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ARTICLE

Oral targeted therapy for cancer

SUMMARY

Oral targeted therapies are increasingly being used to treat cancer. They work by interfering with specific molecules or pathways involved in tumour growth.

It is essential that health professionals managing patients taking these drugs have appropriate training and skills. They should be aware of potential adverse effects and drug interactions, and be able to manage toxicities when they occur.

Despite the selectivity of these targeted therapies, they still have serious adverse effects including skin reactions, diarrhoea and altered organ function.

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Introduction

Targeted therapies block the spread or growth of cancer by interfering with specific molecules or pathways involved in the growth and progression of cancer. The target molecule may be present in normal tissue, but is overexpressed or mutated in the cancer. These drugs can be more effective than cytotoxic chemotherapy as they are specific to the cancer.

Targeted therapies do not damage normal cells in the way cytotoxic chemotherapy does. Nevertheless they are still associated with some toxic adverse effects. These effects are often unique to the therapy and can be severe requiring close monitoring and clinical management. Targeted therapies can also be used in combination with chemotherapy and radiation therapy, and synergistic toxicities such as diarrhoea and skin effects can occur.

Small-molecule inhibitors are given orally. Although treatment is initiated and managed by a cancer specialist, ongoing therapy may not always need to be administered in an oncology setting and patients taking these drugs are increasingly being seen in general practice.

Monoclonal antibodies are another type of targeted therapy for cancer. However, these drugs are given parenterally because they are proteins and would be destroyed by the gut.

Small-molecule inhibitors

Table 1 lists current oral small-molecule inhibitors for specific cancers that are reimbursed by the Pharmaceutical Benefits Scheme (PBS). A large number are also under investigation in clinical trials so it is expected that more will be approved over the next few years.

Mode of action

Small-molecule inhibitors are able to cross the cell plasma membrane and interfere with intracellular targets. They often act on multiple pathways in the cell.

Protein kinases play an important role in regulating cellular activity and are often found to be mutated in cancer. A number of therapies have been developed that block kinase activity and hence block cell growth. These drugs carry the suffix -nib.

BCR-ABL inhibitors

Imatinib was one of the first targeted therapies to be developed for the treatment of chronic myeloid leukaemia. It blocks the BCR-ABL protein kinase which results from a chromosomal translocation (the Philadelphia chromosome) in chronic myeloid leukaemia. Imatinib inhibits the proliferation of leukaemia cells and results in durable responses in over 80% of patients.[1] Imatinib is also active against gastrointestinal stromal tumours and certain types of acute leukaemia.

Epidermal growth factor receptor inhibitors

The epidermal growth factor receptor (EGFR) exists on the outside of cells and is activated by growth factor ligands. Once activated, intracellular tyrosine kinase activity occurs and several signal transduction cascades are initiated which lead to cell proliferation. In many cancers the EGFR activity is increased due to mutations in the receptor or tyrosine kinase protein domains. EGFR tyrosine kinase inhibitors, such as erlotinib and gefitinib, act on the EGFR tyrosine kinase domain. They are used to treat advanced non-small cell lung cancers that have the EGFR mutation.[2,3]

Lapatinib inhibits the tyrosine kinase activity associated with EGFR and human epidermal growth factor receptor 2 (HER2).[4] The HER2 receptor is overexpressed in about 25–30% of breast cancers.

Table 1 **Oral targeted therapies subsidised by the Pharmaceutical Benefits Scheme** [7-11]

Target	Medicine (brand name)	Indication
BRAF	dabrafenib (Tafinlar)	melanoma
BCR-ABL	imatinib (Glivec)	chronic myeloid leukaemia, gastrointestinal stromal tumour
	dasatinib (Sprycel)	chronic myeloid leukaemia
	nilotinib (Tasigna)	chronic myeloid leukaemia
EGFR	erlotinib (Tarceva)	non-small cell lung cancer
	gefitinib (Iressa)	non-small cell lung cancer
	lapatinib (Tykerb)	metastatic breast cancer
MEK	trametinib (Mekinist)	melanoma
mTOR	everolimus (Afinitor)	metastatic breast cancer, renal cell carcinoma
Multi-targeted, including VEGF	pazopanib (Votrient)	renal cell carcinoma, soft tissue sarcoma
	sunitinib (Sutent)	renal cell carcinoma, pancreatic neuroendocrine tumour
	sorafenib (Nexavar)	hepatocellular carcinoma
Immune system (immunomodulators)	thalidomide (Thalomid)	myeloma
	lenalidomide (Revlimid)	myeloma, myelodysplastic syndrome
	pomalidomide (Pomalyst)	myeloma

