ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Lessons Learned From the Accelerated Approval of Cancer Drugs

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H&O What are the principles behind the accelerated approval pathway?

BG The US Food and Drug Administration (FDA) introduced the accelerated approval pathway in the 1990s during the HIV/AIDS epidemic. The premise was that a life-saving treatment should not be kept from patients while it undergoes evaluation for FDA approval, which takes a substantial amount of time. Instead, drugs could be approved relatively quickly based on surrogate endpoints. After a drug receives accelerated approval, another trial would be performed to confirm the benefits to clinical endpoints. If the confirmatory trial shows clinical benefit, then the drug would receive full approval. If clinical benefit is not confirmed, then the approval would be withdrawn.

Although the accelerated approval program started in the context of the HIV/AIDS epidemic, 74% of drugs currently in the pathway are treatments for cancer.[1] The premise behind accelerated approval remains the same for cancer drugs.

H&O Is accelerated approval of cancer drugs more common than it used to be?

BG Accelerated approval is becoming more common, especially for cancer drugs. In a study published in 2019, my colleagues and I found that the percentage of cancer drugs that received accelerated approval increased every year from 2014 until 2017, when accelerated approval constituted 40% of all cancer drug approvals.[2] It is the FDA that ultimately decides whether a drug receives accelerated approval vs full approval. The FDA appears to be more lenient with accelerated approval in the cancer space, where proving that a drug improves overall survival can take time. On average, the use of surrogate endpoints brings a new drug to market 11 to 19 months earlier than using the survival endpoint.[3]

H&O What are the criteria needed to consider a drug for accelerated approval, and how are they applied?

BG According to the FDA, the basis for accelerated approval is that a drug improves a surrogate endpoint that is reasonably likely to predict clinical outcomes and also addresses an unmet need. In the past, the FDA was more stringent with this definition. "Reasonably likely to improve clinical outcomes" was interpreted to mean that the drug improves a validated surrogate endpoint that correlates with a clinical endpoint. More recently, however, the FDA has granted accelerated approval based on unvalidated surrogates, such as overall response rate, from small studies of approximately 30 to 50 patients. Studies have shown that most surrogate endpoints correlate poorly with clinical endpoints. The standard has been dropping, and the criteria are uncertain. There are also cases in which similar data have led to accelerated approval for certain drugs and full approval for others.

The definition of unmet need is also variable. According to the regulatory language, the disease setting should lack an established treatment. In practice, however, the FDA has granted accelerated approval to a drug even when there are other options in the same space.

With this lowering of the bar, it is easier for cancer drugs to apply under the accelerated approval pathway than to apply for full approval, which would require a study that shows an improvement in overall survival. (In recent years, however, the FDA has been granting even regular approval based on improvement in unvalidated surrogate endpoints.) Accelerated approval has become a way to bring marginal drugs to market.

When a drug receives accelerated approval, the manufacturer has several years to conduct a confirmatory trial to show an improvement in clinical outcome. In some cases, confirmatory trials are not completed in a timely manner.[4] Some drugs have remained on the market for more than 5 years without data from confirmatory trials. During the time between accelerated approval and completion of the confirmatory trial, the company has several years to sell the drug. If the confirmatory trial fails and the drug is withdrawn from the market, the company still could have made millions of dollars in profits.

H&O How often do drugs with accelerated approval fail to show benefit in confirmatory trials?

BG My colleagues and I conducted a literature review to assess the clinical benefit of cancer drugs receiving accelerated approval. We identified 93 drugs that received accelerated approval from 1992 through 2017.[5] We found that 20% of the drugs that received accelerated approval went on to improve overall survival in a confirmatory clinical trial. A surprising finding was that for 20% of the drugs that received an accelerated approval, the confirmatory trials used surrogate measures that were the same as those used in the preapproval trials. This finding is strange because the accelerated approval is based on a surrogate for clinical improvement, which presumably was not a clinical endpoint suitable for full approval. In another 21% of drugs with accelerated approval, the confirmatory trial showed improvement in a different endpoint from the one used in the preapproval trials. In 5% of cases, the approval was withdrawn based on results from the confirmatory trial. Postapproval evaluations were ongoing for 40% of the drugs.

