ENGELBERG CENTER for Health Care Reform at BROOKINGS

Conference on Clinical Cancer Research

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Friends of Cancer Research
American Association for Cancer Research
American Society of Clinical Oncology

September 26, 2008

Event Summary

The Engelberg Center for Health Care Reform, in collaboration with Friends of Cancer Research (Friends), the American Association for Cancer Research (AACR) and the American Society of Clinical Oncology (ASCO), hosted a conference to address key challenges facing clinical cancer research.

Four panels of experts came together at the event to discuss recommendations on the specific challenges of data submission standards and evidence requirements, efficacy endpoints, co-development of diagnostics and therapeutics, and a vision for the future of FDA. Issue briefs on the first three topics were developed prior to the meeting, and are available online.

Introduction

In his opening remarks, National Cancer Institute (NCI) Director Dr. John Niederhuber suggested that cancer research should move beyond organ-site based, single agent cancer clinical trials towards a new, molecule- and systems-based era in translational science. In order to achieve the full potential of this new scientific paradigm, researchers will need to adopt drug discovery methods that include mining large datasets and relating genetic information to new targets and pathways. When scientific changes create challenges for the conduct of research, NCI can act as a "safe harbor" where pressing issues can be resolved. The agency has already worked with the CEO Roundtable on Cancer (CRC) to develop common language for clinical trial contracts. The model clauses, which the Justice Department has stated it will not challenge, will reduce the start-up time for clinical trials.

Panel 1 – Data Submission Standards and Evidence Requirements

During this discussion, which was moderated by Dr. Richard Schilsky, associate dean for clinical research at the University of Chicago Medical Center, panelists proposed data collection standards for cancer clinical trials. The panel's recommendations differ depending on whether or not substantial data exist on the safety and efficacy of the treatment being studied. Several panelists noted that streamlined data collection for treatments about which much is already known will make trials faster, less costly, and less burdensome on volunteers. Simplifying data collection may also encourage physician and, in turn, patient participation in clinical trials.

Although the establishment of a standards-based minimum data set will increase the efficiency of trials, potential safety signals must be not overlooked. It was recommended that researchers rely on statistical simulations and post-hoc analyses of previously conducted clinical trials to create a decision tree to guide future data collection, providing sponsors with a mechanism to implement evidence-based data standards. The decision tree, which would take into account factors like whether the treatment was being studied for a new or a supplemental use, would guide sponsors to collect the optimal type and quantity of data on the safety and efficacy of a therapy.

Panel 2 – Improved Insights into Effects of Cancer Therapies

The second panel addressed the issue of auxiliary endpoints, a broad term for endpoints other than overall survival which can potentially be used to help learn about the benefits and risks of cancer therapies in clinical trials. Such endpoints can include progression free survival (PFS), cancer biomarkers, and patient-reported outcomes (e.g., quality of life). As defined by the panel, auxiliary endpoints are not meant to be surrogates for or supplant overall survival, but rather to be evaluated in conjunction with that endpoint.

The panelists focused on PFS because it is now widely used in trials, it has been accepted by the FDA as the basis for approval of some cancer therapies, and it exemplifies many of the challenges in using auxiliary endpoints. PFS, defined by the NCI as the "length of time during and after treatment in which a patient is living with a disease that does not worsen," has been increasingly used to demonstrate efficacy in clinical trials. Compared to overall survival, PFS can often be observed sooner, resulting in less time to show clinical benefit and faster clinical trials. However, since many cancer trials are open-label and progression is typically inferred from radiographic images, that endpoint may be subject to bias.

This concern has prompted debate about whether and to what degree auditing via Blinded Independent Central Review (BICR) is appropriate. As panelists pointed out, BICR is unnecessary in certain situations, but appropriate in others. For example, the FDA has already stated that BICR is unnecessary for double-blinded trials, except when an imbalance in side effects in the treatment arms causes a considerable level of unblinding. In an open-label superiority trial, BICR-based audits of a subset of the PFS endpoints is potentially beneficial; however, the audit would add little or no value if the observed effect size is large enough. Finally, the panelists proposed that an evaluation of PFS at two time points with an audit might reduce bias without much loss of statistical power.

Discussants concluded that researchers should conduct statistical simulations using datasets from previously completed trials to create further standards for what constitutes PFS. This investigation would help develop a more definitive link between PFS and progression, clarify when the use of BICR is appropriate, and yield guidelines on the percentage of cases that should be audited in trials using PFS. If appropriate data sets were compiled, NCI statisticians could complete the necessary analyses within six months, according to Dr. James Doroshow, director of NCI's Division of Cancer Treatment and Diagnosis.

Luncheon Keynote from FDA Commissioner Dr. Andrew von Eschenbach

In his remarks, Dr. von Eschenbach described important changes on the horizon at FDA. He said that the agency is going to upgrade its information technology systems and reassess salary packages and career paths for its most important scientists. The recently launched FDA Fellows program allows professional scientists to learn about the science and policies that underlie the FDA's regulatory decision-making. The FDA has also created the Beyond our Borders initiative, which will result in the opening of FDA offices in Asia, Europe, Latin America and the Middle East.

Panel 3 – Co-Development of Diagnostics and Therapeutics

Panelists discussed steps that should be taken to advance diagnostic test development and regulation, including co-development with cancer therapies. They noted that an unclear, inconsistent regulatory path to clinical acceptance has hampered the development of diagnostic tests with demonstrated clinical utility. Moderator Dr. Daniel Hayes, professor of Internal Medicine at the University of Michigan, noted that FDA approval does not guarantee that an assay is clinically useful, and the "Home Brew" rule means that an assay can be marketed without FDA approval. Furthermore, public and private payers provide poor reimbursement for many diagnostic tests, slowing investment and innovation in potentially high-value tests.

