COMMENTARY

THE AMERICAN JOURNAL of MEDICINE®

The Tradeoff of Cancer Drug Regulatory Policy: Faster Approvals for One Means Less Knowledge for Another

The popular narrative surrounding cancer drugs or other therapies for rare diseases is that patients are willing to assume more risk and uncertainty to gain rapid access to investigational agents. This is, in part, the impetus behind the frequent use of surrogate endpoints by the US Food and Drug Administration (FDA)[1] and European Medicines Agency,[2] as well as the right-to-try legislation.[3] This US law permits patients with terminally ill conditions to receive experimental therapies without the approval of the FDA.

The narrative that cancer drug regulations impose an obstacle on patients was echoed by President Trump, who said, "Our slow and burdensome approval process at the FDA keeps too many advances … from reaching those in need."[4] Here, from the perspective of a medical resident (DLT), a long-time caregiver for family members with cancer (SS), and a practicing hematologist-oncologist (VP), we wish to argue that the current narrative is incomplete. Too often, patients are portrayed as seeking access to untested drugs while regulators insist on careful clinical trials. Instead, we believe the true narrative is that some patients are tolerant of risk and desire fewer regulatory standards, but other patients actually desire increased knowledge regarding their care. In the current system, patients seeking more data to inform their choices are routinely deprived because incentives to generate more data after approval are essentially absent. We begin with the experiences of SS. Over the years, SS has cared for several family members with medical conditions, several with cancer. This is the story of her brother, in SS's words:

> At age 40, my brother was diagnosed with stage IV peripheral T-cell lymphoma, a relatively rare disease. He'd been ill for a year and I'd already turned into a research fiend. PubMed was my new best friend. I read and printed out what became hundreds of pages. The kind oncologist we traveled to see reflexively prescribed 4 rounds of CHOP, a standard chemo that he called a "gold standard." Treatment was discontinued after round 3 owing to progression. The next combination therapy went similarly. The third showed some regression.
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> Trying to evaluate the then-new lymphoma treatments such as gemcitabine, pentostatin, and Bexxar seemed like throwing darts at a dartboard in the dark. Where were the randomized data and trials? Where were they for CHOP? Have things improved? Considering recent drug approvals in peripheral T-cell lymphoma, including romidepsin, pralatrexate, and belinostat, it wouldn't seem so. All are approved based on uncontrolled data. One thing that has improved from that time to this is a better appreciation and articulation of adverse effects.
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> Fourteen months after his original diagnosis, my brother underwent allogeneic donor bone marrow transplantation, a dangerous treatment whose results nonetheless seemed to hold a better survival prospect than available drug regimens. No one wants this treatment if they have any better option. Partially and poorly tested treatments were not a preferable option. For my brother and me, we wanted more information not just more choices.

In VP's clinic, conversations often center on whether a patient with cancer wishes to attempt a therapy that has only been proven to improve progression-free survival, and overall survival or quality-of-life effects are unknown. In VP's words:

Funding: None.

Conflict of Interest: VP receives royalties from his book, *Ending Medical Reversal*. His work is funded by the Laura and John Arnold Foundation; he has received honoraria for Grand Rounds/lectures from several universities, medical centers, and professional societies; and he is a writer for Medscape.

Authorship: All authors had access to the data and a role in writing this manuscript.

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https://doi.org/10.1016/j.amjmed.2018.08.017

> I often explain at length that progression means the time until new tumors grow or existing tumors increase in measurement more than 20% their smallest size. If a tumor increases 19%, that isn't progression, but 21% is. So, it is arbitrary. Feeling bad from cancer and the 20% cut-off don't always go hand in hand. After I explain the evidence base, risks, benefits, and alternatives, patients sometimes throw up their hands: "Why can't you just tell me if this drug will make me live longer or feel better?"

As a resident, DT has seen how frequently prescribing a new medication can be accompanied by optimistic discussions focused on improvement. In DT's words:

> When faced with an ill patient, the treatment team wants to focus on the promising aspects of the novel treatment. It requires great discipline to balance that optimism with consideration for the gamut of possible adverse reactions. During my first intensive care unit experience, it was eye opening to realize the severity and frequency of serious treatment complications and how life-threatening additional side-effects can be for these critically ill patients. The risk of trying an unproven drug cannot be taken lightly.

The current regulatory system fosters uncertainty regarding already available compounds in several ways. First, estimates of FDA drug approvals show that two-thirds of cancer drugs are approved with surrogate endpoints,[5] such as progression-free survival or response rate—in other words, data that are often easier to obtain but not reflective of patient survival or quality of life. The situation with the European Medicines Agency is similar.[2]

Rhetoric by regulators suggests that tolerance of uncertainty is growing. Dr. Scott Gottlieb, FDA commissioner, has also been vocal against FDA restrictions. In a 2012 *National Affairs* paper, Gottlieb wrote that the FDA has an "unreasonable hunger for statistical certainty" and displays a "profound lack of confidence in the ability of doctors to make careful judgments."[6] These comments concern us.

Second, although the regulatory system respects the wishes of those willing to take on more risk, it fails patients preferring more information. The expectation is that the poorly studied drugs continue to be evaluated after they have become available on the market; the reality is that post-market clinical evidence is lacking in quality and quantity. There are few double-blind studies, the highest quality of clinical evidence, and post-approval studies required by the FDA are often not done at all.[7]

One analysis found that 86% (31/36) of drugs approved based on data with surrogate markers failed to show benefit of survival even after an average of 4 years.[5] Over one-third (35%) of drugs approved based on limited evidence (single trial or trials with surrogates) had no controlled studies investigating efficacy even after 5.5 years.[8] In an analysis of 614 post-approval requirements set by the FDA, 20% of required studies were not started and 25% were delayed or ongoing 5 to 6 years later.[9]

When the studies meant to validate the clinical benefit of these drugs are not being published or even performed, patients and their physicians are left wanting. Additionally, drugs receiving accelerated approval are more than twice as likely to have a serious safety risk that is only discovered after their release to the public.[10]

CONCLUSION

We believe the narrative around cancer drugs is incomplete. It is not a case of patients who crave risk facing off with regulators who abhor it; instead, all of us have known people on either end of the spectrum. One can imagine a regulatory system that honors the desires of all patients. It would make drugs rapidly available for dire conditions with few options based on provisional data but would have a firm commitment to generate post-market data for patients seeking more information. The current system has shifted to make more and more drugs available but has failed patients wanting more informed decisions. Reliable data are inconsistently generated, and patients who want drugs proven to prolong or improve quality of life are routinely disappointed or left wondering.

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