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# Beyond chemotherapy

## Demystifying the new 'targeted' cancer treatments

**It has been known for some time that key genetic changes are the principle mechanism of cancer development. These changes lead to abnormalities in the signalling pathways of cells and result in unregulated cell growth, angiogenesis and metastasis.**

Until recently, cancer treatments, ie. surgery, radiotherapy and cytotoxic chemotherapy, although effective, have been relatively nonspecific in their actions. It has long been hoped that an understanding of the molecular basis of cancer would lead to more specific ('targeted') therapies. As a result of decades of research, new therapies are now becoming available.

One of the most spectacular examples of targeted treatment in solid tumours is that of gastrointestinal stromal tumour (GIST), the most common sarcoma of the gastrointestinal system and resistant to conventional chemotherapy. The oral agent imatinib (Glivec) has increased median survival in this disease from 10–20 months to 4.8 years, and is dramatic proof of the 'principle' (*Figure 1a–c*). GIST, however, is a rare tumour. What is the role of these new therapies in the cancers most often affecting our patients?

## General principles

Many receptors exist to control cell behaviour. In cancer cells, the expression or activity of these receptors is deranged and often overactive. The best characterised receptors are transmembrane receptors that receive signals from outside the cell and transmit them (through a complex array of intracellular proteins) to cellular DNA (*Figure 2a*).

There are two main ways to interfere with overactive receptors: antibodies to block the extracellular part of the molecule, and small molecules to inhibit the intracellular activation of the receptor. These so called 'mabs' (monoclonal antibodies) and 'nibs' (tyrosine kinase inhibitors) form the basis of the new cancer treatments (*Figure 2b*).

Different cancers have different aberrant receptor pathways and therefore respond to different 'mabs' and 'nibs'. As a general rule, mabs are given as intravenous infusions (usually weekly or 3 weekly). Nibs are orally active and given every day at home (sometimes with a 1–2 week rest period).

## The EGFR pathway

### EGFR inhibitors

Inhibitors of the epidermal growth factor receptor (EGFR) pathway include cetuximab (Erbitux) and panitumumab (Vectibix) – 'mabs' that have shown activity in colorectal cancer. Gefitinib (Iressa) and erlotinib (Tarceva) are 'nibs' studied extensively in nonsmall cell lung cancer (NSCLC).

### Toxicity

Allergic reactions can occur during intravenous administration of any 'mab' but is less common with the fully humanised antibody panitumumab. Concurrent steroid or antihistamine may help. The most common side effect of anti-EGFR mabs is an acne-like rash involving the face and trunk. The evidence for how to treat this rash is limited and management guidelines have been developed by 'expert opinion'.[1] The rash should be treated differently from acne as it has a different pathophysiology. Simple measures such as using moisturising soaps can ease the discomfort. Topical corticosteroids and oral tetracyclines may be beneficial, particularly if it is thought there is potential for superinfection. In general, the development of a rash correlates with a higher likelihood of response and does not necessarily require alteration in treatment.[1]

Figure 1a–c. CT scan of the liver in a patient with GIST treated with imatinib

Figure 2a. Signal transduction pathway

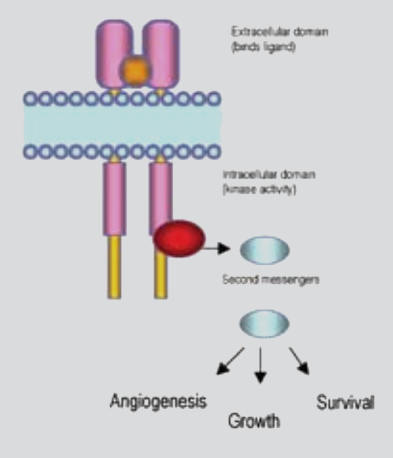
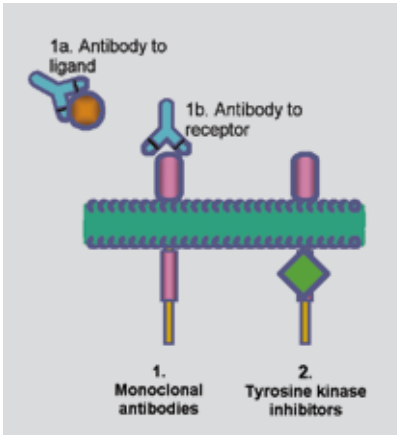



Figure 2b. Strategies to inhibit signal transduction receptors




The 'nibs' (gefitinib/erlotinib) have a class specific toxicity profile. The most common side effects are skin rash (also mostly an acneiform rash), diarrhoea and fatigue, but these are usually mild. Less than 1% of patients require cessation of treatment due to adverse effects. Drug interactions can occur (*Table 1*).

