Targeted cancer therapies

Clinical pearls for primary care

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Patients often have questions about their cancer diagnoses and treatment options. Family physicians are well situated in the health care system to help patients navigate this landscape, but to do this effectively they need to understand emerging cancer treatment options.

There are currently 4 general types of systemic therapy options for cancer treatment: chemotherapy, immunotherapy, endocrine therapy, and targeted therapy, with some overlap among the categories. For example, although immunotherapies are a form of targeted therapy, immunotherapy is a distinct class.[1]

Genetic mutations and resultant changes in cellular proteins can cause cells to divide too rapidly, resulting in malignant growth.[2] To create a targeted therapy, researchers identify the potential genetic mutations and resultant abnormal proteins that drive the growth of certain types of cancer. The targeted therapy drug affects only the abnormal protein, in contrast to chemotherapy, which is nonselective and affects all rapidly dividing cells.[3] Targeted therapies work only if the cancer has the target in question, and many cancers develop resistance to these agents over time. In addition to the cancer type and subtype being identified, potential molecular targets are found by testing the tumour sample for overexpression of biomarkers or for mutations causing cells to multiply rapidly. Identifying these specific targets helps determine management options.

Depending on the specific molecular targets, targeted therapy can act on cell surface antigens, growth factors, receptors, or signal transduction pathways that regulate cell cycle progression, cell death, metastasis, and angiogenesis (**Figure 1**).[4,5] While most targeted therapies are either monoclonal antibodies or small-molecule drugs, they can also be classified as hormone therapies, signal transduction inhibitors, gene expression modulators, apoptosis inducers, angiogenesis inhibitors, immunotherapies, and toxin delivery molecules.[3] Drugs used in molecular targeted therapy can block signals that favour the promotion of cancer cell growth, interfere with the regulation of the cell cycle, or induce cell death to kill the cancer cells.

Types of targeted therapy

The 2 most common types of targeted therapy are monoclonal antibodies and small-molecule inhibitors. Monoclonal antibodies target specific proteins, often receptors, on the cancer cell's surface[6] or in the environment around the tumour. These large molecules are not able to enter the cell. They can prevent cancer cell proliferation by blocking molecules that signal cancer cell growth or angiogenesis.

Monoclonal antibodies can be linked to a toxic substance, such as standard chemotherapy or radionuclides, to deliver the therapy to the cancer cells.[1] Brentuximab vedotin[7] (used in treating Hodgkin lymphoma and some other lymphomas) is an example of a monoclonal antibody–drug conjugate.

Clinical pearl: The names of monoclonal antibodies often end in *-mab* (eg, rituximab, bevacizumab, trastuzumab, pertuzumab, panitumumab).

The other common type of targeted therapy is small-molecule drugs, which, owing to their low molecular weight, pass through the cell surface to intracellular targets to slow proliferation or cause tumour cell death.

Clinical pearl: The names of small-molecule drugs often end in *-mib* (for protease inhibitors) or *-nib* (for kinase inhibitors),[8] such as bortezomib, osimertinib, and vemurafenib.

