OPINION

Personalized medicine in oncology: the future is now

Richard L. Schilsky

Abstract | Cancer chemotherapy is in evolution from non-specific cytotoxic drugs that damage both tumour and normal cells to more specific agents and immunotherapy approaches. Targeted agents are directed at unique molecular features of cancer cells, and immunotherapeutics modulate the tumour immune response; both approaches aim to produce greater effectiveness with less toxicity. The development and use of such agents in biomarker-defined populations enables a more personalized approach to cancer treatment than previously possible and has the potential to reduce the cost of cancer care.

Oncologists have long recognized that each patient with cancer is different from every other patient in clinical presentation, prognosis, tumour response and tolerance to treatment. This is in addition to differences in risk of recurrence, second malignancy and long-term complications of treatment. Yet, only recently have scientists and clinicians begun to understand the biological heterogeneity of human cancer and the inter-individual variation in the human genome to enable a more personalized approach to cancer treatment.

With current technologies enabling interrogation of the cancer genome and examination of variation in germline DNA we are in a better position now than ever before to match the treatment to the tumour characteristics. That is, to select the optimal drug and drug dosage for each patient and thereby to improve patient outcomes. However, significant obstacles remain to the widespread implementation of the vision of personalized cancer care.

Foremost among these are limitations in our understanding of cancer biology and ability to identify molecular targets that are essential for tumour proliferation and progression. Contributing to the slow pace of development of individualized treatment is the paucity of biomarkers that can reliably identify patients who are likely to respond to treatment, as well as the regulatory hurdles to developing biomarker assays for clinical use. This article explores some of the challenges and opportunities in developing personalized treatment for patients with cancer, and asserts that doing so will improve outcomes, reduce toxicity, improve efficiency in drug development and help control the skyrocketing cost of cancer care.

Implications of heterogeneity

Every type of human cancer is comprised of biological subsets that differ in clinical behaviour and response to treatment[1–4], and there are many important examples of treatment regimens that produce better results in some tumour subtypes than others (TABLE 1). Notable examples of tumour subtypes that must be recognized to optimize treatment include oestrogen receptor or HER2 (also known as ERBB2)-positive breast cancer[5]. More recent examples are non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR)-activating mutations[6]; colorectal cancer with KRAS mutations[7]; or malignant gliomas with hypermethylation of the methyl guanine methyl transferase (*MGMT*) gene[8]. In each case, knowledge of the molecular profile of the tumour is necessary to guide selection of therapy for the patient. Expanding knowledge of tumour biology and tumour–host interactions has moved the field of cancer therapeutics in several new directions, including the following:

> "Knowledge of the molecular profile of the tumour is necessary to guide selection of therapy for the patient."

- Development of targeted therapies designed to interrupt molecular pathways known to be critical for cell growth and survival; for example, imatinib (Glivec/Gleevec; Novartis) treatment for chronic myeloid leukaemia and gastrointestinal stromal tumours[9,10].
- Molecular profiling of tumours to better assess prognosis and likelihood of benefit from treatment; for example, the Oncotype Dx assay (from Genomic Health) for breast cancer[11].
- Development of single-gene or multigene expression signatures of response or resistance to particular drug treatments (for example, HER2 and oestrogen receptor) to identify patients with breast cancer who are likely to benefit from adjuvant paclitaxel treatment[12], or ERCC1 expression as a marker of resistance to platinum-based chemotherapy[13].
- Development of vaccine therapies and other immunological approaches that are highly specific to each individual tumour[14].

Similarly, a growing appreciation of inter-individual variation in drug metabolism has begun to provide important insights to guide prescribing practices. Irinotecan (Camptosar; Pfizer), a standard treatment for advanced colorectal cancer is metabolized through a complex pathway that culminates in glucuronidation to facilitate clearance of the drug from the body. Conjugation to the glucuronide is mediated by glucuronosyl transferase, an enzyme encoded by *UGT1A1*, a polymorphic gene in the population. Patients with the *28 genotype, about 10% of the Caucasian population, have low enzyme activity and, therefore, low clearance of the drug and greater toxicity, particularly neutropaenia[15]. Unravelling these relationships has led to the development of commercial tests for *UGT1A1* genotype and revision of the US

Table 1 | **Biomarkers of established or potential clinical utility to guide therapy**

