Leveraging the Success of HIV Drug Development Paradigms for Cancer

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In the 1980s, infection by the human immunodeficiency virus (HIV) was a devastating condition, signifying near-certain lethality; however, people infected by HIV today may have life expectancies typical of the general population (1). A major driver of this progress was the introduction of combination antiretroviral therapy into clinical practice. In contrast, progress for people with cancer has been incremental over the past few decades, although we have recently witnessed improved outcomes in some cancers, owing in part to the development of new therapies. Gains in our fundamental understanding of disease biology, coupled with careful clinical investigations, led to remarkable success in HIV and for certain cancers. Perhaps the development of effective therapies for HIV in the past three decades can provide further insights for continued progress in oncology.

Across the drug development landscape, the focus on oncology has intensified in recent years. Approximately 40% of industry research and development is now devoted to oncology drugs. This intensification began around 2001, with the FDA approval of imatinib, a targeted therapy that transformed the natural history of chronic myeloid leukemia (CML). Since then, drugs targeting oncogenic pathways have improved the treatment of cancers such as melanoma, non–small cell lung cancer (NSCLC), and multiple myeloma. In parallel, unprecedented development of immuno-oncology products have yielded overall survival (OS) advantages in cancers such as melanoma, NSCLC, and kidney cancer. Recently, the FDA approved an antibody inhibiting programmed cell death protein-1 for patients with microsatellite instability (MSI)-high colorectal cancer, for patients with microsatellite instability–high colorectal cancer (MSI-H) colorectal cancer, and for certain cancers. Perhaps the development of effective therapies for HIV in the past three decades can provide further insights for continued progress in oncology.

In oncology, nonsurvival endpoints, such as major molecular response (MMR), durable objective response rate (ORR), and progression-free survival (PFS), are frequently used to assess efficacy. Although MMR is a validated surrogate for CML endpoints in other cancers often lack the same level of established surrogacy. Although demonstration of an improvement in OS remains the gold standard, its use as a primary endpoint has limitations. Because trials examining OS may require large patient numbers, the trend for indications in smaller molecularly defined subsets may require alternative endpoints and trial designs. For example, the FDA approved crizotinib for ROS1-rearranged NSCLC (occurring at a 1% frequency) based on an unprecedented rate of durable response in a small nonrandomized trial (3). Similarly, the FDA recently approved two chimeric antigen receptor T-Cell therapies for patients with certain refractory hematologic cancers based on high rates of durable complete remission, settings where an RCT measuring OS would be infeasible and lack equipoise. In many settings, patients and investigators may demand crossover or refuse to participate in RCTs if early response data indicate substantial improvement over standard therapies, as occurred in EGFR- and ALK-targeted therapy trials in subsets of NSCLC, where interpretation of OS was confounded by crossover. Despite lacking formal surrogacy, measurement of response and progression is used in daily clinical practice to determine whether a patient is deriving benefit and whether to continue therapy, and thus is relevant to patients and oncologists at the point of care.

Another potential lesson from HIV drug development relates to development of combination drug regimens. In HIV, progress was observed after the development of combinations of drugs from different therapeutic classes to circumvent resistance—typically three drugs from two or more classes. The HIV community in the 1980s may have learned this lesson from oncologists, as combination regimens of cytotoxic drugs in the 1970s led to cures for testicular cancer, acute lymphoblastic leukemia, and Hodgkin lymphoma. For other cancer types, combinations of chemotherapy reached a therapeutic plateau with little to no incremental benefit and additive toxicity. In the current era, new classes of targeted and immune-based therapies with fewer overlapping toxicities have renewed interest in combinations. Rather than...
conventional multifactorial RCTs aimed at isolating each drug's contribution to a combination, adaptive trial designs or data external to the RCT may provide sufficient evidence to inform the benefit–risk assessment of combinations (4).

A final potential lesson is the role of engaged, informed, organized, and scientifically driven patient advocacy groups. Motivated by the urgency to discover new therapies, the HIV advocacy community catalyzed greater patient involvement in clinical trial processes including participation in design, endpoint selection, and membership on advisory committees. These advocates argued that trials aimed at demonstrating survival improvements would be at the cost of timely approvals of effective and better-tolerated therapies, leading to unnecessary patient mortality and morbidity. The cancer patient community has frequently championed this message and serves as an active participant in drug development. Recent legislation has called for enhanced patient engagement in drug development, greater transparency in decision-making, and greater public access to trial information (5).

Limitations exist in extrapolating lessons learned from HIV to cancer. HIV has a known etiology providing direction for prevention strategies. The etiological factors for many cancers are multifactorial, and hence, prevention strategies may be less clear. HIV represents a single disease with various clinical manifestations. Cancer represents a spectrum of diseases with diverse etiologies, natural histories, and treatments. HIV-RNA is a validated surrogate, and its effect is captured in the causative pathway of the disease. Intermediate endpoints used in cancer trials, such as ORR and PFS, have not always established surrogacy to OS, but can be clinically meaningful to patients if associated with deep and durable tumor regression, symptom improvements, or delays in administration of more toxic therapies. Furthermore, when multiple active drugs are approved based on improvements in intermediate endpoints such as PFS, survival gains can be observed through observational studies, as occurred in cancers such as CML and multiple myeloma (6, 7).

These two therapeutic areas share the challenges of developing drugs for life-threatening diseases and the risk inherent in balancing timely access to drugs with generating evidence necessary for approval. As life expectancies of patients with HIV have improved to approximate those without the disease, it is natural that patients, physicians, and regulatory agencies would shift from focusing predominantly on efficacy to focusing on more tolerable and less toxic regimens while maintaining efficacy. In contrast, for most patients with advanced cancer, this efficacy benchmark has not been met, necessitating continued acceptance of greater assumption of risk when developing novel therapies, balancing the need to increase chances for cure or long-term control while concurrently attempting to de-escalate and reduce toxicities of therapy when possible.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

References
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