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editorial

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An introduction to stratified medicine

It has been 44 years since Richard Nixon declared war on cancer and 14 years since imatinib (the tyrosine kinase inhibitor that targets the Bcr-Abl oncogene in chronic myeloid leukaemia) made the front page of Time magazine. Are we now in the era of personalised anti-cancer therapy? And what exactly do we mean by stratified or personalised medicine in terms of cancer treatment?

Personalised medicine suggests a truly individual treatment regimen based on both tumour and host characteristics. Stratified medicine is a major step on the road to this medical utopia; a commonly accepted definition is 'the targeting of treatments (both pharmacological and non-pharmacological interventions) according to the biological or risk characteristics shared by subgroups of patients' [1].

In clinical trials this may mean either restricting entry to patients with the desired characteristics [2] (Fig. 1b), or performing a pre-planned analysis as to the impact of the biomarker on outcome [3]. In oncology over the last 10–20 years stratified medicine has in many ways become synonymous with the development of the mechanism targeted agents (MTAs). The rationale behind these agents is to kill cancer cells by exploiting potential 'Achilles heels' of the cancer. This is normally by blocking the activity of a mutated or over-expressed oncogene (oncogene addiction), or a pathway the tumour has become overly reliant on, potentially as a compensatory mechanism for other molecular abnormalities (synthetic lethality).

An example of the move to more personalised medicine is exemplified by the treatment of non-small cell lung cancer (NSCLC), where in the past several chemotherapy regimens were evaluated in an unselected population [4]. More recently clinical trials suggested that patients with non-squamous histology may benefit from the treatment with platinum/pemetrexed rather than platinum–gemcitabine, which seemed to be more effective in tumours with squamous histology [5]. Over the last 5–10 years we have been able to give molecular targeted therapy to the small number of patients with NSCLC (at least in the Caucasian population) that have activating mutations in the EGFR or translocations in the ALK gene [6]. MTAs targeting these abnormalities have high response rates and are associated with better outcomes than chemotherapy [3]. This has led to the search for additional subpopulations of patients where the tumour may have molecular abnormalities that could respond to MTAs.

Technological advances in genetic testing methodologies such as the increasing utility of next-generation testing are providing the high-quality diagnostic support necessary for rapidly establishing the genetic signature of individual tumours. Analysis of patient's tumours for multiple molecular abnormalities within the auspices of umbrella protocols (Fig. 1d; such as the Stratified Medicine Programme 2 and the Lung Cancer Mutation Consortium in NSCLC, or the MOSCATO trial (NCT01566019) in patients who have exhausted standard therapies) has proven to be feasible, and genotype directed therapy may be associated with a better survival [7]. Tailored guidelines for the roll-out of such diagnostic approaches that would underpin and guide therapeutic decisions

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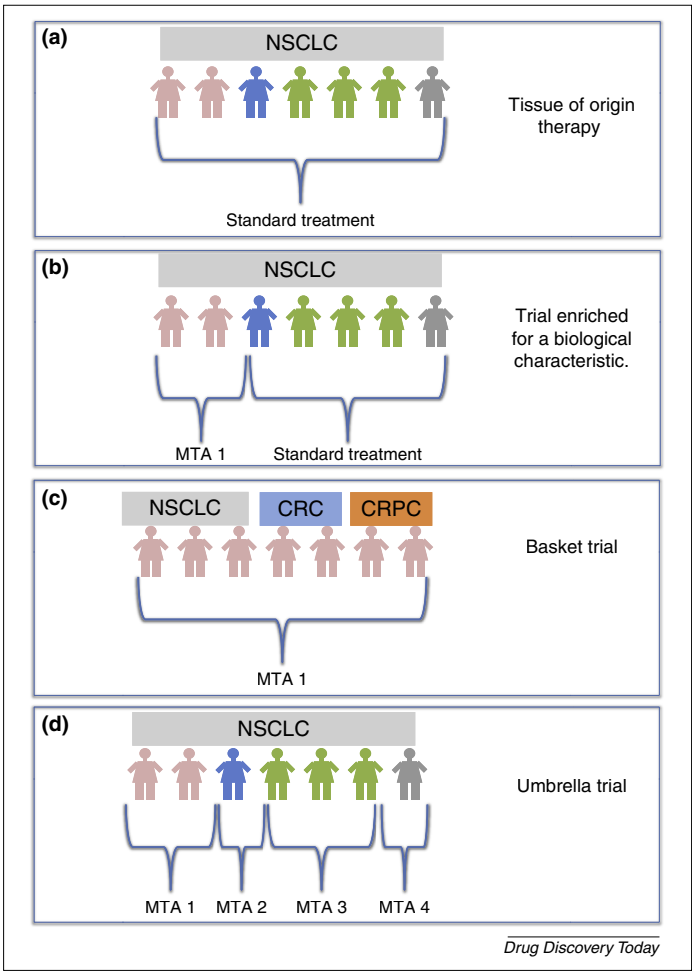

