Perspective

That's how you make drugs!

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Abstract: Although the science is able to proof that a drug works for the BRCA mutation in breast cancer, prostate cancer and pancreatic cancer (and maybe in other BRCA-mutated cancers) we stick to the registration path of doing phase 1, 2 and 3 trials based on organs. With the knowledge of today and the practice of personalized medicine we are able to give the drug olaparib much faster and save lives or at least extend lives with a good quality of life. This can be done differently if patients are involved in the process of determining the research, designing the trials and organizing the trials. If done properly we help patients in the first place and all the stakeholders will benefit as well.

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I want my olaparib and I want it now!

'Because I have cancer above the midriff, I can go and whistle for that drug, but it would have been given to me if the cancer had been under the midriff'. It's an emotional outburst from a patient with breast cancer and a BRCA mutation. A new drug is available on the market—'a wonder drug' to treat BRCA-mutated cancers [olaparib, (1)]. In the Netherlands this drug is registered for ovarian cancer, but not for any other sorts of BRCA-mutated cancers (including breast cancer, prostate cancer and pancreatic cancer). It's not my conclusion that it's a 'wonder drug', but the conclusion of leading scientists and doctors. A study by a geneticist from the Erasmus Medical Centre shows that although they did not go into remission, the drug has allowed several hundred, possibly over one thousand patients to live significantly longer. The side effects are relatively mild, so the patient's quality of life during this time is also good. 'The drug has to be made available'…

However, the drug will not for the time being (in the Netherlands in any case) be made available to patients with breast cancer, prostate cancer and other BRCA-mutated cancers. This is because the phase 3 trial for olaparib in these types of tumors must first be conducted, concluded and evaluated, and the drug may only be prescribed after it has proved to be effective on these organs (and then there must be a significant difference from a placebo or other efficacious drug). So this means many more patients will die earlier than necessary. But we did at least follow the rules…

A drug's path

It's a well-known fact that the path a drug has to travel from its early beginnings until it reaches the patient is a long one. It begins with research, which is often carried out by a biotech firm, as the pharmaceutical industry does not conduct much research any more (2,3). The medicine undergoes three phases of clinical trials, and must then be registered for the disorder in a specific organ. All different types of institutes are responsible for monitoring quality, applying and maintaining rules and again adjusting these rules. The medicine ultimately reaches the patient, and in many cases it doesn't actually prove to be efficacious (4). This can be explained by the fact that the inclusion rules for patients are so strict that only a limited number of patients suffering from this disorder in a specific organ can meet the requirements. By the time the medicine can actually be prescribed it is given to all the patients with a tumor in

a specific organ. While still being efficacious for 20% of patients in this select group, the medicine's effectiveness in reality is most disappointing.

The entire process is divided into dozens of stages, possibly even hundreds. The effect of this is that responsibilities are also divided into many different small parts. No one monitors or takes responsibility for the entire process. However, the patients are the ones who pay the price, as they end up not receiving the drug or getting it too late. They aren't given the drug during the trial as they don't meet the inclusion criteria. They don't get it after the trial as they don't have cancer in the organ for which the drug is registered. They don't receive the drug after it has been registered because it is too expensive and the health insurer refuses to pay for it, or the Minister of Health refuses to allow health insurers to cover the costs of the drug, as was the case in the Netherlands with nivolumab for 7 months and the early death of many patients.

This whole process isn't right. It means we can say to a dying patient that he or she is not allowed the medicine because for example we don't yet know the long-term effects. This is the case, even though the same patient would be happy with effects over 5 years, because then they would at least still be alive. The splitting up of responsibilities, and the accompanying absence of having to consider what happens next leads to this remarkable and at the same time justifiably cautious approach. I do not doubt that it is justified. I base myself in this respect on the fact that there is nobody, or in any case very few people who deliberately withhold medicines from patients.

Where is the patient?

Patients do not really have a say in any of the groups that are involved in bringing a drug to the market. They are not involved in the question of which drug is truly necessary for the patient, the design of the drug or the trial, assessing the results of the trial, determining which patients qualify to receive the drug, or in the question of whether the health insurer covers the cost of the drug. Patients are involved in the discussion with the physician about whether the medicine should be prescribed as part of the treatment, but their involvement is not crucial. Ultimately, the patient may participate in a trial under certain conditions and if the drug is registered they are able to take it if the physician has prescribed it. This is hardly an enviable position to be in.

It can be done differently

In an article in *Chinese Clinical Oncology* (*CCO*) of 2014 I already gave some hints about alternative roads for the development of new drugs (5). Let me elaborate here a bit more about possibilities and ways to change this.

