ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Repurposing Drugs in Oncology

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H&O What is drug repurposing, and how is it used in oncology?

EV Drug repurposing describes the phenomenon of using drugs that are already approved or available for a different purpose. In the context of oncology, the basic idea is to expedite the drug development process by exploring alternative approaches that could benefit patients. In general, it involves taking existing drug with known side effects, chemistry, and dosing protocols and, based on a scientific rationale, investigate whether they can be beneficial in treating cancer patients.

H&O How does the process of repurposing drugs differ from traditional drug development?

EV Traditional drug development begins with identifying a target of vulnerability in a cancer cell, which can be challenging because cancer cells and normal cells are 99.9% the same. The next step is to identify either an antibody or a chemical compound that can interact with the identified target.

Once such a compound is found, the real work begins. Researchers need to find a molecule that effectively inhibits the target and that can be formulated to administer to patients. The process typically starts by studying cell lines and then progresses to animal studies. Afterwards, phase 1 clinical studies are conducted using the selected formula, with a focus on assessing the pharmacokinetic and toxicity profiles to ensure they fall within acceptable limits. In the end, the main concern is whether the drug works in patients or not. The entire drug development process can take anywhere between 8 to 12 years, depending on the specific entity being studied.

In contrast, drug repurposing leverages existing drugs that are already approved and are known to be safe for other purposes. This significantly shortens the timeline because researchers can skip the early stages of drug development and instead focus on investigating whether the repurposed drug can effectively treat cancer patients, streamlining the overall process considerably.

H&O Are there any challenges or limitations associated with repurposing drugs, and how are those addressed?

EV The results have been disappointing with attempts to take drugs from outside oncology and repurpose them for use in oncology, as we discussed in an article in *Cancer Discovery*. We described a few examples of agents that initially appeared to have anticancer properties, such as metformin and aspirin, but were never shown to be effective cancer treatments.

Another approach involves repurposing drugs already used within oncology. We have been working on programs aimed at establishing drugs that are already on the shelf for specific cancer types as potential treatments for different cancer types or even alternative targets. This approach can significantly speed up the process, as we already know these drugs are effective against cancer. In our ongoing studies in the Netherlands, now expanding across several European locations, we have shown that such repurposed drugs can indeed provide benefit.

Yet, there are problems. When starting with a drug that is already approved and is ending its patent lifespan, generally there is not much incentive for pharmaceutical

companies to test it in clinical trials for different tumor types. This situation negatively affects patients with rare cancers the most, because those with more common cancer types already have access to the bigger market of approved drugs tailored to their condition.

To address this issue, our Drug Rediscovery Protocol seeks to facilitate access to these potentially beneficial drugs for patients with rare cancers. In the DRUP study, we make drugs which have been approved for a specific cancer available for a broader population outside the designated label. This allows patients with rare cancers to participate in our study. In these patients, there is a consistent clinical benefit rate (defined as a complete response, a partial response, or stable disease >4 months) of 32%. This success spanned across all tumor types and treatments, and encompassed more than 1350 treated patients.

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Although this approach does not strictly fit the formal definition of drug repurposing, it ensures that we make the most of existing drugs. Like I said, the traditional drug development process takes 8 to 12 years to get it to the market and on the shelf, resulting in drugs sometimes being approved for one type of cancer and then left unused for others. The most salient historic example is the 12-year gap between the approval of trastuzumab (Herceptin, Genentech) for breast cancer and for gastric cancer. This delay underscores the importance of finding novel uses for existing drugs to avoid wasting resources and to expand treatment options for patients, especially in light of the fact that approximately 93% of all new drugs entering a phase 1 are discarded owing to toxicity, pharmacokinetics, and/or lack of efficacy. That is a huge waste of resources. A lot of science is not reaching the patients, and that is a shame.

Advancements in technology, such as single-cell sequencing, whole-genome sequencing (WGS), panel sequencing, and RNA sequencing, have allowed us to better understand the responsiveness of certain tumors to specific drugs. This knowledge opens the possibility of giving discarded drugs a second chance when we can identify the specific patient profiles that respond well to them. For instance, a drug that appears ineffective in 9 out of 10 patients might show promise if we can pinpoint why it works exceptionally well in 1 patient, and then seek similar cases for more successful outcomes.

H&O How do researchers identify potential drug candidates for repurposing, and what role do genomic-sequencing technologies play?

EV As a medical oncologist, one of my main concerns is that scientific progression is currently outpacing the use of these findings in the clinic. For example, small DNA sequencing panels or gene panels are commonly used, but they generally do not cover all the relevant targets.

Therefore, I am a proponent of WGS, which offers a comprehensive view of the genetic landscape of the tumor and is done at an acceptable price, similar to the smaller tests. With WGS, we gain access to a wealth of information that allows us to create tailored treatment plans. For instance, we can identify potential drug candidates for very rare targets, which may occur in only 1 in 1000 cases. Individual testing for infrequent targets may not be cost-effective, but when dealing with a larger pool of targets, it becomes more justifiable. The power of WGS lies in its ability to reveal a broader range of potential targets for drug repurposing. Another advantage is the potential to create a compressive database integrating WGS data, clinical information, and treatment outcomes. This database could lead to more affordability by enabling us to identify resistance profiles upfront and prevent exposing patients to unnecessary toxicities.

