Development of Therapeutics for Heart Failure: Expedited Commentary

Precision Medicine for Heart Failure

Lessons From Oncology

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In his State of the Union Address in January 2015, President Barack Obama launched the Precision Medicine Initiative "to bring us closer to curing diseases like cancer and diabetes." Francis Collins, the Director of the National Institutes of Health, noted that advances in molecular biology, genomics, and bioinformatics and converging trends of increased connectivity through social media and mobile devices had set the stage for the President's visionary initiative.[1] The initiative would start by focusing on cancer. Although cardiovascular disease remains the leading cause of death in the United States, the decisions to focus initially on cancer highlighted the advances in precision medicine for cancer that have clearly outpaced that for any other field of medicine. In fact, cardiology in general and heart failure (HF) specifically have made little progress toward precision medicine. Nonetheless, important lessons can be learned from both the success and failures of precision oncology, which will potentially provide a template for advances toward a precise approach to the therapy of HF and other cardiovascular diseases.

The fundamental principle that underlies cancer precision medicine is that molecular analysis of an individual patient's tumor can enable the identification of the appropriate drug for that tumor which would in turn lead to improved efficacy. Molecular analysis of cancer has been facilitated by the confluence of technological and analytic advances, including the completion of the Human Genome Project,[2] the introduction of high-throughput and relatively inexpensive next-generation sequencing,[3] and the development of sufficient data storage and computational analytics.[4] The Precision Medicine Initiative at the National Cancer Institute has also been facilitated by the Exceptional Responders Initiative and new constructs for clinical trials. In the Molecular Analysis for Therapy Choice (MATCH) program, patients undergo a tumor biopsy followed by next-generation sequencing supplemented by immunohistochemistry or fluorescence in situ assays for 200 genes that align with targeted agents that have demonstrated effectiveness against human tumors having the specific genetic abnormalities.[5] Other designs include basket trials that target a single genetic alteration using a single drug to treat tumors in different organs[6] and umbrella trials that target multiple genetic alterations using different agents in a single cancer type. Basket and umbrella hybrid trials are designed with multiple subprotocol arm targets: each arm testing a single genetic alteration with a single drug but against multiple different tumors.

The early wins that Precision Medicine Initiatives have brought to the care of patients with cancer have been in the treatment of nonsmall-cell lung cancer associated with mutations in either epidermal growth factor receptors[7] or anaplastic lymphoma kinase gene,[8] metastatic melanoma with mutations in the proto-oncogene B-RAF (BRAF),[9] and BCR-ABL translocation-positive myelogenous leukemia.[10] For example, 20 years ago, investigators reported that the overexpression of the epidermal growth factor receptor in nonsmall-cell lung tumors was associated with worse survival.[11,12] Clinical trials that were first reported in 2003 suggested that epidermal growth factor receptor tyrosine kinase inhibitor gefitinib might benefit patients with nonsmall-cell lung cancer leading to accelerated approval by the Food and Drug Administration. However, when subsequent trials met with mixed results, the approval was withdrawn.[13] However, after the sequencing of receptor tyrosine kinase genes revealed somatic mutations in epidermal growth factor receptor that predicted response to gefitinib, and clinical trials demonstrated improved survival, the Food and Drug Administration reinstated approval of the drug in 2014.[14]

The early success of precision medicine was enticing. Cancers were ideal targets for precision therapy because mutations could be identified in genes that had already been defined as potential targets and thus useful drugs were in the pipeline. Centers of Personalized Medicine and Precision Medicine grew in both academia and the private sector—attracting patients, pharmaceutical partners, investment groups, and donors. Unfortunately, cancer has proven to be surprisingly complex, and initial optimism has been tempered by more realistic expectations.[15,16] An innate ability of cancers to develop resistance to a single drug by activating alternative pathways or by upregulating partially inhibited pathways, a toxicity threshold that is below the therapeutic threshold, and an inability to combine 2 agents because the combined toxicity precludes the dosing of either drug at an optimal level have challenged oncologists and drug development.[15] In addition, both primary tumors and metastases show substantial

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heterogeneity—a Darwinian model of tumor evolution that has been compared with a branching tree.[17] Cutting off 1 branch of the tree can simply enhance growth from another part of the tree.

