

# Personalised Medicine in Cancer Treatment: Hype or Hope?

**Edwin Klumper of SMS-oncology discusses the developments that have taken place in personalised medicine, reviewing the impact they have had on the industry and the challenges that lie ahead**

Cure rates in cancer are improving steadily but slowly. Early diagnosis and removal of the primary tumour remain the cornerstone of cures. The efficacy of systemic treatment in advanced disease is modest, despite the discovery of many new molecular targets and the development of new drugs. There is a need for both more effective drugs and for a better understanding of how to use them to improve treatment outcome. The number of publications discussing personalised medicine is skyrocketing. Why do we need personalised drugs? What do we mean by personalised medicine? What are the challenges? How successful has it been so far? What will the future bring? In exploring these questions it is important to bear in mind that personalised medicine is not the Holy Grail, but is another modest step in a long journey to further improve the outcome for patients who suffer from cancer.

## **WHY DO WE NEED PERSONALISED DRUGS?**

There is an increased demand for more effective drugs to treat advanced cancers. In the majority of advanced cancers chemotherapy will not cure patients, with a few exceptions such as cases of leukaemia, lymphoma and testicular cancer. The efficacy of anticancer drugs is low compared to other therapeutic areas such as cardiovascular disease or asthma, and as a result, a better understanding is needed of how to use the available drugs to improve the treatment outcome.

Traditionally, anticancer drugs that show objective response rates of 20 per cent or more have been considered effective. The dilemma oncologists face every day is that one would not want to withhold a patient a fair chance of being treated with an effective drug. However, as it cannot be predicted who will respond, all patients will receive the drug. The result is that many cancer patients are treated with drugs that are ineffective for them, while being exposed to toxicity including severe side-effects or even toxic deaths. To illustrate this point, it has been estimated that each year in the US alone around 20,000 women with breast cancer might be spared the side effects of Paclitaxel without significantly

raising the risk that their cancer will return. So, how can we personalise treatment to improve the outcome through better efficacy and less toxicity?

## **WHAT IS PERSONALISED MEDICINE?**

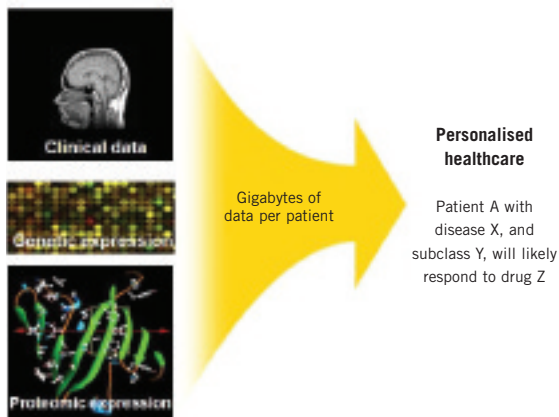
Strictly defined personalised medicine is truly customised individual treatment, though it is still experimental and thus may have limited effect. Studies are still underway with gene therapy, which involves replacing a set of defective genes with functional ones, and autologous cancer vaccines, which use unique antigens from an individual patient's tumour to stimulate a tumour-specific immune response. Despite new and improved technologies, mixed results have been reported. It is fair to say that a breakthrough technology has not yet reached mainstream commercial markets, and even when proven to be successful in the future, it is unlikely that every patient will qualify for such a therapy. The treatment of cancer is complicated due to the heterogeneity within and between tumours caused by aberrant protein expression and multiple genetic defects, many of which remain to be identified.

Within a wider context, personalised medicine is nothing new. Simply put, it

is no more than the use of all available personal medical information in order to choose the optimal treatment for each cancer patient. Consider a cancer patient with pre-existing cardiac disease: the common practice of replacing anthracyclines by other drugs or a liposomal packaged anthracycline to avoid damage to the heart is personalised medicine. Cure rates of children suffering from acute lymphoblastic leukaemia rise to 90 per cent when treated with different intensive chemotherapy regimens stratified to high-, medium- and low-risk groups. This is also a form of personalised medicine.

So, why the hype? It is probably our human optimism. It is fuelled by the promises made by molecular biology to further unravel the mechanisms of cancer and to eventually find a cure. Indeed, molecular biology has revolutionised the amount of new data available for exploration as illustrated by sequencing the genome. Emerging insights have provided new and exciting ways to fight cancer, such as the understanding of aberrant proteins as products from fusion genes, or angiogenesis promoting tumour growth. Sophisticated new technologies enable us to collect a staggering amount

**Figure 1: Increase in patient data to personalised medicine**



of data for each cancer patient (see Figure 1), but the question remains – can we use such data to improve personalised cancer treatment?