BRAF Intracellular protein kinase that forms part of the mitogen-activated protein (MAP) kinase pathway and drives cell proliferation
BCR-ABL BCR = breakpoint cluster region, ABL = abelson murine leukemia oncogene-1 (BCR-ABL is a fusion gene created by the ABL1 gene on chromosome 9 to the BCR gene on chromosome 22)
EGFR Epidermal growth factor receptor (member of the ErbB family of receptors that promotes cell proliferation)
MEK MAPK/ERK kinase (MAPK = mitogen activated protein kinase, ERK = extracellular-signal-regulated kinase)
mTOR Mammalian target of rapamycin (protein kinase that regulates cell growth)
VEGF Vascular endothelial growth factor (protein produced by cancer cells that stimulates angiogenesis)

BRAF and MEK inhibitors

Other targeted drugs inhibit pathways that occur downstream of the EGFR receptor. Dabrafenib inhibits the activity of BRAF, an intracellular protein kinase of the RAF kinase family that drives cell proliferation and can be mutated in melanoma cells (Aust Prescr 2014;37:28-35). Dabrafenib significantly improves progression-free survival (by approximately two months) in melanoma compared to standard chemotherapy.[5]

Trametinib inhibits the MEK pathway and has been combined with dabrafenib in an effort to reduce resistance to dabrafenib, and to reduce some of the adverse effects associated with BRAF inhibition.[6]

Multi-targeted drugs including vascular endothelial growth factor inhibitors

Sunitinib, sorafenib and pazopanib are kinase inhibitors that affect multiple pathways involved in cancer cell growth. In addition to blocking tyrosine kinase pathways they block the vascular endothelial growth factor (VEGF) protein which promotes angiogenesis. These drugs are active in a variety of cancers due to their diverse activity (Table 1).[7-11]

Adverse effects

Despite their selectivity, targeted therapies still have adverse effects, ranging from mild skin reactions to fatal gastrointestinal perforation (see Table 2). Toxicity depends largely on the target of the drug and the drug's individual properties. Most targeted therapies, with the exception of immunomodulatory drugs, are known to cause nausea, diarrhoea and skin problems. Adverse effects of individual drugs and the management of these can be found in the eviQ Cancer Treatments Online website (www.eviq.org.au).[12]

Patients require constant monitoring while on therapy. All healthcare professionals who see the patient should be aware of the toxicity profile of the therapy and the appropriate management. Many targeted therapies can adversely affect liver and renal function so laboratory results should be monitored regularly. It is usual for the treating haematologist or oncologist to review blood tests monthly.
Some targeted therapies are used in combination with cytotoxic chemotherapy. For example, the

Table 2 **Common adverse affects associated with oral cancer therapies**

Adverse effect	Drug (affects >1% of patients)
Diarrhoea	dabrafenib, dasatinib, erlotinib, gefitinib, lapatinib, nilotinib, pazopanib, sorafenib, sunitinib
Hypertension	pazopanib, sorafenib, sunitinib
Prolongation of QT interval	dabrafenib, dasatinib, lapatinib, nilotinib, pazopanib, sorafenib, sunitinib
Bleeding	dasatinib, erlotinib, gefitinib, pazopanib, sorafenib, sunitinib
Constipation	lenalidomide, thalidomide
Fever	dabrafenib
Hypothyroidism	imatinib, pazopanib, sunitinib
Oedema	dasatinib, everolimus, imatinib, nilotinib
Pulmonary complications	dasatinib, imatinib, erlotinib, gefitinib, lapatinib
Venous thromboembolic events	lenalidomide, pazopanib, sorafenib, sunitinib, thalidomide
Reduction in left ventricular ejection fraction	dasatinib, lapatinib, pazopanib, sorafenib, sunitinib, trametinib

combination of lapatinib and capecitabine is used in breast cancer and these patients require a regular check of their blood counts before each cycle of chemotherapy.

Dermatological effects

Skin reactions are common with targeted therapies that affect the EGFR pathways since the EGFR is found in the skin. These effects tend to develop a few weeks after starting therapy and include rash, itching, and changes in hair and nails.[13] Table 3 details common dermatological effects of targeted therapies.

Patients taking EGFR inhibitors should use a mild soap that is free from alcohol and perfume, and apply a bland moisturiser as a preventive measure at least twice a day. Skin can be extra sensitive to the sun and patients should be advised to use a broad spectrum sunscreen (SPF 30+). Hydrocortisone cream and oral antibiotics such as doxycycline which have an anti-inflammatory action are alternatives for skin rashes not responsive to moisturising creams.

The BRAF inhibitors have a potential to cause skin malignancies. These patients should be regularly checked for signs of malignant skin changes such as the development of a squamous cell carcinoma.

