What Level of Evidence: The Elusive Balance in Drug Development

Many dichotomies have prevailed throughout the history of medicine, certainly exemplified in modern times by the contest between the development of a robust body of evidence to support a treatment intervention versus the rapid availability of interventions for routine patient use. Whether addressing AIDS, cancer, or another life-threatening or incurable disease, the tension between access to new treatments for desperate individuals versus safeguarding the public for the common good prevails. In the spirit of hastening the FDA approval process for drugs to treat serious diseases including cancer, legislation was passed nearly 2 decades ago introducing the concept of accelerated approval based on surrogate end points.1,2

Several recent publications have reviewed the FDA experience with accelerated approval of oncology products.3–5 To summarize, the accelerated approval regulations require that agents under consideration must be “better than available therapy” (i.e., show improved efficacy).5 Surrogate end points as predictors of clinical benefit include prolongation of life or better quality of life; however, regulations also require post-approval clinical trials to confirm clinical benefit, a requirement that has generated controversy because of variable compliance.

Review of the FDA database for accelerated approval of oncology products from December 1992 through July 2010 shows that the FDA granted accelerated approval of 47 new indications for 35 antitumor drugs. Of these, 28 were based on single-arm trials.3 The array of surrogate end points for accelerated approval of the 47 new indications included objective response rate and duration, time to event, safety, time to progression, and disease-free survival. Of the 47 new indications, 26 received regular approval based on clinical benefit shown in post-approval clinical trials, and 21 did not receive regular approval because the clinical benefit was not confirmed.

Another effort to enhance drug development in the United States was implemented in 1983, with the introduction of the Orphan Drug Act. This act provided clinical trial grants, a tax credit for clinical testing costs, and exclusivity rights for drugs that specifically target rare diseases, defined as diseases affecting fewer than 200,000 people.6 In addition, drug application fees may be waived, and there is a possibility for faster FDA review. That oncology represents an important area for orphan drug development is not surprising, as summarized in a recent review of approval of orphan versus non-orphan drugs for cancer.7 This study, of new orphan and non-orphan drugs approved between 2004 and 2010 for the treatment of cancer, showed a nonsignificant difference in the median total clinical testing phase favoring orphan drugs. The median FDA review time was identical, and no difference was seen in the number of trials in each of the 2 groups undergoing usual versus accelerated review. Compared with those for non-orphan drugs, orphan drug clinical trials had smaller numbers of patients, and were often nonrandomized, most likely not double-blind, more likely to evaluate disease response rather than survival, and more likely to have more patients with serious adverse events.

Another recent study, from Friends of Cancer Research, addressed the median time of approval for cancer medicines. This analysis included 35 new oncology drugs approved from 2003 to 2010 by either the FDA or the European Medicines Agency (EMA).7 The median time from submission date to approval date for the FDA was 182 days, compared with 350 days for EMA. The authors concluded that the perception that new cancer drugs are available more quickly in Europe than the United States is unfounded. They argued that there should be “strong financial and public support” of the FDA to enhance rapid availability of new drugs for U.S. cancer patients and that

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“difficulties in carrying out clinical trials in the field of oncology,” rather than delayed review processes, have resulted in delays in bringing new agents to the U.S. public.

The controversy surrounding accelerated drug approval was rekindled during the February 2011 FDA Oncology Drugs Advisory Committee (ODAC) meeting. The committee consensus urged the FDA to improve the standards for granting accelerated approval for oncology drugs, suggesting that accelerated approval should be granted based on randomized studies rather than single-arm trials; that, in general, 2 randomized post-marketing studies should confirm clinical benefit and that these studies should be in progress at the time of accelerated approval; and that cooperative groups may conduct confirmatory trials but the companies must maintain post-marketing responsibilities.

The concepts of accelerated approval for cancer drugs and incentives to encourage orphan drug development are laudable and have brought new agents to the forefront of care. Potential benefits of early market access for new agents include opportunities for further investigations, such as combination therapies, prognostic and predictive marker development, exploratory use in other malignancies, and accumulation of additional acute and long-term toxicity data. The pervasive development of clinical trials incorporating “off-label” uses has resulted in numerous regimens across malignancies that have become standard of care.