### WHAT ARE THE MAJOR CHALLENGES?

One of the main challenges to personalised medicine in cancer treatment is the availability of effective drugs and predictive biomarkers. Pancreatic cancer is the fourth leading cause of cancer-related deaths in the Western world with a median survival of around six months. At diagnosis, 80 per cent of pancreatic cancer patients present with unresectable disease. Gemcitabine is considered standard chemotherapy, but the lack of other effective drugs leaves few, if any, options for personalised treatment. This issue affects many other relatively drug-insensitive cancer types such as advanced cancers of the prostate, head and neck, stomach, liver, bladder, brain, bone, ovaries, melanoma and sarcoma, to name a few. Despite increased R&D efforts driven by molecular biology and the discovery of new cancer targets, the number of anticancer drugs that have achieved market authorisation is somewhat disappointing (see Table 1). From 2000 to 2009, 25 drugs for common cancer types have been approved by the FDA – on average less than three new compounds annually. The fact is that without a choice of effective drugs there is not much room to personalise cancer treatment.

Predictive biomarkers are not necessary in themselves to select the drug of choice. Take chronic myelogenous leukaemia (CML) for example. All CML patients will be treated with Imatinib, because all but a few CML patients carry the

Philadelphia chromosome. The chromosome is characterised by a translocation between the long arms of chromosomes 22 and 9 that results in the fusion protein *bcr-abl* with a strong tyrosine kinase activity, promoting tumour growth. Imatinib selectively blocks the tyrosine kinase activity of *bcr-abl* in CML patients.

In most cases, however, predictive biomarkers are

lacking even when a choice of effective drug is available, such as in relatively drug-sensitive cancer types like lung, breast, or colorectal. The good news is that the response rates to single agent Paclitaxel or Doxorubicin in advanced breast cancer are in the range of 50 to 60 per cent. The bad news is that the lack of predictive biomarkers leaves no option to tailor chemotherapy to women that will most likely respond. The recent surge in the development of targeted therapies may introduce a step forward to personalised treatment. The identification of specific cancer targets or pathways in human biopsies will help to prescribe drugs to those patients who are most likely to

respond. This sounds like a great promise, but the reality is that the number of predictive biomarkers that have been approved by authorities, is still limited (see Table 2, page 48). Tumour marker antigens have been in clinical use since the 1970s. The carcino-embryonic antigen (CEA) blood test used to monitor colon cancer reoccurrence was first approved by the FDA in 1973. Three decades later, only about a dozen of the FDA approved biomarkers are being used in clinical practice. Not all of the new generation of targeted therapies are guided by a set of predictive biomarkers. Take Bevacizumab, for example – the first angiogenesis inhibitor and one of the most prescribed targeted drugs to date; it does not have a validated predictive biomarker.

Probably the biggest gain of personalised therapy is avoiding over-treatment of the non-responders who lack the specific targets, thereby reducing unnecessary toxicity, rather than improving the outcome for the responders who would have been treated anyway. A difficult argument is cost savings. While targeted therapy may reduce costs by avoiding over-treatment, companies may charge extra for better personalised drugs as economics demand that we pay more for better products in the future.

**Table 1: Cancer drugs approved by the FDA in 2000 to 2009**

Year	Generic name	Trade name	Company
2009	Everolimus	Afinitor	Novartis
	Ofatumumab	Arzerra	GlaxoSmithKline
	Pazopanib	Votrient	GlaxoSmithKline
2007	Ixabepilone	Ixempra	Bristol-Myers Squibb
	Nilotinib	Tasigna	Novartis
	Temsirolimus lapatinib	Torisel Tykerb	Wyeth GlaxoSmithKline
2006	Dasatinib	Spyrcel	Bristol-Myers Squibb
	Sunitinib	Sutent	Pfizer
	Panitumumab	Vectibix	Amgen
2005	Sorafenib	Nexavar	Bayer/Onyx
2004	Pemetrexed	Alimta	Eli Lilly
	Bevacizumab	Avastin	Genentech
	Clofarabine	Clolar	Genzyme
	Cetuximab Erlotinib	Erbix Tarceva	Imclone, Bristol-Myers Squibb Genentech, OSI Pharmaceuticals
2003	Tositumomab	Bexxar	Corixa, GlaxoSmithKline
	Gefitinib	Iressa	AstraZeneca
	Bortezomib	Velcade	Millennium Pharmaceuticals
2002	Fulvestrant	Faslodex	AstraZeneca
	Ibritumomab	Zevalin	Biogen IDEC
2001	Alemtuzumab	Campath	Berlex Laboratories
	Imatinib	Gleevec	Novartis
	Zoledronic acid	Zometa	Novartis
2000	Gemtuzumab ozogamicin	Mylotarg	Wyeth