The Multinational Association of Supportive Care in Cancer (www.mascc.org) provides useful clinical practice guidelines for the prevention and treatment of EGFR inhibitor-associated dermatological toxicities.[14] Therapy may need to be interrupted or reduced for severe reactions. This decision will be made by the treating haematologist or oncologist in consultation with the patient.

Gastrointestinal effects

Gastrointestinal-related toxicity is prominent with many targeted therapies. Complications include diarrhoea, constipation and nausea.

Diarrhoea affects up to 80% of patients. In many cases the diarrhoea can be managed with antidiarrhoeal medication, such as loperamide. If not controlled, it can quickly develop into serious dehydration and electrolyte imbalance. Patients must be educated about self-monitoring and self-treatment of diarrhoea when they start therapy. It is usual to provide the patient with a supply of loperamide to use should diarrhoea develop. Patients must be advised to seek advice from their specialist if diarrhoea lasts for longer than 24 hours or does not respond to medication.[15] Patients who develop severe diarrhoea may require a dose adjustment, treatment interruption or even discontinuation of the therapy.

Bleeding risk and implications for surgery

Because angiogenesis inhibitors (e.g. pazopanib, sorafenib, sunitinib) affect blood vessels, patients can have problems with bleeding and wound healing.

These drugs should be stopped before any planned surgery or invasive procedures including dental surgery. It is generally recommended that therapy is stopped a week before major surgery and at least 3–4 days before minor surgery. Treatment is generally restarted four weeks after surgery to reduce complications with wound healing, but this may vary according to the therapy, surgery and the patient. Advice should always be sought from the treating oncologist or haematologist with regard to stopping and starting of therapy and for surgical or dental procedures.

Table 3 **Common skin problems with oral cancer therapies**

Skin problems	Presentation
Papulopustular (acneiform) rash	Erythematous pustules with or without pruritus Occurs on scalp, face, upper chest and back Onset occurs 1–6 weeks after treatment commences
Xerosis (dry skin) and fissures	Dry, scaly, itchy skin Often follows the acneiform rash Painful fissures on tips of fingers and toes Onset 1–2 months after treatment commences
Pruritus	Often accompanies acneiform rash and dry skin
Paronychia	Tender and oedematous inflammation of the nail folds of fingers and toes Lesions can become infected Onset about 6 weeks after treatment commences
Hand–foot syndrome	Redness in the palms of the hands and soles of feet Blisters and cracked peeling skin can develop May be accompanied by painful paraesthesia Onset 1–2 months after treatment commences
Hair changes	Trichomegaly (elongation and curling of the eyelashes) Hypertrichosis (usually as facial hair) Hyperpigmentation Scalp hair changes including brittle hair, slowed growth and alopecia Onset 2–5 months after treatment commences

Immunomodulatory drugs

Lenalidomide, thalidomide and pomalidomide are immunomodulatory drugs mainly used in the treatment of myeloma in combination with steroids.[16] They may also be combined with cytotoxic chemotherapy. They block several pathways that drive the progression of myeloma and have anti-angiogenic properties.

Due to the well-documented risk of birth defects associated with these drugs, only specialists and pharmacists registered with the Pharmion Risk Management Program are allowed to prescribe and dispense thalidomide, lenalidomide and pomalidomide.

There is an increased incidence of thromboembolic events in patients treated with the combination of dexamethasone and lenalidomide, thalidomide or pomalidomide, and prophylactic antithrombotic therapy is routine for these patients.[17] These drugs are associated with constipation and diarrhoea. Haematological toxicities are more common with lenalidomide, while dose-dependent peripheral neuropathy is associated with prolonged therapy with thalidomide.

All-trans retinoic acid

All-trans retinoic acid is an oral therapy used in the treatment of acute promyelocytic leukaemia,[18] usually in combination with arsenic trioxide and/or cytotoxic chemotherapy. It is a derivative of vitamin A with a distinct mode of action. All-trans retinoic acid binds to the retinoic acid gene receptor and induces the differentiation of acute promyelocytic leukaemia cells into normal mature cells. Common adverse effects include headache, fever, weakness and fatigue. All-trans retinoic acid should only ever be prescribed by a haematologist experienced in managing acute promyelocytic leukaemia.

Drug interactions

Interactions between targeted therapy and other prescribed and over-the-counter medicines, complementary medicines and food can affect the efficacy and safety of both the targeted therapy and other therapy. It is important that an assessment is made of potential interactions when a patient is started on therapy, or when any new medications are started.

The bioavailability and absorption of many tyrosine kinase inhibitors is affected by food and the acidity

of the stomach environment. The concomitant use of acid suppressive treatment decreases absorption of dasatinib, erlotinib, gefitinib, lapatinib and pazopanib.[19] The combination of these drugs and an H_2 antagonist, proton pump inhibitor or antacid should be avoided. Food can enhance the absorption of lapatinib in an unpredictable manner and lapatinib should be taken on an empty stomach.

