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EDITORIAL

Precision Medicine

Where have we reached and where are we headed?

*Ikram A. Burney[1] and Ritu Lakhtakia[2]

الطب الدقيق

إلى أين وصلنا و إلى أين نتجه؟

إكرام بيرني و ريتو لكتاكيا

The diagnosis and treatment of cancer continues to pose profound challenges. Over the past 50–60 years, significant advances have been made in the screening, early detection, diagnosis and treatment of cancer, resulting in the current cure rate of 40–60%.[1–3] Together with surgery and radiotherapy, systemic chemotherapy has been the mainstay of cancer treatment for over half a century. However, conventional cytotoxic chemotherapy is fraught with both short- and long-term side-effects, to the extent that many patients and caregivers consider the option of cancer treatment to represent a choice between 'the devil and the deep sea.' Although combinations of cytotoxic chemotherapy are developed following rigorous evidence-based testing, a significant number of patients may not benefit from the combination and develop side-effects due to the non-selective nature of the treatment. Personalised and individualised treatment therefore remains a much desired but elusive goal for cancer patients, caregivers and healthcare professionals alike.

Precision or personalised medicine aims to overcome the 'one-size-fits-all' approach to cancer care and tries to match the treatment with specific genotypic and/or phenotypic targets on the tumour so as to maximise efficacy and minimise side-effects.[4] Notably, the genetic profile of the cancer may change over time and hence this method of treatment also needs to be dynamic. Another important aspect of the personalised approach, beyond the individual tailoring of therapy, is the capacity to provide prognostic information. With gene-on-a-chip technology, the analysis of multiple biological determinants such as growth, metastatic potential and microenvironment regulators can be used to stratify tumour behavior. The seminal work by Perou *et al.* on the molecular characteristics of breast cancer opened the floodgates for genomic signature determinants to enable prognostication.[5]

There are several dimensions of personalised medicine. First and foremost, it is important to ask ourselves whether, in the prevailing bio-psycho-social model of health and illness, we can rely solely on genetic code to inform the choice of treatment, or if we also need to take into account other factors, such as environment and lifestyle, which have a very strong influence on overall health. Secondly, it may be prudent to distinguish between prognostic and predictive markers, although this may not always be possible. Whereas the intrinsic characteristics of the patient or disease are known as prognostic biomarkers which identify the likelihood of a clinical event, predictive biomarkers indicate whether a favourable or unfavourable effect would result from exposure to a certain therapeutic agent. While both of these aspects are important, for the purposes of this article, the focus of discussion will lie on predictive biomarkers which help not only in predicting the response to treatment, but also to tailor the treatment itself.

So, what is our current understanding of an individual's predictive biomarkers? In general, cancer denotes a heterogeneous group of diseases. Since the outcomes of treatment are overtly different in different patients, attempts have been made to classify and subclassify cancers based on either histological or biological characteristics and, more recently, molecular phenotype. As a result, some common cancers, such as breast cancer, colon cancer and non-Hodgkin's lymphoma are no longer considered a single disease entity, but have been classified into several molecular types [Table 1].[5–8] These molecular subtypes may provide either prognostic or predictive information, or both. A further refinement is that 'actionable' predictive targets have been identified in many cancers, including non-small-cell lung cancer, Hodgkin's lymphoma, melanomas and gastric, ureteral and uterine cancers [Table 2].[9,10] For certain other cancers, molecular aberrations have become the *sine*

[1]*Department of Medicine, Sultan Qaboos University Hospital, Muscat, Oman;* [2]*College of Medicine, Mohammed Bin Rashid University, Dubai Healthcare City, Dubai, United Arab Emirates*

**Corresponding Author e-mail: ikramburney@hotmail.com*

Table 1: Molecular subtypes of common cancer[5–8]

Type of cancer	Molecular subtype
Breast cancer	ER/PgR-positive and HER-2/neu-negative
	ER/PgR-positive and HER-2/neu-positive
	ER/PgR-negative and HER-2/neu-positive
	Triple-negative
Colon cancer	Wild-type *Ras*
	Mutant *Ras*
Non-Hodgkin's lymphoma	B cell, CD19 and CD20
	T cell and CD52
	Anaplastic large-cell and CD30

ER = estrogen receptor; PgR = progesterone receptor; HER = human epidermal growth factor receptor; CD = cluster of differentiation.

qua non for diagnosis, for example the *breakpoint cluster region-Abelson murine leukaemia* (*BCR-ABL*) translocation in chronic myeloid leukaemia and the *c-kit* mutation in gastrointestinal stromal tumours.[11,12] These are only a few examples, with the list of such cancers continuing to grow. These molecular targets not only guide treatment using targeted therapy, but may also help to determine the choice of conventional cytotoxic chemotherapy.