Tumour type	Biomarker	Potential clinical use
Breast	Steroid hormone receptors	Select hormone therapy
Breast	HER2	Select trastuzumab use
Breast	Oncotype Dx gene profile	Assess prognosis; select chemotherapy
Colon	KRAS mutation status	Guide EGFR-specific antibody use
Colon	Microsatellite instability	Assess prognosis or utility of 5-fluoruracil adjuvant treatment
Non-small cell lung	EGFR mutation	Guide selection or use of EGFR tyrosine kinase inhibitors
Non-small cell lung	ERCC1	Select platinum-based chemotherapy
Glioblastoma	MGMT methylation	Guide temozolomide use
Melanoma	BRAF V600E mutation	Select therapy

EGFR, epidermal growth factor receptor; ERCC1, excision repair cross-complementation group 1; HER2, also known as ERBB2; MGMT, methyl guanine methyltransferase.

Food and Drug Administration (FDA) label for irinotecan to recommend initiating treatment at a reduced dose for patients with the *28 genotype.

More recently, increasing attention has been paid to the pharmacogenetics of tamoxifen, a highly effective drug for the treatment and prevention of breast cancer. Tamoxifen is metabolized by cytochrome P450 2D6 (CYP2D6) to biologically active metabolites: 4-OH tamoxifen and endoxifen. CYP2D6 is involved in the metabolism of many commonly used drugs and, like *UGT1A1*, the gene is polymorphic in the population, yielding groups of patients who are limited or extensive metabolizers of tamoxifen[16]. Slow metabolizers may be at increased risk of cancer progression when receiving tamoxifen therapy[17] and alternative treatments, such as aromatase inhibitors, might be preferred in such individuals. Whether or not women should routinely be tested for *CYP2D6* genotype before receiving tamoxifen is a matter of ongoing debate, but the controversy illustrates the importance of the need for better understanding of the genetics of drug metabolism before assuming that all patients will benefit from treatment to the same extent.

Biomarkers and clinical trial design

A better understanding of cancer biology and drug metabolism has enormous potential to improve the efficiency of drug development. The clinical development of gefitinib (Iressa; AstraZeneca) for treating NSCLC illustrates both the challenges and opportunities in the development of targeted therapies for cancer.

In the case of gefitinib, the target (EGFR) was known and ample preclinical and early clinical data existed to indicate that the target was inhibited at pharmacologically achievable drug concentrations that were clinically tolerable. Initial clinical trials showed promising, even dramatic, results in some patients[18] and the drug received marketing approval in the United States of America according to the accelerated approval pathway.

Subsequently, large-scale, prospective, randomized Phase III trials failed to confirm the clinical benefit of gefitinib when added to standard chemotherapy for advanced NSCLC[19,20] and marketing approval for the drug was effectively withdrawn in the United States and Europe. All of these actions occurred before the recognition of the importance of activating EGFR mutations to identify individuals who are likely to benefit from treatment with this class of agents[6], and more recent studies have confirmed the importance of tumour genotyping to identify likely responders[21]. Indeed, the weight of such evidence was sufficient for European regulatory authorities to once again license gefitinib for marketing for the treatment of patients with advanced NSCLC who have an activating mutation of the EGFR tyrosine kinase.

Contrast the clinical development of gefitinib to that of trastuzumab (Herceptin; Genentech) — a molecule that also inhibits EGFR pathway signalling but the development of which was restricted to study of patients with *HER2* overexpression — and the value of having a validated biomarker to improve the efficiency of drug development becomes clear.

Many ways to fail

Despite these important advances in understanding tumour biology and using biomarkers to identify and select patients who are likely to benefit from or be resistant to treatment, there remain few examples of clinically useful biomarkers that can identify drug sensitivity and predict clinical benefit. Indeed, clinically useful biomarkers, such as HER2 and KRAS, are far more useful to identify patients who are unlikely to respond to treatment. Why is it so difficult to identify positive predictive biomarkers? Once again, the challenge lies primarily in understanding the heterogeneity of cancer and the plasticity of the cancer genome (BOX 1).

Tumours with drug-sensitizing mutations can simultaneously harbour or develop drug resistance mutations as in the case of the EGFR T790M mutation[22], or there may be downstream pathway-activating mutations as in the case of KRAS[23]. Activation of a parallel pathway that circumvents a pharmacological block is known to occur as in the case of MET amplification, thereby causing resistance to small-molecule EGFR inhibitors[24]. In addition, pathway blockade can result in feedback upregulation of the pathway to overcome the block[25].

