Molecular mechanisms and clinical use of targeted anticancer drugs

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SUMMARY

The last decade has seen the introduction of several new classes of targeted anticancer therapies for routine clinical use.

Unlike chemotherapy, which generally targets all dividing cells, these drugs are specific for a molecular characteristic of a cancer such as a growth factor receptor or signalling molecule.

Although targeted therapies do not cause the antiproliferative toxicities typical of chemotherapy, they do have adverse effects of their own.

These new drugs include monoclonal antibodies, such as bevacizumab and rituximab, and the small molecule tyrosine kinase inhibitors, such as dasatinib and sorafenib.

Targeted therapies are often taken for long periods of time. Many of the drugs, such as the tyrosine kinase inhibitors, are orally administered so patients receiving these therapies are increasingly being seen in general practice.

Introduction

Historically, the treatment of cancer was based on an understanding of the differences in cell kinetics between normal and malignant cells. The largely fortuitous discovery of cytotoxic therapy resulted in a class of drugs that has become known as chemotherapy. Most chemotherapy drugs have a direct action on DNA or proteins involved in DNA replication, translation and transcription. Although it was hoped that chemotherapy would selectively treat the disease and not normal tissue, this was not the case. As chemotherapy generally targets all dividing cells, highly proliferative normal tissues are also affected and common toxicities develop such as myelosuppression and mucositis.

The search for more targeted cancer therapies has been supported by a better understanding of malignancy at the molecular level. Cancers exhibit acquired characteristics that enable their malignant phenotype. These have been called the hallmarks of cancer and traits include:

- replicative immortality
- sustained proliferative signalling
- evasion of growth suppressors
- angiogenesis induction
- tissue invasion and metastases
- resistance to cell death
- deregulated cell metabolism
- genomic instability
- tumour-promoting inflammation
- ability to evade the immune system.

Cancers interact with their local microenvironment or stroma through angiogenesis, inflammation and immune responses. Each of these hallmarks of cancer provides a target for drug therapy.

The targeted therapies can be broadly divided into two classes:

- monoclonal antibodies (Table 1)
- small molecules – predominantly tyrosine kinase inhibitors (Table 2).

Monoclonal antibodies

Monoclonal antibodies are denoted by the suffix –mab, for example trastuzumab for breast cancer. They typically require intravenous or subcutaneous administration. 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.

Monoclonal antibodies target cell surface molecules, usually receptors, or their ligands. They may exert their effects through interference with a receptor pathway or through immune mechanisms such as antibody-dependent cellular cytotoxicity.

Small molecules

The small molecules typically block pathways that are continuously activated in cancer cells. The tyrosine kinase inhibitors are the most common and work by

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* antibodies that contain polypeptides from different species

inhibiting kinases that phosphorylate key proteins to activate signal transduction pathways. They are denoted by the suffix –nib, for example imatinib for chronic myeloid leukaemia, and are typically developed for oral administration. These inhibitors block a number of different tyrosine kinases.

Another class of small molecules is the inhibitors of mammalian target of rapamycin (mTOR). They have the suffix –imus, for example everolimus for pancreatic neuroendocrine tumour or temsirolimus for renal cell carcinoma. These molecules bind to an intracellular protein (FKBP-12). This complex then blocks the activity of mTOR kinase which inhibits angiogenesis and tumour cell growth, proliferation and survival.

Table 1 **Monoclonal antibody therapies for cancer**

Drug	Target	Indication	Companion diagnostic test	Adverse effects	Monitoring and precautions
Bevacizumab	VEGF	First-line therapy of colorectal cancer in combination with chemotherapy*	—	Hypertension, arterial and venous thromboembolism, haemorrhage, gastrointestinal perforation, poor wound healing	Blood pressure, urinalysis Discontinue several weeks before elective surgery
Cetuximab	EGFR	Second- or third-line therapy of colorectal cancer with or without concurrent chemotherapy*	Patient must have wild-type KRAS[#]	Acneiform rash, diarrhoea, hypomagnesaemia, severe hypersensitivity reactions at time of infusion, interstitial lung disease (rare)	Electrolytes (magnesium), pre-emptive management of rash and management of secondary complications e.g. cutaneous infection
		As concurrent therapy with radiation for head and neck cancer where cisplatin is contraindicated or not tolerated*	—		
Ipilimumab	CTLA-4	Metastatic melanoma*	—	Autoimmune effects including colitis, dermatitis, hepatitis, endocrinopathy and neuropathy	Clinical monitoring for rash and colitis Liver function tests Regular check for thyroid dysfunction, adrenal and pituitary dysfunction
Panitumumab	EGFR	Colorectal cancer	Patient must have wild-type KRAS	Acneiform rash, diarrhoea, hypomagnesaemia, hypocalcaemia, interstitial lung disease (rare)	Electrolytes (magnesium), pre-emptive management of rash and management of secondary complications e.g. cutaneous infection
Rituximab	CD20	Diffuse, large B cell non-Hodgkin's lymphoma*	CD20 expression[#]	Lymphopenia (B cell depletion), Stevens-Johnson syndrome, HBV reactivation	Full blood count Avoid live vaccines Check HBV status pre-treatment
		Low grade B cell or follicular cell non-Hodgkin's lymphoma*			
		CD20 positive chronic lymphocytic leukaemia*			
Trastuzumab	HER2/ neu	HER2 positive breast cancer in adjuvant and metastatic settings*	HER2 positivity on in situ hybridisation assay[#]	Cardiomyopathy	Regular assessment of left ventricular ejection fraction
		Advanced gastric cancer			