Therefore, it became possible to treat a subtype of tumour with a drug which has been specifically tailored to the tumour target. The first two drugs in this class of targeted therapy are monoclonal antibodies against the receptors expressed on the cell surface. Trastuzumab, a monoclonal antibody directed against epidermal growth factor receptor (EGFR)-2 or human epidermal growth factor receptor (HER)-2/neu, was found to improve progression-free survival in patients with breast cancer expressing the protein.[13,14] Moreover, rituximab, a monoclonal antibody directed against the cluster of differentiation (CD)20 antigen expressed on activated B lymphocytes, was shown to improve both progression-free and overall survival in several types of B cell non-Hodgkin's lymphoma.[15,16] At almost the same time, a small-molecule tyrosine kinase inhibitor (TKI), later christened imatinib, was described; this agent inhibits phosphorylation at the adenosine triphosphate-binding site of the protein translated as a result of the *BCR-ABL* translocation in chronic myeloid leukaemia.[11] The introduction of imatinib in 2001 forever changed the landscape of treatment and outcomes for patients with chronic myeloid leukaemia as allogeneic bone marrow transplantations, with their attendant morbidity and significant mortality, were

Table 2: Actionable targets and targeted therapy in selected cancers[9,10]

Type of cancer	Target	Treatment
Non-small-cell lung cancer	EGFR mutations	EGFR TKIs
	ALK translocation	*ALK* TKIs
	ROS1 fusion	*ROS1* TKI
Anaplastic large-cell lymphoma	CD30 expression	Anti-CD30 antibody
	ALK translocation	*ALK* TKI
Hodgkin's lymphoma	CD30 expression	Anti-CD30 antibody
Melanoma	*BRAF* mutation	*BRAF* inhibitors
Gastric cancer	HER-2/neu expression	Anti-HER-2 antibodies
Uterine cancer	Microsatellite instability	Immune checkpoint inhibitors
Ovarian cancer	*BRCA1* and *BRCA2* mutations	PARP inhibitors

EGFR = epidermal growth factor receptor; TKI = tyrosine kinase inhibitor; ALK = anaplastic lymphoma kinase; CD = cluster of differentiation; HER = human epidermal growth factor receptor; BRCA = breast cancer; PARP = polyadenosine diphosphate-ribose polymerase.

replaced by a tablet with very few, if any, significant side-effects and an equal degree of efficacy.[17,18]

These three drugs are regarded as the frontrunners of modern day precision medicine. Since then, a plethora of monoclonal antibodies and TKIs have been investigated, reported and approved for use in a variety of cancers and have resulted in improved response rates and progression-free and overall survival, in addition to reducing and, in some cases, alleviating toxicities associated with conventional cytotoxic chemotherapy.[19] Nevertheless, although the side-effect profile of monoclonal antibodies and TKIs is different from that of conventional cytotoxic chemotherapy, it may sometimes be just as devastating. In addition to improving survival rates of common cancers, these medicines have also provided opportunities for therapy for individuals with otherwise difficult-to-treat cancers.[19]

However, challenges remain and treatment is often 'hit or miss', as not all patients with a certain target respond, or respond similarly, to a specific drug. For example, *BRAF* inhibitors produce remarkable responses in cases of metastatic malignant melanoma, but so far have not proved particularly effective in *BRAF*-mutant colon cancer.[20] Some tumours continue to exhibit primary resistance to the specific molecularly-targeted drug and may even develop

secondary resistance during the course of treatment. There are several reasons for this; some cancers may have more than one pathway of oncogenesis and others, especially solid tumors, may not have one specific driver mutation leading to oncogenesis.[20] These cancers may be dependent on tumour-environment interactions for progression. Furthermore, infiltration, invasion and metastasis remain the primary reason for dissemination in some cancers. Invariably, a metastatic tumour may harbor a different type of mutation and the elimination of one clone of cells may not be sufficient.[20]

