**SPECIAL SECTION**

**Biomarkers, Surrogate End Points, and the Acceleration of Drug Development for Cancer Prevention and Treatment: An Update**

Prologue

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**INTRODUCTION**

Remarkable progress has been made over the past two decades in our understanding of the molecular, cellular, and tissue processes involved in precancer and cancer (neoplastic) progression. Nonetheless, the development of effective and safe therapies for the prevention and treatment of cancer remains slow, inefficient, and costly. For example, data from the Tufts Center for the Study of Drug Development show that new cancer chemotherapy drugs approved in the United States between the years 1998 and 2001 were in clinical development for a mean of approximately 75 months and required another 7.6 months to obtain approval (1). The high attrition rate of promising new drugs in late-stage clinical trials is a prominent example of the problems faced in drug development. Although hundreds of oncology drugs have been under development in the United States during the past decade, only a few new drugs are approved every year [by early 2003, there were fewer than 100 approved oncology drugs (2)]. Many of these drugs fail because they are tested in inappropriate patient populations and/or in settings where a clinical endpoint cannot be reached; hence, clinical benefit required for marketing approval for a new drug is not demonstrated. This growing unmet medical need for cancer therapies has spurred collaboration among scientists and advocates in the public and private sectors to define strategies for more effective cancer drug development, including the application of biomarkers in risk stratification, clinical trial design, end points, clinical networks, use of new technologies, and criteria for tissue and data collection and dissemination (3–14).

This special section of *Clinical Cancer Research* addresses the potential of biomarkers, especially as surrogate end points, to facilitate the development of effective and safe oncologic drugs. Its aim is to review the state of the science, identify needs, and propose strategies regarding the application of biomarkers. The focus is on surrogate endpoint and other biomarkers that can be commonly accepted as standards for regulatory review and action for both new, molecularly targeted agents and cytotoxic drugs; practical issues and strategies for the use of these biomarkers to advance oncologic drug development are also considered. Several general themes emerge from these pages, particularly the need for multisector, cooperative processes for the identification, validation, review, and implementation of surrogates in cancer drug development.

Two articles in this section provide general approaches to the definition and evaluation of biomarkers. One reviews the uses of mechanism-based biomarkers in all phases of cancer drug development (15), whereas the other presents a strategy for identifying and evaluating potential biomarkers associated with response to therapy (16). The remaining articles present strategies for the application of already well-developed and highly promising surrogate end points [adenomas in prevention of colorectal cancer (17), CA-125 in progressive ovarian cancer (18), and prostate-specific antigen doubling time (PSA-DT) in progressive prostate cancer (19)].

**RATIONALE FOR BIOMARKERS AND SURROGATE END POINTS IN MECHANISM-DRIVEN ONCOLOGY DRUG DEVELOPMENT** (15)

The development of four examples of molecularly targeted agents/agent classes (trastuzumab, imatinib, epidermal growth factor receptor inhibitors, and angiogenesis inhibitor) highlights the potential as well as the challenges of using mechanism-based biomarkers in oncology drug development. In their rationale for using biomarkers, Park et al. (15) recommend that they be applied throughout the drug development process to identify and validate therapeutic targets; screen and optimize candidate agents; provide proof of concept for agents and models; enhance mechanistic understanding of drug or drug combinations; identify optimal target populations; predict response, resistance, and toxicity; and rapidly distinguish responders from nonresponders to therapeutic intervention. A collaborative enterprise among pharmaceutical, biotechnology, government, ac-
admic, and patient advocacy groups is needed to advance research in biomarker methodology and validation. In addition, the collaborative effort should facilitate information and technology flow among different sectors and partners; encourage integration of complementary efforts such as diagnostics and therapeutics; establish consensus regarding standards, processes, and validation; and develop frameworks for using biomarkers in clinical trials. Correlative biomarker development and validation studies in Phase I, II, and III oncology drug trials should be encouraged, with funding from pharmaceutical companies as well as government agencies such as the NIH. New mechanisms of funding should be established to foster interdisciplinary research in this area.