VEGF	vascular endothelial growth factor		EGFR	epidermal growth factor receptor
KRAS	Kirsten rat sarcoma-2 virus oncogene		CTLA-4	cytotoxic T-lymphocyte associated antigen 4
CD20	lymphocyte antigen		HBV	hepatitis B virus
HER2	human epidermal growth factor receptor 2			

* indicates listing on the Pharmaceutical Benefits Scheme (PBS) at the time of publication. Companion diagnostics are listed as per PBS authority restrictions.

[#] use guided by companion diagnostic test

Table 2   **Small molecule therapies for cancer**

Drug	Target	Indication	Companion diagnostic test	Adverse effects	Monitoring and precautions
Bortezomib	26S proteasome	Multiple myeloma*	–	Emesis, peripheral neuropathy, rash, myelosuppression, gastrointestinal disturbance, peripheral oedema	Full blood count, check for neuropathy
Crizotinib	ALK	Non-small cell lung cancer	ALK gene rearrangement	Nausea, vomiting, diarrhoea, hepatotoxicity	Liver function tests
Dasatinib	BCR-ABL (Philadelphia chromosome)	Chronic myeloid leukaemia*, acute lymphoblastic leukaemia*	PCR evidence of BCR-ABL transcript#	Diarrhoea, rash, pleural effusion, oedema, myelosuppression, mucositis, QT interval prolongation	Full blood count, liver function test; ECG as clinically indicated; Physical examination
Erlotinib	EGFR	Non-small cell lung cancer (after prior chemotherapy*)	Activating EGFR mutation in absence of KRAS mutation	Acneiform rash, diarrhoea, transaminitis, interstitial lung disease (rare)	Liver function test; Pre-emptive management of rash and treatment of complications e.g. secondary infection
Everolimus	mTOR	Pancreatic neuroendocrine tumour	–	Mucositis, rash, electrolyte abnormalities, transaminitis, dyslipidaemia, diarrhoea, constitutional symptoms, pneumonitis, peripheral oedema	Electrolytes, urea, creatinine, liver function test, full blood count, glucose
Gefitinib	EGFR	Non-small cell lung cancer (after prior therapy*)	Activating EGFR mutation# in absence of KRAS mutation	Acneiform rash, diarrhoea, transaminitis, interstitial lung disease (rare)	Liver function test; Pre-emptive management of rash and treatment of complications e.g. secondary infection
Imatinib	BCR-ABL	Acute lymphoblastic leukaemia*	PCR evidence of BCR-ABL transcript#	Rash, oedema, pleural effusion, decreased left ventricular ejection fraction, emesis, myelosuppression, myalgias and arthralgias	Full blood count, liver function test, physical examination; Possible role for therapeutic drug monitoring
		Chronic myeloid leukaemia*	PCR evidence of BCR-ABL transcript#		
		Gastrointestinal stromal tumour in adjuvant setting and for unresectable metastatic disease*	CD117 (c-kit) expression on immunohistochemical staining#		
		Hypereosinophilia and eosinophilic leukaemia*	FIP1L1-PDGFRA fusion gene#		
		Myelodysplastic or myeloproliferative syndrome*	PDGFR gene rearrangement#		
		Systemic mastocytosis with eosinophilia*	FIP1L1-PDGFRA fusion gene		
		Dermatofibrosarcoma protuberans*	–		