## The HER2 pathway

The HER2 receptor is related to the EGFR and is present in increased number in about 20–25% of breast cancers (so called HER2 positive cancers). Without treatment, these cancers have a worse prognosis than HER2 negative breast cancers. However, they are generally more sensitive to chemotherapy and when treated with targeted therapies, prognosis can be significantly improved.

### HER2 inhibitors

Trastuzumab (Herceptin) is a humanised monoclonal antibody that targets the HER2 pathway. Lapatinib (Tykerb) is a nib that targets the intracellular protein kinase domains of both EGFR and HER2. Trastuzumab has been shown to improve survival in both early (postoperative) breast cancer and advanced (metastatic) breast cancer. Lapatinib has shown promise and is still being tested.

### Toxicity

Trastuzumab is well tolerated. Hypersensitivity reactions are rare and usually occur with the first infusion. Cardiotoxicity, particularly

Table 1. EGFR tyrosine kinase inhibitors – adverse effects and drug interactions[10,12]

| Category | Adverse effect | Management |
|---|---|---|
| Gastrointestinal | Diarrhoea<br>Nausea<br>Anorexia | Hydration, loperamide<br>Antiemetic<br>Small frequent meals |
| Skin | Pustular (acneiform) rash<br>Itchy, erythematous, dry skin | Topical hydrocortisone cream 1% (no more than 14 days)<br>Doxycycline 100 mg twice per day orally if rash is moderate to severe<br>If rash is severe (interferes with function) EGFR inhibitor dose may need reducing – discuss with medical oncologist |
| Eyes | Conjunctivitis and blepharitis- mild<br>Reversible corneal erosion | Topical antibiotics if severe<br>Specialist referral |
| Haematological | Mild epistaxis, haematuria | Check full blood count<br>No action usually required |
| Laboratory tests | Liver function abnormalities – asymptomatic and mild | LFTs are monitored at hospital visits |
| Drug interactions | CYP3A4/EGFR TKIs are metabolised by CYP3A4 enzymes | Potential for increased toxicity |
| | CYP3A4 inhibitors (eg. ketoconazole, itraconazole, rionavir) increase EGFR TKI concentrations | |
| | CYP 3A4 inducers eg phenytoin, carbamazepine, St John's wort decrease EGFR TKI concentrations | Potential for decreased efficacy |
| | CYP 2D6/EGFR TKIs may increase blood concentrations of drugs metabolised by CYP 2D6 | Watch beta blockers |
| | Elevations in INR | Review need for warfarin, change to enoxaparin or check INR weekly |

Table 2. Bevacizumab adverse effects and drug interactions[18]

| Category | Adverse effect | Management |
|---|---|---|
| Cardiac | Hypertension – common | Antihypertensives |
| Vascular | Arterial thromboembolism (including myocardial infarction, cerebrovascular accident) | Low dose aspirin is being studied. It does not appear that aspirin increases bleeding risk[26] |
| | Venous thromboembolism | Consider anticoagulation (it does not appear that warfarin increases risk of haemorrhage)[27] |
| | Haemorrhage (eg. gastrointestinal, respiratory, genitourinary) | Emergency measures if required, specialist advice |
| Gastrointestinal | Gastrointestinal perforation and poor wound healing | Stop bevacizumab 6 weeks before elective surgery |
| Laboratory tests | Leukopaenia, neutropaenia<br>Proteinuria | Generally no specific treatment required |
| Drug interactions | No formal drug interaction studies have been conducted in humans | Monitor for potential drug interactions |

congestive cardiac failure (CCF), is the most important adverse effect, although it is uncommon. In patients on trastuzumab the left ventricular ejection fraction (LVEF) is regularly monitored with either an echocardiogram or a gated heart pool scan (GHPS). In clinical trials using trastuzumab as adjuvant therapy, the rates of severe CCF ranged 0.3–3.4%. For this reason it is not used concurrently with anthracycline chemotherapy, which is also known to cause CCF.[2–4]

