COMMENTARY

Imaging in drug development: will it deliver on the promise of personalised medicine?

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Over recent years, many new techniques have been applied to drug development in an effort to provide safer and more effective therapies to the patient. In addition, the intense competition between commercial interests continues to drive this search for new and effective technologies. The common goal is the provision of personalised medicine: an approach based on our growing understanding of the molecular basis of disease.

Accurately predicting the behaviour of disease is a fundamental aspect of medical management. Response markers have, in part, reached their popularity because of the confluence of several independent technologies. Advances in our understanding of the molecular basis of disease and miniaturised automation of diagnostic tests have made this task a reality.

Conventional anatomical imaging has justly been criticised for being insensitive to molecular events and lagging in response to cytostatic agents. Despite these challenges, imaging presents distinct and unique characteristics that complement molecularly based assays. Importantly, imaging allows the non-invasive, serial morphological characterisation of disease and remains the principal means by which objective response is assessed in clinical trials.

As future planning depends on an assessment of the present, it is worth assessing the current status of imaging in the development of anticancer drugs. A commentary, of course, is no substitute for an in-depth review and is biased by the author's outlook, but nevertheless has a role in stimulating debate and discussion. A successful strategy depends on a clearly defined aim, which in drug development translates into drug commercialisation. An endeavour recently

estimated to cost on the order of US\$1 billion [1]. By any measure this is a vast sum of capital, given it takes ten or so years to bring a drug to market: a process better known for its attrition than by success. So, although new oncology drugs are afforded preferential regulatory review, development times are on average longer than for other therapeutics and close to 50% of Phase III trials fail [2]. A considerable array of technologies, including imaging, are being adopted in the hope of bringing a competitive advantage to the development stream. Either by providing an early marker of response, a prognostic indicator or a measure of molecular activity. On this basis, imaging is categorised as a biomarker and represents one of several technologies promoted as a means of delivering on disease-specific therapy. By these criteria, the definitive role and impact of imaging can only be determined by judicious review of prospectively acquired data. A categorical judgement is difficult to make given the fast pace of drug development, but enough experience exists to critically assess these efforts. The competitive world of drug development, however, is rarely forgiving and swiftly disposes of strategies failing to deliver on expectations or added-value.

It is with good reason that medical imaging is acknowledged with having revolutionised medical practice following the development of cross-sectional technology and is now an essential condition of patient management. By the same token, imaging assessment remains the principle method by which objective response is measured in clinical trials of solid tumours. Furthermore, response affects surrogates of survival, such as progression-free survival and time to progression.

Clinical trials proceed at a fast pace and require continuous monitoring to negotiate the complex operational requirements and demand for accurate reporting of data. Confidence in the process needs to be supported by an effective audit trail. This might, for example, mean providing images for review by an independent third

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party or regulatory authority. The timely need for objective assessment of data explains the rapid expansion of imaging contract research organisation (CRO) services that ensure standardised practices in the execution, transmission and analysis of data. Recent events have highlighted the need for standardised assessment of imaging studies [3]. The RECIST 1.1 criteria aim to provide such a basis by the harmonisation of clinical trials imaging data [4]. These are expert-based recommendations, but more importantly have a strong evidence base for their conclusions. Modifications based on trial-specific design and criteria are not uncommon and need to be taken into account when planning a study. Just as it is important to maintain a critical eye, it is essential not to lose sight of the maturity the RECIST criteria have brought to clinical trial reads.

It takes little more than the experience of one clinical trial to appreciate the logistical challenges required to provide timely data for internal and regulatory review. It has been the author's experience that imaging experts are employed most effectively by leading on the design and execution of imaging trials. Furthermore, they need to ensure that both CROs and trial teams have a common understanding of the goal of imaging. Imaging experts are also required to provide oversight of the CROs and to facilitate a smooth and efficient flow of information. A clearly defined scope of work and communication structure is essential to an effective service. Much of the work of pharmaceutical imaging groups has focused on formalising these processes. Properly organised, a clinical team should expect on the order of 70% of the planning, implementation and management of a clinical trial to be formulaic and follow standardised templates. A common hurdle includes the transfer of data from sites to the CROs. Such problems can be overcome and be dealt with proactively. The practice of co-opting expert external imaging advice to the clinical trial team is required on occasion, but for the most part is effectively managed by CROs.