The opportunities for biomarker-directed drug development are exciting, offering the potential to limit enrolment of candidates for clinical studies to those most likely to benefit from the treatment under study. This enables the design of studies that demonstrate larger effects, but with smaller numbers of patients required[26]. However, the risks associated with this approach are considerable. An invalid biomarker (for example, EGFR expression for cetuximab (Erbitux; Bristol-Myers Squibb, Merck Serono, ImClone Systems)); a suboptimal technology to assess the biomarker (for example, immunohistochemistry rather than fluorescence *in situ* hybridization to assess HER2); or a technically difficult assay that provides inconclusive or unreliable results can all confound the clinical trial design. Therefore, confidence in the biological relevance of the marker and extensive analytical validation of biomarker assays are required to move forward.

Regulatory challenges

Biomarker-driven clinical trials also introduce regulatory challenges when the aim is to co-develop a biomarker assay with the drug. This is because both the test and the drug must meet regulatory standards for marketing approval and clinical use. Within the FDA, review of *in vitro* diagnostic tests

Box 1 | **Potential mechanisms of resistance to targeted therapies**

The mechanisms listed below contribute to the challenges in identifying clinically useful biomarkers that can be used to select patients who are most likely to benefit from or be resistant to treatment:

- Mutation at drug binding site
- Downstream pathway mutation and/or activation
- Feedback upregulation of target
- Parallel pathway activation
- Pharmacological resistance

and drugs occur in different divisions of the agency (that is, the Center for Devices and Radiological Health, and the Center for Drug Evaluation and Research, respectively) that apply separate review processes and have different approval standards. Investigators and sponsors may find it challenging to design clinical trials that are acceptable to both divisions and to provide conclusive evidence of the safety and effectiveness of both the test and the drug.

Recently, a group of clinical investigators, scientists, drug developers and regulatory experts, convened by the Brookings Institution, proposed a novel strategy for drug and biomarker co-development designated "Targeted Approval" (*Accelerating Development and Approval of Targeted Cancer Therapies*; see Further Information). The objective of this approach is to facilitate the accelerated development and approval of a cancer therapy that is used in a population defined by a specific biomarker test.

The proposed criteria for targeted approval are that the drug must be indicated for use in cancer treatment; the assay must be analytically validated; and the drug must demonstrate, in a population defined by the test, a prespecified statistically significant change in a clinical end point that is reasonably likely to predict clinical benefit. Under such circumstances, it is proposed that the FDA would approve the drug for use in the population identified by the biomarker test, as well as approve the test for identifying the patient population for treatment with the drug. However, the caveat of approval of the assay is that the test has not been proved useful to identify patients with expected lack of benefit from the drug. Post-marketing studies would be necessary and required to establish the utility of the test and the drug in the biomarker-negative population. The Brookings Institution panel proposed that, in these circumstances, reimbursement by insurers for off-label use of the drug would not occur until completion of the post-marketing studies. At present, it is not clear whether or not this proposal will be accepted by the FDA, or any other regulatory authority. What is clear is that revisions to regulatory policies and procedures are essential to enable a more rapid development of targeted anticancer therapies and the biomarker assays that are essential for their optimal use.

Personalized care to reduce cost

The use of biomarkers to identify patients who are most likely to respond or be resistant to treatment has significant cost implications as well. The NCIC Clinical Trials Group BR.21 trial demonstrated the clinical utility of erlotinib (Tarceva; Genentech, OSI Pharmaceuticals) in the treatment of advanced NSCLC[27,28]. The trial, which found an improvement in median overall survival of 2 months for erlotinib treatment compared with placebo, led to the marketing approval of the drug in the United States and other countries. An economic analysis conducted as part of the clinical trial assessed resource utilization by patients in the trial and determined that the incremental cost-effectiveness ratio for erlotinib treatment was CA$94,638 per life-year gained. However, subgroup analyses revealed that the drug is much more cost-effective if used in non-smokers or in patients whose tumours have a high EGFR copy number[28].

The clinical development and use of cetuximab further illustrates the complexity and value of biomarker-based drug development. Perhaps based on the experience with trastuzumab, initial clinical trials with cetuximab were limited to patients with *EGFR*-overexpressing colorectal tumours. Indeed, the FDA-approved label for cetuximab limits its use to this patient population. Post-marketing studies demonstrated similar activity of cetuximab in patients with low or non-expressing tumours, suggesting that the level of *EGFR* expression was irrelevant to the clinical effectiveness of the drug.

