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Biological surrogate end-points in cancer trials: Potential uses, benefits and pitfalls

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Abstract

New technologies have led to the development of an increasing number of targeted therapies and interest in combining these with conventional therapy to provide individualised patient treatments. New drug or treatment regimens must, however, undergo rigorous testing under strictly controlled conditions before they can be adopted as standard. This can be expensive, time-consuming and inefficient. Surrogate end-points have been proposed as an alternative, which could be measured earlier or more conveniently than true end-points. The aim of this paper is to review the definition, advantages, disadvantages and potential pitfalls of biological surrogate end-points in the context of cancer treatment.

Keywords: Surrogate end-points; Biomarkers; Cancer

1. Introduction

With the development of new technologies including genome sequencing, DNA microarrays, proteomics and imaging modalities such as positron-emission tomography (PET), we have a greater understanding of tumour biology and behaviour. This, in turn, has led to the development of an increasing number of targeted therapies and interest in combining these with conventional therapy to provide individualised patient treatments. However, any new drug or treatment regimen must undergo rigorous testing under strictly controlled conditions before it can be adopted as standard. Testing usually takes the form of a series of phase I, II and III trials, each with well-defined end-points. In most phase III trials, efficacy over the standard treatment is proven by showing a statistical improvement in an outcome, such as survival or local control, or a reduction in toxicity, a process which is both time-consuming, expensive and in some cases inefficient. In order to overcome these problems, it has been proposed that surrogate end-points, which could be measured earlier or more conveniently, might be an alternative to true end-points [1]. In addition, there has been great interest in developing and incorporating biomarkers into clinical trials to aid in the selection of compounds for testing and defining appropriate patient groups for trials or treatment [2]. The incorporation of the measurement of biomarkers in prospective trials might be helpful in determining the mechanism of treatment effect, lack of effect or toxicity. With these points in mind, a Surrogate End-point Group was established as part of the European Organisation for Research and Treatment of Cancer (EORTC) Radiotherapy Translational Research Group. The aim of this group is to identify where surrogate end-points might be appropriately investigated or incorporated into the trials of the Radiotherapy Group.

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The aim of this paper is to review the definition, advantages, disadvantages and potential pitfalls of biological surrogate end-points.

2. What is the definition of a surrogate end-point?

Surrogate literally means 'to substitute for' [3]. Therefore, in the simplest terms a surrogate end-point is a measurement that can be substituted for a true end-point to predict either benefit (e.g., survival) or harm (e.g., late toxicity). However, the lack of consistency in defining surrogate end-points has led to confusion. Recently, the Biomarkers Definitions Working Group proposed a general definition of a surrogate end-point as a 'biomarker that is intended to substitute for a clinical end-point and is expected to predict clinical benefit (or harm or lack of benefit) based on epidemiological, therapeutic, pathophysiological, or other scientific evidence' [4]. Furthermore, any changes induced in the surrogate end-point by a treatment must accurately reflect changes in the true end-point [5].

There should be a clear distinction between surrogate end-point and surrogate marker. Bentzen *et al*. [6] distinguished between a surrogate marker and a surrogate end-point in the context of late effects of radiotherapy. They defined a surrogate marker as a biological effect of treatment that, if it occurs, changes the probability of an individual developing a late effect, whereas a surrogate end-point does not necessarily predict development of an effect at the individual level, but is an indicator of the toxicity of a treatment at the trial level. This definition of surrogate marker corresponds more closely with the definition of a biomarker as a characteristic that is measured and evaluated as an indicator of normal processes, pathogenic processes or as a response to treatment [4]. In fact, it has been proposed that the term 'surrogate marker' be avoided as this suggests that the substitute is for a 'marker', rather than for a clinical end-point [4]. Clearly, this is an area which requires further clarification.

In 1989, Prentice [7] published an important paper which set down strict statistical criteria to define surrogate end-points. He defined a surrogate end-point as a response variable for which a test of the null hypothesis of no relationship to the treatment groups under comparison is also a valid test of the corresponding null hypothesis based on the true end-point. That is, if we reject the null hypothesis that the surrogate end-point is associated with the treatment, meaning there is an association then there is most likely to be an association with the true end-point. Furthermore, a surrogate end-point must fully 'capture' the relationship between the treatment and the true end-point. This definition with respect to evaluation of surrogate end-points is discussed further below.

Various biological and clinical phenomena could potentially serve as surrogate end-points. These include molecular markers (specific mutations in cancer-related genes, gene expression products), cellular and nuclear phenomena (proliferation, apoptosis, DNA ploidy), serum markers (prostate-specific antigen (PSA), carcinoembryonic antigen (CAE), CA125, β human chorionic gonadotropin (βHCG), α fetoprotein (αFP), tumour characteristics detected by (functional) imaging (magnetic resonance imaging (MRI), PET) and clinical assessments (tumour response, time to progression).

3. What is the definition of a true end-point?

A true end-point is any characteristic or variable that reflects how a patient functions, feels or survives [8]. In radiotherapy trials, this usually means survival, local recurrence or development of toxicity. Time is usually measured from the start of treatment or date of pathological confirmation of disease. End-points such as time to progression and response (complete, stable or progression) are not true end-points but ought to be considered as surrogate end-points. Although, whether in most circumstances they qualify as such given the definitions and criteria discussed in this paper is highly disputable.

4. When can a biological surrogate end-point be used as a substitute for a true end-point?

Prior to evaluation of a potential surrogate end-point statistically, three criteria need to be satisfied: (i) is the potential surrogate associated with the true end-point biologically; (ii) is the treatment associated with the potential surrogate end-point; and (iii) does the potential surrogate mediate the effect of the treatment on the true end-point [8]?

To satisfy the first criteria we need to show that there is good biological evidence or a sound rationale to suppose that the surrogate is associated with the true end-point. Data to support this are most likely to be obtained from pre-clinical and animal studies as well as previous retrospective and epidemiological studies.

To satisfy the second criteria, we must be able to show that there is some relationship between the surrogate end-point and the treatment, that is the treatment changes the surrogate end-point. This information might be obtained from previous studies or relatively smaller studies designed to answer this question.

Finally, we need to show whether the effect of treatment on the true end-point is mediated via the surrogate end-point. This is important in situations where the effect of the treatment on the true end-point is mediated through mechanisms other than the surrogate or where the effect is mediated through a number of mechanisms