Examples of commonly used targeted therapies

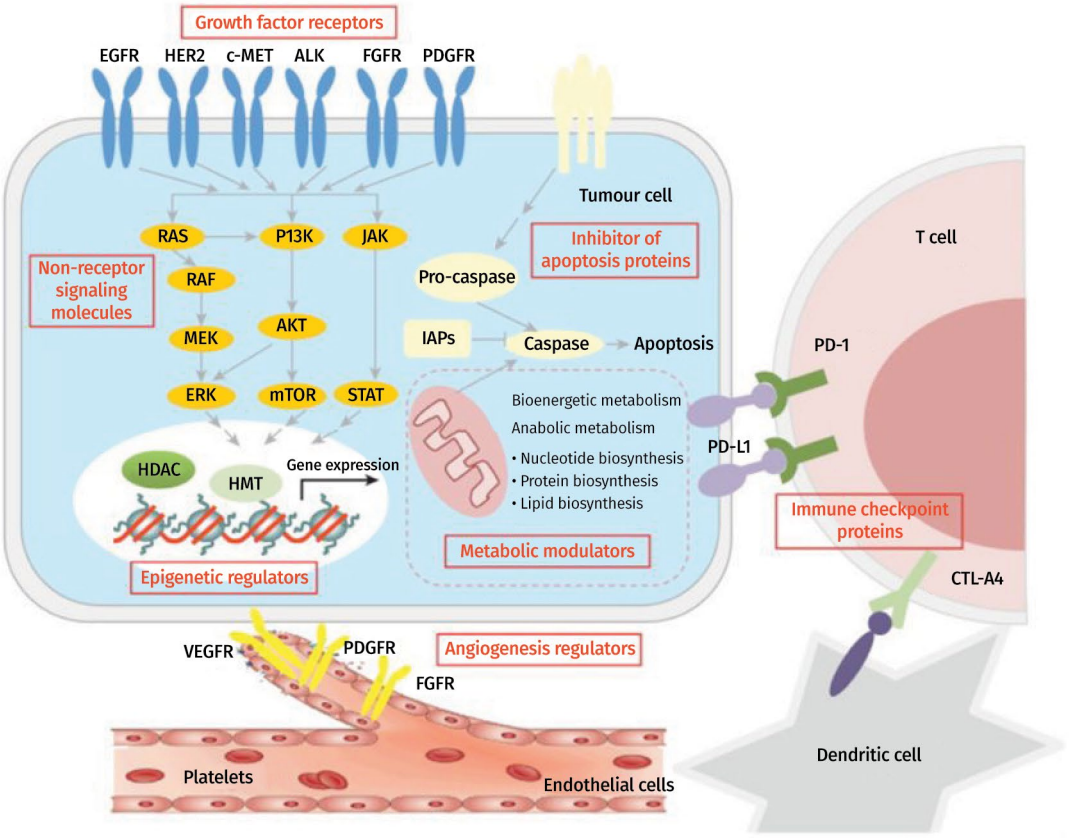
An overexpression of the human epidermal growth factor receptor 2 (*HER2*) gene (now known as erb-b2 receptor tyrosine kinase 2 [*ERBB2*]) exists in *HER2* mutation–positive breast cancers and gastric cancers. The monoclonal antibodies trastuzumab and pertuzumab can be used to treat *HER2* mutation–positive breast cancers and target different regions of *HER2*.[9] Trastuzumab emtansine is an example of a monoclonal antibody–drug conjugate used to treat breast cancer that targets *HER2* and delivers the cytotoxic drug to tumour cells.[10]

Cyclin-dependent kinase 4 and cyclin-dependent kinase 6 inhibitors (eg, palbociclib, ribociclib) are used to treat hormone receptor–positive, *HER2* mutation–negative breast cancers.

Poly(adenosine diphosphate ribose) polymerase inhibitors (eg, olaparib, niraparib) target an enzyme that repairs DNA damage and are used to treat some ovarian cancers.[11,12] Olaparib is also indicated in *BRCA* mutation–positive breast cancer treatment.

In non–small cell lung cancers, epidermal growth factor receptor (*EGFR*) mutation–positive tumours exhibit rapid cell division and growth; *EGFR* tyrosine kinase inhibitors (eg, osimertinib, gefitinib, erlotinib) are small-molecule drugs that target *EGFR* mutation–positive tumours. Another protein targeted in treating non–small cell lung cancer is anaplastic lymphoma kinase (ALK). Cells with ALK mutations can be targeted by ALK inhibitors

Figure 1. Targets for molecularly targeted cancer therapy



AKT—protein kinase B, *ALK*—anaplastic lymphoma kinase, *c-MET*—mesenchymal–epithelial transition factor, CTL-A4—cytotoxic T-lymphocyte–associated antigen 4, *EGFR*—epidermal growth factor receptor, ERK—extracellular signal-regulated kinase, *FGFR*—fibroblast growth factor receptor, HDAC—histone deacetylase, *HER2*—human epidermal growth factor receptor 2, HMT—histone methyltransferase, IAPs—inhibitors of apoptosis, JAK—Janus kinase, MEK—mitogen-activated protein kinase, mTOR—mammalian target of rapamycin, PD-1—programmed cell death 1 protein, *PDGFR*—platelet-derived growth factor receptor, PD-L1—programmed cell death 1 ligand 1, PI3K—phosphatidylinositol 3-kinase, RAF—rapidly accelerated fibrosarcoma, RAS—rat sarcoma virus, STAT—signal transducer and activator of transcription, *VEGFR*—vascular endothelial growth factor receptor.

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(eg, crizotinib). There are several other potential molecular targets noted in non–small cell lung cancers.

