

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

Section Editor: Mark J. Ratain, MD

Generic Sirolimus: A Future Opportunity to Decrease the Cost of Oncology Care?



Laurence H. Baker, DO
 Collegiate Professor, Cancer Developmental Therapeutics
 Professor, Internal Medicine and Pharmacology
 University of Michigan School of Medicine
 Ann Arbor, Michigan
 Chair, SWOG

H&O What are some of the current major challenges regarding access to oncology drugs?

LB One major challenge is that there are not enough effective drugs. There are a lot of expensive drugs that are of very marginal benefit. There are current discussions of advances in this arena, and the US Food and Drug Administration (FDA) is proud of its list of approved cancer drugs. However, most oncologists and patients find these treatments to be of more modest benefit than hoped. Thus, we need better drugs.

H&O What are the underlying causes of these challenges?

LB One issue that needs to be addressed is our tendency to use buzzwords. Many want to describe drugs as being antiangiogenic, irrespective of whether or not these drugs act through an angiogenic mechanism to produce benefit. Why? It is a marketing term that sounds good. In talking about so-called personalized medicine, what is really meant by that is biomarker-driven medicine and rational decision-making. Some type of test is performed and the results guide decisions regarding treatment with a particular drug. This is not personalized. I aim to practice personalized medicine. I sit with a patient, get to know who they are, what their environment is, and what kind of access to resources they have before I make a treatment plan.

Another problematic phrase is to say that a drug is reasonably well tolerated. I often make the joke that “reasonably well tolerated” means I would not give this treatment to a dog, because we downplay the side effects of

the drug. The immediate side effects of a drug are reported very quickly, but the adverse events that evolve over time often go unrecognized due to decreased vigilance. That leads to published data claiming that the drug is reasonably well tolerated. An example of this includes several of the tyrosine-kinase inhibitors, where there is a significant degree of hypertension and heart failure. However, these drugs are often described in initial publications as reasonably well tolerated. Such buzzwords and incorrect labels are hindering progress. In reality, every new idea is not a paradigm shift, nor is every new drug a novel agent.

In our preclinical experiments, we often do not have the right controls, and so we identify wonderful new things that are, in fact, incorrect. There is a great deal of pressure on university faculty to get grants, which means to have publications, which means to slant the data because journals want positive information to produce in order to attract readers and advertisers. These somewhat cyclical events are preventing further progress in this field.

H&O Can you provide an overview of the history of rapamycin?

LB Rapamycin is a mammalian target of rapamycin (mTOR) inhibitor that was identified in the 1970s. Rapamycin was being investigated as a new antibiotic, but it was found to have immunosuppressive properties. It was ultimately approved for the prevention of allograft rejection in recipients of organ transplants. Preclinical and early clinical studies showed that rapamycin alone and in combination inhibited tumor cell proliferation, suppressed tumor angiogenesis, and induced apoptosis

of some cancer cells. However, as the patent on rapamycin was about to expire and extensions were being reviewed, it was no longer financially feasible to continue its development as a cancer therapeutic. As such, other mTOR inhibitors emerged.

H&O Why has interest in the development of rapamycin resurfaced?

LB As other mTOR inhibitors continue to be investigated in a variety of areas and in different combinations, it is evident that they have more similarities than differences. Importantly, they all act on the signaling pathways in cancer in the same way as rapamycin. Because these mTOR inhibitors have demonstrated activity in certain cancers, there has been a renewed interest in developing rapamycin, the generic predecessor of agents in this class.

H&O What are some examples of the potential use of sirolimus?

LB Perivascular epithelioid cell tumors (PEComas) represent a family of mesenchymal neoplasms, which are mechanistically linked through activation of the mTOR signaling pathway. Sirolimus has demonstrated activity in patients with PEComas.

H&O What impact might sirolimus have on the rising costs of cancer treatment?

LB At doses currently utilized, it would cost approximately \$1,000 per month to treat a patient, but the cost could decrease dramatically when the patent for rapamycin (US patent number 5,100,899) expires in 2013. It does not make financial sense for the current manufacturer to develop rapamycin for cancer therapy, given the looming patent expiration and amount of time required to garner approval for an oncology indication, especially when the patent for rapamycin in malignant disease has already expired. A lack of patent protection means that there is little commercial incentive for the private sector to develop this agent. However, in comparing the price of conducting clinical trials against escalating non-generic drug costs, it is clear that substantial long-term savings could be generated by public or philanthropic intervention.

H&O What are the biggest remaining challenges?

LB One remaining issue is the interruption in the supply of generic drugs. This was a major problem last

year where, sporadically, drugs were not available for cancer patients. Shortly before the presidential election, however, this concern was largely improved. The FDA started allowing shipments of drugs from India and Australia to fill the gap. The White House issued an Executive Order that directed the FDA to expand its authority to police drug shortages. This included requiring all manufacturers to notify the FDA of impending shortages and having the FDA report any violations of the government's price controls on generic drugs. The FDA's Early Notification Program of potential disruptions in drug supply has made a difference.

However, costs remain high for cancer drugs. Middle-class Americans struggle to afford treatment. Many physicians know that their patients are often faced with making the decision to eat or continue treatment. This is a horrible situation, and it needs to be further addressed in a national way. The pharmaceutical industry is very important to our society as an economic engine, and like most important components to our society, it is well represented by lobbyists. Aside from politics, there is no reason why the United States cannot purchase these drugs as a single purchaser. Some have tried to call attention to this problem, but there have not been any consistent answers as of yet.

Perhaps the Affordable Care Act will actually lead to serious solutions to serious problems. I certainly hope so. In his second inaugural address, President Obama talked about our need to make tough choices when it comes to health care. If we start to eliminate the waste and the gouging of prices with these oncology drugs, we will be left with much clearer choices. There will still be hard decisions to be made, but whether or not we have the resolve as a society to address that remains to be seen.

Suggested Readings

Cohen EE, Wu K, Hartford C, et al. Phase I studies of sirolimus alone or in combination with pharmacokinetic modulators in advanced cancer patients. *Clin Cancer Res.* 2012;18:4785-4793.

Wagner AJ, Malinowska-Kolodziej I, Morgan JA, et al. Clinical activity of mTOR inhibition with sirolimus in malignant perivascular epithelioid cell tumors: targeting the pathogenic activation of mTORC1 in tumors. *J Clin Oncol.* 2010;28:835-840.

Bhattacharyya GS, Biswas J, Singh JK, et al. Reversal of tamoxifen resistance (hormone resistance) by addition of sirolimus (mTOR inhibitor) in metastatic breast cancer. *Eur J Cancer.* 2011;47:9.

The American Society of Clinical Oncology Response to U.S. Supreme Court Ruling on Healthcare Reform Law. ASCO in Action Website. <http://ascoaction.asco.org/Home/tabid/41/ArticleType/ArticleView/articleId/313/ASCO-Response-to-US-Supreme-Court-Ruling-on-Healthcare-Reform-Law.aspx>. Published June 28, 2012. Accessed January 23, 2013.