

Disease Interception: Myths, Mountains, and Mole Hills

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Abstract

Malignant diseases develop slowly over time and are often preceded by identifiable premalignancies. As malignancy progresses, so does genomic complexity and the ability of cancers to evade most therapeutic interventions. Accordingly, with some notable exceptions, a relatively low percentage of advanced cancers are effectively treated and even fewer are cured. Despite this appreciation, much less attention has been

paid to intercepting the disease process compared with that of treating well-established and refractory disease. One frequently cited reason is that the pharmaceutical industry is not interested in these pursuits. In this commentary, we attempt to define the true hurdles, the degree of difficulty inherent in each, and some important approaches to be considered. *Cancer Prev Res*; 9(8): 635–7. ©2016 AACR.

Conventional wisdom suggests that industry is not interested in developing products for prevention or disease interception because the hurdles are simply too high. This is despite compelling evidence that as a neoplasm progresses, it gets more difficult to treat due to increased genomic complexity (1), which allows tumors to adapt to and evade therapeutic interventions (Table 1). Budish and colleagues (2) provide an economic explanation for the low investment in prevention research that was highlighted by a front page article in the *New York Times* that trumpeted, "Why Preventing Cancer is Not the Priority in Drug Development" (3).

These perceived hurdles include myths, mountains, and molehills, such as: (i) the drugs will be used chronically and therefore must be impossibly safe (myth); (ii) the clinical trials are too long and too expensive (molehill); (iii) the regulatory agencies will make it difficult to gain approval (molehill); (iv) the market is large, but the prices will be low and therefore difficult to make a profit (myth) and; (v) diagnostics are not sufficiently sensitive or specific to identify those individuals who are at the greatest risk of progressing to disease versus those who will never have significant disease (mountain).

As is often the case, conventional wisdom is only partially true and overly simplistic. In addition, the seductive simplicity of this nihilistic view is damaging to disease interception efforts that could lead to transformative medical developments. It is only by exploring the complexity of this issue that a path forward emerges. So although there are hurdles, each one needs to be understood. Some perceived obstacles are myths that we need to debunk. Others are molehills that we need to walk over. Finally, some are mountains that we need to climb. It is only by knowing the

difference between the myths, mole hills, and mountains that we can uncover the path forward.

Chronic use/impossibly safe

Several prevention drugs are used daily for long periods of time, including statins for treatment of hypercholesterolemia and prevention of atherosclerotic vascular disease, selective estrogen receptor modulators (SERMs) such as tamoxifen and raloxifene for prevention of breast cancer, and bisphosphonates for the prevention of osteoporotic fractures. All have untoward side effects, including muscle disorders for statins, thrombosis and uterine cancer for SERMs, and jaw necrosis for the bisphosphonates. In contrast, other products do not require daily use, such as the hepatitis B and human papillomavirus vaccines for the prevention of viral infections that lead to hepatocellular carcinoma and cervical, respectively. Although many current treatments of serious diseases require systemic and chronic use, novel approaches and technologies are being developed to prevent disease using short-term, intermittent, localized, or low-dose therapy (4). Nonetheless, safety is always critically important, and we recognize that in many instances, this is amplified when drugs must be used chronically.

Studies are long and expensive

This oversimplification is based on the concept that surrogate endpoints cannot be validated for use for regulatory approval or ultimately for reimbursement. Yet, the original approval for the statins was based on a biomarker that was initially unproven to be a surrogate for prevention of cardiovascular mortality (5). Recently, approvals were granted by the FDA for two proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitors (alirocumab and evolocumab), based on lowering of low-density lipoprotein (LDL) cholesterol in patients at high risk for heart attack or stroke and who were receiving MTDs of a statin. For alicumab alone, the sponsor was willing to conduct five placebo-controlled randomized trials involving 2,476 participants. Both alicumab and evolocumab, which are given by injection, cause large reductions in LDL cholesterol levels, as compared with placebo (39%–62% reduction for alicumab and 47%–56% for evolocumab). These

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doi: 10.1158/1940-6207.CAPR-16-0049

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Table 1. Cancer interception manifesto

Cancers develop over many years, often decades
A cancer diagnosis is preceded by premalignancy
Cancers become more complex over time
Complexity makes cancers more adaptable
Adaptable cancers are harder to eradicate
Early disease is less complex and therefore less adaptable
Treating cancer and premalignancy earlier leads to better outcomes for patients

NOTE: From P. Lebowitz. The Economist "War on Cancer" Conference, London, 2015.

drugs received standard approval without completion of ongoing studies that are designed to demonstrate clinical benefit beyond lowering the surrogate marker.

