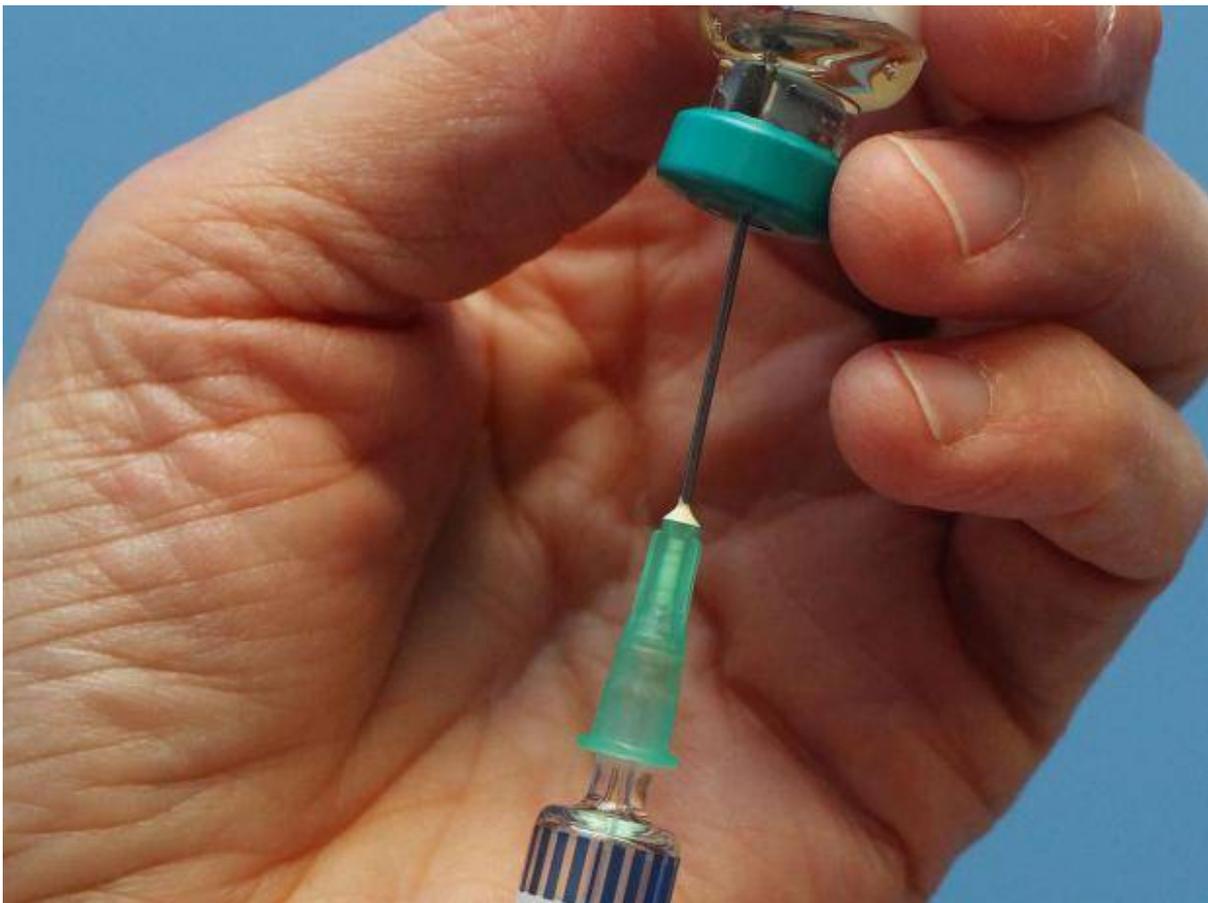# *When my son died of cancer I decided to wage war on the disease myself*

Precisely because cancer is so complex, giving patients one targeted therapy does not make much biological sense - that's why we need to test new treatments urgently

Catherine Bresson
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The WIN Consortium is trialing the possible use of new combinations of cancer therapies *Getty*

This story begins when my son was diagnosed with cancer at the age of eight. Like most patients who are lucky to be in an international city, he received nine consecutive lines of treatment, one after another, prescribed in the exact order of "cancer textbooks": from nasty chemotherapy to sophisticated targeted drugs.

Were these drugs the right match for the tumour of my child? No, they were just thrown at him in a blind manner, hoping for the best.

The worst happened - my son Gaspard died.

I kept asking myself how cancer could remain a fatality in an era when the human genome – our genetic code – has been deciphered and can be manipulated to cure rare diseases; when AIDS is under control; when cars do not need drivers; and man is conquering space?

Here started my personal war against cancer. I had no strategy, no troops, no weapons to face the enemy, only my grief and determination to make things change.

Yet I knew change was needed. Treatment options have not really varied for years; research silos remain unbreakable; the costs of treatment are exorbitant; and advances in genomic-based treatment of cancer are unacceptably slow.

And so it came to pass that a year after my son's death, in October 2010, a small group of prominent oncologists established a global collaboration of cancer centres, drug makers, technology and insurance companies built on refusal of the status quo. The network was ambitiously named the Worldwide Innovative Networking (WIN) Consortium in personalised cancer medicine, and I soon joined as director of operations.

The good news when it comes to cancer is that some important breakthroughs have been achieved recently with the introduction of targeted and immune drugs. Indeed, evidence is building in clinical trials, research and case reports to suggest that patient outcomes are improved when a specific targeted medicine can be matched to an identified anomaly of the tumour's DNA (a "genomic aberration").

However, the bad news is that in the majority of cases, this does not work or it works only briefly. Not all advanced solid tumours harbour potentially "actionable" genomic anomalies

that can be treated with a targeted therapy. So far the approach has benefited only a small portion of patients, for a variety of confounding factors. We lack tools to understand which DNA anomaly is important versus not important, we have difficulties to predict whether a drug that targets an identified anomaly will be effective in terms of patient's outcome. In other words we still do not know how to match a patient's cancer to the right drug.