Although improvements in instrumentation, data processing and display will no doubt improve the speed and efficiency of anatomical visualisation, most clinical imaging modalities lack the resolution to deconvolve molecular events. Although molecular imaging is well-established in cell and animal systems, only a handful of these strategies have been translated to the clinic and even fewer have addressed questions central to the drug developer. These include an understanding of the modulation of cellular events that in a clinically measurable and validated way will support trial needs. Furthermore, such technologies should be widely available, standardised and comply with robust scientific and regulatory review. 18-Fluoro-2-deoxyglucose positron emission tomography (¹⁸FDG-PET) and dynamic contrast-enhanced MRI (DCE-MRI) are arguably the two most mature experimental technologies available for implementation and supported by the recommendations of expert groups [5, 6]. The majority of other molecular-based techniques require resources rarely available beyond one site. In addition, the challenges involved in translating events at the molecular level to clinical end-points will continue to present a higher barrier to the widespread regulatory approval of molecular diagnostics.

Should the drive towards personalised medicine rely exclusively on tissue biomarkers? Although there have been notable successes, the field remains challenged in translating science to the clinic. Just as any diagnostic, tissue biomarkers must also face the rigours of commercial validation. In this respect, the richness of imaging data contrasts sharply against the monochromatic output of *in vitro* tests. There has been a real drive by academic and regulatory authorities to shift the paradigm of drug development towards a biomarker-driven process. There have been notable successes (BCR-ABL protein translocation, and overexpression of the cytokine receptor c-KIT and growth factors HER2 and EGFR), but equally there have been many cautionary experiences. There is no doubt that imaging and laboratory biomarkers can work synergistically to provide insight into drug action, but this approach will require considerable validation before it becomes commonplace [7]. This leads on to the issue whether to advocate experimentally mature rather than speculative technologies. From the author's perspective, only DCE-MRI and FDG-PET are currently applicable to early clinical trials. These modalities have a strong basis on which to clinically interpret results and have been successfully managed across multiple centres. In the author's experience these two characteristics are the essential features by which to challenge the value-added of an experimental imaging strategy.

This is not to say that innovative imaging strategies should be rejected without any more thought. Many aspects of tumour behaviour have been successfully explored both in animal systems and the clinic. Radiotracer technologies, for example, have consistently shown their value in assessing receptor-ligand interactions, and techniques such as MR spectroscopy and diffusion-weighted imaging have been successfully used to probe drug metabolism and therapeutic target modulation. Creating novel radiotracers, however, requires specialist resources such as radiochemistry, a cyclotron and a dedicated research unit. Only a handful of projects, if that, can reasonably be expected to meet the required timelines. Furthermore, results from a small radiotracer study might not necessarily translate to the patient population as a whole. Finally, imaging is considered expensive next to cheap and simple molecular assays. Although the validity of that last statement is debatable, the missing factor of most novel technologies is a clear relationship between results and clinical outcome. Is validation against survival outcome a reasonable target to aim for? Ideally yes, but the necessary trial design makes this a very challenging undertaking. As discussed earlier, imaging is best served by focusing on its strengths, namely the early assessment of response and defining the mechanism of action of a drug. Other key factors such as dosing, scheduling and patient stratification will require further development.

In summary, anatomical imaging is an established feature of clinical trials in solid tumours and a promising functional marker of tumours. The majority of clinical trials now, and for the next few years, will continue to depend on assessment of objective response. How the resources for future biomarker development will be distributed will depend on a balance between objective results and rising costs. For the time being, imaging

continues to be a powerful technology and likely to be at the forefront of personalised medicine.

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