However, although the use of surrogate endpoints to predict clinical benefit is important in advancing prevention, this approach comes with caveats, that is, sometimes surrogate endpoints do not perform as expected even when there is a strong scientific rationale. One example is the use of class I antiarrhythmics in the setting of postmyocardial infarction. These agents decrease aberrant ventricular activity (a surrogate for serious arrhythmias), but this practice ultimately was found to cause an increase in mortality (6). The key learning here is not to abandon surrogate endpoints. This would ignore the successes of new therapies that have been provided to patients many years earlier using surrogate endpoints, such as cholesterol, blood pressure, blood glucose, and tumor response. When one considers these examples, it is likely that far more people have benefited from acceleration of new therapeutics with the use of surrogate endpoints than those that have been harmed. However, the use of surrogate endpoints requires a thoughtful assessment of their ability to predict the magnitude of clinical benefit. This, however, should not be interpreted as an impossible hurdle to overcome. For example, after the first HMG-CoA reductase inhibitor, compactin, entered the clinic, studies were discontinued because of severe animal toxicities (the true cause remains uncertain). Merck then promptly stopped its studies of lovastatin (Mevacor), a structurally similar natural product, and carried out additional animal studies and clinical studies in ultra-high risk patients. Ultimately, the drugs were proven to be well tolerated, and the statin era was begun.

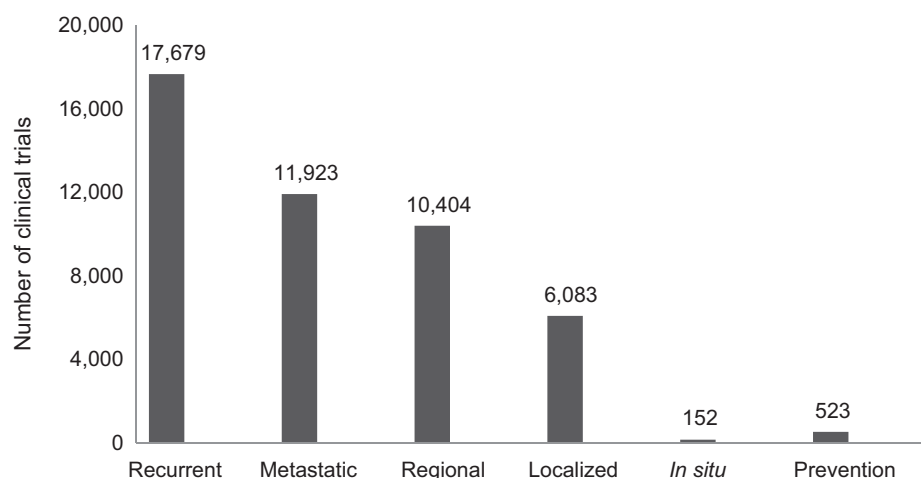


Figure 1. The number of clinical trials conducted between 1973 and 2011 in decreasing order of 5-year overall survival. Adapted with permission from Budish and colleagues, 2015 (2).

Regulatory agencies

As noted above, regulators have precedent for approving drugs based on surrogate endpoints. This is particularly true for oncology indications, where response rate and progression endpoints have often been used for approval. Agencies are far more open to creative discussions than some might believe and can offer constructive ideas to help industry meet an important unmet medical need.

Profitability

Lipitor, a disease interception product, has been one of the most lucrative drugs in history. In fact, during its patent life, Lipitor sales topped \$130 billion, which is double that of the number two drug, clopidogrel (Plavix), which is also indicated to prevent complications of atherosclerotic cardiovascular disease (7). Yet, many overlook this fact when considering the future of disease interception. Similarly, alendronate (Fosamax), a bisphosphonate approved for both the treatment and prevention of osteoporosis, produced peak sales of over \$3 billion: "Although the number of patients at risk for a specific malignancy would be much smaller than the population at risk for atherosclerotic vascular disease or osteoporosis, this smaller patient population may allow for a somewhat higher price if there was an overall health economics benefit from intercepting a cancer-causing process."