Table 2 **Small molecule therapies for cancer (continued)**

Drug	Target	Indication	Companion diagnostic test	Adverse effects	Monitoring and precautions
Lapatinib	HER2/neu	HER2 positive breast cancer after progression on prior trastuzumab*	HER2 positivity on in situ hybridisation assay#	Decreased left ventricular ejection fraction, rash including palmar-plantar erythrodysesthesia (hand-foot syndrome), diarrhoea, emesis, transaminitis	Regular assessment of left ventricular ejection fraction, electrolytes, urea, creatinine, liver function test
Sorafenib	Multiple targets including BRAF, VEGFR, EGFR, PDGFR	Hepatocellular carcinoma*, renal cell cancer	–	Hypertension, rash including palmar-plantar erythrodysesthesia (hand-foot syndrome), diarrhoea, emesis, myelosuppression, delayed wound healing, hypophosphataemia, elevated amylase and lipase	Blood pressure, dermatologic assessment, full blood count, phosphate level. Consider pancreatitis if symptomatic
Sunitinib	Multiple targets including VEGFR, PDGFR, proto-oncogene c-kit, FLT3	Renal cell cancer*, gastrointestinal stromal tumour after progression on imatinib*	–	Hypertension, emesis, myelosuppression, hypothyroidism, adrenal dysfunction, decreased left ventricular ejection fraction, yellow discolouration of skin, mucositis, elevated lipase, transaminitis	Blood pressure, full blood count, electrolytes, urea, creatinine, liver function test, thyroid function test. Consider pancreatitis and adrenal dysfunction if symptomatic
Temsirolimus	mTOR	Renal cell cancer	–	Emesis, myelosuppression, dyslipidaemia, diarrhoea, rash, arthralgias and myalgias, and nephrotoxicity	Electrolytes, urea, creatinine, liver function test, full blood count, glucose, lipids
Vemurafenib	BRAF	Metastatic melanoma	BRAF V600E mutation	Arthralgias, rash, photosensitivity	Physical examination

BCR-ABL	breakpoint cluster region-Abelson
EGFR	epidermal growth factor receptor
KRAS	Kirsten rat sarcoma-2 virus oncogene
PDGFR	platelet derived growth factor receptor
BRAF	proto-oncogene B-Raf
FLT3	FMS-like tyrosine kinase 3
PCR	polymerase chain reaction
mTOR	mammalian target of rapamycin
FIP1L1-PDGFRA	fip1 like1-platelet derived growth factor receptor alpha
HER2	human epidermal growth factor receptor 2
VEGFR	vascular endothelial growth factor receptor
ALK	anaplastic lymphoma kinase

* indicates listing on the Pharmaceutical Benefits Scheme (PBS) at the time of publication. Companion diagnostics are listed as per PBS authority restrictions.

use guided by companion diagnostic test

Principles of targeted therapy

Targeted therapies are developed on the premise that a particular target is important in the pathogenesis of a malignancy. The relevance of a target may have been determined through basic scientific research or through epidemiological studies in patients with tumours that express the target. Often targets are prognostic biomarkers. For example, human epidermal growth factor receptor 2 (HER2)/neu amplification is associated with poor prognosis in breast cancer. Also, the KRAS (Kirsten rat sarcoma-2 virus oncogene) mutation is associated with poor prognosis in colon cancer.

Ideally, targeted therapies have very high specificity for their target. If the tumour does not express the target then the therapy will be ineffective. Target molecules are predictive biomarkers for efficacy of the therapy. For example, trastuzumab is ineffective in treating breast tumours that do not have amplified HER2/neu. On the other hand, cetuximab is only effective for colorectal cancers that have wild-type (normal) KRAS, but not tumours that have mutant KRAS (Table 1).

As targeted therapies are dependent on their target it should be possible to tailor therapy to suit individual patients. This therapeutic strategy avoids treating patients who will not benefit and may only experience adverse effects. In addition more selective use of the therapy results in improved cost-effectiveness.

In Australia, prescribing of many targeted therapies requires evidence that the patient's cancer is expressing the target molecule. This is confirmed using a companion diagnostic test. Future government registration and reimbursement of targeted therapies will include parallel assessment of any associated diagnostic test.

Adverse effects

In general, targeted therapies do not cause the antiproliferative toxicities of chemotherapy, but they all have toxicities of their own (Tables 1 and 2). Some of the toxicities are common to the classes of drug. For example:

- acneiform rash with drugs that target the epidermal growth factor receptor
- cardiac toxicity with drugs targeting HER2/neu
- hypertension and other vascular toxicities with angiogenesis inhibitors such as bevacizumab.

Some of the small molecules have multiple targets and have a greater potential to cause adverse effects than monoclonal antibodies. Angiogenesis inhibitors such as bevacizumab may interact with a patient's pre-existing medical condition, for example hypertension.