Genomic sequencing technologies, particularly WGS, play a crucial role in identifying potential drug candidates for repurposing and optimizing treatment plans based on a patient's unique genetic makeup. Embracing advanced technologies can help us bridge the gap between scientific discoveries and their effective application in clinical practice.

H&O What other examples are there of repurposing drugs?

EV Outside of oncology, examples of drug repurposing are very limited. The only notable example is aspirin, which has been studied for its potential in preventing colorectal cancer. The effect is minimal, so it is not something I would strongly promote, but there are studies supporting this notion.

Within oncology, there are instances where drugs initially developed for one target have shown effectiveness

against a different target. For example, imatinib, which was developed for chronic myelogenous leukemia, also demonstrated activity in gastrointestinal stromal cell tumors. Similarly, some MET inhibitors were found to interact with alternative targets, such as ROS1.

Advances in our understanding of cancer cells and drug interactions are improving. For example, artificial intelligence programs such as AlphaFold are significantly reshaping drug development. We can now predict, based on molecular structure, which targets are hit by which drugs. This opens the door to new possibilities for precision medicine with repurposed drugs.

H&O Can you speak on the importance of collaboration between academia, industry, and regulatory bodies in the drug-repurposing process?

EV Collaboration among those entities poses a challenge owing to the polarized nature of the system. Pharmaceutical companies develop drugs, but often face criticism for perceived high prices. Healthcare insurance companies approach accepting new drugs with caution and consider their cost-effectiveness. Regulatory authorities focus on determining the drug's efficacy. Medical oncologists seek to conduct meaningful trials.

Our experience has shown that productive initiatives can come about when all stakeholders come together. Here in the Netherlands, we have established a personalized reimbursement model within our protocols for rare cancers. Under this system, when we administered off-label drugs to patients, the pharmaceutical companies provide the treatment for free for the first 4 months. If the treatment works, the insurance company then takes over the reimbursement. Such collaborative efforts ensure that drugs reach the patients who benefit from them.

However, this is not easy, especially when dealing with low patient numbers. To address this, we need to identify strong signals of drug activity, and design schemes that incorporate both clinical trials and real-world data. By understanding each perspective, we can seek out creative solutions to make effective treatments more accessible. Ultimately, we should recognize that we all share a common goal, and that is to create better treatment options and outcomes for patients. Collaboration among academia, industry, regulatory bodies, and medical professionals is vital to achieving this objective and improving patient care.

H&O Are there any financial or regulatory barriers that can limit the adoption of repurposing drugs, and how can those be overcome?

EV Yes, as I mentioned earlier, there are financial and regulatory barriers that can limit the adoption of repurposed drugs, particularly when dealing with extremely rare populations. Conducting trials with only 10, 20, or 30 patients poses challenges in terms of study design, which is generally single-arm, and statistical significance. Pharmaceutical companies may be hesitant to invest in these rare indications, as running these trials can be both difficult and costly. The regulatory authorities are also cautious about relying solely on single-arm studies. However, medical oncologists, upon seeing positive outcomes in their patient on a particular drug, desire access to those medications for further treatment. So yes, there are financial hurdles, but I think the biggest problem is the number of patients that you can identify for treatment. In cases of common targets or diseases, randomized clinical trials are employed, providing a well-established roadmap for drug evaluation. However, for rare cancer patients, the low number of eligible patients makes traditional trial design impractical.

H&O What do you see as the future of drug repurposing in oncology?

EV In the future, it would be great if we could lower the attrition rate of phase 1 studies from 93% to around 85% or 80%. Ideally, if we could increase the success rate from 7% to 14%, we could significantly enhance the number of drugs that reach the market. However, I am ambitious. Even with a 20% success rate, there is still room for improvement. We must strive to do better on multiple levels. Ultimately, I envision a future where we can bring a more substantial percentage of repurposed drugs to the market, providing more treatment options for cancer patients and improving overall patient care.

Disclosures

Dr Voest is the co-founder of Mosaic Therapeutics.

Suggested Readings

AlphaFold Protein Structure Database. https://alphafold.ebi.ac.uk. Accessed August 1, 2023.

Hoes LR, van Berge Henegouwen JM, van der Wijngaart H, et al. Patients with rare cancers in the Drug Rediscovery Protocol (DRUP) benefit from genomics-guided treatment. *Clin Cancer Res.* 2022;28(7):1402-1411.

Schipper LJ, Zeverijn LJ, Garnett MJ, Voest EE. Can drug repurposing accelerate precision oncology? *Cancer Discov.* 2022;12(7):1634-1641.

van der Velden DL, Hoes LR, van der Wijngaart H, et al. The Drug Rediscovery Protocol facilitates the expanded use of existing anticancer drugs. *Nature.* 2019;574(7776):127-131.

van Waalwijk van Doorn-Khosrovani SB, Pisters-van Roy A, van Saase L, et al. Personalised reimbursement: a risk-sharing model for biomarker-driven treatment of rare subgroups of cancer patients. *Ann Oncol.* 2019;30(5):663-665.