Some Real Problems (Mountains)

In our experience, there are real problems that must be overcome.

Lack of validated targets

A major problem to be overcome for the development of prevention and interception drugs in noncommunicable disease is the lack of validated targets. Here again, cancer represents one of the most compelling areas for investigations, as for most malignancies, there is a well-defined premalignant condition for both solid and even hematologic diseases. For example, *in situ* carcinomas, also referred to as intraepithelial malignancies, are histologically identifiable. In addition, the transition from a normal but susceptible epithelium to colon cancer has been elegantly

described (8). Yet, limited information currently exists on the altered genome of high-risk colonic polyps. Similarly, premalignant conditions of the oral epithelium and bronchi are well described (e.g., leukoplakia and atypical adenomatous hyperplasia, respectively), yet far less information exists as to the potentially actionable targets for these entities (9). Myeloma is preceded by a progression from polyclonal production of plasma cells to monoclonal proliferations that begin with a monoclonal gammopathy of undetermined significance, through smoldering myeloma, which is then further stratified according to risk. Again, the actionable targets in these conditions are far less clear than even the relatively little we know for the full-blown malignancy, multiple myeloma.

Existence of validated surrogate endpoints

If survival is the only endpoint, then conventional wisdom would hold as these trials could be very long, expensive, and difficult to conduct effectively, as the results would be confounded by the variety of treatments that patients would receive following progression. For example, assume that smoldering myeloma was treated with a new drug versus a standard-of-care regimen and after 2 years, there was a marked decrease in progression to multiple myeloma for the experimental treatment. Upon relapse in both groups, patients would be treated with several different types of therapy that could not be legitimately proscribed at the start of the smoldering myeloma study. If these drugs were effective, then the benefit from treating the premalignancy might be confounded.

Diagnostic tests

Today, there are a limited number of diagnostic tests that can identify those individuals with premalignancies who are most likely to progress (10). This concept fails to take into account how much things have and will change. For example, before the roentgenogram was invented, lung cancer was often a postmortem diagnosis. With the advent of the chest X-ray, more people were diagnosed while still alive and potentially operable. With high-resolution CT and PET scanning, the disease and even the premalignancies are now diagnosed. In addition, we can now classify carcinoma *in situ* of the breast histologically according to risk, and data are emerging using transcriptomics that can further

stratify patient risk of progression to invasive disease. Similar work is ongoing in prostate cancer, colon cancer, and many others. One can readily envision a time in the near future where those individuals at the highest risk of disease progression will be readily identified and targeted for more precise treatments. At the same time, those at low risk will be spared unnecessary interventions.

The Path Forward

If the cause of the problem is that we do not have validated targets, surrogate endpoints, or accurate diagnostic tests, then the solutions must address these with a greater sense of rigor and urgency than in the past.

Why is there no sense of urgency? As a statistics colleague, Weichung "Joe" Shi, once said, "the problem with prevention is that nothing happens." In contrast, the success of statins is based on "something happening," that is, a decrease in serum cholesterol. Similarly, dual-energy X-ray absorptiometry, commonly known as the DEXA scan, allowed people to measure their risk of developing osteoporotic fractures based on degree of bone loss and to select patients most likely to benefit from bisphosphonates, which are by no means perfectly safe. Similar pharmacodynamic endpoints for cancer interception, such as decreases in the quantity of a monoclonal immunoglobulin in smoldering myeloma, therefore, would be highly desirable.

Finally, with the mounting costs of health care becoming problematic even in the wealthiest countries, it is our responsibility to make the health care economic case for preventing, intercepting, and curing disease, rather than managing chronic disease for a lifetime.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

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Writing, review, and/or revision of the manuscript: W.N. Hait, P.F. Lebowitz

Received February 15, 2016; revised March 31, 2016; accepted April 14, 2016; published OnlineFirst May 2, 2016.

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