Targeted and individualised therapies

PROGRESS IN TARGETED THERAPIES FOR CANCER: OVERVIEW

Benjamin Solomon and John Zalcberg
Peter MacCallum Cancer Centre, East Melbourne, Victoria.
Email: ben.solomon@petermac.org  john.zalcberg@petermac.org

Abstract
The explosion in knowledge about the molecular and cellular biology of cancer has led to the identification of many molecules or physiological processes that can be therapeutically exploited to treat cancer using so called ‘targeted therapies’. While the concept of targeted therapy is not a new one, it is only in the last decade that these agents have become established in standard clinical practice. An overview of progress in the development of targeted agents to date and challenges faced in the future application of targeted therapy to cancer treatment is provided in this article and is the subject of this issue of Cancer Forum.

Targeted therapies for cancer can be broadly defined as treatments directed against abnormally activated molecules or physiological processes required for maintenance or progression of tumours. In recent years, many targeted therapies have become established in daily clinical practice and a huge number of agents are in various stages of pre-clinical and clinical development. The concept of targeted therapy however, is not a new one. Just over a hundred years ago Paul Erlich developed the concept of ‘magic bullets’ to specifically target disease while sparing normal tissues (Erlich also coined the term chemical therapy or ‘chemotherapy’). Although treatment with radioiodine in the 1930s or tamoxifen in the 1970s perhaps represent the origins of targeted therapy for cancer, the modern era of targeted therapy was ushered in by the trials of rituximab, trastuzumab and imatinib at the beginning of this century. Since then there has been steady clinical progress with targeted therapies, used alone or in combination with conventional therapies, finding new indications in many tumour types, including cancers previously considered untreatable.

The development of targeted agents and their use in cancer treatment have been made possible by major advances in the understanding of cancer biology, in particular the identification of targets important for cancer maintenance and progression, and technological innovations that have allowed these targets to be therapeutically manipulated. However, significant challenges in the clinical application of targeted therapies remain, including finding predictive markers to identify which patients are likely to benefit from which treatments, the development of acquired resistance, management of long-term toxicities and the financial costs of these agents.

Historical backdrop
The recent progress in targeted therapies must be viewed against the backdrop of the achievements of cytotoxic chemotherapy over the last half century or so (see timeline, figure 1). The observation of profound lymphoid and myeloid suppression in World War I soldiers exposed to nitrogen mustard led to the use of mustine in patients with lymphoma in the 1940s. Since then, a range of cytotoxic drugs have been developed, including alkylating agents, vinca alkaloids, podophyllotoxins, antimetabolites, topoisomerase inhibitors, platinum analogs and taxanes. The largely empiric use of these drugs resulted in cures in germ cell tumours and certain leukaemias and lymphomas. Concurrent chemotherapy with radiotherapy provided potentially curative treatment for head and neck cancer, lung cancer, cervical cancer, anal squamous cell carcinoma and other cancers, albeit at the expense of significant toxicity. Adjuvant chemotherapy after surgery in breast, colon, or lung cancer improves survival. Additionally, in many tumour types, chemotherapy can improve survival and quality of life in patients with metastatic disease. However, limitations of traditional cytotoxic chemotherapy include low response rates and frequent toxicities to normal tissue. Efforts to combine different cytotoxic agents or increase dose (by techniques including the use of growth factor support, autologous bone marrow or peripheral stem cell transplantation) have in general not resulted in further improvements in outcomes, indicating a ceiling of efficacy for current cytotoxic drugs.

Tamoxifen
Tamoxifen is arguably the first and most successful targeted therapy to date. For over a century it was
recognised that oophorectomy, hypophysectomy and adrenalectomy were effective treatments in some women with breast cancer. The identification of the estrogen receptor in the 1950s and the development of an assay for the estrogen receptor led to a method to identify patients who would benefit from endocrine ablative surgery. Tamoxifen (initially called ICI-46,474) was developed as a post-coital contraceptive (it failed as it caused ovulation). Pre-clinical studies demonstrated that tamoxifen was able to block estrogen from binding to estrogen receptors in tumours and prevented the growth of mammary tumours in rats. These findings led to clinical studies beginning in the 1970s that established the use of tamoxifen in metastatic breast cancer and in the adjuvant setting for women with hormone receptor positive tumours. Tamoxifen has also been reported to prevent the development of new breast cancers by 50% in high risk women.