Treatment of colorectal cancer may include bevacizumab, a monoclonal antibody that binds to vascular endothelial growth factor (VEGF) and inhibits the growth of tumour blood vessels.[13] Panitumumab, another monoclonal antibody, targets *EGFR*. Since mutations in the Kirsten rat sarcoma virus gene may be associated with reduced effectiveness of panitumumab, testing for these mutations is indicated.

Approximately half of melanomas have mutations in the B-type Raf proto-oncogene (*BRAF*),[14] resulting in an altered *BRAF* protein that promotes cancer cell growth. B-type Raf proto-oncogene protein inhibitors (eg, vemurafenib, dabrafenib) are small-molecule targeted therapies that can be effective against *BRAF* mutation–positive cancers. Mitogen-activated protein kinase inhibitors (eg, trametinib) can also work against *BRAF* mutation–positive melanomas and can be combined with *BRAF* inhibitors.

Other targeted therapies worth mentioning are rituximab, a monoclonal antibody that targets the CD20 pathway and is commonly used to treat certain types of lymphoma and chronic lymphocytic leukemia[15]; daratumumab, which is used in the treatment of multiple myeloma and targets CD38[16]; and bortezomib, which is used to treat multiple myeloma and some lymphomas.[17] Sunitinib is a tyrosine kinase inhibitor used to treat renal cell cancer.[18]

Targeted therapy administration

Most small-molecule drugs are conveniently formulated as tablets or capsules, whereas most monoclonal antibodies are administered intravenously. However, some monoclonal antibodies, such as rituximab,[15] can be given subcutaneously if no contraindication exists, allowing for shortened treatment day times. Trastuzumab is also given subcutaneously in some remote areas, resulting in less travel and less time away from home for patients.

Side effects

Despite the expectation that targeted therapy would have fewer adverse effects than traditional chemotherapy, substantial toxicities are still seen. These targeted therapy toxicities differ from those seen with chemotherapy and vary according to the targeted therapy's mechanism of action. Patients may present to their family physicians with these adverse effects (eg, bleeding), and oncologists may enlist family physicians' help in patients' ongoing side effect management (eg, hypertension). Skin problems are commonly seen with *EGFR* inhibitors and can consist of acneiform rash (**Figure 2**),[19] nail changes (**Figure 3**),[19] hair discolouration, dry skin, and yellow discolouration of the skin.[18] **Box 1** summarizes preventive measures and considerations for managing rash associated with *EGFR* inhibitor use.[20] Congestive heart failure is a known adverse effect of trastuzumab. Side effects commonly seen with VEGF inhibitors and VEGF receptor inhibitors include hypertension, thromboembolic events, impaired wound healing, and increased risk of bleeding (including tumour-associated hemorrhage).[21]

Treatment of side effects

Management of side effects often depends on severity. Mild adverse effects can often be treated symptomatically, while moderate effects may require a treatment break or dose reduction. Severe side effects are more likely to require ceasing the use of the offending agent and looking for alternative treatment options.

Conclusion

As the number of new cancer diagnoses rises[22] and cancer treatment options rapidly emerge, family physicians are likely to find themselves helping patients navigate questions about treatment options. Understanding how targeted therapy works, why specific therapies may or may not be options, and what adverse effects are possible is essential to helping patients navigate their cancer care journeys.

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Competing interests

Dr Sian L. Shuel receives contract support from BC Cancer as Medical Education Lead for BC Cancer's Primary Care Program.

References

1. Dahan R. *Monoclonal antibodies, antibody-drug conjugates, and bispecific antibodies.* New York, NY: Cancer Research Institute; 2021. Available from: **https://www.cancerresearch.org/immunotherapy/treatment-types/targeted-antibodies**. Accessed 2022 Jan 21.

