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Challenges and methodology in the incorporation of biomarkers in cancer clinical trials

Charlotte S. Wilhelm-Benartzi[a,b,*], Shahrul Mt-Isa[b], Francesca Fiorentino[b], Robert Brown[c], Deborah Ashby[b]

[a] CRUK Imperial Centre, Department of Surgery and Cancer, Imperial College London, UK
[b] Imperial Clinical Trials Unit, School of Public Health, Imperial College London, UK
[c] Epigenetics Unit, Department of Surgery and Cancer, Imperial College London, UK

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ABSTRACT

Biomarkers can be used to establish more homogeneous groups using the genetic makeup of the tumour to inform the selection of treatment for each individual patient. However, proper preclinical work and stringent validation are needed before taking forward biomarkers into confirmatory studies. Despite the challenges, incorporation of biomarkers into clinical trials could better target appropriate patients, and potentially be lifesaving. The authors conducted a systematic review to describe marker-based and adaptive design methodology for their integration in clinical trials, and to further describe the associated practical challenges. Studies published between 1990 to November 2015 were searched on PubMed. Titles, abstracts and full text articles were reviewed to identify relevant studies. Of the 4438 studies examined, 57 studies were included. The authors conclude that the proposed approaches may readily help researchers to design biomarker trials, but novel approaches are still needed.

1. Introduction

Considerable challenges exist in the incorporation of biomarkers into clinical trials. This explains why they are mostly included as exploratory endpoints into current oncology clinical trials (McShane et al., 2009). Individual patient heterogeneity, both between primary and sites of metastasis as well as within metastatic lesions, is a major concern for successful treatment of advanced tumours (Kummar et al., 2015). As patient biopsies often target a single piece of tissue at one time point only, and not at multiple ones longitudinally, tumour heterogeneity and alterations over time are not properly addressed, although they likely contribute to the evolution of drug resistance (Kummar et al., 2015). Furthermore, biomarkers can represent molecular aberrations that

* Corresponding author at: 3rd Floor Radiotherapy Building, Hammersmith Hospital Campus, Du Cane Road, London W12 0NN, UK.
E-mail addresses: c.wilhelm-benartzi@imperial.ac.uk, charlottewilhelm@gmail.com (C.S. Wilhelm-Benartzi).

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can be driver or passenger events (Kummar et al., 2015). Other issues include the percentage of cells and the method of obtaining a tumour sample, and in what sequence multi-combinatorial agents as well as their dose levels should be used to target multiple aberrations (Kummar et al., 2015). Despite this, biomarkers can be used to establish more homogeneous groups using the genetic makeup of the tumour to inform the selection of treatment for individual patients (Mandrekar and Sargent, 2009).

Biomarkers are classified into a few categories in the literature: prognostic, predictive, surrogate, screening or diagnostic, pharmacodynamic efficacy and resistance, and integral and integrated biomarkers (Mandrekar et al., 2013; Hong and Simon, 2013; Mankoff et al., 2015). For the purposes of this article, we mainly focus on prognostic and predictive markers; with a brief overview of the others. A surrogate marker is a biomarker accepted by regulatory agencies as a substitute for a clinical endpoint and, when used as an early indicator of treatment efficacy, is potentially attractive in terms of cost-effectiveness (Mandrekar et al., 2013); e.g. HIV load. Screening or diagnostic markers are used in the monitoring of disease including PSA levels in prostate cancer. Pharmacodynamic efficacy and resistance biomarkers are used to measure response and resistance to treatment, respectively (Hong and Simon, 2013). Finally, integral biomarkers determine patient incorporation and/or directs clinical trial procedures, while integrated biomarkers are not used to determine patient treatment (Mankoff et al., 2015). Prognostic markers provide an early indication of the clinical course of a patient independent of any specific intervention and may be considered in the clinical management of a patient; e.g. BRCA1/2 mutation-which can also be predictive of PARP inhibitors. These are prevalent in the literature, and guidelines for their evaluation are available with the gold standard being the REMARK criteria (McShane et al., 2005; McGuire, 1991). Predictive biomarkers are measured prior to an intervention and identify patients who are susceptible to a particular drug effect; however they are not necessarily prognostic of post-treatment clinical course (Mandrekar and Sargent, 2009), e.g. HER2 or KRAS (Khambata-Ford et al., 2007). Predictive markers can only be properly validated in a prospectively designed randomized controlled trial testing for a marker-by-treatment interaction (Altman and Lyman, 1998); but a very large sample size is often required (Polley et al., 2013). A biomarker can be both prognostic and predictive such as Estrogen Receptor status and its prognostic association with relapse and its predictiveness of treatment benefit from tamoxifen (Hayes et al., 1996).