H&O What happens when confirmatory studies fail to meet the outcomes that led to accelerated approval?

BG Per the statute of accelerated approval, if the confirmatory trial fails, the drug must be withdrawn. However, we have seen that the withdrawal of the drug is not automatic. The FDA convenes a committee of experts to discuss whether the accelerated approval should be withdrawn. The term "dangling accelerated approval" refers to drugs that failed to show clinical benefit in confirmatory trials but remain on the market. It is rare for the FDA to revoke approval.

My colleagues and I performed a study that focused on drugs that did not meet the primary endpoint of the confirmatory trial.[6] We were expecting that all of these drugs would be withdrawn. Instead, we found that several of the drugs remained in the market under a dangling accelerated approval. A few drugs were withdrawn voluntarily by the manufacturer (most likely based on guidance from the FDA). The FDA revoked approval of only 1 drug.

A few drugs received full approval despite failing to show clinical benefit in the confirmatory trial. An example is bevacizumab in glioblastoma. The primary endpoint of the confirmatory trial was overall survival. The study showed that bevacizumab did not improve survival or health-related quality of life.[7] It delayed progression by a few weeks. Other drugs in this category included immunotherapy agents, which reflects a bias in oncology that most patients should receive some type of immunotherapy. Immunotherapy drugs can cost $15,000 a month. For a drug that does not improve clinical outcomes to remain on the market with such a high price tag is a societal failing.

Another disadvantage to the accelerated approval program concerns the large amounts of money spent by the government, the health care system, and patients on treatments that ultimately show no benefit in confirmatory trials. The cost of a cancer drug does not reflect whether it has full approval or accelerated approval.

H&O Do accelerated approvals from the FDA have implications for the treatment of patients worldwide?

BG Discussions about the FDA often focus on the US health care system. However, there are global repercussions, particularly in low- and middle-income countries, that are sometimes ignored. My colleagues and I recently published an article on how drugs with accelerated approval are incorporated into management in India.[8] The manufacturer can promote the accelerated approval of a drug in other countries. Oncologists in other countries might then start using the drug, without appreciating the nuances between accelerated approval and full approval and because they do not want to deprive their patients of a potential treatment option available for clinical use in the United States.

Our research found that in several cases, a drug that was withdrawn from the US market was still promoted in other countries. The manufacturer informed the other countries that the withdrawal was limited to the United States, and encouraged oncologists in low- and middle-income countries to continue use of the drug.

The FDA appears to be more lenient with accelerated approval in the cancer space, where proving that a drug improves overall survival can take time.

H&O Are there any notable successes associated with accelerated approval?

BG A successful example would be the immunotherapy drugs in melanoma and lung cancer that were initially approved under the accelerated approval pathway. Pembrolizumab (Keytruda, Merck) received accelerated approval for lung cancer, and this drug has substantially improved outcomes.

H&O What are some ways that the accelerated approval process can be improved?

BG I like the accelerated approval pathway in theory. Ideally, this process allows rapid approval of a drug with promising clinical benefit to fill an unmet need. The drug is withdrawn if a confirmatory trial is not completed in time or fails to confirm benefit. The accelerated approval program provides a good balance between allowing early access to a drug and confirming safety and efficacy in the future.

There are a few ways to improve the process, which we have highlighted in detail in previous articles.[9,10] First, the FDA should clearly define which surrogate endpoints are good enough for accelerated approval and which clinical endpoints are needed for full approval. Second, when a drug receives accelerated approval, the confirmatory trial should already be underway. Without that mandate, the company can take several years to complete a confirmatory trial. Third, if the confirmatory trial is not completed in time, there should be some penalties for the company. Fourth, when the confirmatory trial fails to show clinical benefit, the withdrawal should be automatic and immediate. Cost is not within the purview of the FDA, but another point is that drugs that receive accelerated approval should be less expensive than those that receive full approval. Medicare can make this adjustment.

H&O Are there any other ways to bring new treatments to patients as quickly as possible?

BG Accelerated approval is one of the best pathways. The only problem is the implementation. If the accelerated approval pathway is implemented according to what the legislation says and improved based on these recommendations, it could work as a great system. A new accelerated approval pathway is not needed; the existing one should be refined.

Disclosure

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