Patients who were not previously suitable for chemotherapy may now receive treatment with one of the new drugs. Targeted therapies are also more suitable as maintenance therapies than cytotoxics.

How effective are targeted therapies?

Response to traditional chemotherapy is usually determined by a change in tumour size. While this is still possible with targeted therapies, many of the drugs stabilise tumours rather than shrink them. Sometimes these drugs are referred to as cytostatic rather than cytotoxic. An example is sorafenib for hepatocellular carcinoma. Fewer than 2% of patients achieve a partial response, but their time to progressive disease is significantly longer than with placebo. This leads to improved survival.

Drugs such as imatinib for gastrointestinal stromal tumours can alter radiological appearance on CT scan, making tumours more hypodense compared to baseline. Specific response criteria, called the Choi criteria, use change in the appearance of the tumour, rather than change in size, as one of the response measures.[1] Positron emission tomography may show gastrointestinal stromal tumours have also become hypometabolic after a short period of treatment despite no objective change in tumour size.

Sometimes it is difficult to measure a patient's response to therapy and newer measures of treatment response are being developed. For example, patients receiving immunotherapy with the anti-cytotoxic T-lymphocyte associated antigen 4 (CTLA-4) monoclonal antibody ipilimumab for metastatic melanoma may have objective evidence of disease progression before an immune response occurs. The immune-related response criteria have been developed to take this observation into account.[2]

Implications for primary care

All of the common cancers and many rare tumours now have at least one line of systemic therapy. GPs will routinely encounter patients receiving a targeted therapy and it will be useful to be aware of common toxicities (Tables 1 and 2). Perhaps more important is the role the doctor can play in ensuring treatment compliance. Many targeted therapies are given continuously, for example imatinib for gastrointestinal stromal tumour and erlotinib for non-small cell lung cancer. If treatment is interrupted, the patient's disease may progress. Although the tumour may respond when rechallenged, resistance to therapy may emerge. As such the GP can encourage patient adherence and also liaise with the cancer specialist before stopping therapy because of toxicity.

Future directions

It is expected that many more targeted therapies will come into routine clinical use. A future direction for small molecule tyrosine kinase inhibitors will be to combine them to overcome treatment resistance. Monoclonal antibodies will be modified to become carriers for radiation or cytotoxic drugs and will be enhanced to increase their immune effects. The use of these medicines will be improved by further development of companion diagnostic tests. ◄

Winston Liauw has received funding from Merck-Serono and has ongoing participation as an investigator in numerous clinical trials associated with the development of targeted drugs. He provides drug development and medical advice to Clinical Network Services. He serves on the board of directors of NPS MedicineWise.

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FURTHER READING

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Q:

SELF-TEST QUESTIONS

True or false?

5. Lapatinib is only prescribed for patients with breast cancer expressing the KRAS mutation.

6. Acneiform rash can occur with gefitinib and erlotinib.

Answers on page 143

Book review

Therapeutic Guidelines: Cardiovascular. Version 6.

Melbourne: Therapeutic Guidelines Limited; 2012. 228 pages

These guidelines provide the reader with an overview of salient cardiovascular topics, from the management of risk factors to acute management of chest pain and arrhythmias.

The guidelines are sensibly structured into succinct and manageable sections, and flow diagrams and tables effectively support written text. Most useful are the clinical pearls in highlighted boxes, which for example, remind the reader that life-threatening hyperkalaemia can occur when adding an aldosterone antagonist to an ACE inhibitor or angiotensin II antagonist in patients with renal impairment.

The new features of the current edition are the standout. 'Type 2 diabetes and cardiovascular disease risk' is a new focus that explores the assessment and management of risk factors in patients with diabetes, while new information has been included on the management of antithrombotic therapy in patients with cardiac implanted electronic devices undergoing non-cardiac procedures or operations. This section is valuable for answering that often difficult question of what to do with a patient's anticoagulation before surgery. Revised information on bariatric surgery has been included, which is important for GPs tackling the rising problem of obesity.

Particularly useful is the section on antithrombotic therapy, which summarises the various types of anticoagulants and antiplatelets and includes the newer drugs such as dabigatran, rivaroxaban and ticagrelor. It provides a short summary of salient points such as clinical utility, monitoring, determinants and management of bleeding and over-anticoagulation. This is great for the busy GP needing quick access to concise information during a consult, particularly as the newer drugs are used with increasing frequency.

Overall, the Cardiovascular Therapeutic Guidelines is a comprehensive and useful resource for GPs, medical students and other health professionals.

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