While generally well tolerated, side effects of lapatinib can include diarrhoea, hand-foot syndrome, nausea, vomiting, fatigue and rash. The long term cardiotoxicity of lapatinib is not known but cardiac events are rare in trials conducted so far.[5]

## The VEGF pathway

Angiogenesis is a fundamental event in the process of tumour growth and metastasis. The vascular endothelial growth factor (VEGF) and its receptor (VEGFR) are key regulators of this process, promoting endothelial growth, migration, survival and blood vessel permeability.[6] Over expression of VEGF is associated with tumour progression and poor prognosis in a number of cancers, and is thus a logical target for treatment.

Table 3. Progress in the treatment of advanced NSCLC[24]

| | Median overall survival (months) | 1 year survival % | 2 year survival % |
|---|---|---|---|
| 1980s | 4–6 | 10 | 5 |
| 2000 | 8 | 30–35 | 10–15 |
| 2005 | 10 | 40 | 20 |
| 2010 | Personalised medication and targeted treatment | | |

### VEGF/VEGFR inhibitors

Anti-VEGF therapies reduce tumour vascularisation and therefore can inhibit tumour growth and metastasis. They can also reduce microvascular permeability and help to normalise irregular and leaky blood vessels and allow better delivery of chemotherapy to the tumour.[7] Bevacizumab (Avastin) is a humanised recombinant monoclonal antibody to VEGF. Sunitinib (Sutent) and sorafenib (Nexavar) are oral multitargeted VEGFR and platelet derived growth factor receptor (PDGFR) nibs used in the treatment of metastatic renal cell carcinoma.

### Toxicity

The VEGF/VEGFR pathway inhibitors have a class specific toxicity profile. Their toxicity generally does not overlap with chemotherapy (*Table 2*).

## Targeted therapies in specific cancers

### Breast cancer

#### Metastatic disease

In patients with HER2 positive breast cancer trastuzumab, either as a single agent or in combination with chemotherapy, can provide

Table 4. Important trials of targeted agents in metastatic renal cell carcinoma[25]

| Trial | Number of patients | Benefit of targeted therapy | Main adverse effects of targeted therapy |
|---|---|---|---|
| Sorafenib vs. placebo | 903 | Yes | Fatigue, skin rash, hand foot syndrome, diarrhoea, nausea, hypertension |
| Sunitinib vs. interferon | 750 | Yes | Fatigue, nausea, diarrhoea, vomiting, lymphopaeina, neutropaenia, anaemia |

significant clinical benefit. Two studies confirm that the addition of trastuzumab to chemotherapy improves overall survival.[8,9] In one study, adding trastuzumab to the taxane docetaxel improved median survival from 23 to 31 months ($p$=0.033).[9] The use of trastuzumab with aromatase inhibitors is also being explored for those with tumours that are both HER2 positive and oestrogen receptor positive.

In patients whose cancer progresses after trastuzumab, an all oral combination of capecitibine chemotherapy and lapatinib can improve survival.[5]

### Early breast cancer

In the five randomised controlled trials studying trastuzumab in early breast cancer there has been a striking and reproducible reduction in the risk of recurrence of 39–52% at follow up ranging 1–3 years.[2–4] This translates into an absolute risk reduction of up to 12.8%. The large benefit derived from trastuzumab may mean that less aggressive and safer chemotherapy may be used in the future. At present, trastuzumab is given intravenously every 3 weeks for 1 year. Cardiac function is assessed every 3 months.