A number of targeted therapies are substrates for the cytochrome P450 (CYP) 3A4 enzyme.[20-22] Simultaneous use with other CYP3A4 inhibitors, such as grapefruit juice, can increase concentrations of many targeted drugs and cause toxicity. A warning label alerting the patient not to consume grapefruit-containing products is required on many targeted therapies including lapatinib, nilotinib, pazopanib and sunitinib.

Other CYP3A4 inhibitors that patients with cancer may be taking include:

- azole antifungals – fluconazole, itraconazole, posaconazole, voriconazole
- macrolide antibiotics – clarithromycin, erythromycin
- antiemetics – aprepitant.

Concomitant use of CYP3A4 inducers can reduce concentrations of tyrosine kinase inhibitors and lower their efficacy. CYP3A4 inducers include:

- antiepileptic drugs – carbamazepine and phenytoin
- oral dexamethasone
- rifampicin
- St John's wort.

$5HT_3$ antagonists (for nausea), antibiotics (clarithromycin, erythromycin) and azole antifungals (such as fluconazole) are commonly used by patients with cancer and these can have a fatal interaction with targeted therapies by prolonging the QT interval (Aust Prescr 2015;38:20-4). QT prolongation with the serotonin $5HT_3$ antagonist ondansetron occurs in a dose-dependent manner. Single intravenous doses of ondansetron should not exceed 16 mg in patients under 75 years and 8 mg in patients over 75 years. If concurrent use of these drugs cannot be avoided then an ECG should be obtained before, and one week after, starting concomitant medication.

Targeted therapies with anti-angiogenic activity can increase the risk of bleeding. Any co-administered drug or complementary therapy that interferes with blood clotting adds to this risk. Caution should be used when prescribing or dispensing antiplatelet medication, and anticoagulants including dabigatran, rivaroxaban and apixaban.

Vaccination

Live vaccines are contraindicated in patients with impaired immune function and those who have poorly controlled malignant disease. Inactivated vaccines are generally safe, but patients may have a diminished immune response to the vaccine. The recommended schedule of vaccination for cancer patients is outlined in the 10th edition of the Australian Immunisation Handbook.[23]

Patient information and labelling

The majority of oral targeted therapies will be self-administered at home by the patient. As with oral cytotoxic therapy, patients should be given verbal information and a written plan that includes when the drug should be taken and if it should be taken before or after food, adverse effects and any drugs or foods that need to be avoided.

The labelling of oral targeted therapy, like cytotoxic therapy, should clearly state the dose and the number of tablets to be taken. It is important that the patient understands when continuous dosing may be required or when the drug is given on a cyclical basis. For example, in renal cell cancer, sunitinib is taken as a daily dose for four weeks followed by a two-week break, whereas pazopanib is taken continuously. In pancreatic neuroendocrine tumours, sunitinib is taken continuously.

Targeted therapies are not cytotoxic and do not require cytotoxic handling precautions. Some are known to be teratogenic, for example thalidomide, while for others there is limited or no evidence of safety. The product information should always be consulted.

Adherence to treatment

Many targeted therapies are taken continuously for a number of months or years until disease progression or resistance occurs. Adherence to treatment plays a pivotal role in the success of therapy. Treatment failure can develop with some therapies, such as imatinib for chronic myeloid leukaemia, if they are not taken as prescribed.[24] This is due to the loss of the cytogenetic response because of the inconsistent exposure to imatinib.

Non-adherence increases with longer duration of therapy and when patients experience adverse effects. Adherence should be discussed regularly with the patient to identify any difficulties they may be having complying with the dosing.

Drug resistance

Acquired resistance to molecularly targeted drugs can develop over time and occurs with almost all therapies. Specific mutations often contribute directly to this, however cellular and physiological mechanisms also play a significant role. Resistance to therapy remains a significant challenge in the clinical management of cancer with targeted therapy.

Conclusion

As with oral cytotoxic therapy, the delivery of oral targeted therapy requires a multidisciplinary approach.[25,26] Treatments should only be initiated by a cancer specialist who has experience with these drugs.

It is essential that health professionals managing these patients have appropriate training and skills in the use of these therapies in cancer care. They should be aware of the adverse effects and the potential for drug interactions. Healthcare professionals should seek advice from the prescribing cancer specialist when required. If a patient unknown to the doctor or pharmacist presents for therapy, a full patient review must be conducted and the oncologist or haematologist who initiated treatment should be contacted for further advice. ◁

Christine Carrington is an advisory board member for MSD and has also served on advisory boards for Gilead and Amgen.

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