Figure 2. Acneiform eruption seen with epidermal growth factor receptor inhibitor use: *A) Papular lesions on the chest, B) V-shaped papulopustular eruption on the back, C) close-up of follicular pustules, and D) confluent pustules on the nose.*

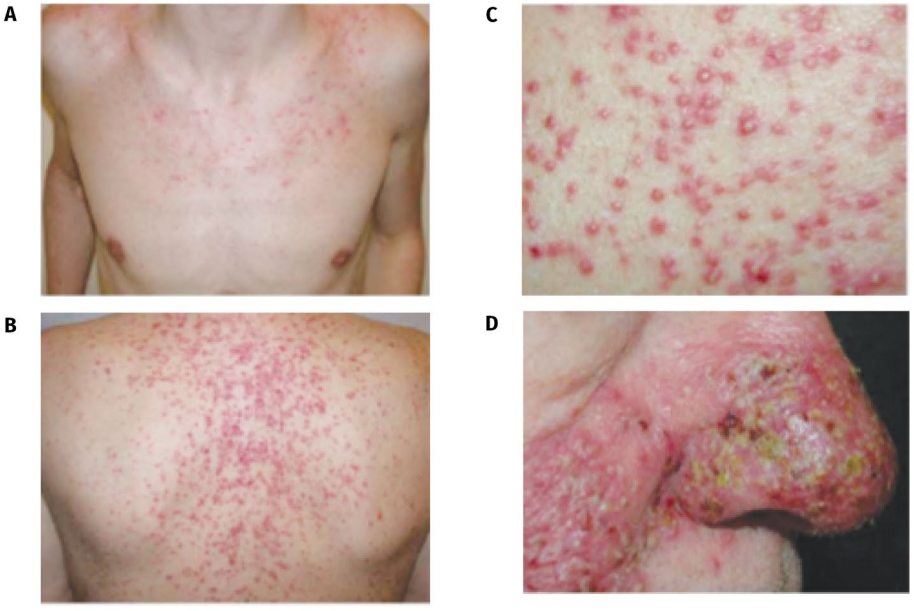
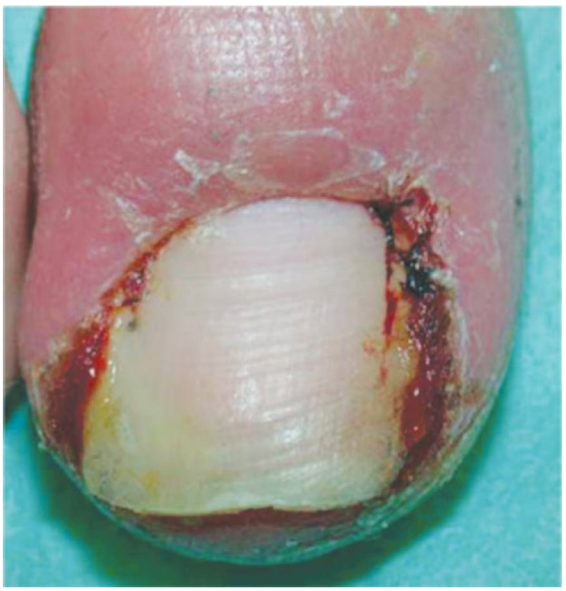


Figure 3. Paronychia and pyogenic granuloma of the nail fold of the big toe caused by epidermal growth factor receptor inhibitor use



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Box 1. Addressing rash associated with *EGFR* inhibitor use

Preventive measures for rash associated with *EGFR* inhibitor use can include assessing patients for skin conditions such as acne, rosacea, and psoriasis that can worsen with *EGFR* inhibitors.[20] Education around moisturizing, avoiding excessive sun exposure, wearing a hat and long sleeves, and using sunscreen is important.

Prophylaxis (eg, with minocycline 100 mg by mouth twice daily and hydrocortisone cream, 1%, at bedtime for the first 6 weeks followed by a taper) can be initiated.

Management of the rash can include a topical lotion with clindamycin, 2%, and hydrocortisone, 1%, twice daily with or without minocycline 100 mg by mouth twice daily, or doxycycline 100 mg twice daily for 4 weeks with or without prednisone 0.5 mg/kg by mouth once daily for 7 to 14 days, depending on the severity of the rash. Also:

- Obtaining a bacterial culture for secondary infection is recommended for severe rashes (grade 3 or higher).
- Consider referral to a dermatologist if there is no improvement after 4 weeks.
- Therapy dose modification or interruption may need to be considered.
- Management should include input from the patient's medical oncologist.

EGFR—epidermal growth factor receptor.