## WHAT ARE SOME OF THE SUCCESSES?

Successes in personalised cancer treatment are still limited to a handful of drugs and indications that have resulted in guiding treatment algorithms. The most prominent success is the treatment of advanced breast cancer with Trastuzumab, which was first approved by the FDA in 1998. Trastuzumab is an inhibitor of the HER2/neu-receptors, which are over-expressed in breast cancer and promote tumour growth. Around 20 to 25 per cent of women with HER2 positive breast cancer can be selected up-front for treatment with Trastuzumab, thereby avoiding unnecessary treatment of the 75 per cent or so HER2 negative patients. The principle however, is not new. In the late 1970s, Tamoxifen, an antagonist of the estrogen receptor, received FDA approval to treat women with estrogen receptor positive breast cancer and has since saved many lives.

In colorectal cancer, KRAS mutations have been validated and approved by the FDA as a predictive biomarker. Mutations in the gene that encodes KRAS, a protein that transmits growth signals from epidermal growth-factor receptors (EGFR), occur in 40 per cent of colorectal cancers. Tumours that express the mutated version of the KRAS gene will not respond to anti-EGFR therapy. In July 2009, the FDA and EMEA updated the labels of two anti-EGFR monoclonal antibody drugs, Panitumumab and Cetuximab indicated for treatment of metastatic colorectal cancer to include prescribing information about KRAS mutations.

In non-small cell lung cancer, patients with EGFR-activating mutations are sensitive to Gefitinib, a tyrosine kinase inhibitor of EGFR. In July 2009, the EMEA granted market authorisation to treat this specific subset of patients with Gefitinib.

**Table 2:** Predictive biomarkers approved by the FDA to prescribe drugs for treatment

Biomarker	Cancer type
Estrogen receptor	Breast
Progesteron receptor	Breast
HER2/NEU	Breast
KIT	GIST
KRAS	Colon
EGFR	Colon

## WHAT WILL THE FUTURE BRING?

It is anticipated that a limited number of companion diagnostics, co-developed in tandem with a drug to screen patients for clinical studies and commercialised alongside the drug for diagnostic and treatment purposes, will come to the market. A strong drug candidate in development is PLX4032 which targets the V600E mutated oncogene BRAF in melanoma with promising response rates. The number of new companion diagnostics will be limited as the identification of clinically useful predictive biomarkers for solid tumours has proven challenging, with many initially promising biomarkers failing to translate into clinically useful applications. The use of companion diagnostics for patient screening in clinical trials remains surprisingly infrequent. However, many of the big pharmaceutical companies are including the use of biomarkers in early stage clinical drug development. For example, around 90 per cent of the molecules in development at Eli Lilly, Pfizer and Bayer have biomarker strategies associated with them. Incorporating a search for 'potential' predictive biomarkers in early clinical trials will increase complexity and costs, thus raising hurdles for many small biotech firms without any guarantee of the future success of the drug or indeed biomarker validation.

Stratification based on gene expression profiling will be another tool for treatment personalisation. Examples for use in breast cancer treatment are MammaPrint by Agendia (which is a prognostic test for recurrence) and Oncotype Dx by Genomic Health (which predicts the response rate to chemotherapy). Several other products are in development, and advances in technology make these types of tests more sophisticated and cost-effective for individual patient screening.

## CONCLUSION

Clinical development will be more complicated and more critical in support of commercialisation and

## About the author



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reimbursement: will the clinical data warrant premium prices? For the development of personalised medicine, it is essential to specify the subset of patients that are likely to respond through the use of biomarkers. It is also critical to do the right study in smaller subsets of patients with additional complex endpoints, and more tumour sampling for biological validation of targets. The fulcrum of clinical development may shift from hinging on large Phase III regulatory trials to smaller and smarter Phase I and II programmes requiring smaller confirmatory Phase III trials to get market approval.

Despite the potential that exists for personalised medicine, we must still be modest as we face the future of cancer treatment. While personalised medicine has been around for 30 years, it only gained new momentum through the molecular revolution, and the fact remains that gains in cancer treatment have been modest when compared to the worldwide research conducted by thousands of scientists, and the billions of dollars spent by the industry. A long journey and hard work still lies ahead. This is definitely not a time to hype, but a time to hope.