In some context, cardiomyopathies would appear to be more amenable to precision medicine than cancer: failing hearts are thought to be generally homogenous, many of the signaling pathways responsible for regulating cardiac function have been identified, mutations in at least 40 genes have been shown to cause familial dilated cardiomyopathy, and the various forms of heart muscle disease have been well characterized phenotypically using easily obtained and noninvasive measurements. Although not performed on a regular basis, endomyocardial biopsies can provide access to tissue. Nonetheless, there is almost a complete absence of precision in the care of patients with dilated cardiomyopathy because of an absence of specific disease-modifying therapies. To date, there is only a single therapeutic drug recommendation that is specific to a subset of the HF with reduced ejection fraction population: the fixed dose combination of hydralazine and isosorbide dinitrate that is recommended as a class 1 agent for the treatment of self-identified blacks with HF with reduced ejection fraction.[18] However, classifying the use of hydralazine and isosorbide dinitrate in blacks as precision medicine is an oversimplification because self-reported race is a crude surrogate for genotype. For example, the G-protein β-3 subunit genotype predicted enhanced benefit of hydralazine and isosorbide dinitrate in the A-HeFT trial (African American Heart Failure), but only 52% of self-identified blacks in the study carried 2 alleles (T/T) of the polymorphism (C825T) that is linked to enhanced α-adrenergic tone and improved outcomes with hydralazine and isosorbide dinitrate.[19] Therefore, the possibility exists that 48% of black were treated unnecessarily, whereas 14% of non-Hispanic white Americans who have the advantageous genotype were not treated. The value of the GNB3-TT genotype is now being tested in the prospective GRAHF-2 (Genomic Analysis of Enhanced Response to Heart Failure Therapy in African Americans-2 trial).

A principal difference between the translational sciences in HF and in cancer biology that might explain in part the relative lack of precision therapy in the treatment of HF is that HF research has been driven in large part by discoveries in investigational models of HF, whereas drug discovery in cancer has been driven by the elucidation of altered biology of human tumors. For example, animal models with left ventricular dysfunction secondary to a myocardial infarction, transaortic constriction, pacing-induced tachycardia, or transgenic overexpression of selected proteins have provided therapeutic targets for drug discovery. By contrast, new therapeutic targets in cancer have arisen in large part from studies of human cancers either in situ or in vitro. The convergence of oncological and cardiovascular research might provide a unique opportunity for furthering the development of precision medicine in both fields by balancing strengths and weaknesses inherent in each.

The BAG3 (Bcl2-associated athanogene-3) gene provides a prime example. BAG3 is a key mediator of protein quality control, and loss-of-function mutations in BAG3 are associated with the development of dilated cardiomyopathy. Protein quality control is a critical function for the survival of both cardiac and cancer cells; however, the therapeutic goal is to block it in cancer cells and enhance it in the heart. Protein quality control is performed in all cells by 2 complementary mechanisms: the ubiquitn–proteasome system and the aggresome-autophagy pathway involving the BAG3/heat shock protein cochaperone complex. The ubiquitn–proteasome system degrades intracellular proteins, both native and misfolded, in a process that involves polyubiquitination and subsequent degradation by the proteasome.[20] BAG3 is expressed in the heart, the skeletal muscle, and in many cancers and serves as a cochaperone with heat shock proteins to facilitate the selective transport of misfolded proteins and organelles, including damaged mitochondria for eventual degradation.[21] BAG3 also binds Bcl-2, thereby inhibiting apoptosis, sustains nuclear factor κB activity,[22] facilitates excitation–contraction coupling by enhancing the β-adrenergic ability to activate receptors with the L-type Ca^{2+} channel,[23] and protects the heart from ischemia–reperfusion injury.[24] Thus, BAG3 is prosurvival for both cardiac cells and cancers as evidenced by the fact that loss-of-function mutations in BAG3 are now recognized as a major dilated cardiomyopathy locus, whereas overexpression of BAG3 in cancers affords resistance to chemotherapy.[25,26] Functional abnormalities in the proteasome have also been identified in models of HF and in failing human heart; however, a direct relationship between mutations in the core of the proteasome has not been identified.[20]