Modern era of targeted therapy

In the last three decades there have been major advances in unraveling the molecular processes that underpin cancer. Increasingly detailed appreciation of the biology of cancer has led to the identification of specific molecules or processes (eg. angiogenesis) that are crucial to the maintenance and progression of tumours. Coinciding with this has been the development of new technologies such as high throughput screening, structure-based design and monoclonal antibody technology, that have allowed discovery of agents that modulate these targets (so called targeted therapies). Small molecules designed to inhibit signal transduction pathways by inhibiting protein kinases and monoclonal antibodies targeting cell surface receptors represent the most commonly used approaches to date. These agents have demonstrated efficacy across a broad range of tumour types.

This issue of Cancer Forum provides an update about the current status of targeted therapy in breast cancer, lung cancer, colorectal cancer, ovarian cancer, renal cancer, sarcoma and haematologic malignancies. At the time of writing, 15 such therapies are approved by the Therapeutic Goods Administration (TGA) (see table 1).

Early success for the use of targeted therapies as single agents was seen with trastuzumab in breast cancer, imatinib in chronic myeloid leukaemia (CML) and rituximab in B-cell lymphomas. Tumour types considered resistant to standard cytotoxic treatments, such as gastrointestinal stromal tumours (GIST) and renal cell carcinoma, have responded to agents such as imatinib and sunitinib. Survival benefits observed with the epidermal growth factor receptor (EGFR) inhibitors erlotinib in non-small cell lung cancer (NSCLC) and cetuximab in colorectal cancer indicated that these agents might be beneficial in a broader set of tumour types.

Notably, the strategy of combining targeted therapies with cytotoxic chemotherapy and radiotherapy has proved to be fruitful. This is particularly the case for monoclonal antibodies, where combinations of rituximab, trastuzumab, bevacizumab and cetuximab with chemotherapy (as well as radiation in the case of cetuximab) have become important and in many cases standard of care regimens in lymphoma, breast cancer, colorectal cancer, lung cancer and head and neck cancer. Less promising results have been seen with small molecules, where to date many combination studies have not demonstrated improved outcomes.
(with the exception of lapatinib in combination with capecitabine in breast cancer and possibly erlotinib in combination with gemcitabine in pancreatic cancer).21-22

The application of targeted therapies to cancer has required a shift from empiricism and a ‘one treatment fits all’ algorithm, to one based on understanding the mechanism of disease and targeting pathogenesis. This is exemplified by the clinical development of imatinib, the first tyrosine kinase inhibitor to be used in humans.

Imatinib was developed to target the molecular abnormality responsible for CML, but has found applications in other malignancies. Screening of chemical libraries and medicinal chemistry efforts in the 1980s led to the identification of a compound (now known as imatinib, formerly known as STI571 and CGP57148B) that potently inhibited BCR-ABL (the fusion protein product of the t 9:22 translocation known as the Philadelphia(Ph) chromosome which is the molecular driver of CML).23 Encouraging pre-clinical studies with this drug24 led to a Phase I clinical trial that was conducted in patients with Philadelphia chromosome positive (Ph+) CML.6 Significant efficacy with minor toxicities was observed in these patients.6 Soon after this, imatinib was studied in and found to have activity in CML in blast crisis and Ph+ Acute lymphocytic leukaemia. This led to US Food and Drug Authority (FDA) approval of imatinib for Ph+CML in 2001. Imatinib also inhibits two other kinases C-KIT (CD117) and platelet derived growth factor receptor (PDGFR). This lead to the study of imatinib in gastrointestinal stromal tumours, where it received accelerated FDA approval on the basis of response rates in tumors with mutations in either C-KIT or PDGFR.8 Since then, further mechanism-based studies led to exploration of the use of imatinib in tumours with activating mutations or gene rearrangements, resulting in increased expression of receptor or ligand.25 As a result of these studies imatinib is now approved for: chronic myelomonocytic leukemia (TEL-PDGFRα fusion gene); aggressive systemic mastocytosis (C-KIT mutations); hypereosinophilic syndrome and/or chronic eosinophilic leukemia (FIP1L1-PDGFRα fusion kinase); and dermatofibrosarcoma protuberans (COL1A1/PDGFB fusion).

