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Perspective

Precision Drugs are Needed for Precision Medicine to Work

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ABSTRACT

Precision medicine (PM) tailors disease prevention and treatment to people's genes, environments, and lifestyles, claiming to target the right treatments for the right patients at the right time. However, it needs precision drugs with molecular structures that interact with precisely defined disease targets to do so.

Keywords
Precision medicine; Precision drugs; Molecular targets.

INTRODUCTION

It was postulated in 1999[1] that the human genome would be used to predict, prevent, and treat disease more precisely in 2010. It was further suggested that the next 15 or 20 years would witness a "*complete transformation in therapeutic medicine*".[2] The promise of precision medicine (PM) is to improve patient care through therapies specifically designed to match the individual's disease conditions and even to prevent diseases.[3]

The premise of PM links the alterations in DNA sequences to disease causation. However, gene variants failed to explain common complex diseases. For example, genome-wide association studies demonstrated that hypertension, diabetes, cardiovascular disease, and many cancers are each associated with hundreds of gene variants that explain only a fraction of the disease's origin, progression, and frequency.[4]

As we enter 2023, there is little evidence available of a "*complete transformation in therapeutic medicine*".[2]

How the goals of PM could be achieved has not yet been defined. A vital factor in the future success of precision therapies–precision drugs (PDs)–must be created.

PRECISION DRUGS

PDs are needed to support the promise of PM to prevent and treat disease by targeting patients' disease-related genes, environments, and lifestyles at the right time. However, the concept, design, and availability of "PDs" are rarely considered. The rationale for and the approach to developing PDs have been discussed previously.[5] The molecular structure of PDs needs to be defined and shown to interact with a precisely defined disease target with the appropriate pharmacokinetics to be efficacious. "Targeted" drugs approved to date only act on pathways assumed to be involved with the disease.[6]

However, some progress has been made by using targeted therapies to treat specific types of cancer cells, such as human epidermal growth factor receptor 2 (HER2)-positive breast cancer cells, or using tumor marker testing to help diagnose cancer. "Targeted therapies"[7] use drugs[8] to attack specific cancer cells.[9] Such therapies usually cause less harm to normal cells than chemotherapy[10] or radiation therapy.[11] For example, chronic lymphocytic leukemia (CLL) is now treated successfully using monoclonal antibodies[12] that bind to a specific target on cancer cells. The antibodies kill the cancer cells, block their growth, or keep them from spreading. Rituximab, ofatumumab and obinutuzumab alone or combined with chemotherapy are used to treat symptomatic or progressive, recurrent, or refractory CLL, an indefinite article targeting cluster of differentiate 20 (CD20), a protein found on the surface of B-lymphocytes.

Incidentally, accuracy and precision are both used to measure results. Accuracy measures how close results are to the true or known value. Precision, however, measures how close results are to one another. So, perhaps we should be talking about "accuracy" medicines and drugs.

The conventional drug discovery process has advanced our ability to treat many diseases. However, to advance to PM,

PDs are needed. It is unlikely that any existing drugs could be repurposed to serve as PDs. For example, several approaches have been used to modulate the immune system, including immune checkpoint inhibitors and monoclonal antibodies.

Immunotherapy is expected to aim the immune system against cancer cells. However, applying immunotherapy is not compatible with the PM principle of "*right dose for the right patient at the right time*".[13]

PM requires detailed information about the biological mechanisms of the disease. At present, good biomarkers to predict a patient's response to immunotherapy are not available. Further, PM requires the treatment to be applied at the right time. Adjuvant immunotherapy trials can last for 1-3-years. The pharmacokinetics of a PD needs to be fully known and documented. However, a dose-response relationship is often not established with immunotherapy.[14] T-cell transfer therapy uses immune cells taken from the patient's tumor to boost the natural ability of T-cells[15] to fight cancer. Immunotherapy is anything but precise.

Using PDs could make promising immunotherapy treatment more precise and effective.

PARADOXICAL EFFECTS OF CHEMOTHERAPIES

D'Alterio et al[16] reviewed in 2020 the paradoxical pro-metastatic effects of chemotherapy. In summary, the authors stated that the "*therapeutic efficacy on the primary tumor may in fact be counter balanced by the induction of tumor/host reactive responses supportive for survival and dissemination of cancer cell subpopulations*".

In several tumor types, chemotherapy has failed to counteract and control metastatic dissemination even when a partial or complete primary tumor response has been achieved.[17] Consequently, patients develop distant metastases despite efficient local disease control.[18] Therefore, the broader detrimental effects of chemotherapy must be considered when developing PDs.

At the primary tumor site, chemotherapy induces cell selection from the intra-tumor heterogeneity of specific clones or cellular subsets possessing intrinsic drug resistance.[19,20] In addition, specific subsets of cancer stem cells (CSC) have been shown to self-renew and have an increased ability to initiate and sustain primary tumors.[21-23]

Further, extrinsic resistance can also develop stimulated by the microenvironment, directly activating CSC self-renewal pathways, leading to the induction of the epithelial-mesenchymal transition (EMT), giving tumor cells enhanced disseminating properties, CSC features, and chemoresistance.[24,25] EMT links chemoresistance and metastatic potential, although this connection is not fully understood.[26]

D'Alterio et al[16] classified the paradoxical role of chemotherapy in metastasis according to various settings: selection/generation of disseminating CSC both *via* tumor- and stromal-mediated mechanisms; mobilization and recruitment of pro-tumorigenic immune cell subsets; regulation of circulating tumor cells (CTC) phenotype, and contribution to the generation of pro-metastatic niches favoring extravasation or survival and proliferation at distant sites.

Let us Examine Specific Examples

In breast cancer, cytokines released by tumor cells after chemotherapy can activate both Wnt/j3-catenin and NF-KB pathways that amplify the secretion of further cytokines to establish an autocrine inflammatory forward-feedback loop enriching for chemoresistant CSCs. This feedback loop can be interrupted by targeting the IL8/CXCR1/2 axis resulting in tumor inhibition and prevention of the generation of paclitaxel-enriched CSCs.[27]

In bladder cancer, Kurtova and co-authors demonstrated that CSCs actively contribute to therapeutic resistance by promoting cell division of a quiescent pool of CSCs that ultimately re-populate residual tumors between chemotherapy cycles. This effect is driven by prostaglandin E2 (PGE2) release by apoptotic cells after chemotherapy that paradoxically promotes neighboring CSC repopulation. In vivo cotreatment with a PGE2 inhibitor enhances the chemotherapeutic response of bladder xenograft models by abrogating tumor repopulation.[28] All the above suggests that the existing anti-cancer chemotherapy drugs are unlikely to serve as PDs.

NEW PARADIGM

PM is either a fantasy or bad propaganda without recognizing the need for PDs and precisely defining what is needed. In developing disease-targeted drug therapies, it is critical to make the task very clear and define it in terms of unique molecular structures present in specific disease-associated cells. However, a question does remain: "*Can this be done using the approaches employed so far?*"

A new paradigm for developing truly disease-targeted PDs needs to be developed[29,30] and adopted. The key steps will include new approaches to identifying unique molecular structures present in a narrowly defined population of cells and a practical algorithm for identifying such unique structures relevant to diseases (e.g., cancer). A high-level of artificial intelligence at the level of human intelligence will need to be an integral part of this effort.

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