**REANALYSIS OF APPROVED CANCER DRUGS: OLD DRUGS, NEW TRICKS (16)**

Neoadjuvant settings are a promising arena for using new molecular and imaging technologies to identify and establish surrogate end points or other biomarkers (or signatures) to measure and potentially predict efficacy for approved, effective antitumor drugs. The availability of both pre- and posttherapy validating tissue biopsies makes noninvasive imaging, both molecular (functional) and clinical (anatomical), particularly valuable in this reanalysis. Retrospective studies will be feasible if adequate specimens and rigorous clinical and demographic data are available. However, for the most part, efficient, small prospective studies will be needed and are anticipated to be very productive. A collaborative initiative among pharmaceutical companies, biotechnology firms, the National Cancer Institute (NCI) and other government agencies, and academic scientists is needed to facilitate immediate access to such novel technologies as genomic, proteomic, and functional imaging technologies as they develop, and access to clinical trial samples such as serum, biopsy tissue, and DNA imaging data. This collaboration could leverage the knowledge and resources of the NCI’s existing initiatives in technology (e.g., Cancer Bioinformatics Informatics Grid project), clinical networks (e.g., Cooperative Oncology Groups), and translational research (e.g., the Specialized Programs of Research Excellence program). Comparable efforts in the United Kingdom could also inform the initiative. Together, these efforts will promote the discovery of surrogate end points or other biomarkers to predict and measure effectiveness of therapies.

**COLORECTAL ADENOMAS: A PROTOTYPE FOR THE USE OF SURROGATE END POINTS IN THE DEVELOPMENT OF CANCER PREVENTION DRUGS (17)**

There is compelling evidence establishing the adenoma as a surrogate end point biomarker for colorectal cancer. Revision or improvement of existing policy is recommended to accommodate and encourage earlier approval for marketing drugs designed to treat or prevent precancerous lesions in many target organs because this will address an unmet medical need. This article on colorectal adenomas also provides sample trial designs (17). It is anticipated that preventive drugs will be administered long term to diverse populations at varying risk for disease, and thus the establishment of longstanding safety and efficacy is critical. A two-phase drug approval process may be appropriate, with accelerated approval based on demonstrated efficacy against adenomas in a relatively short-term study (3 years for sporadic adenomas or 6 months for familial adenomatous polyposis patients). Full approval would require planned, rigorous postmarketing surveillance, in addition to follow-up trials in defined study populations (e.g., beyond 3 years and up to 5–6 years). The complementary roles of screening and drug intervention need to be addressed in clinical research and future public policy. In addition, current and future efforts should focus on the identification, validation, and implementation of end points that are reached even sooner than the adenoma (e.g., aberrant crypt foci). The parallel application of molecular, genomic, and proteomic techniques will allow characterization of the genetic, pharmacogenomic, phenotypic, and histological properties underpinning the drug response of early lesions and their risk of progression. Such research will facilitate the identification and validation of critical targets for intervention. This, in turn, may stimulate the development of much-needed molecularly targeted therapies with promise in colorectal cancer prevention and treatment.

**CA-125 IN CLINICAL TRIAL EVALUATION OF NEW THERAPEUTIC DRUGS FOR OVARIAN CANCER (18)**

Data exist to support the acceptance of CA-125 as a surrogate end point marker in clinical trials for the evaluation of oncologic drugs for progressive ovarian cancer, and this article (18) defines the CA-125 response and suggests its use as a complementary tool to standard criteria for disease measurement. The use of the defined CA-125 response is not recommended in trials of initial chemotherapy because the CA-125 response is to both surgery and chemotherapy. CA-125 should be considered in Phase I–II trials to identify the biologically optimal dose and cytostatic activity of nonconventional therapies such as signal transduction inhibitors. The proposed CA-125 response definition should be used routinely in Phase II clinical trials to support “go/no go” decisions for further development. Trials to determine response rates using both CA-125 and Response Evaluation Criteria in Solid Tumors (RECIST) criteria would be designed so that if the CA-125 response rate provides >90% power to detect the minimal acceptable rate, the trial would be continued so that response can be measured with the same power by RECIST criteria. Consideration should be given for early discontinuation of those study arms with significantly inferior prognosis defined by CA-125. Progression-free survival and, specifically, the date of progression should be defined according to the CA-125 and RECIST criteria. Trial data that demonstrate CA-125 response and an improvement in progression-free survival defined according to the CA-125 and RECIST criteria proposed by the Gynecologic Cancer Inter-group should be used to support accelerated approval of promising therapies. These trials would be designed to allow continuation of evaluation to survival or quality of life end points or to be followed in Phase IV confirmatory trials using these standard end points.
PSA-DT AS A SURROGATE MARKER FOR EVALUATION OF ONCOLOGIC DRUGS TO TREAT PROSTATE CANCER (19)