A concern was that the dramatic responses seen with imatinib in CML and GIST represented the exception rather than the rule and that few solid tumours would be dependant on or ‘addicted’ to a single oncogenic mutation and therefore contain a targetable molecular ‘Achilles heel’.6,8,26 This scepticism is supported by large-scale genomic studies of cancer genomes which show that individual tumours may contain multiple potentially pathogenic mutations.27,28 These data emphasise the importance of developing bio-informatic tools that can provide an assessment of complex signalling networks to identify which pathways drive a particular cancer and the necessity of developing combinations of drugs that inhibit multiple different pathways.

Another approach is to identify small subsets of patients within a tumour type that are driven by the mutation of interest. Again, imatinib provides an instructive example. Phase II studies of imatinib in unselected patients with melanoma were conducted with disappointing results.29,30 However, recently KIT-activating mutations were reported in a small subset of patients with acral and mucosal locations.31,32 Phase II studies of imatinib in patients with melanomas found to have KIT mutations have commenced with preliminary positive results.33

<table>
<thead>
<tr>
<th>Table 1: TGA approved targeted therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Small molecules</strong></td>
</tr>
<tr>
<td>Imatinib (Glivec)*</td>
</tr>
<tr>
<td>Gefitinib (Iressa)*</td>
</tr>
<tr>
<td>Erlotinib (Tarceva)*</td>
</tr>
<tr>
<td>Sorafenib (Nexavar)</td>
</tr>
<tr>
<td>Nilotinib (Tasigna)</td>
</tr>
<tr>
<td>Dastinib (Sprycel)*</td>
</tr>
<tr>
<td>Lapatinib (Tykerb)*</td>
</tr>
<tr>
<td>Sunitinib (Sutent)</td>
</tr>
<tr>
<td>Bortezomib (Velcade)*</td>
</tr>
<tr>
<td>Octreotide (Sandostatin)*</td>
</tr>
</tbody>
</table>

| **Monoclonal antibodies**               |
| Rituximab (Mabthera)*                  | CD20                   |
| Trastuzumab (Herceptin)*               | erbB2 (HER2)           |
| Cetuximab (Erbitux)*                   | EGFR                   |
| Bevacizumab (Avastin)                  | VEGF                   |
| Alemtuzumab (Campath)                  | CD52                   |

TGA approved targeted therapies for cancer as of July 2008. Note this list excludes hormonal therapies for breast and prostate cancer. Asterisk (*) indicates Pharmaceutical Benefits Scheme approval for specific indications.
Challenges for targeted therapy

The concept of individualised medicine involves selection of the right drug for the right person at the right dose and schedule (figure 2). Current molecular modelling and medicinal chemistry efforts have enabled the development of inhibitors of many kinases implicated in cancer; monoclonal antibody technology allows for design of specific humanised antibodies to target essentially any protein. Previously ‘un-druggable targets’, such as those involving protein protein interactions are now ‘druggable’, allowing the development of new classes of targeted agents such as proapoptotic BH3 mimetics. The challenge moving forward is to identify which patients will benefit from this growing armamentarium of targeted therapies.

It is however, fair to say that the progress in the molecular characterisation of tumours has not been matched by the development of clinically useful predictive biomarkers. For example, although much has been learned about the mechanisms of angiogenesis in tumours and bevacizumab has been shown to be of clinical benefit in combination with chemotherapy in colorectal cancer, in non small cell lung cancer and perhaps breast cancer, there are no predictive markers that predict which patients are most likely to benefit from this therapy. The importance of predictive and prognostic biomarkers is explored in the article by Sally Lord and colleagues.

To date, tests for specific genetic markers (ie. mutations, amplifications or gene rearrangements) conducted in tumour tissue have proven the most robust predictive markers. However, it is likely that ongoing genomic and proteomic studies will uncover other suitable biomarkers as illustrated by tests such as Oncotype Dx in breast cancer. It is also likely that high throughput platforms which allow cheap and rapid screening for hundreds of mutations, or next generation sequencing that allows sequencing of entire cancer genomes (as discussed by David Bowltell in this issue of Cancer Forum) and non-invasive molecular profiling methods in circulating tumour cells, plasma DNA, or utilising proteomic studies of plasma, will be valuable sources of predictive and prognostic markers that will direct treatments in the near future. In addition, as Rod Hicks and Rob Ware point out in their article, molecular imaging with technologies such as positron emission tomography will also provide important means to select patients for treatment and to monitor response to therapy.

