Introducing new molecular technologies into routine clinical cancer care. What new technology and what for?

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introduction

Practising clinicians always feel an urgency to introduce innovations into clinical practice in order to help their patients, by reducing either mortality or morbidity. However, that urgency is balanced by a prudent caution, whereby we all require a certain level of objective evidence before we are willing to fully embrace innovation. It is now widely accepted that new drug treatments should only be accepted into clinical practice on oncology once evidence from randomized clinical trials shows clear benefit from the new treatment. In general this practice is widely accepted by the profession, patients and their families, charities and the pharmaceutical industry. Massive investment in R&D is made both by charitable and commercial sectors. However, the introduction of new diagnostic and prognostic testing methodologies into clinical practice is much less clear-cut, and the acceptable pathways are not as transparent as they are for therapeutics. This paradox has been highlighted recently by the tremendous explosion we have seen in the success of molecular biology in unravelling many of the fundamental secrets of the process of carcinogenesis and metastasis. The majority of working clinicians do not have the knowledge or expertise to properly assess the laboratory science behind these discoveries. The lack of agreed and transparent regulatory pathways causes widespread concern to those working in the field of cancer, because we all wish to strike a proper balance between introducing innovation which will improve care and not introducing new practices until there is an adequate body of evidence.

In this paper we will examine a number of classes of innovation, focusing on genetics, which will affect the lives of practising clinicians within the next decade. We will broadly divide these innovations by the type of technologies involved, but will not make any attempt to explain or examine the detailed specifications of the technology. We will discuss examples of each innovation, and briefly consider the possible advantages and disadvantages of introduction into clinical care, with a superficial assessment of the professional and public response to these advances.

We will look at: (i) the search for mutations in known cancer predisposition genes; (ii) the introduction of web-based technology to enable relatives to access information on personal risk; (iii) the impact of the inherited genotype on treatment options; (iv) founder mutations; (v) mutation analysis of metabolizing enzymes predicting toxicity; (vi) mutation analysis of metabolizing enzymes predicting efficacy; (vii) mutation analysis of receptors giving information on treatment response; (viii) analysis of gene expression arrays in tumour tissue.

analysis of known cancer predisposition genes

The management of individuals with a strong family history of breast and ovarian cancer, including the protocols for offering of genetic testing, has been extensively discussed over the last decade [1–4]. The general oncology community was initially wary of active involvement, leaving the clinical work to a few specialist cancer geneticists. Recently, however, the UK charity Cancerbackup has developed a user-friendly program called OPERA (Online Personal Education and Risk Assessment; available on the website http://www.cancerbackup.org.uk) [5]. This program is based on guidance issued by the National Institute of Health and Clinical Excellence (NICE) to the UK National Health Service [6]. This guidance is relatively specific but is similar to other guidelines which have previously been used [2–4]. The program gathers information on an individual’s personal and family history of breast and ovarian cancer, and then derives a personal information sheet based on an analysis of the information given. This information sheet outlines the available options for the individual using the program without making any reference to the traditional label for the group, thus avoiding possible misleading reassurance caused by the ‘low-risk’ label. Considerable attention has been paid within the program to the possible triggers which would drive an individual to search for and spend time on such a program, particularly for those individuals who actually do not have a significant family history. The theoretical basis underlying the information sheet comes from the ‘theory of argumentation’ initially expounded by Toulmin [7], and this program is unique in the quality of personal information it provides [8, 9].

The Director of the Cancer Risk Clinic at the University of Chicago Medical Centre suggested to the 2008 Annual Meeting of the American Association for the Advancement of Science that primary care providers should embrace genetic risk assessment and BRCA mutation testing [10].
Recent laboratory experiments [11–13] have suggested that tumour cells in carriers of the BRCA1 and BRCA2 mutations are more sensitive to platinum-containing chemotherapy. An international randomized clinical trial examining the toxicity and efficacy of platinum and taxane in known gene carriers with relapsed metastatic breast cancer is now running. It is coordinated by the Cancer Research UK Cancer Trials Centre at University College London, and hopes to recruit widely from as many countries as possible across Europe and further afield [14]. Further elucidation of these pathways in the laboratory has led to the identification of the poly (ADP) ribose polymerases (PARP) as important components of the available repair mechanisms. Inhibition of these polymerases by a class of drugs known as PARP inhibitors is theoretically attractive [15, 16] and is being trialled with encouraging early results [17].

These studies are the first in the world to examine the contribution of inherited genetic variation to treatment response in oncology. If these early trials are successful then it is likely that we will see more patients coming forward for genetic testing, and therefore the service will be forced into increasing speed of throughput, hopefully without reducing the quality of the information given.

It has been known for some time that certain populations have an increased frequency of certain specific mutations in the BRCA genes, so-called ‘founder mutations’ [18]. Probably the best known examples of such populations are the Ashkenazi Jewish people [19, 20] and the population of Iceland. The presence of founder mutations in populations facilitates the speedier and cheaper identification of mutations in individuals from these populations. As evidence mounts that gene carriers should be offered specific drug treatments for disease, we will face a complex political and possibly ethical problem where treatment may partially be determined by the race of the affected patient. The differing cost of various treatment regimes can only exacerbate this problem, with certain racial groups being offered cheaper regimes than other groups. It will become inevitable that society will have to address and solve these problems as more and more information on the contribution of inherited genetic variation to the response to disease treatment becomes available and scientifically validated.