Several measures that could be taken to create a clear pathway for the development of cancer assays were recommended. Panel members suggested that such a pathway be developed with input from FDA advisory panels, professional societies, and clinical investigators. They also emphasized that approvals for diagnostic tests should be based on demonstrated clinical benefit, but were open to various methods of measuring demonstrated benefit. Finally, panelists recommended that an advisory committee similar to the Oncologic Drugs Advisory Committee (ODAC) be created in order to facilitate the development of a coordinated process for tumor marker clearance. When diagnostic tests are co-developed with therapies, coordination of the regulatory process across FDA centers is especially important.

Dr. Ray Woosley, president and CEO of the Critical Path Institute, presented a method that could facilitate the development and approval of diagnostic and therapeutic companions through biomarker certification and the use of quantitative disease models. For example, if a disease model predicted that a diagnostic test was likely to correctly identify populations responsive to a hypothetical drug, then the FDA could qualify the test for use in developing a therapy that has the same characteristics as the hypothetical drug. Next, clinical trials would be conducted to determine the test's clinical utility in conjunction with the therapy. Ultimately, positive trial results of the diagnostic-therapy combination would be submitted to the FDA for approval as a "strategy" – that is, the drug would only be used when the assay predicts a beneficial response. This is not the only approach, therefore a formal dialogue is needed among professional societies, NCI, FDA, and diagnostics developers to identify and evaluate the range of alternatives.

Panel 4 – Vision for the Future of the FDA

The final panel outlined a vision for the FDA that incorporated the ideas discussed in the previous panel presentations, including panelists' own perspectives on the agency. Each noted the FDA's need for additional resources, and several mentioned that such resources could help the agency hire and retain additional scientific staff whose capabilities reflect the current state of biomedical science.

For example, current and future breakthroughs in cancer research are being built on the disciplines of systems-based biology, genomics, and nanotechnology. Dr. Robert Young, chancellor of Fox Chase Cancer Center, suggested that the FDA should create positions equivalent to Chief Science Officer and Chief Medical Officer and a board of external scientific advisors. Dr. Ellen Sigal, chairperson and founder of Friends of Cancer Research, also backed the idea that the FDA should solicit more input from outside advisors. Dr. Anna Barker, NCI's deputy director, highlighted the NCI-FDA Interagency Oncology Task Force's work on nanotechnology, standards for electronic data submission and biomarker qualification – and called for more collaboration between these influential organizations. Dr. Sigal recommended this task force be expanded to include external representation.

There was also consensus that the FDA's Centers need to work more closely with one another to advance regulatory science in light of rapidly advancing product development science. To ensure that new treatments are developed efficiently and maximally effective, more biomarkers and auxiliary endpoints need to be validated through consistent evaluation across public and private research programs. Dr. David Kessler, former FDA Commissioner, pointed out the importance of developing endpoints that can be measured quantitatively, rather than subjectively. David Epstein, president and CEO of Novartis Oncology, added that the issues linked to auxiliary endpoints need to be addressed soon in order to provide support for conducting clinical trials of treatments for rare diseases and better-defined subgroups of patients.

Dr. Kessler outlined the process by which the next FDA Commissioner could accelerate innovation in cancer therapies. He suggested the commissioner make a public commitment to finding more treatments that work for patients with cancer. To win the necessary public support for this effort, the FDA will need to concentrate on treatments for the most aggressive cancers. Finally, the FDA must develop a drug development roadmap for sponsors and regulators to follow. For cancer therapies, the roadmap should ensure that trials "get the science right," that accelerated approvals are granted where appropriate, and that models of success are identified for others to follow. A similar roadmap, Kessler said, was crucial to the rapid testing and approval of AIDS drugs in the early 1990s.

Next Steps

Dr. Mark McClellan, director of the Engelberg Center for Health Care Reform, summarized the conference discussion with a series of recommended next steps for making clinical cancer research more effective and efficient:

Data Submission Standards and Evidence Requirements

1. Building on the proposals from the first panel, efforts should be made to ensure that data are collected consistently and accurately, and that the data that are gathered are actually useful. To accomplish this goal, researchers should use data from completed trials to develop a decision tree that would help sponsors design optimal data collection protocols.

Improved Insights into Effects of Cancer Therapies

2. Researchers should perform simulations on data from a series of completed PFS trials involving BICR, to quantify the potential for bias. This analysis should yield evidence-based recommendations for when BICR will meaningfully reduce bias, and on what percentage of cases should be reviewed. The approach to improving auditing procedures for PFS suggests a method for increasing the consistency and quality of data produced in clinical trials utilizing other auxiliary endpoints: researchers should strive to make auxiliary endpoints standardized and quantifiable. Studies, analogous to those needed for PFS, should be carried out to validate other auxiliary endpoints.

Co-Development of Diagnostics and Therapeutics

3. The FDA, relevant FDA advisory panels, and professional societies should begin to discuss ways to clarify the development pathway for cancer diagnostics in general and those co-developed with targeted therapies in particular. This discussion should address methods for generating reliable evidence to show that diagnostics influence treatment decisions and impact health outcomes. Such evidence can influence reimbursement of diagnostic tests.

4. An ODAC-like committee could help improve consistency and intra-FDA coordination in tumor marker clearance and approval. An initial item of business for this committee and FDA staff should be to define a clearer pathway initial validation, further development, and approval for diagnostic tests that seem to have demonstrated clinical utility.