Another challenge is the development of acquired resistance to initially effective therapies. Patients receiving imatinib for CML or GIST may develop resistance to imatinib after many months or even years of successful treatment. Similarly, patients with NSCLC responding to EGFR TKIs gefitinib and erlotinib invariably become resistant to these agents. Recently, the mechanisms responsible for acquired resistance have begun to be appreciated and new strategies to overcome this problem are under development. In CML and in GIST, a frequent observation in patients with acquired resistance to imatinib is a point mutation in the ABL, KIT or PDGFR kinase domain that interferes with the binding of imatinib. This approach may be overcome by structurally distinct second generation inhibitors such as nilotinib, dasatinib or sunitinib. In NSCLC resistance occurs through secondary mutations in the EGFR that prevent binding of gefitinib or erlotinib to the active site of the EGFR tyrosine kinase; or through subversion of alternative signaling pathways such as occurs with amplification of c-met. Strategies under investigation to overcome acquired resistance to EGFR inhibitors include the use of irreversible inhibitors of the EGFR, such as PF00299804 or BIBW 2992, or combinations of EGFR inhibitors and met inhibitors. For other classes of targeted agents such as antiangiogenic therapies, the mechanisms of resistance (both intrinsic and acquired) remain poorly understood.

There has also been appreciation of the distinct profile of toxicities of targeted therapies. Examples of common toxicities include: rash toxicity and diarrhoea from EGFR inhibitors; hypertension from VEGF inhibitors; congestive cardiac failure from trastuzumab; hypothyroidism and hair depigmentation from sunitinib; and hand foot syndrome from multitargeted tyrosine kinase inhibitors. In addition, there are rare but serious complications of targeted therapies such as fatal haemorrhage or reversible posterior leukoencephalopathy with VEGF inhibitors. Long-term management of toxicities of targeted agents are particularly relevant, as unlike cytotoxic chemotherapy, which is typically used for a limited number of cycles, targeted agents are frequently used in ongoing maintenance treatments for months or years.

Finally, the financial costs of targeted therapies are significant. Novel targeted agents are frequently many times more costly than their cytotoxic predecessors. Trastuzumab, imatinib, bevacizumab and rituximab together accounted for over $8 billion in sales in 2005. Treatment with cetuximab or bevacizumab can currently cost patients in excess of $4000 a month. These considerable costs raise issues of how much individuals or the broader community are prepared to pay for sometimes incremental benefits provided by these drugs, as well as ethical issues regarding equity of access to treatment.

Figure 2: The role of predictive markers in individualised medicine. If a given drug is only active in 30% of unselected patients of a given tumour type, a predictive marker can be used to identify those patients prior to treatment. This allows the therapy to be delivered to a selected population more likely to benefit and spares patients unlikely to benefit from receiving an ineffectual treatment.
Conclusions

While there has been remarkable progress in a relatively short time in the application of targeted therapies to cancer treatment, there remains a long way to go before cancer can be considered a chronic disease. Few targeted agents (with the exception of adjuvant tamoxifen or trastuzumab) have been shown to cure patients. The survival benefits from the addition of targeted agents to chemotherapy, while significant, are generally incremental and measured in months. Further progress requires understanding of the molecular drivers of cancer and development of clinically useful tools to identify which patients will benefit from which treatments. Combinations of agents acting on different targets alone or in combination with conventional agents will need to be developed and tailored to the particular genetic makeup of individual tumours. Strategies will be needed to prevent or overcome acquired resistance to treatments and to manage long-term toxicities of targeted agents. These challenges will need to be addressed to realise the promise of targeted therapies in delivering individualised medicine for all patients with cancer.

Conflict of interest statement: Ben Solomon is on the advisory boards for AstraZeneca, Sanofi-Aventis, Novartis and receives research funding from Novartis. J ohn Zalberg is on the advisory boards for Amgen, Ariad, Novartis, Pfizer, Roche, Sanofi-Aventis and receives research funding from Agen, MerckSerono, Novartis, Pfizer and Sanofi-Aventis.

References