Even those cancer patients who are "lucky enough" to have a tumour harbouring an anomaly that can be treated with a targeted therapy, are almost guaranteed to relapse once the disease develops resistance.

In the meantime the statistics are staggering. 14 million new cancer cases are registered every year. By 2030, the global burden is expected to grow to 21.7 million new cancer cases. This means that cancer will affect everyone in the world, sooner or later, directly or indirectly. The 'emperor of all maladies' already claims 8.8 million deaths per year, making cancer a leading cause of death worldwide, with lung cancer being the top killer.

Lung cancer develops silently and when the first clinical symptoms appear, it is often too late - the patient is already in an advanced stage of the disease that is then incurable.

Over the past 50 years lung cancer treatment has been largely ineffective. As Dr. Razelle Kurzrock, senior deputy director for clinical science at UCSD's Moores Cancer Center and Head of WIN Clinical Trials Committee, said in a recent interview: "we were blindly throwing drugs at [patients] hoping something will stick".

Around 14 per cent of non-small cell lung cancer (NSCLC) patients with stage IIIA disease survive five years after diagnosis; with stage IIIB disease the five-year survival rate is only 5 per cent. When the disease has spread to other parts of the body, the five-year survival rate drops to 1 per cent. Unfortunately 60% of patients are diagnosed at late stage IV.

With the current path of drug and biomarker development, it will take decades to achieve significant improvement in cancer outcomes. Personalised oncology, aimed at giving the right treatment to each patient, is therefore a long and winding road that has left many patients on the side.

Strategy

Cancer is complex and pernicious, yet it does not develop in vacuum, but rather in an individual. Precisely because cancer is so complex, giving patients one targeted therapy does not make much biological sense. It may produce response in some patients, but responders will inevitably develop resistance and succumb to the disease. It is time to look at patients as individuals and to develop combination treatments, or 'cocktails'. But how can we determine personalised therapy combinations that can be used to treat lung cancer, or other deadly malignancies? There is no clear answer yet.

The easiest way to cure cancer is to prevent it. Global tobacco control is critical to achieve this goal. When lung cancer is detected at an early stage, surgery and adjuvant therapies are enough to achieve cure. But what if the patient arrives too late, having an advanced form of the disease? How can we deliver the gift of time and quality of life that my son was denied? The strategy here resides in switching from the current monotherapy rule given in consecutive lines, towards the rational combination(s) of targeted drugs. But how many drugs do we need to combine together?

There are many trials under way exploring combinations of two drugs. With few exceptions they do not yet achieve the goal of prolonging life significantly. Patients and their families are expecting more than only a few additional weeks or months of life.

The strategy for lung cancer treatment and all other solid tumours has to be multiple modalities and multiple drugs that are optimized for each individual. Like in any war we need a strategy adjusted to the enemy who is shrewd, mutable and agile.

Our research team hypothesised that three targeted therapies with different modes of action, hitting different biological pathways simultaneously, will overwhelm cancer. This strategy is expected to achieve what targeted single agents have failed to do so far in precision oncology, especially in lung cancer — stave off cancer resistance and prolong long-term survival. The triple-therapy hypothesis is that all patients could be treated in a personalised way (and not only a minority whose tumour harbours a known targetable DNA anomaly), and that the patient outcomes would be significantly improved. Indeed, the strategy has been successfully implemented in patients with AIDS, whose viral load is effectively controlled with triple-therapy thus reducing AIDS to a chronic disease.

However, cancer is far more complex than AIDS, and one triple-therapy will not fit all lung cancer patients. The pathways that cancer uses to thrive are many more than we thought before, propelling us to conclude that patients will need several tri-therapy combinations to fight cancer.

Tactics

Two innovative tactics and weapons were developed to make this tri-therapy approach possible. First, three drugs were selected among those already existing on the market; second, an algorithm based on a new biomarker technology was put in place. The latter explores a broad spectrum of analyses that 'imprint' the disease, a routine procedure even in the most advanced clinical trials. They include the investigation of the tumour DNA but also the gene expression of the tumour tissue in comparison to the healthy tissue of the patient.

The algorithm is able to integrate billions of bytes of data with the purpose of identifying meaningful individual biological anomalies or pathways that can be targeted with a 'cocktail'. In terms of military strategy and tactics, the objective being pursued is to '*hit them (the relevant pathways) where it hurts*'.

This novel strategy is ready to be tested. The US Food and Drug Administration (FDA) has already given its blessing to the launch of a unique WIN Consortium trial in first line therapy (that is for non-treated patients) of metastatic NSCLC.

While the first proof of concept trial is getting off the ground with the first tri-therapy, a second combination is coming. The more tri-therapy combinations are studied, the faster we obtain more options for patients and elucidate the ability of the algorithm to match patients to the right combinations. With more than one therapeutic option, patients will be able to switch to different combinations as resistance emerges and extend survival for many more years than is currently possible.

One could say that this is a nice strategy but still a hypothesis until proven by clinical trials. The major risk here is losing time – to be too late for those who wait for a miracle. For the sake of the patients, we cannot afford to wait for the results of the first tri-therapy trial before we move to the next. My dream is to have within 5 years clear answers and build substantial knowledge to make a quantum jump in treating lung cancer patients who have been left without significant survival improvement for the past 50 years.

We need many more strategies to win the war against cancer, apart from research intuition and foresight. Tough political battles lie ahead of us: we have to convince drug developers to collaborate; we will need ambassadors and supporters to convey our message; we have to persuade governments to help. We are all at war against a common enemy.

Catherine Bresson is Director, Operational Team of the WIN Consortium