## Nonsmall cell lung cancer

### Advanced NSCLC after chemotherapy

In an important study of gefitinib compared with placebo in the second line treatment of locally advanced or metastatic NSCLC there was no difference in overall survival between the two groups.[10] However, there was a significant survival benefit in those who had never smoked, in those of Asian origin, and in those with EGFR gene mutations.[11] In contrast to gefitinib, a study of erlotinib showed an increase in overall survival from 4.7 to 6.7 months (HR 0.7, $p$=–0.001) among all comers compared with placebo.[12] Again, patients of Asian origin, those with adenocarcioma, and those who never smoked, derived the most clinical benefit. These patients are more likely to harbour a mutation in the EGFR gene, causing constant activation of the signalling pathway. Mutation testing is available to determine which patients are likely to benefit most from these drugs. Erlotinib and gefitinib do not appear to potentiate the effects of chemotherapy.[13–16]

### Advanced NSCLC in addition to chemotherapy

In one study of NSCLC, a combination of chemotherapy and the angiogenesis inhibitor bevacizumab was compared with chemotherapy and a small survival benefit was seen.[17] Unfortunately, there were a number of treatment related deaths in this trial, and much remains to be learnt about how to best use these drugs (*Table 3*).

## Colorectal cancer

### Metastatic colorectal cancer

The median survival of patients with metastatic colorectal cancer has been extended beyond 24 months with the advent of newer chemotherapeutic agents and the development of targeted therapies. In one study, bevacizumab combined with first line chemotherapy including irinotecan resulted in an improved median survival from 15.6 to 20.3 months.[18]

Bevacizumab has also been studied in an infusional chemotherapy regimen called 'FOLFOX' (oxaliplatin and infusional flurouracil and leucovorin) and shown to be beneficial in first and second line settings.[19] Ongoing trials are exploring the combination of bevacizumab with cetuximab.

Cetuximab has been extensively studied in patients already treated with multiple lines of chemotherapy and shown modest survival benefit over best supportive care in patients with no further chemotherapy

Table 5. Targeted therapies currently available on the Pharmaceutical Benefits Scheme*

| Cancer | Drug | Setting approved |
|---|---|---|
| Breast | Trastuzumab (Herceptin) | Initial treatment for HER2 positive early breast cancer commencing concurrrently with adjuvant chemotherapy following surgery<br>First line treatment of metastatic breast cancer in combination with chemotherapy or as a single agent in subsequent lines of therapy |
| NSCLC | Gefitinib (Iressa) | Single agent therapy of locally advanced or metastatic NSCLC in patients with a performance status of two or less where disease progression has occurred after at least one chemotherapy agent and there is evidence of an activating mutation of the EGFR gene in tumour material |
| GIST | Imatinib (Glivec) | Metastatic or unresectable malignant GIST which has been histologically confirmed by the detection of CD117 on immunohistochemical staining |
| Chronic myeloid leukaemia | Imatinib (Glivec) | Chronic, blastic and accelerated forms of chronic myeloid leukaemia expressing the Philadelphia chromosome or the transcript bcr-abl tyrosine kinase |
| Non-Hodkin lymphoma | Rituximab (Mabthera) | Relapsed or refractory low grade or follicular B-cell non-Hodgkin lymphoma<br>Untreated CD20 positive diffuse large B-cell NHL in combination with chemotherapy<br>Symptomatic patients with untreated CD20 positive stage II or IV follicular B-cell NHL in combination with chemotherapy |

* Other access programs are available for some drugs via the relevant pharmaceutical company

options. Cetuximab plus irinotecan shows still greater activity than cetuximab alone in these patients, with improvement in time to disease progression of 4.1 months versus 1.5 months in one study.[20]

Panitumumab has shown similar single agent activity to cetuximab and is currently being studied in combination with chemotherapy as first and second line treatment.[21]

### Adjuvant therapy

Ongoing clinical trials are examining the benefit of bevacizumab in addition to standard adjuvant chemotherapy in patients with potentially curable colorectal cancer.

## Renal cell cancer

### Metastatic renal cell cancer

As a result of advances in the understanding of the genetics of renal cell cancer, novel targeted approaches for the treatment of metastatic renal cell cancer have been developed. The USA Federal Drug Administration has approved two targeted agents, sunitinib and sorafenib, for the treatment of metastatic renal cell cancer. In Australia, sunitinib has become the standard of care for metastatic disease with a proven survival advantage over other treatment such as interferon[22,23] (*Table 4*).

## Conclusion

Chemotherapy has been available for decades to treat solid tumours in a nontargeted fashion. The aim of the new targeted therapies is to better define which patients will benefit from specific therapies, thereby allowing individualised therapy with improved clinical outcomes and less toxicity (*Table 5*).

Conflict of interest: none declared.

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