

In medicine today – Cancer and the prorogation of clinical reality in favour of probabilistic outcomes

Review

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Abstract: How essential is the randomised trial in cancer therapeutics? Is it conceivable that *prospective randomised clinical trials* in cancer medicine could, one day, safely be abandoned in favour of Phase II studies supplemented with real-world data from cancer centres, without detriment to the progress of cancer therapeutics or the welfare of cancer sufferers? If feasible, such practice could reduce the cost of new drug development, while freeing clinical investigators from the ethical burden of random allocation of treatment or indeed providing no therapy with the administration of a placebo to cancer sufferers.

Keywords: cancer • probabilistic • randomised • trials

1. Introduction

In the final game of the 2022 Australian Open, during the third set, the organisers of the tournament projected to the audience a *win predictor* with the statistical probabilities for the winner. For Daniil Medvedev, the favourable score was 96%; for Rafael Nadal, it was just 4%. Nadal went on to win the championship, the 21st in his illustrious career, making tennis history. It remains to be seen whether organisers of similar events will indulge in the future with the liberal use of probabilistic *win predictors*.

The definition for *probabilistic* is given as ‘based on, or affected by probability, randomness or chance’ and synonyms are given as *stochastic*, *model-based*, *heuristic*, *theoretic*, *Bayesian*; another synonym would be *pithanotic* from the Greek *πιθανότης* for *probability*.

During the coronavirus disease 2019 pandemic, the development of vaccines against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was based on probabilistic outcomes from studies employing participants who volunteered to receive the vaccine under investigation and controls, allocated to no vaccination or a placebo.

The probability of a vaccine being effective was predicted reasonably accurately from these studies and

was largely confirmed in the field, an unprecedented achievement for the development of effective vaccines in a remarkably short period of time! But how effective a particular vaccine really was, the ability to prevent transmission, the quality and duration of protection and side effects that did not emerge or were not noted during the initial trials had to await the application of the vaccines in the wider field of the real world.

In medicine, generally, and in oncology, particularly, probabilistic rather than actual outcomes dominate research influencing clinical practice. Perhaps the best example of such probabilistic medicine in the last 30 years is the widespread prescription of statins, in the hope of preventing cardiovascular disease and stroke^[1]. An outcome statistically demonstrable in a cohort, but not easily verifiable in the individual patient anticipating the benefit, while experiencing the side effects^[1]. In contrast, in the case of antihypertensive therapy, despite some side effects^[2], the treatment benefits may be early and more readily apparent.

2. The issue

The development of new drugs against cancer usually follows three phases.

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In a typical Phase I clinical trial, the objective is to determine the safety, tolerability and the way the body handles the new compound under investigation, its pharmacokinetics.

If tolerance is established, a Phase II study follows, during which evidence of activity of a new drug is sought against different types of cancer. Participants in Phase I and II trials are, usually, patients whose disease progressed or did not respond to an earlier established treatment.

A promising Phase II, or even a Phase I study, is likely to trigger interest in a potentially effective new treatment and instigate a Phase III randomised study, controlled either with a placebo or a comparator-approved treatment, which may have also been established probabilistically!

However, once a new treatment is approved or established, it is uncommon to seek results emanating from studies with real-world experience and long-term follow-up, the actual, rather than the probable or predicted outcomes. This appears to be the case especially in the treatment of cancer. Once a new drug is licensed for a specific indication, a race begins for the development of new compounds or promising analogues competing for endorsement, with the aim of providing greater efficacy and improved tolerance.

This perfectly reasonable, legitimate and justified aspiration results, however, in a plethora of new clinical trials, while there is rarely an opportunity or interest in looking back at what has been achieved in the real world of everyday clinical practice.

The real world of everyday clinical practice can be distant to the constructed world of the prospective randomised controlled trial, where treatment may be constrained by selection of subjects on grounds of age, without comorbidities, or similar considerations. Subsequent treatments influencing survival could affect outcomes of real-world data as well as of randomised trials, but such issues could be addressed depending on the quality of deposited data.

Furthermore, if not a placebo, the choice of the comparator arm in prospective randomised cancer trials investigating a new drug is made by the investigator, virtually always these days, a sponsoring pharmaceutical company^[3].

The chosen comparator is often determined by licensing regulations emanating primarily from agencies such as the Food and Drug Administration (FDA) in the USA or the European Medicines Agency (EMA) in the European Union (EU), but may not always enjoy universal acclaim^[3]. An example of this is interferon, widely used in the past in the adjuvant treatment of melanoma in the USA, but, despite some enthusiastic

proponents of this treatment, was not equally popular for the same indication in Europe^[4-5].

In oncology, concern has been expressed about discrepancies between the promising therapeutic outcomes predicted from controlled randomised studies and the true efficacy of the *latest treatment advance* in everyday clinical reality^[6,7].

In a systematic evaluation of approved cancer drugs by the EMA in the years 2009–2013, Davis *et al* argued that most drugs entered the market without evidence of benefit on survival or quality of life^[6]. At a minimum of 3.3 years after market entry, there was, according to their study, no conclusive evidence that these approved and marketed drugs either extended or improved life for most cancer indications. When there were survival gains over existing treatment options or placebo, they were, according to the same authors, often of marginal benefit^[6,7].

Such concerns expressed by Davis *et al* are by no means new or unique and may relate to methodological or statistical pitfalls in the design of randomised studies^[4-5].

Unlike statins, the outcome of intervention in the treatment of cancer is promptly evident and often easily measurable in the individual patient. A response to a particular drug or treatment may be complete, partial, short-lived or durable, or the disease may manifestly progress against the treatment.

There was hardly a need for a placebo-controlled, prospective, randomised trial to demonstrate the activity of the tyrosine kinase inhibitor, imatinib, against gastrointestinal stromal tumours. The evidence was there for everyone to see even in Phase I trials^[8].

Would advances in the treatment of cancer suffer a catastrophic collapse, detrimental to the welfare of patients and to medical science, if randomised controlled studies were abandoned tomorrow in favour of Phase II studies? Considering the findings of Davis *et al*.^[6], this would be highly unlikely.

As already mentioned, recruitment of patients in a Phase II trial happens, as a rule, when all else has failed from conventional or standard care against a particular cancer.

Consequently, results of Phase II studies providing information on the efficacy, safety and tolerance of a new drug may contribute reliable, if not more robust, information about the real value of a new treatment, while curtailing the cost, time and resources. This information can be intelligently applied in the real world by clinical experts in the field, instead of transforming cancer care into a perpetual question mark with endless randomised studies, often of predictable outcomes. This may not be the perfect world, but is probably a better

world than that provided by the randomised study, freed also from the ethical burden of distributing, at random, treatment to cancer sufferers or indeed *no treatment*.

Information may also continue to flow from studies with real-world data and outcomes, providing a clearer picture of the true value of a treatment against cancer, an approach that is increasingly favoured by clinical researchers^[9].

Furthermore, and as importantly, others have argued that in contrast to the belief that randomised controlled trials are more reliable estimators of the efficacy of a treatment, investigators have found that, in some settings, observational studies did not overestimate the size of the treatment effect compared to their randomised counterparts^[10].

Since the streptomycin trial conducted for the treatment of tuberculosis in the 20th century^[11],

the randomised trial has been the blunt instrument of researchers and licensing authorities in the service of evidence-based medicine. Its methodology and deontology have rarely been challenged^[10-14].

Perhaps the time has come to review and re-examine the true value and ethics of the randomised trial, especially when it comes to the treatment of cancer.

Conflict of interest

I declare, I have no conflict of interest.

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