Conversely, in some cases the required post-marketing studies have not been performed or have taken extended periods of time for completion. Further, in some cases, agents did not show clinical benefit in confirmatory studies. The recent ODAC recommendations, therefore, appear reasonable as efforts to secure critical data to confirm efficacy at least in an era of less targeted, empiric clinical trial design using traditional efficacy end points.

As mentioned, the Friends of Cancer Research concluded from their recent analysis of FDA and EMA drug approval timelines that perhaps delays in the introduction of new agents to patients with cancer is not because of the regulatory review processes but rather significant problems in conducting oncology clinical trials in the United States. It is certainly true that the United States has been in an ongoing clinical trials crisis for a number of years. However, equally true is that we are faced with a multitude of issues profoundly affecting drug development. These issues encompass a host of factors such as regulations, cost, reimbursement, public perception, an evolving oncology practice environment, policy, government funding, globalization of the pharmaceutical industry, and, perhaps foremost, the need for new paradigms in clinical trial design to enhance the understanding of human tumor biology and subsequent patient selection for interventions.

Despite advances in cancer treatment, we are still not curing most individuals with metastatic disease. Therefore a pervasive “unmet need” remains as justification for more rapid drug development in oncology. In addition, as smaller and smaller subsets of patients within a given disease category are identified by molecular parameters, more oncology agents will, by definition, achieve orphan disease status, with distinct limitations in the number of patients available for clinical trial participation. New paradigms of trial design, and thus new regulatory approval strategies, will be of paramount importance.

Determination of clinical benefit will remain crucial as the cornerstone of drug approval, whether accelerated or “usual” approval; however, demonstration of clinical benefit could conceivably include single-arm clinical trials based on biologically driven patient selection strategies with efficacy end points that may be assessed using molecular markers or functional imaging. Randomized clinical trials will remain important tools, but they may also involve new design concepts with much smaller numbers of patients based on much more precise selection criteria. The pharmaceutical industry and regulatory
agencies will be required to address complexities of drug development and regulatory approval in which individual agents are linked to particular diagnostics for patient selection, and in which biologic pathways or markers are essential to measure efficacy.

Improved patient selection based on individual patient and tumor characteristics may indeed result in superior overall survival. However, surrogate end points may remain necessary in situations in which overall survival benefit is a product of multiple regimens administered over the duration of illness. This raises the issue of the importance of incremental benefits of therapy to patients and clinicians alike. True, clinical trials for breast and colon cancer, for example, have shown survival benefit; however, also true is that we have transformed these cancers into chronic diseases because of incremental benefits of multiple regimens administered over time. Given the relatively unselected populations of patients historically chosen for clinical trials participation, there is consistent compromise of ability to denote the actual benefit of an intervention. Empiric clinical trials usually do not show why one group of patients experiences improved efficacy but a sizeable group of patients experiences minimal or no benefit, thus potentially “diluting” the significance of results such as overall or progression-free survival.

For clinicians to meet the increasing pressure on them to practice evidence-based medicine, much greater public acceptance of evidence and willingness to participate in clinical trials is needed by clinicians and patients alike. That so many individuals invest so much in unproven or so-called alternative approaches to their care without scientific evidence is fascinating. The reasons for such choices are, of course, complex, but this phenomenon does suggest the need to invest in new approaches to engage the public (and clinicians) to embrace scientifically sound clinical research to truly accelerate access to new drugs in this country.

Cancer drug development has been ensconced in silos. Rather than promoting segregation of cancer treatment stakeholders, further advances cultivating more rapid introduction of new cancer interventions will require a committed alliance of all involved: pharmaceutical, device, and diagnostics industries; radiology; FDA and the overall regulatory establishment; government; clinicians and clinical trialists; patients and advocacy groups; statisticians; laboratory scientists; and the reimbursement establishment, both public and private.

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