No other interest can take precedence — a patient's perspective on oncology drug development

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My husband's diagnosis with melanoma and our struggle to access effective therapy challenged what I had learnt about medical research. I have since founded a patient network, becoming a vocal advocate for patient-centric drug development. Herein, I discuss some of the lessons I have learnt.

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I clearly remember the first lecture about evidence-based medicine I attended. I was a third-year medical student, and after 2 years of theoretical training I was now seeing my first patients. Patients were considerably harder to 'read' than textbooks and the realization that my decisions one day would have far-reaching consequences haunted me.

Scientific rigour in the form of blinded, placebo-controlled randomized clinical trials seemed to be the solution to my worries: I would be able to test whether treatments were actually as effective as hoped. The structured approach would protect me from falling prey to my own biases and my patients would be safe! I was sold.

In the spring of 2011, and without any warning, the little hard lump under my husband's arm turned out to be a melanoma that had already spread to his lungs and spine. We were told not to hope for a cure and that any treatment would be palliative. Less than half an hour from returning from the appointment, my computer-savvy husband found what I hadn't had the heart to tell him. "I won't be here for Christmas," he said. The melanoma would soon grow at an alarming rate — a medusa of a tumour reaching out in any possible direction, every morning larger than the evening before.

Chemotherapy, the then standard-of-care therapy, was largely ineffective, as I knew since medical school. It was also the comparator in any available clinical trial. Friends referred to it as a 'nocibo', a non-effective treatment with adverse effects. All this happened while, for the first time, not one but two new therapeutic classes were making tumours 'melt' in early phase clinical studies that were not even intended to evaluate efficacy — tumours like the one I watched growing daily in despair. What ensued was the hardest, brutally instructive and most humbling year of my life. Having to tell your 3-year-old and 5-year-old daughters that their father is dying, and being the one tightening the screws of his coffin to never be opened again, all before you have even reached your thirty-sixth birthday, leaves indelible traces.

He did, however, live to see Christmas — thanks to clinical trials or, rather, thanks to us learning how to use clinical trials to obtain what he desired most: more time with his daughters. Receiving a life-shortening diagnosis causes unbelievable suffering for patients and families. Withholding effective therapies in this setting, all in the name of 'good science', is inhumane. It was an eye-opening experience to be at the receiving end of what I had once considered the solution to, not the cause of, suffering. Knowing that I could have been the person inflicting this experience on others horrifies me to this day and has become the driving force behind my advocacy efforts. In this Comment, I discuss some of the lessons I have learnt.

In my experience, patients with melanoma join clinical trials for one of several reasons: a largely ineffective standard-of-care therapy (as is currently the case for uveal melanoma), the patient has exhausted all existing lines of therapy, or the therapy is approved but not reimbursed in a given country. The motivation invariably is access to treatment. The alternative? Death. While it takes a considerable amount of cynicism to claim that this scenario leaves 'free choice', patients can choose which trial serves their interests best (usually, a promising therapy in a nonblinded, nonrandomized trial) and also when to leave such a trial. In this context, patients are often accused of therapeutic misconception, a situation defined by Appelbaum et al.[1] in 1987 as "[the denial of] the possibility that there may be major disadvantages to participating in clinical research that stem from the nature of the research process itself"[1]. Nowadays, however, therapeutic misconception is more commonly used as the patient's failure to understand the difference between a therapeutic intervention and a research setting[2].

While slightly different, both definitions fail to acknowledge what Article 8 of the Declaration of Helsinki[3]

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clearly states: “While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.” If the interest of a patient is to seek the most promising treatment, then an ethical cancer trial design needs to ensure this, independently of the wishes of other stakeholders. Furthermore, a situation of high unmet need alters our perceptions of acceptable benefit and risk, a fact that is also increasingly acknowledged and accounted for by decision makers such as the European Medicines Agency (EMA)[4].

Healthy people like to think of control arms in clinical trials as risks, but patients think about them as hazards: if they enrol in a clinical trial because the existing standard of care is inefficient, receiving that standard of care in the trial defeats the purpose of participating in the first place and becomes a hazard that should be avoided. The scientific community consistently fails to recognize that a null hypothesis is a valuable scientific construct but, ultimately, a hypothesis. No judicious academic, let alone a pharmaceutical company, will initiate a clinical trial to demonstrate that a novel therapy is inferior. Thus, the mere existence of a clinical trial implies a more or less realistic (and, at times, unduly optimistic) assumption of potential benefit. For a chance to survive, patients with melanoma prefer an unknown risk to a known risk with insufficient benefit, in the full understanding that the novel therapy might turn out worse — acknowledging Applebaum’s statement of a potential disadvantage owing to the research process itself[1]. My husband participated in a clinical trial of a MEK inhibitor, at the time thought to be superior to earlier BRAF inhibitors. While this hypothesis turned out not to be true, the choice of the trial remains correct — it was the most promising option at the time.

In times of increasing demand for civic participation, public as well as private entities (such as the EMA, national Health Technology Assessment (HTA) bodies, pharmaceutical companies and research institutions) are formalizing mechanisms of patient engagement. From a patient advocacy perspective, patient input that draws on a combination of disease experience and technical expertise is particularly effective. However, despite best intentions from all parties, patient engagement is not trivial because experiences and preferences can vary greatly even within the same community and need to be adequately captured through solid methodology.

Most European cancer patient advocacy groups welcome structured patient involvement and have started to systematically learn from strong patient communities that have been able to shape the drug development process through a combination of expertise and high internal organization in the past. A notable example is the community of patients with HIV or AIDS, which successfully challenged prevalent clinical trial designs by introducing novel surrogate end points, kick-started the testing of combinations of unapproved therapies and pushed for expanded access programmes[5].

Although the demands for time, expertise and commitment can become challenging (because most groups of patients with cancer predominantly work with volunteers), the European Patient Academy for Therapeutic Innovation (EUPATI), a 14-month-long training programme in drug development for patient advocates, has been a success. Communities of patients with cancer are now implementing European Community Advisory Boards (ECABs), a board of highly trained patient advocates that advise pharmaceutical companies and academic researchers on topics such as patient selection, acceptable comparators and end points. Originally developed by the community of patients with HIV or AIDS in 1992, Community Advisory Boards were adopted by groups of patients with rare diseases and now by the cancer advocacy community.

Thanks to the Internet, nowadays patients are better educated and connected than ever before. High-quality medical, scientific and technical knowledge is widely accessible, often at low or no cost. Online platforms facilitate not only communication but also the collection of data and the generation of evidence, enabling patient communities to impose their wishes with increasing sophistication and to an unprecedented degree — as in the case of patients with amyotrophic lateral sclerosis who initiated their own clinical trial and who used data-sharing platforms to unblind clinical trials[6].

Today’s research subjects are becoming emancipated and able to enforce their preferences. Drug development and clinical trial designs will have to follow suit. I am a firm believer that we will end up with a faster, more relevant and very different approach: none of the fervent supporters of randomization I have met so far has ever participated in a cancer clinical trial. Is this a coincidence? As with any progress, resistance is to be expected and new trial designs and data sources will come with their own challenges. However, it will become increasingly hard to ignore what should have always had precedence: a patient’s best interest.

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