the individual's compliance with these targeted therapies. The SCN needs to be proactive in the management of skin toxicities and provide information and support.[32, 33]

Learning Activities	
Completed	Activities
☐	1 Search the literature to identify interventions to prevent, minimise, and/or manage skin toxicities associated with monoclonal antibody administration.
☐	2 Outline the evidence based information and supportive care strategies to prevent and manage dermatological effects associated with EGFR inhibitors in the following circumstances: • mild skin toxicity • moderate skin toxicity • severe skin toxicity.

Cardiotoxicity

Angiogenesis inhibitors exert their effect by either neutralising VEGF (bevacizumab) or blocking signaling within the endothelial cell (sunitinib or sorafinib).[12] This results in a unique group of cardiac effects such as:[34]

- hypertension
- reduced left ventricular ejection fraction (LVEF)
- cardiovascular events including:
- myocardial ischemia
- myocardial infarction
- congestive heart failure
- arrhythmia.

Although the exact mechanism is unknown, theories that have been proposed include:

- blockade of nitric oxide, which is required for the walls of arterioles and other resistance vessels to relax[11]
- direct toxicity to cardiomyocytes.[34]

Cardiac toxicity associated with trastuzumab can range from an asymptomatic reduced LVEF to congestive heart failure.[9, 34] Although the exact mechanism of cardiotoxicity is unknown, the damage has been described as a type II antineoplastic agent-related cardiac dysfunction (CRCD), which appears mostly reversible with improvement on discontinuation of therapy.[34]

The risk of cardiotoxicity increases with the concomitant administration of antineoplastic agents such as anthracyclines and paclitaxel. The two most significant risk factors have been identified as age and combination of trastuzumab and anthracycline therapy. The two agents should therefore not be given together.[34] A feature of trastuzumab cardiotoxicity is its reversible nature, which may allow therapy to be reintroduced in certain individuals after improvement in LVEF.

The significance of the cardiotoxic related events has led to warnings with regards to the use of these agents in individuals with a history of cardiovascular events and exposure to other cardiotoxic agents.[34]

Learning Activities	
Completed	Activities
☐	1 Outline the evidence based information and supportive care strategies to prevent and manage cardiac toxicity in the individual receiving targeted therapies.

Immunosuppression

Alemtuzumab is a monoclonal antibody targeting the CD52 antigen expressed on the surface of both normal and malignant T and B lymphocytes, natural killer cells and cells of the myeloid lineage.[25, 35]

Alemtuzumab therapy results in bone marrow suppression and a profound lymphopaenia. This puts individuals at increased risk of developing serious bacterial, fungal, viral and protozoan infections.[36]

Management strategies include:[25, 35]

- prophylaxis for pneumocystis pneumonia with trimethoprim / sulfamethoxazole, dapsone or pentamidine
- prophylaxis for varicella zoster and herpes simplex infections with acyclovir or valacyclovir
- antifungal therapy as required
- monitoring for signs and symptoms of cytomegalovirus (CMV) infection during therapy and for 2 months post completion
- CMV surveillance, CT scans, and bronchoscopy.

Learning Activities	
Completed	Activities
☐	1 Outline the evidence based information and supportive care strategies to prevent and manage consequences of immunosuppression in the individual receiving targeted therapies.

Other effects

Fluid retention is common and presents as periorbital and lower extremity oedema in at least 50-60% of individuals treated with imatinib. Serious effects of fluid retention include:[25, 28]

- pleural effusion
- ascites
- rapid weight gain
- pulmonary oedema.

Fluid retention and oedema has also been reported in the second generation TKI dasatinib. Management includes monitoring for signs of fluid retention and oedema during therapy. Individuals need to be educated to weigh themselves daily at home and to report weight gains of 1 kg in one week and symptoms of dyspnoea.[12] Symptom management strategies may include diuretics for periorbital and lower extremity oedema and ice packs or haemorrhoid preparations for periorbital oedema.[28]

A group of rare but significant side effects has been associated with the use of bevacizumab including:[10, 12, 34]

- development of potentially fatal gastrointestinal perforations
- complicated wound healing and tissue repair such as wound dehiscence, tracheoesophageal fistula, and perforation of nasal septum
- haemorrhage - epistaxis, haematemesis, haemoptysis, bleeding at tumour sites, subarachnoid, and haemorrhagic stroke.

This has led to black box warnings being listed with the use of this agent. Although rare, at times these serious adverse events can be fatal and require the SCN to develop skills in assessing for alterations and educating individuals on the importance of reporting symptoms early. The following management strategies should be considered:[12, 34]

- assess baseline bowel and skin integrity and signs of delayed wound healing each visit
- assess for conditions that place the individual at risk for bleeding
- assess baseline mental status and neurological signs and monitor during therapy for CNS haemorrhage, reversible posterior leukoencephalopathy and fatal encephalopathy
- educate individuals on signs to report immediately - wound dehiscence, bleeding tendencies such as epistaxis, haematemesis, and haemoptysis, abdominal pain associated with nausea, vomiting and constipation
- treatment should be interrupted prior to surgical procedures, although the exact time interval required is not known.

Learning Activities	
Completed	Activities
☐	1 Identify an agent from each of the following categories: • cytokines • monoclonal antibodies • molecular targeted therapies • angiogenesis inhibitors • miscellaneous agents and complete the following activities: • identify adverse effects of these agents • select one adverse effect of each agent and discuss the evidence based nursing interventions required to prevent, detect and manage the effect.

Challenges for targeted therapies in cancer treatment

The development of targeted therapies has seen incremental improvements in the response of some cancers. It has also seen opportunities for treatment of other cancers considered refractory to traditional therapies, and challenged perceptions regarding traditional cancer control efforts.[37]

The focus in the future may not be the identification of new drugs, but progressing our understanding of the molecular pathways that regulate cell growth, apoptosis, angiogenesis, and metastasis, and the communication or cross talk between these mutated pathways and receptors.[10, 11, 17] Several critical steps need to be realised in the application of targeted therapies in cancer control:[11, 38, 39]

- developing clinically useful prognostic markers to identify individuals needing treatment
- developing predictive markers that identify and select individuals who will benefit most from these therapies
- avoiding treatment in those unlikely to respond or at risk of unacceptable toxicity
- combining agents that target different key pathways
- combining agents with conventional therapies
- developing strategies to overcome acquired resistance.

Clinical trials are vital and play a key role in addressing these issues, identifying new agents and the individuals who will benefit. Clinical trials give individuals access to new agents before they become routinely available. Individuals participating in clinical trials help answer critical questions such as who will benefit, what are the effects, and which individuals are unlikely to respond.[9]

Another challenge is the financial cost of targeted therapies. These agents can be considerably more expensive than traditional therapies, with the duration of therapy for some agents lasting years. Clinical trials investigating targeted therapies usually include these agents free, at no cost to the individual. As more of these agents become available the following issues will need to be addressed:[9]

- how much an individual or the general community is prepared to pay for progress in cancer therapy
- how agents will be reimbursed by the government and private insurance companies
- ensuring access to these agents is equitable.

The SCN has a key role in educating individuals on the importance of clinical trials, promoting participation, and supporting individuals during trials, when they withdraw, or when they find the toxicities unacceptable.

Learning Activities		
Completed	Activities	
☐	1	Access Targeted therapies, aspects of pharmaceutical and oncological management[5] and summarise the current and future challenges for targeted therapies.
☐	2	Discuss potential implications for the SCN with increasing numbers of people being treated with targeted therapies.

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