It is critical that proper preclinical work and stringent validation be done before taking forward only the most promising biomarkers into confirmatory studies. The aim of this article is to provide an overview on the methods to incorporate biomarkers into clinical trials and to further describe the challenges.

2. Materials and methods

Study selection followed the process described in the diagram in Fig. 1. The design name, whether they are marker-based, adaptive, used in design in or testing during a trial, their description, advantages and disadvantages and trials using those designs were retrieved.

3. Results

Fifty-seven articles were included in the review, and methods of incorporating biomarkers were identified (Table 1). Broadly, the methods fall into marker-based or adaptive, and being used as design or testing methods; and other novel designs.

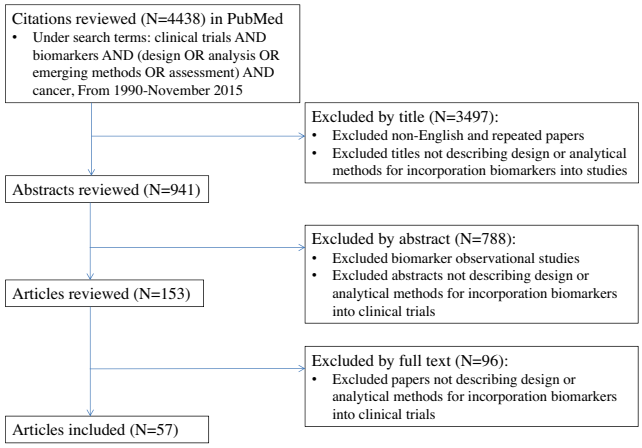

Fig. 1. Study selection diagram.

3.1. Overview of marker-based methods

One of the most commonly used marker-based designs is the enrichment or targeted design (Fig. 2a), which is appropriate when there is compelling preliminary evidence to suggest that treatment benefit or lack of toxicity is restricted to patients with a certain biomarker profile (Rothmann et al., 2012). An ideal biomarker for this design would need a well-established cut-off point and have an assay with a rapid turnaround time (Mandrekar et al., 2013). A successful enrichment design is very efficient, increases the power of a study as compared to the unselected/all comers design, and may require only a small sample size if the treatment effect is large in the biomarker positive subgroup, even if the biomarker positivity prevalence is low in the population of interest (Freidlin et al., 2010a). Conversely, if the assay is imperfect, the treatment may actually have an effect in the negative subgroup or whole population which will remain unknown as only the positive subgroup is recruited (Simon, 2014; Lin and He, 2015). Furthermore, this design may require a large population to be screened to identify the biomarker positive subgroup; moreover, it cannot determine whether the biomarker is predictive or not. A slight modification to the enrichment design is the hybrid or mixture design (Fig. 2b) allowing the treatment effect of the intervention therapy in the biomarker positive subgroup to be compared with the treatment effect of the control arm in both the biomarker positive and negative population (Lin and He, 2015); this design would still require a well-established biomarker.

The vast majority of currently conducted trials collecting biological specimens for marker measurements use the Unselected or All Comers design (Fig. 2c) as all patients meeting the eligibility criteria are entered into the trial independent of previous testing or the resulting status of the biomarker of interest. Furthermore, one does not need to be certain about the benefit of the marker in either the overall population or the biomarker defined subgroups as it provides the treatment effect in the overall population as a whole (Rothmann et al., 2012). Less established biomarkers needing further validation of their performance or having a slower assay turnaround times could be used in this design (Mandrekar et al., 2013). However, the cost of measuring the biomarker in the whole population will be large if a high proportion of patients are not able to contribute biomarker measurements, hence the prevalence of the biomarker should be high (Lin and He, 2015).

The Marker-Based Strategy Design recruits eligible subjects regardless of their biomarker status, just like all-comer design and then randomly assigns the patients to either to have therapy determined by their marker status, in the biomarker directed arm, or to receive therapy independent of marker status (Freidlin et al., 2010a)