In April 2013 I visited David Tuveson in Cold Spring Harbour. David is a leading pancreatic cancer researcher. After spending some time as a fundamental researcher at the Memorial Sloan Kettering Cancer Centre and speaking to patients there, he asked me what the most important thing was that pancreatic cancer patients had to deal with (apart from the fact that they all barring a few exceptions die within six to twelve months). My answer was short and direct: "Pain!" and indeed; that was also David's conclusion; "Pain!" "If I can take away the pain I give them 6 to 12 months more Peter". However, nobody apart from David does any research into the pain related to pancreatic cancer. This is because, to begin with, pain cannot be patented, and secondly because patients do not have a say in the focus of the research. Patients should be the ones who decide what assignments the fundamental researchers carry out to ensure the research remains within relevant areas. And researchers cannot determine what is relevant. That can only be decided by the patients, in consultation with physicians and scientists, but patients should be decisive in this respect. This also applies to fundamental research. When you allow researchers to set the research agenda, you do end up with interesting and scientific studies, but the question that only patients can answer is whether they actually benefit from them.

Relevant research and the relevant drugs and clinical trials that result from them arise through cooperation between patients, physicians, scientists and representatives of the pharmaceutical industry. The first question to be asked is what the largest problem for patients is. And research is conducted based on this outcome. This is followed by trials that are set up on the basis of cooperation between the patients and the pharmaceutical industry. Trials are then set up for drugs that will be relevant and in which patients are willing to participate. After all, they are set up by patients, for patients, and don't just serve to register drugs (which has unintentionally and inconspicuously become the aim of most trials). The outcome of these trials will in most cases be better than the results of the current trials, as they are set up by patients and for patients. And patients will act as the best possible ambassadors for these

results, as they will result in drugs that actually work and provide benefits. Drugs that can actually extend the life of patients, and not just by a few months (because this does not satisfy patients in any way) and which above all have limited side-effects, as this is something patients should also take into account during the development stage. After all, they are the ones who have suffered these terrible side-effects and will not accept them so readily.

It can be done quicker

Patients will also indicate that the introduction of new medicines takes far too long and can be much quicker. After phase 1 and 2, why add phase 3 for every organ that the medicine might be effective for? In the case of olaparib it can be immediately prescribed after registration for ovarian cancer, for BRCA-mutated prostate, breast, pancreatic and stomach cancer. Administer it immediately after phase 1 and 2. It is after all safe and we know the doses that should be prescribed. Perhaps we can carry out an accelerated phase 3 trial, and then administer it to all patients with a BRCA mutation. And we should also make sure we keep a good record of how this treatment progresses in patients. Carefulness and speed are not mutually exclusive. Most scientists would agree that there is not one good scientific reason to suggest that olaparib would also not work for BRCA-mutation breast, prostate, pancreatic and stomach cancer patients. We can already establish that it would take 30, 40 or 50 patients with, for example pancreatic cancer, to establish whether the drug is efficacious. If it works then we proceed with the treatment and if it doesn't then we stop treating this group of patients with olaparib. So drugs should therefore be registered on the basis of the gene mutation and no longer based on the organ affected by the tumour. Treatment and registration. Patients want to cooperate in this respect, because no patient is willing to wait for a treatment that doesn't work. The patients we're talking about here have run out of alternatives. If this process is controlled and the patients are kept well informed then this is certainly possible and very morally responsible. Moreover, it is actually morally unacceptable to refuse these patients the drug. They are dying and they deserve our help. This offers real hope, and not just false hope. There's a chance the drug works and this is a chance we can offer the patient. In the worst case the drug does not work, but we've done all we can to offer the patient the opportunity to see their children and grandchildren grow up, or in any case to enjoy their company for a longer time.

If it is possible to do this differently and quicker then it must change

It's now time for action. We have carefully considered the options and now we have to act, placing patients who have a decisive say in matters in crucial positions in each stage of the drug development process. We must stop speaking with patients, and then leaving them out of the discussions that actually matter and making decisions in their absence. No, from now on we must discuss matters with patients and make the decisions in the same meeting. The patient must be involved in decisions about the research agenda, the design of the trial, inclusion in the trial, the registration of the drug and reimbursing the costs of the drug. This increases the quality of the decision-making and the acceptance.

In conclusion, patients do not need treatments that don't work or which have horrific side-effects. This is however the effect of most treatments so far. To date this has involved spending considerable amounts of money, which in most cases has just led to misery. Listening to and cooperating with patients is not only beneficial for them, but also for the healthcare services and the related costs.

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Footnote

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