The use of PSA-DT in prostate cancer drug development is supported by current data. PSA measures have a role in screening, early detection, diagnosis, staging, monitoring progression, and evaluating the effects of treatment. Whereas PSA measures predict extent of disease, PSA-DT after definitive local treatment by surgery or with radiotherapy is correlated with survival. In addition, emerging data suggest that PSA-DT is a valuable prognostic parameter after hormonal ablation and in hormone-refractory patients. Thus, therapeutic modulation of PSA-related parameters (especially PSA-DT) produces clinically meaningful benefits to the patient. In addition, posttreatment PSA-DT can be used as a criterion to identify trial cohorts (e.g., those at high risk for progression in whom hormone therapy with or without a new agent can be tested). PSA-DT in the rising PSA population can also be used as a Phase III endpoint for studies comparing local treatments in newly diagnosed patients, if the cohort has been appropriately defined. Furthermore, the effect on PSA-DT can be used in go/no-go decisions in Phase II trials. Trial data that demonstrate significant changes in PSA-DT should be used to support accelerated approval of promising therapies. These trials would be designed to allow continuation of evaluation to improvement in disease-free survival (as assessed anatomically), survival, or quality of life end points or to be followed in Phase IV confirmatory trials using these standard end points.

FUTURE DIRECTIONS

This special section was developed to assess the current promise of surrogate end points in three different clinical oncology settings and to highlight critical research needs and growth areas pertaining to biomarker use in oncology drug development. One particularly promising avenue for biomarker development is the molecular analysis of responders to therapy that may define patient groups most likely to be responsive to certain therapeutic interventions. This effort may also identify molecular targets and stimulate development of therapies directed at these lesions. Examples include work by Staudt (20) to characterize gene expression profiles that can be used prospectively to define lymphomas responsive to standard chemotherapy, as well as studies conducted in other disease settings such as acute myeloid leukemia (21, 22) and breast (23) and testicular cancer (24). This research arena will be greatly facilitated by current and developing molecular profiling approaches to define the molecular signature of cancer—patterns of gene and protein expression and DNA alterations (e.g., gene hypermethylation, single-nucleotide polymorphisms, microsatellite instability, and gross chromosomal aberrations) associated with cancer diagnosis, prognosis, or response to therapy. Novel molecular and functional imaging technologies are also expected to foster biomarker identification and application. The combination of imaging with molecular approaches is an intriguing strategy that is being explored in several disease settings. For example, the application of spiral computed tomography imaging in combination with molecular analysis of endoscopic biopsies and sputum to detect atypia or aberrant DNA methylation may be useful in lung cancer screening (25, 26). In breast cancer, the application of 99mTc probes to image molecular lesions (e.g., c-MYC, c-Erb-B2, and epidermal growth factor receptor) is being investigated in preclinical models (27–29). Future reviews of developing biomarkers in breast and lung cancer, as well as other promising clinical settings, are planned to highlight these and other areas of development. Biomarkers have enormous potential to influence cancer diagnosis, prognosis, and treatment. Formal, multidisciplinary scientific review panels are needed to foster the development of sound, science-based strategies to apply biomarkers to advance oncology drug development. These expert panels could take a lead role in developing consensus regarding the definition of the surrogate endpoint biomarkers and their measurement, clinical trial design, and specific efficacy and safety criteria for establishing clinical benefit for both new full drug approvals and accelerated approvals. These advances would allow the earliest possible access to important new cancer drugs. Existing oncology drug development expert panels include RECIST (30), the AACR Intraepithelial Neoplasia Task Force (9), and the NCI/Food and Drug Administration (FDA) Interagency Oncology Task Force. Recent initiatives supported by the NCI of the NIH include the aforementioned Cancer Bioinformatics Informatics Grid project,12 which is seeking to develop resources and methods, as well as standardized procedures, for collecting and disseminating critical basic sciences and clinical data that promise to be useful in evaluating cancer biomarkers. Another relevant initiative is the Cancer Fellowship Training Programs,13 which will contribute to the training of clinical trialists to be expert in the use of new technologies and the application of these new methods as well as biomarkers to clinical trials of new drugs. A collaborative FDA/NCI/ASCO/AACR effort is also sponsoring a series of public workshops to review clinical end points in major cancer settings, which will then be discussed at FDA Oncologic Drug Advisory Committee meetings. Surrogate end point biomarker expert panels would complement these efforts by providing a forum targeted toward discussion and review of advances in biomarker development and implementation. It is expected that an ongoing format would be best to provide continuing oversight and direction to accommodate and analyze the data that new drugs and technologies are providing in this important area.

REFERENCES


13 http://www.nci.nih.gov/newscenter/pressreleases/FriendsFDANCI.


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