2. *What is targeted therapy?* Alexandria, VA: American Society of Clinical Oncology; 2022. Available from: **https://www.cancer.net/navigating-cancer-care/how-cancer-treated/personalized-and-targeted-therapies/what-targeted-therapy?** Accessed 2022 May 27.
3. What is targeted therapy? In: *Targeted therapy to treat cancer.* Bethesda, MD: National Cancer Institute; 2021. Available from: **https://www.cancer.gov/about-cancer/treatment/types/targeted-therapies/targeted-therapies-fact-sheet**. Accessed 2022 Jan 21.
4. Saijo N. Progress in cancer chemotherapy with special stress on molecular-targeted therapy. *Jpn J Clin Oncol* 2010;40(9):855-62. Epub 2010 Jul 22.
5. Huang M, Shen A, Ding J, Geng M. Molecularly targeted cancer therapy: some lessons from the past decade. *Trends Pharmacol Sci* 2014;35(1):41-50. Epub 2013 Dec 19.
6. What are the types of targeted therapy? In: *Targeted therapy to treat cancer.* Bethesda, MD: National Cancer Institute; 2020. Available from: **https://www.cancer.gov/about-cancer/treatment/types/targeted-therapies#whatare-the-types-of-targeted-therapy**. Accessed 2022 Jan 21.
7. Firer MA, Gellerman G. Targeted drug delivery for cancer therapy: the other side of antibodies. *J Hematol Oncol* 2012;5:70.
8. Scott GN. Sorting through the confusion of biologic drug names. *Medscape* 2016 Aug 19. Available from: **https://www.medscape.com/viewarticle/867446_1**. Accessed 2022 Jan 21.
9. Keating GM. Pertuzumab: in the first-line treatment of HER2-positive metastatic breast cancer. *Drugs* 2012;72(3):353-60.
10. *Trastuzumab emtansine* [product monograph]. Vancouver, BC: BC Cancer; 2018. Available from: **http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Trastuzumab%20Emtansine_monograph.pdf.** Accessed 2022 Jan 21.
11. *Olaparib* [product monograph]. Vancouver, BC: BC Cancer; 2020. Available from: **http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Olaparib_monograph.pdf.** Accessed 2022 Jan 28.
12. *Niraparib* [product monograph]. Vancouver, BC: BC Cancer; 2021. Available from: **http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Niraparib_monograph.pdf**. Accessed 2022 Jan 28.
13. Shih T, Lindley C. Bevacizumab: an angiogenesis inhibitor for the treatment of solid malignancies. *Clin Ther* 2006;28(11):1779-802.
14. *Targeted therapy drugs for melanoma skin cancer*. Atlanta, GA: American Cancer Society; 2019. Available from: **https://www.cancer.org/cancer/melanoma-skin-cancer/treating/targeted-therapy.html**. Accessed 2022 Jan 21.
15. *Rituximab* [product monograph]. Vancouver, BC: BC Cancer; 2021. Available from: **http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Rituximab_monograph.pdf**. Accessed 2022 Jan 21.
16. *Daratumumab* [product monograph]. Vancouver, BC: BC Cancer; 2019. Available from: **http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Daratumumab_monograph.pdf**. Accessed 2022 Jan 21.
17. *Bortezomib* [product monograph]. Vancouver, BC: BC Cancer; 2021. Available from: **http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Bortezomib_monograph.pdf**. Accessed 2022 Jan 21.
18. *Sunitinib* [product monograph]. *BC Cancer drug manual.* Vancouver, BC: BC Cancer; 2019. Available from: **http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Sunitinib_monograph.pdf**. Accessed 2022 Jan 21.
19. Segaert S, Van Cutsem E. Clinical signs, pathophysiology and management of skin toxicity during therapy with epidermal growth factor receptor inhibitors. *Ann Oncol* 2005;16(9):1425-33. Epub 2005 Jul 12.
20. *Prevention and treatment of acneiform rash in patients treated with EGFR inhibitor therapies*. Edmonton, AB: Cancer Care Alberta; 2020. Available from: **https://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-supp003-egfri-rash.pdf**. Accessed 2022 Jan 21.
21. *Bevacizumab* [product monograph]. Vancouver, BC: BC Cancer; 2021. Available from: **http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Bevacizumab_monograph.pdf**. Accessed 2022 Jan 21.
22. Canadian Cancer Statistics Advisory Committee, Canadian Cancer Society, Statistics Canada, Public Health Agency of Canada. *Canadian cancer statistics 2021.* Toronto, ON: Canadian Cancer Society; 2021. Available from: **https://cancer.ca/Canadian-Cancer-Statistics-2021-EN**. Accessed 2022 Jan 21.

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