An interesting juxtaposition of cancer and heart disease is seen in the development of proteasome inhibitors for the treatment of multiple myeloma and other cancers. Bortezomib, the first targeted therapy for multiple myeloma, inhibits the proteasome and in so doing significantly extended the time to disease progression from 16.6 to 24 months with a median duration of response of 19.9 months. However, bortezomib had an interesting off-target effect—it increased levels of BAG3 in tumor cells, thereby increasing drug resistance. The limitations of bortezomib led to the development of the next generation of proteasome inhibitors: carfilzomib. As might be expected, carfilzomib had no effect on BAG3 levels and demonstrated a significantly more robust effect on multiple myeloma when compared with bortezomib in a phase 3, open-label, multicenter trial.[27] Although the methodology for assessing HF in the various treatment groups was somewhat opaque, it is instructive to note that the incidence of grade 3 or greater HF with reduced ejection fraction was 1.3% to 4% with bortezomib but ≈7% with carfilzomib.[28,29]

I would argue that we can implement precision care for patients with HF with reduced ejection fraction by adopting approaches used by our colleagues in cancer. First, we should emulate the aggressiveness with which our colleagues in oncology and related disciplines have pursued an understanding of the genetics that underlie the development of cancer. The development of centralized core facilities with the technical know-how and the informatics support to serve as a regional referral center has clearly helped. These centers perform sample processing, sequence analysis of known mutations, and next-generation sequencing when appropriate and provide a repository for both data and for stored DNA. Second, the National Cancer Institute seeks to establish 1000 centers for precision medicine. While I think that number is not achievable for studying HF because there are far fewer HF centers and

fewer HF doctors, the Heart Failure Society of America should be bold and attempt to create a consortium of centers focused on precision medicine that at the least numbers in the hundreds. The development of these centers will most likely require public–private partnerships, as well as development dollars, because the Heart, Lung, and Blood Institute receives less support than the National Cancer Institute, and National Cancer Institute–designated cancer centers have a political standing in most academic medical centers that exceeds that of the cardiovascular programs. Nonetheless, an approach that is equivalent in boldness to the cancer moon shot would help enormously. A substantial number of these centers should be located in urban areas with populations that are under-represented in clinical trials so that no particular populations are under-represented. In fact, an absence of black participation in genetic studies is a significant health disparity that needs to be addressed.

Third, we should take advantage of novel opportunities to obtain patient samples so that our translational research can be bidirectional—going from the patient to the laboratory rather than the laboratory to the patient. One underappreciated opportunity is to study tissue obtained at the time of left ventricular assist device placement. Left ventricular assist devices are sometimes placed in patients who have had HF for a shorter period of time when compared with hearts removed at the time of transplant, the number of left ventricular assist devices placed each year is increasing significantly, and recent reports point to a small subset of left ventricular assist device patients whose cardiac function improves after placement—the super responders. Finally, there is a pressing need for cardiovascular geneticists and genetics counselors to evaluate and counsel patients with familial disease, and efforts should be put forth to create subspecialty training opportunities and board certification.

The Heart Failure Society of America and the American Heart Association should seize the opportunity afforded by the current interest in precision medicine to promote the value of precision medicine and the importance of genetic testing—much as the National Cancer Institute– designated cancer centers and the American Society for Clinical Oncology has championed the value of precision medicine. Hopefully, a decade from now, we can point to a group of patients with HF in whom we used precision medicine to cure their disease.

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