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Regulatory issues in the evaluation of antimetastatic and other novel anticancer therapies

Abstract This article outlines some of the complexities and challenges confronting researchers and the US Food and Drug Administration (FDA) in the area of evaluation of antimetastatic and other novel anticancer therapies. The scientific regulatory matrix utilized by the FDA is outlined. Subsequently, the complications encountered when designing and interpreting studies of antimetastatic drugs are described, and finally changes in the regulatory landscape both within the USA and internationally are considered.

Key words Antimetastatic drugs · US Food and Drug Administration · Clinical trials · Regulation

Introduction

This article is intended not so much to define how the US Food and Drug Administration (FDA) reviews new antimetastasic agents but rather to outline some complexities and challenges we jointly confront. The primary problem is that because our understanding of cancer cell biology is limited, albeit improving rapidly, our ability to identify clinically effective agents is also limited. This is a fascinating area but is outside the purview of this article. First, to provide an understanding of how drug development programs in the USA are structured, the scientific regulatory matrix utilized by the FDA is described. Then, the complications of designing and interpreting studies of antimetastatic drugs are considered, and finally how the regulatory landscape is changing both within the USA and internationally is outlined.

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Drug development

Drug development in the USA begins with the discovery of a novel molecule by the sponsor, usually a pharmaceutical company. In the preclinical stages, the sponsor performs the studies necessary to characterize the molecule and conducts the animal studies necessary to estimate its activity and side effects.

To bring the new product to clinical use, certain characteristics need to be defined. This characterization requires that as the new drug is developed, the sponsor must perform a series of studies:

1) in vitro studies to identify the drug's activity and toxicity and provide clues to any potential novel toxicity it may have;
2) studies in animals to expand the understanding of the drug's biological activity (ideally in an appropriate animal model) and also to describe the drug's toxicity an intact organism; and
3) the sponsor must also gather preliminary information that describes the composition, manufacture, and control of the drug.

Before the sponsor initiates clinical testing of the drug in humans, it must first receive permission from the FDA. The application must include a protocol for the proposed clinical study, provide adequate information about the properties and toxicities of the drug based on the laboratory and animal studies in the preclinical phase, and describe the chemical's composition and how it is manufactured.

Once the FDA is satisfied that the compound is sufficiently safe to test in humans, its development generally

proceeds through a series of clinical studies. The first step is a phase I trial, which is primarily (but not exclusively) a safety study to:

1) determine the proper therapeutic dose and various dose/toxicity profiles in humans; and
2) recommend the therapeutic dose to be used in the next phase of clinical trials.

A phase I study also is designed to determine quantitative and qualitative toxicities (pharmacodynamics) and the drug's distribution and metabolism (pharmacokinetics). The importance of obtaining accurate information about the appropriate dose and schedule is described elsewhere in this supplement. Typical pharmacokinetic information is too frequently crude and unsatisfactory, and requires either further biological insights or luck.

If the product proves sufficiently safe to continue testing in humans, the next phase of studies investigates whether the drug has a salutary biologic effect. In phase II studies, researchers measure the biological activity of the new drug against disease: does it appear to cause tumor shrinkage or to cause the patient to live longer than expected? These studies determine whether the drug is worth definitive testing in larger, more expensive and time-consuming phase III trials. In the past, important details, such as exactly which patients with which tumors are to be studied, have not always been adequately considered. As a result, choices sometimes have been largely empirical and based on convenience. However, if a well-executed phase II trial is conducted, it can lead to a more complete and definitive stage in the development of a new pharmaceutical: a sophisticated phase III study.

In phase III studies the best data about effectiveness are gathered and physicians learn the most about how to use a new therapy. These are typically large-scale studies, often involving thousands of volunteer patients with a substantial fraction of them belonging to a control group that does not receive the new treatment being tested. Phase III trials are expensive and time consuming, but they are the best way to show that a new treatment works.

What constitutes sufficient evidence to prove that a new drug is safe, effective, and worthy of approval for widespread use? Typically, the FDA requires substantial, scientifically valid studies, and this generally means controlled clinical trial data. A prospective, contemporaneously controlled, randomized clinical trial remains the gold standard of clinical trial design. There are many other types of clinical study designs that can be used when the prospective, randomized trial may not be appropriate, such as a historically controlled trial in which a well-recognized pattern of disease is used as a comparison for patients receiving a new drug.

In a controlled trial, there are many different ways to determine whether the drug is working. Most simply, do patients receiving the new treatment live longer? If the treatment does not lengthen life, it may be worthy of approval and widespread use if it improves the quality of life for a person with cancer, e.g., by ameliorating pain. These seem to be clear endpoints: the person is alive or dead or requires less analgesia. However, these endpoints can be difficult to measure if the drug is only partially effective, provides only temporary benefit, or is useful only for a subgroup of patients.

Alternatively, instead of waiting to see if more patients die in the control group, surrogate endpoints for clinical effectiveness have been increasingly used to approve cancer drugs. The principal surrogate endpoint has been tumor shrinkage. If the treatment results in tumor shrinkage, then it is likely that the therapy will be of some clinical benefit to cancer patients and may be worthy of approval. Other useful surrogate endpoints may include measuring a decline in serologic markers, but these measures tend to be indirect and easily affected by factors other than clinical benefit from the treatment. Currently, the FDA does not have sufficient confidence in these surrogate markers to use them as the sole basis for approving new cancer treatments.

Finally, after the drug studies are complete, the sponsor files a New Drug Application (NDA) which causes the FDA to review all of the data from all of the relevant studies and then decide whether the new product can go into widespread use. The NDA describes the composition of the drug and how it is manufactured, the nonclinical pharmacology and toxicity, pharmacokinetics and bioavailability, and the clinical effects of the drug, both in terms of effectiveness and adverse reactions. Statistical analysis is also included to provide the scientific rigor needed to be confident that the drug works.