**mutation analysis in tumours**

Scientific attention initially focused on unravelling the complex pathway involving activation of the epidermal growth factor receptor (EGFR) in a number of human cancers. The EGFR is a member of the HER/Erb-B family of receptor tyrosine kinases, and is involved in the regulation of numerous cellular processes. Disruption of this regulatory activity is heavily implicated in human tumourigenesis, and EGFR amplification has been reported in 40–80% of non-small-cell lung cancers (NSCLC) [32]. In colon cancerogenesis, the EGFR is activated by the binding of a ligand to the extracellular domain, which causes the receptor to dimerize; this results in autophosphorylation of specific tyrosine residues within the tyrosine kinase domain of the EGFR. This activity leads to the activation of several downstream signalling pathways [33]. EGFR overexpression in NSCLC is associated with poorer clinical outcome, and points to a important role for these pathways as possible targets. Tyrosine kinase inhibitors competitively bind to the ATP-binding site in the tyrosine kinase domain, and inhibit activation of downstream pathways, thus reducing cellular growth. The best known tyrosine kinase inhibitors are gefitinib and erlotinib. Over the last 4 years a number of somatic mutations across the whole of the EGFR gene have been described [22–24], and several mutations in the gene coding for DPD have been described [25, 26]. At least one of these mutations can lead to relative DPD deficiency, and a combination of two similar or different mutations can lead to severe absolute DPD deficiency, resulting in extreme toxicity even with the administration of low drug dosages.

The selective oestrogen receptor modulator (SERM) tamoxifen is a prodrug which undergoes extensive primary and secondary metabolism mediated by the cytochrome P450 (CYP) enzyme system to generate metabolites with varying potencies as anti-oestrogens. Hydroxylation of tamoxifen by CYP2D6 and CYP2C9 generates the highly potent anti-oestrogen 4-hydroxy tamoxifen [27]. Secondary metabolism of N-desmethyl tamoxifen mediated by CYP2D6, and of 4-hydroxy tamoxifen mediated by CYP3A4/5 produce a number of metabolites including 4-hydroxy-N-desmethyl tamoxifen or endoxifen [28, 29]. Several studies have suggested that endoxifen may be more important than 4-hydroxy-tamoxifen in the over-all cancer effect of tamoxifen. There is a specific genotype of CYP2D6, labelled 4*, which can be relatively easily identified in the laboratory. Patients who carry two copies of this 4* genotype (i.e. are homozygous for this variant) have significantly lower plasma levels of endoxifen after 4 months’ treatment with tamoxifen compared with patients with other genotypes. Data from a retrospective study of post-menopausal women treated with adjuvant tamoxifen demonstrate that carriers of the 4*/4* genotype had a significantly shorter time to breast cancer recurrence [30]. These intriguing results suggest that tamoxifen may be less effective in patients with certain genotypes. If substantiated, this suggestion may be very important not only in breast cancer patients treated with adjuvant tamoxifen, but also in those at-risk patients being offered tamoxifen as a chemo-preventative agent [31].
in tumour tissue have been reported. Many of these have been identified in the tyrosine kinase-binding domain, and it has been suggested that mutations close to the ATP-binding cleft may give the most direct information on sensitivity to tyrosine kinase inhibitors [34]. Several clinical studies have examined the relationship between the identification of EGFR mutations in tumour tissue and the response to tyrosine kinase inhibitors, but overall these trials have proved inconclusive; the general consensus is therefore that EGFR mutation testing should not be mandatory before treatment [35].

An alternative mutation testing strategy involving the same pathway concentrates on an analysis of the Kirsten RAS (KRAS) gene. This gene is one of the family of RAS proto-oncogenes, and is intimately involved in regulating cell growth. In approximately 17–25% of human cancers there is evidence of an activating KRAS mutation. The recent introduction of anti-EGFR monoclonal antibodies has caused some excitement amongst oncologists, as these compounds are active in metastatic colorectal cancer, which is resistant to drugs such as irinotecan. There is now growing evidence to suggest that tumours carrying a mutation in the KRAS gene will also be resistant to these monoclonal antibodies such as cetuximab and panitumumab. Whether KRAS mutation analysis should be offered to all colorectal cancer patients with resistant metastatic disease remains an unanswered question at present.

**examining multi-gene expression in tumours**

Recent advances in the techniques of gene expression array analysis allow the accurate determination of the expression of thousands of genetic sequences at the same time. These genetic signatures offer a real insight into the detailed biology of individual tumours, and naturally there is detailed discussion at learned meetings, but there seems to be a lack of consensus within the community over the evidence base required before widespread adoption of these techniques is acceptable.

Cancer of unknown primary is a well recognized clinical entity which presents problems to clinicians, patients and their families and friends. As current management is so heavily dependent on clinico-pathological identification of the primary site, it is difficult to know how far to pursue possibly fruitless diagnostic testing, including expensive imaging [36]. It has been suggested that gene expression array analysis may be very helpful in this clinical situation, but more definitive evidence is awaited [37]. Gene expression technologies show ‘considerable potential for improving prognostic and therapeutic prediction’ in early breast cancer, according to a recent systematic review published in the *Annals of Internal Medicine*, but the authors conclude that more needs to be done before it is clear how best to incorporate these technologies into clinical decision-making [38].

**conclusions**

Recent technological advances in genetic analysis have attracted considerable interest from oncology professionals and the public. These advances may well result in dramatic improvements in the quality of clinical care. It is important for major international societies such as the European Society for Medical Oncology to highlight these advances, but also to ensure that they are only widely adopted into clinical practice when a secure evidence base has been established.

**disclosures**

James Mackay was Managing Director of Opaldia Ltd, a healthcare company which distributes products for Agenda BV, Diagenic ASA.

**references**

14. Protocol for The BRCA Trial, a randomised phase II pilot trial of carboplatin compared to docetaxel for patients with metastatic genetic breast cancer. Available from Cancer Research UK and UCL Cancer Trials Centre, 90 Tottenham Court Road, London W1T 4TJ, UK.