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Editorial

Defining a New Role for the National Cancer Institute Cooperative Groups: More Science, Fewer Trials

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Disclosures of potential conflicts of interest may be found at the end of this article.


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Over the past decade, the Cooperative Group program of the National Cancer Institute (NCI) has been subjected to intense scrutiny and significant change, despite its six-decade history of significant contribution to cancer treatment. The first cooperative group, Cancer and Leukemia Group B (CALGB), was formed in 1957 by the NCI to expedite the larger-scale testing of leukemia drugs, many of which were forthcoming from the NCI's own drug development program. CALGB served as a precedent for establishing a dozen such groups, which were defined by their interest in specific diseases and by geographic regions. For much of the last half of the 20th century, the groups answered the need for large, well-controlled, randomized, phase III trials and contributed crucial knowledge about optimal therapies for childhood and adult leukemia, lymphomas, and solid tumors. At their peak, their trials entered 25,000 new patients in trial each year and drew thousands of community and academic oncologists into their effort.

The common perception of group activity changed after the year 2000. The adult groups were inefficient in starting and completing trials; overlapped in their scientific interests; had redundant infrastructure for statistics, data management, and auditing; and reimbursed a modest $2,000 per patient, much below the cost of data management and oversight for individual members, who chipped in the additional dollars. In addition, scientifically, their trials lacked the excitement of the targeted drug studies coming from the corporate world of biotechnology. These industry trials were an entirely different sort: patients were selected on the basis of a well-defined molecular target, high initial response rates, rapid progression to approval, and generous reimbursement. NCI's drug discovery and development program was no longer the dominant source of interesting compounds.

A report from the Institute of Medicine (IOM) in 2010 called for major changes in group organization and trial prioritization and highlighted the need for improved funding [1]. The NCI has instituted many of these changes over the past 4 years [2], reducing the number of adult groups to four, speeding the process of trial review and initiation, consolidating data management, and establishing a groupwide process for prioritizing studies. A funding increase for high-accruing sites is being implemented. The next step in the restructuring of the groups, as detailed in the report on IOM workshops elsewhere in this issue [3], will be to bring the groups into the mainstream of targeted cancer drug development.

The reform of the groups is happening in the context of a major change, if not a revolution, in the process of cancer drug development. Basic research, much of it sponsored by the NCI, has provided the molecular foundation for building successful targeted therapies. New drugs—when appropriately tested against patients with tumors of the right molecular profile—are now marching through the drug development process with increasing speed, as recognized in these pages [4]. With a receptive U.S. Food and Drug Administration [5], it is now possible to win approval after phase I (as for ceritinib)—an expectation unimaginable in the past—and approval after phase II is now commonplace. Many of these definitive trials are conducted by pharmaceutical and biotechnology companies in conjunction with academic investigators. Companies are able to organize ad hoc multisite consortia to find the necessary number of patients with relatively rare mutations in lung, melanoma, breast, and colon cancer and other tumors, all without the direct help of the NCI groups, although the academic collaborators are usually from NCI-funded cancer centers. The cooperative groups have been offered access to these exciting new drugs for post-approval development of combination therapies and other objectives.

In this new era of industry-driven drug development, the group program was confronted with the choice of either redefining its role or becoming irrelevant. NCI leadership has accepted

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this challenge and, after 3 years of a major reorganization and with the advice of a series of IOM workshops in 2011 and 2013, has given us a roadmap for future trials.

The report of the IOM's Workshop Series on "Implementing a Cancer Clinical Trials System for the 21st Century," found elsewhere in this issue [3], offers a number of possibilities for new directions: comparison of multiple different agents for a given tumor subset; "basket" trials for a selected mutation (e.g., *b-RAF* or *RET*) and its targeted drug across multiple tumor histologies; trials in often neglected patient populations, such as children or the elderly; adjuvant trials in rare patient subsets; and combinations of drugs (with chemotherapy or with other targeted agents from different firms). Examples are provided of three new NCI group trials (L-MAP, MATCH, and ALCHEMIST) that require screening of extremely large patient populations (e.g., up to 8,000 in the L-MAP trial) to identify those with uncommon mutations and then assign appropriate patients to the logical new drug. In the ALCHEMIST trial (aptly named), two drugs—erlotinib (Tarceva) and crizotinib (Xalkori)—will be tested and randomized against placebo after standard adjuvant therapy in early stage lung cancer with appropriate mutations. The logistics of ALCHEMIST and other targeted trials represent a new challenge for the groups, with their widely distributed membership, limited reimbursement, and nonacademic community participants. It will be an important test of the new group strategy to show that they can enlist, procure, distribute, and test samples from widely scattered participants and efficiently screen these samples on a massive scale in the proposed trials.

All of this change is occurring in an environment of fiscal stringency, with no prospect of improvements in the NCI budget in the near future. The increased reimbursement for accruals, if it happens, will be modest and selective. To cope with the limited budget, one would have to predict that there will be further consolidation of the existing four adult groups, fewer accruals to a more limited set of highly prioritized trials, and a greater emphasis on discovery as opposed to proof of superiority of modestly different regimens. At the same time, funding for the large cancer centers, which have been the focus for targeted drug development, is likely to be capped. A question remains unanswered: Would the NCI get a bigger bang for its buck by increasing its funding for the cancer centers, which already have a strong track record for translational research in targeted drug development, rather than continuing to fund the groups at the current level?

In the context of these major changes and with their new mandate, it is likely that the groups will not have the resources to perform many of the traditional, definitive, randomized, phase III trials of the past. Industry will have to play a greater role in refining drug sequences or combinations. At a price tag of $220 million per year (considering all associated costs) [6], the new National Clinical Trials Network will have an opportunity to produce results with a major impact on cancer drug development. Likely $1 billion will be spent before we have an answer, but if the NCI is to play a larger role in modern drug development, this is a logical step forward.

Disclosures

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Editor's Note: See the related article, "Expanding Public-Private Collaborations to Enhance Cancer Drug Development: A Report of the Institute of Medicine's Workshop Series, 'Implementing a National Cancer Clinical Trials System for the 21st Century,'" on pages 1179–1185 of this issue.