Once the sponsor has filed an NDA, the FDA spends up to one year reviewing the application for substantial evidence of effectiveness, a legal criterion that leads to the conclusion that the new drug works and that the risks of using it are worth the benefits. Products designated as "priority," which potentially offer important benefits for patients with serious disease and no acceptable alternatives, are reviewed in ≤6 months. There have been a variety of regulatory changes over the past few years affecting drugs intended for people with serious and life-threatening diseases, and new cancer agents have been among those affected by the changes.

When the clinical trials for a new agent have progressed sufficiently to suggest that the treatment is working, the FDA can allow the sponsor to make the drug widely available under a so-called Treatment IND. This allows critically ill patients to be treated with the drug as soon as possible, and allows the sponsor to gather additional information on the drug's safety and effectiveness. This is intended to allow compassionate use in people with serious illnesses so that they can obtain access to a new treatment while the FDA reviews the NDA. Under a similar program called parallel tracking, the FDA allows manufacturers (under certain circumstances) to make new drugs available to patients who cannot participate in clinical trials.

Under a policy called accelerated approval, the FDA is able to give conditional approval to a promising new drug for seriously ill patients based only on surrogate endpoints, such as tumor shrinkage. This policy allows the sponsor to market the drug as soon as possible. However, because the FDA lacks confidence in the adequacy of surrogate endpoints alone, the manufacturer must conduct additional studies to confirm that the drug helps people in a meaningful way before final approval is given. Meanwhile, patients and researchers have access to the new intervention, sometimes years earlier than would otherwise have been possible. Everyone benefits, particularly patients.

The FDA works actively with companies to make promising cancer treatments approved in other countries available to patients in the USA. In practice, this means that once the FDA identifies a promising drug approved elsewhere, it works quickly to make it available to US patients.

Even after a drug has been approved for widespread use, and especially when it has received accelerated approval, the FDA can require a company to continue to collect data from patients in ongoing clinical trials. These so-called phase IV studies are often intended to answer specific questions about the toxicity of a new product. At the same time, the FDA includes the new drug in its ongoing postmarketing surveillance system which is designed to detect unpredicted adverse events that are sometimes discovered after a new therapeutic agent is marketed.

Application of the scientific/regulatory framework to new antimetastatic drugs

The general scientific/regulatory framework outlined above is applied to the evaluation of new antimetastatic drugs and other cancer therapies in a similar fashion. The FDA needs to see proof that drugs designed to prevent or treat metastasis clearly demonstrate safety and effectiveness. However, in some ways it is more difficult to prove the efficacy of antimetastatic drugs. Adjuvant therapies are a common part of definitive treatment after a tumor is detected. The principal goal of all adjuvant treatment is to reduce the appearance of microscopic tumor that has spread to other parts of the body, and the results of such treatments are mixed. Metastatic spread remains the most common reason for treatment failure and death. Physicians, researchers, and regulators alike need to find ways to provide better, more effective therapeutic agents to patients faster.

Study design and interpretation

The field of antimetastatic agents is in its infancy and there are more regulatory questions than answers. For example, what are the appropriate clinical endpoints for a drug that is intended to prevent or treat metastasis? With a measurable tumor, shrinkage can be detected. But what can be measured in metastatic disease, particularly early in the disease when no tumors are evident? Does that mean that only clinical trials that demonstrate delay of disease progression or increased survival are valid indicators of effectiveness? These types of trials tend to take the longest, require the largest number of patients, and cost the most.

Can surrogate markers be useful? There has been considerable discussion about the value of and need for valid surrogates of efficacy to improve the development process for new oncology products, and objective tumor regression has been used in phase II and phase III therapeutic trials. What has not been so clearly articulated is the urgent need for useful surrogates in phase I trials. As new biologic therapies with novel mechanisms of action are initially tested, the goal is to determine the optimal dose and schedule (not necessarily the most intensive or most toxic). If the phase I study fails to do this, subsequent studies become a tragic waste of patients' resources and time (and their hopes and generosity), as well as the loss of opportunities to study other promising products. Appropriate biochemical surrogates of molecular targets (such as angiogenesis growth factor receptor interference, apoptosis, etc.) should be seriously considered as an integral part of phase I trials of presumed antimetastatic agents.

For all types of trial surrogates, the utility of simple serologic measures of disease activity should be viewed with initial skepticism. As useful as tests such as prostate-specific antigen, chorioembryonic antigen, or CA-125 may be in untreated patients, the possibility that antimetastatic treatment could biochemically elevate or lower their levels should be recognized. Clinical conclusions based on such naive assessments could be not only incorrect, but also misleading.

Other questions to be addressed include whether particular types of cancer patients should be evaluated in phase I trials. Depending upon the identification of distinct cellular or biochemical targets, certain types of patients with specific types of tumors may be the perfect (even necessary) candidates for ideal phase I studies.

What type of trial will be needed for cancer prevention by vaccine? The papillomavirus is known to cause cervical cancer in women, and vaccines can prevent viral infections. What will it take to demonstrate that a papillomavirus vaccine is able to prevent cervical cancer? It will probably require a large, prospective, controlled clinical trial to determine whether the vaccine reduces the incidence of cervical cancer in the treatment group. However, is there an easier, cheaper way? It is likely that antibodies to the vaccine (and thus the virus) can be measured in the serum. Is this sufficient?

Conclusions

In conclusion, the questions with which the FDA struggles are increasingly being confronted by regulatory

authorities in other countries as well. Through the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, the major drug-producing and -regulating countries of the world have taken great strides toward consensus. Although consensus has not been reached on all issues, progress has been dramatic and the problems faced by one are increasingly faced by all.