EUROPEAN JOURNAL OF CANCER 46 (2010) 2143–2144

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Editorial Comment

How to improve the cost effectiveness of oncology drug development
A commentary on Tan et al. Anti-cancer drug resistance – Understanding the mechanisms through the use of integrative genomics and functional RNA interference

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ARTICLE INFO

Article history:
Received 3 May 2010
Accepted 10 May 2010
Available online 9 July 2010

Why do treatments work for some people but not others? Why do treatments stop working? Finding the answer to these questions is central to any attempt to control cancer. The ability to match the right drug to the right patient and optimise the treatment in response to changes in the individual's tumour biology is the nirvana of oncology practice. The unfulfilled hope was that the huge investment in biomarker discovery and development would realise this dream.

A group led by Charles Swanton and his colleagues[2] in this issue provide a thorough and thought-provoking review of the current state of knowledge in drug resistance research. They show how our understanding of the determinants of drug resistance has increased exponentially over the last decade. They review four broad but distinct determinants of drug resistance: common molecular pathways which influence response, or lack of it, to groups of cytotoxic agents; cancer stem cell differentiation; genetic alterations in the tumour itself and protective changes in the tumour microenvironment. The literature that Tan et al. review demonstrates that all four can be subject to direct measurement *in vivo* as well as *in vitro*, using integrative genomics and functional imaging techniques. Up until recently, the difficulty has been in elucidating which molecular pathways active in the genomic complexity of the tumour and its microenvironment may be relevant and potentially predictive of drug response in patients. Importantly, the team suggest that distinct genes, expression of which may influence drug sensitivity, can be determined using functional RNA interference (RNAi) approaches. RNAi can be used in laboratory drug resistance screening approaches to identify distinct genetic regulators of drug response in cultured tumour cell lines. Indeed, Swanton et al recently demonstrated that RNAi screening technology can be used to derive predictive mRNA expression signatures of drug response in breast cancer.[1]

Tan and colleagues argue convincingly that these technologies should be used for the prospective identification and validation of biomarkers for drug response and the development of drug resistance, within trial programmes rather than as an afterthought to try to improve drug efficacy. We would go further and argue that the utilisation of these technologies should herald a revolution in the process of drug development, driving success rates up and most importantly

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2010.05.023

delivering treatments to market with the knowledge necessary to identify which patients they will treat successfully, and the biomarkers that will signal acquired or intrinsic drug resistance.

The current model of oncology drug discovery is not economically sustainable. Development costs are continuing to rise whilst the markets for new treatment are shrinking and health care budgets are struggling to afford the prices that manufacturers wish to charge. The costs of manufacture are an increasingly important cost driver, as biotherapies replace small molecule medicines. However, the biggest single cost driver continues to be late failures – i.e. those treatments that are found to be insufficiently effective or unsafe during Phase 3 trials. The hundreds of millions of dollars lost are recouped in the price of the 1 in 3 Phase 3 drugs that succeed.

Our enhanced understanding of the determinants of drug resistance demonstrates that current approaches to Phase 3 trial design are little more than a lottery. High levels of molecular and genetic heterogeneity between patients are a credible explanation of why treatments that appear to work in Phase 2 trial populations fail to work sufficiently well in Phase 3 trials. Knowledge of the molecular and genetic determinants of drug resistance prior to Phase 3 could substantially reduce or even eliminate this lottery from the drug development process.

As well as reducing the risk of failure, understanding molecular and genetic determinants of drug resistance would allow for smaller and thus quicker Phase 3 trials due to a larger expected effect size, as non-responders could be prospectively excluded from trial samples. Smaller trials cost less, providing further opportunities for cost savings in the R&D process.

As well as allowing for more efficient development of new oncology treatments, ensuring an adequate understanding of the mechanisms of drug resistance for candidate treatments prior to undertaking Phase 3 trials will protect those patients who will not benefit from treatment from potential harmful drug exposure relative to the standard of care. Where this can be done, there is an ethical imperative that it should be done.

Clinical practice, economics and ethics all point towards undertaking research into the mechanisms of drug resistance much earlier in the research and development process. The drug development process is very nearly bust; now may well be a good time to fix it.

Conflict of interest statement

None declared.

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