FIGURE 1

The changing paradigm of cancer treatment from chemotherapy chosen according to the tumours tissue of origin, with no reference to molecular profile **(a)** to stratified medicine. This can be as part of a clinical trial enriching for a single biological characteristic within one tumour sub-type **(b)**, a basket trial where patients with tumours with a specific molecular profile receive the same targeted agent regardless of the tumour's tissue of origin **(c)** or an umbrella trial where patients with tumours with different molecular characteristics can all be treated with targeted therapy as part of one trial **(d)**. (MTA, molecular targeted agent; NSCLC, non-small cell lung cancer; CRC, colorectal cancer; CRPC, castrate resistant prostate cancer. Patients of the same colour have identical driver mutations.)

are beginning to be introduced [8]. This shows in one disease the move over the last 10 years from site-directed therapy to molecular based therapy, but similar work is being conducted in other solid tumours [9,10]. However, we have come to realise that many challenges exist to the implementation of stratified medicine in cancer; this special issue addresses how we are now meeting these challenges.

What treatment to give

Unfortunately it is increasingly clear that the some of the assumptions behind stratifying patients on a molecular basis are not necessarily true. It was originally hoped that all tumours identified to have an abnormality in an important or 'driver' oncogene would respond to therapy regardless of the tissue that the tumour arose in. This would allow 'basket' trials where all patients with a similar molecular profile receive the same treatment regardless of the cancers' primary site of origin (Fig. 1c). This approach may have some validity, for example drugs targeting Her-2 have been shown to have activity in several tumour types with over-expression of this oncogene [11–13]. However, tissue context may be vitally important; a prime example of this is that patients with B-Raf mutated colorectal cancer do not respond to drugs such as vemurafenib, which has an approximately 60% response rate in B-Raf mutated melanoma. This is due to a feedback loop, which drives EGFR activity in the malignant colorectal cells, rescuing them from the impact of B-Raf inhibition [14,15]. Basket trials may have the most utility in either rare tumour types or rare molecular abnormalities where it is not feasible to perform evaluations in cohorts of patients with tumours arising from a single tissue of origin.

An even bigger issue to be addressed is that of temporal and spatial intra-tumour heterogeneity. When choosing chemotherapy directed according to a tumour site of origin, a biopsy of any site (either primary or metastasis) can be performed to confirm the diagnosis. However, molecular profiling may show dramatic differences in the genotype between the primary and metastases, and even within different areas of the primary tumour [16,17]. Whilst convergent evolution may be seen, with abnormalities found in the same key driver oncogenes, the nature of the abnormality may differ even within the different areas of cancer within a same patient [16]. Whether these abnormalities will respond equally to targeted therapy is unclear, but it is unlikely.

Equally it is clear that the tumour evolves over time particularly under the selection pressure of therapy. Selection of drug resistant clones that are probably present at diagnosis occurs rapidly, and may even be associated with a change in histology [16,18–21]. The impact of this intra-tumour heterogeneity on the efficacy of stratified medicine is not known, but it is clear that a small biopsy taken at the time of diagnosis is unlikely to be truly representative of the overall molecular profile of the cancer particularly after multiple lines of therapy [22,23].

The choice of therapy to give may be obvious in the context of a mutated oncogene that is well known to be an oncogenic driver. However, the question arises when confronted by a complicated tumour genotype as to what is the most appropriate therapy to give, and who makes this decision? For many years oncologists have worked with physicians, surgeons, clinical nurse specialists, radiologist and pathologists as part of the multi-disciplinary team (MDT). This MDT has been particularly concerned with diagnosing cancer and deciding on the initial modalities of therapy. The choice of palliative therapy has then been made by oncologists guided by tumour site, patient characteristics and a few licensed predictive biomarkers (such as Her-2 and K-Ras status). Most oncologists will not have the knowledge to interpret complicated genotypes. The average carcinoma has approximately 50–100 somatic mutations depending on the patient's age and tumour type [24,25], although only somewhere between 3 and 7 of these may be driver mutations [26]. Molecular abnormalities can consist of different forms of mutations (i.e. nonsense, missense), chromosomal aberrations (amplifications, deletions and translocations) and this does not even take account of changes in haplotype and the extensive epigenetic abnormalities that also occur.