Nevertheless, the paradigm of cancer care is changing. Instead of classifying tumours by histological or biological behaviour, molecular targets are now being employed to classify tumors. Because of a common target, and the availability of tailored treatment for the target, different tumour types charcterised by the same molecular target respond similarly. For example, in addition to breast cancer, HER-2/neu is overexpressed in gastric, bladder and several other cancers and trastuzumab (the monoclonal antibody binding to the EGFR-2 receptor) has been shown to improve survival in cases of HER-2/neu overexpressing gastric cancer, although not to the same extent as in breast cancer.[21] Similarly, patients with tumours with mutations in the *breast cancer* (*BRCA*) *1* and *BRAC2* genes, such as high-grade epithelial ovarian cancer, triple-negative breast cancer and prostate cancer, have exhibited prolonged progression-free survival when treated with the poly-adenosine diphosphate-ribose polymerase inhibitor, olaparib, which induces a state of synthetic lethality.[22] Another example is microsatellite instability in mis-match repair (MMR) genes. Data are beginning to emerge that MMR-deficient tumours may be more responsive to immunotherapy using anti-programmed cell death protein 1 (anti-PD1) antibodies, even if the mutation occurs in tumours as diverse as those seen in cancers of the colon, uterus, bladder or ureter.[23]

Although molecular targets provide an opportunity for cancers to be treated with target-specific drugs, a significant number of tumours do not respond. Is personalised therapy therefore 'illusive' or 'elusive'? It may be crucial to clearly distinguish between targeted therapy and precision medicine. On the one hand, targeted therapy is directed towards a molecular target in an individual, albeit one shared by a significant number of patients with a particular type of tumour or even across multiple types of tumours; therefore, it may be not be necessarily personalised in the true sense of the word. On the other hand, if personalised medicine needs to be precise enough to be individualised, then treatment such as chimeric antigen receptor T cell therapy may be an example. This first-of-its-kind drug was recently approved for the treatment of relapsed acute lymphoblastic leukaemia in children and young adults and has shown remarkable response and long-term survival rates among patients whose disease relapsed after a bone marrow transplant.[24] However, the drug is prohibitively expensive at the moment and may produce side-effects requiring transfer to the intensive care unit.

Also, there may be an economic dichotomy in the implementation of precision medicine. On the one hand, precision medicine is likely to identify susceptibility, preventative strategies, prognosis and appropriate targets for treatment, and hence may be cost-effective. As former USA President Barak Obama said in the mission statement for his precision medicine initiative: "It must enable a new era of medicine through research, technology, and policies that empower patients, researchers, and providers to work together toward the development of individualized care".[25] On the other hand, precision medicine initiatives require vast resources, such as the incorporation of extensive molecular profiling tests into clinical practice, which is clearly beyond the means of many healthcare programmes around the world, especially those in low- and middle-income countries.

In conclusion, the journey to personalised cancer treatment continues and, happily, this goal may no longer be quite so elusive. The advent of immunohistochemistry and monoclonal antibodies were torchbearers for tailored treatment. Gene sequencing, the identification of genetic mutations and the development of small-molecule TKIs have also allowed us to move away from the beaten path of cytotoxic chemotherapy.[26] The identification of other targets such as proteasomes and cyclin-dependent kinases has also helped significantly in this regard. Other areas of research in precision medicine include the Cancer Genome Atlas, integrated proteogenomic analysis, next-generation sequencing, clustered regularly interspaced short palindromic repeat (CRISPR) mechanisms and translational research; these may result in designer drugs that pave the way for the near future.[26] Nevertheless, while we seem to be moving in the right direction, we are still not past the winning post. Critically, all new drugs need to be validated in proper trials before they can be considered for clinical use, particularly as the detection of a target and the availability of a drug to hit that target does not guarantee clinically relevant efficacy.[26]

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