Timing is money

For lower drug prices, something better than outrage

By Anette Breindl, Senior Science Editor

Cutting pills in half is currently an act of desperation by those who can’t afford the full amount their doctor has prescribed.

But for some of the most expensive drugs on the market – cancer drugs – there are a number of drugs where cutting the dose by half, or by more, can result in treatment that is just as effective, and cuts financial toxicity and, possibly, other toxicity risks as well.

An opinion piece in the June 20, 2019, issue of *JAMA Oncology* coins a new term, interventional pharmacoeconomics, and describes “strategies and challenges for interventional pharmacoeconomics to reduce prescribing costs while maintaining efficacy.”

In their *JAMA Oncology* opinion piece, authors Mark Ratain, Daniel Goldstein and Alan Lichter described four strategies that could reduce drug costs at no loss of efficacy.

The first was lowering doses outright in cases where the response to the drug does not change over a large range of doses. An example is Imbruvica (ibrutinib, Pharmacyclics LLC/Janssen Biotech Inc.) whose maximum clinical effect occurs well below its approved dose of 420 mg, and which frequently needs to be taken at reduced doses due to toxicity issues. Pilot studies indicate that the dose could possibly be reduced by two-thirds, to 140 mg a day – a simple fix, if larger studies confirm, as the drug comes in 140-mg tablets.

In a 2018 study, Ratain, who is a professor of medicine at the University of Chicago, and his colleagues had demonstrated that one-quarter of Zytiga (abiraterone, Johnson & Johnson) was as effective as the full dose at reducing PSA levels in men with metastatic prostate cancer if the drug was taken with food instead of on an empty stomach, which is what the label prescribes. (See *BioWorld*, April 9, 2018.)

Another possibility for drugs whose doses cannot be as easily reduced is to take them less frequently. In an abstract at this year’s annual meeting of the American Society of Clinical Oncology (ASCO), Ratain and Goldstein reported that modeling studies indicate Opdivo (nivolumab, Bristol-Myers Squibb Co.) could likely be given at a dose of 420 mg every 12 weeks, and “certainly,” Ratain said, every eight, rather than the every four weeks in current clinical practice.

Furthermore, the authors wrote in their ASCO abstract, “as responding patients generally have a 35-45% decrease in clearance over the first 6 months of treatment, even less frequent dosing may be required for subsequent doses.” They also noted that “similar opportunities may exist for other checkpoint inhibitors.”

A third possibility is decreasing treatment duration, including halting treatment after a defined period rather than treating indefinitely, a strategy whose success was reported for the combination of Venetoclax (venetoclax, Abbvie Inc./Roche Holding AG) and Gazyva (obinutuzumab, Roche Holding AG) in first-line treatment of chronic lymphocytic leukemia at the 24th Congress of the European Society of Hematology last week. (See *BioWorld*, June 18, 2019.)

Therapeutic substitution rounds out the possibilities described by the trio.

‘No penalty for being too high’

Getting drugs approved at higher doses than necessary is a strategy that has come about with the rise of targeted therapies, whose toxicities are mild enough to make the approach feasible.

Too-high doses are one side effect of applying market principles, however halfheartedly, to drug development. Both the finite life span of patents and competition between companies result in a system that rewards development speed more than it penalizes doses that are too high.

“Unless you are very smart in how you do your phase I, you are probably adding a year to your development” if the goal is to find the lowest possible effective dose, Ratain told *BioWorld*.

“Companies are going as fast as they can, and they don’t really care about getting the dose right.”

Higher doses still mean, in all likelihood, worse toxicities. But
in oncology, such toxicities are assumed to come with the territory by doctors, patients and regulators alike.

Goldstein, who is senior physician in medical oncology at Rabin Medical Center noted that currently, “from the company perspective it makes sense – they don’t want to miss, and there is no penalty for being too high.”

From the financial side, Goldstein told BioWorld that “it’s never been worth it to go after it until the prices have gotten so wacky.”

In oncology, drug costs have doubled in recent years and now account for half of all heath care costs, as opposed to 20% of health care costs over all indications.

Under those circumstances, “the message to pharma is [that] if you don’t bother to optimize your dose, your drug is going to be subject to interventional pharmacoeconomic strategies to reduce revenue,” Ratain said.

Ratain acknowledged that because the cost of manufacturing, at least for small molecules, is a trivial contributor to their price, interventional pharmacoeconomics would come to a screeching halt if companies took the time for precise dose-finding during clinical development, and said he would welcome such a development.

But with incentives aligned as they are, he predicted that the current state of affairs with respect to dose-finding “will continue for many years.”