Recently, a series of studies have clearly demonstrated that colorectal tumours that harbour KRAS mutations fail to respond to cetuximab and related treatments, and that patients with KRAS-mutated tumours do not benefit from such treatment[29–32]. These findings led the American Society of Clinical Oncology to issue a provisional clinical opinion recommending against the use of EGFR-directed monoclonal antibodies in patients whose colorectal tumours harbour KRAS mutations[33] — a recommendation recently accepted by regulatory authorities in the United States and in Europe.

The revised drug labelling translates into a more limited commercial market for these drugs, and a recent estimate suggests that the US health-care system could save as much as US$700 million annually in drug costs by limiting the use of these drugs to patients with KRAS wild-type tumours[34]. A formal economic analysis of cetuximab treatment in patients with advanced colorectal cancer demonstrated an incremental cost-effectiveness ratio of cetuximab treatment compared with best supportive care of CA$199,742 per life-year gained[35]. This could be reduced to CA$120,061 by limiting use of the drug to patients with KRAS wild-type tumours.

Recent data suggest that colorectal tumours with BRAF or phosphatase and tensin homolog (PTEN) mutations are

Box 2 | **Challenges of the targeted therapy era**

As more epigenetic targets are identified, and with more than 800 anticancer therapeutics in clinical development, the obstacles to targeted therapy include the following:

- More drugs
- More diseases
- More use of placebo controls
- More use of randomized screening trials
- Longer time to reach end points
- More expensive documentation
- Multiple effective lines of therapy
- Greater regulatory complexity

also resistant to EGFR-directed antibodies. These data raise the possibility of further limiting the use of these agents to patients with wild-type genetic markers in each of these segments of the EGFR signalling pathway[36]. Ongoing and future clinical trials with cetuximab will be limited to enrolling patients with KRAS wild-type tumours, thereby increasing the possibility of demonstrating benefit from the drug by excluding a non-responsive patient population.

Conclusion

Personalized cancer care is rapidly becoming a reality in the clinical assessment and management of patients. As a consequence, the expectation is that this approach will improve treatment efficacy, reduce toxicity and minimize cost. Ongoing genome-profiling activities such as the National Cancer Institute's Cancer Genome Atlas and the Sanger Institute's Cancer Genome Project hold promise to reveal more drug targets than ever before. Indeed, the number will grow even more as epigenetic targets are identified. With more than 800 anticancer drugs already in clinical development, the challenges of the targeted therapy era (BOX 2) are formidable and include the following:

- The identification of more biologically and clinically discrete tumour subsets.
- An increasing number of drug targets and agents in development.
- Greater use of placebo controls and randomized trials that require more patients and present greater recruitment challenges.
- A longer time to reach time-to-event end points for agents that do not produce tumour regression.
- More expensive clinical documentation to record progression events.
- The availability of multiple lines of effective therapy making it challenging to demonstrate a survival advantage in many trials.
- Greater regulatory complexity for studies that seek approval of both drugs and diagnostic tests.

New paradigms of cancer biology, such as the concept of tumour stem cells, will further challenge the clinical investigator community to develop clinical end points that can be used to assess the activity of agents that may have no immediate effect on tumour mass or progression, even if they effectively eradicate the stem cell population. The cancer research, clinical and regulatory communities have an obligation to work together to meet these challenges. Patients with cancer are not all the same and each person deserves nothing less than a personalized approach to their care.

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Competing interests statement
The author declares no competing financial interests.

DATABASES

Entrez Gene:
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene
BRAF | *CYP2D6* | *EGFR* | *ERCC1* | *HER2* | *KRAS* | *MGMT* | *PTEN* | *UGT1A1*

OMIM:
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM
Breast cancer | chronic myeloid leukaemia | colorectal cancer | gastointestinal stromal tumours | non-small cell lung cancer

FURTHER INFORMATION

Accelerating Development and Approval of Targeted Cancer Therapies: http://www.brookings.edu/~/media/Files/events/2009/0914_clinical_cancer_research/Panel3%20ApresFINAL.pdf
The Brookings Institute: http://www.brookings.edu
The Cancer Genome Atlas:
http://cancergenome.nih.gov
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