Cancer drugs, survival and ethics: a critical look from the inside

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The recently published article by Dr Peter Wise in the British Medical Journal (BMJ) is a very strong criticism of the cancer community at large, including governments, pharmaceutical industry, regulatory agencies, cancer trialists and medical oncologists in relation to cancer drug development and the cost, approval process and, ultimately, prescription to patients.1 In short, the view of this well-respected endocrinologist is that patients with cancer have a poor understanding of their benefits and risks as clinical trial participants, that they are provided with unrealistic expectations regarding drug efficacy, which he purports are marginal at best, and that the world of cancer research is dominated by market interests rather than true health benefits. A plea is made for raising the efficacy bar in trial design and drug approval criteria and for giving more weight to research in prevention, early diagnosis and supportive care, as the latter, in Dr Wise’s opinion, has likely contributed more than drugs to improve the 5-year survival rates of many solid tumours. In this editorial we will examine these criticisms, evaluate their pertinence and, when applicable, discuss current attempts at repositioning the needs of patients with cancer at the heart of innovation efforts.

For a new cancer drug to reach the market, it has to demonstrate an improved therapeutic index when compared with ‘standard of care’ in a well-conducted randomised clinical trial. This involves a succession of critical, complex steps and multiple stakeholders. The responsibility for designing, conducting, analysing and reporting pivotal cancer clinical trials has progressively moved away from academia and is mostly today in the hands of pharma, with very little, if any, governmental support. The history behind this worrisome evolution is summarised and discussed in the article ‘Academic research worldwide: Quo vadis?’ which does share some of Dr Wise’s concerns.2

Because cancer trials have become outrageously expensive, academic investigators interested in scientific issues of unquestionable importance to patients—such as improved treatment tailoring based on innovative diagnostic tests or safe de-escalation of treatment—struggle to find the few million euros needed for their trials. The pharmaceutical industry, meanwhile, is obsessed by the nightmare of a negative registration trial that costs well over €50–€100 million and is under considerable pressure, given the recent fierce competition among drugs that share a common target. The numerous anti-programmed death (PD)1 or PD-ligand 1 immune checkpoint inhibitors in clinical development are just the most recent examples of this race. Moreover, the few drugs that eventually get approved also have to compensate for the many that fail.3 Governments, with only few exceptions, prefer to stay out of the ‘risky business’ of cancer clinical research until they are faced with huge increases in cancer drug costs, which they then try to decrease, for example, by supporting national trials investigating shorter treatment durations. These often fail, as demonstration of ‘non-inferiority’ is quite challenging and requires a very large number of patients willing to take a risk for themselves.1 Considering these worrisome developments, it is not surprising that today’s clinical trials feature risk-averse and conservative designs and generate modest ‘benefits’, the nature of which could indeed be seriously questioned by well-informed patients.

Overall survival (OS), as Dr Wise mentions, is the ‘golden standard’ end point in cancer research. The complex methodological problems behind the use of surrogate end points are, however, overlooked in his article.5 Extending ‘progression-free survival’ (PFS) in the context of metastatic disease is an example of a popular, yet weak end point and as such it has not been given a lot of weight in the construction of the ‘ESMO Magnitude of Clinical Benefit Scale’.6

But why was not PFS ignored altogether? There are two reasons: first, PFS can be associated with improvements in quality of life (QoL), which are meaningful to patients,
even if 'transient' and, second, OS gains can be obscured by 'crossover', a phenomenon which will be increasingly difficult to control in view of parallel, competitive trials investigating compounds of the same molecular class. It is important also to note that evaluation of QoL end point remains problematic, despite increasing integration into cancer trials. In practice, reduction of specific tumour-related symptoms and/or less therapy-related toxicity is often used as surrogate for QoL. Additionally, non-oncologists may not realise the vital importance of 'positive trials' in advanced malignancies as the way to open the door for new drugs to be tested in the early disease setting, with a curative intent. Indeed Dr Wise’s appeal for more radical local treatment (surgery) is misguided, especially in breast cancer where radical surgery did not prove to be superior to conservative surgery. It is in systemic therapy (as well as in screening) that significant gains were made.

Defending ‘PFS’ as a reasonable, although suboptimal, end point in advanced cancer clinical trials is not saying that it has a lot of ‘value’ for patients nor that it can be the sole basis for drug approval and huge financial returns. This is the precise reason why tools like the ESMO Magnitude of Clinical Benefit Scale are valuable. The ESMO Magnitude of Clinical Benefit Scale indeed hopes to serve three purposes:

1. Provide a ranking of new anticancer drugs in relation to their ‘value’ for patients, with the highest scores allocated to drugs that do prolong the life of patients with cancer and/or significantly improve their QoL.
2. Ameliorate the design of future clinical trials and, in particular, promote patient-reported outcomes as well as the selection of more meaningful 'HR' and absolute gains in PFS and OS.
3. Facilitate the dialogue between the medical oncologist and his or her patient, so that the latter will no longer have unrealistic expectations from the treatment being discussed.

That we need to markedly improve the way we inform our patients about their treatment options or lack thereof is true, for all medical specialties. In many countries, cultural barriers on truth-telling still remain. For patients facing their own mortality, it can often be difficult to accept the limited effectiveness of cancer treatments, a problem with which oncologists have struggled since the inception of the specialty. For clinical trial participants, the ‘informed consent’ has become a 40-page to 50-page complex document that often protects the sponsor more than the patient and initiatives consisting of providing more accessible information through videos, for example, have to be encouraged. The development of similar user-friendly, didactic information tools for busy cancer clinics is also highly desirable as only a minority of patients are enrolled in clinical trials.

But what if truly innovative and valuable anticancer drugs become inaccessible in view of exponentially rising cancer care costs? And how will this impact the care of other chronic diseases? Here is where fundamentally different reimbursement models need to be put in place, such as reimbursement based first on ‘value’ as established through clinical trials and subsequently based on real-world performance of the drug.

Last, but not least, there is room for improvement in the complex interplay among governments, pharma, doctors and patient organisations. At the research level, innovative partnerships should be put in place, where patients have a say in terms of trial design, doctors have a say in terms of relevant ‘treatment arms’ and access to patient samples, pharma and academia agree for earlier “data sharing” and governments provide funding for the most ‘risky’ treatment arm. At the ethical level the entire process of drug approval should be protected from pharma influence. At the same time, universities should give more recognition for authorship on trials run by Academia as opposed to trials fully controlled by pharma, in order to discourage close ties between clinical investigators and pharmaceutical companies and provide alternative path to career development and peer recognition.

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REFERENCES