The “war on cancer” was launched by the 1971 passage of the National Cancer Act and by President Richard Nixon’s call for a U.S. commitment to eradicating the disease equaling that brought to bear on placing a man on the Moon (Fig. 1). As it turned out, bringing cancer under control has been a much more formidable challenge than a lunar landing. Although the ensuing substantial federal investment in cancer research—$100 billion since 1971—has yielded remarkable progress in our understanding of the molecular basis of cancer, this knowledge has not yet been translated into effective strategies for preventing and treating the most common cancers. Although there have been isolated dramatic successes, including cures for many childhood cancers, testicular cancer, and some acute and chronic leukemias, there has been little change in the overall survival rate among patients with cancer.

Many believe that the primary focus of the war on cancer should be the identification of new, clinically useful drug targets that can take us beyond the current plateau of survival advances. We suggest that an equally crucial step toward success in cancer therapy is the development of new methods and strategies for matching new and existing drugs with the characteristics of individual patients—what is frequently termed personalized cancer treatment. On one level, personalizing treatment would improve efficacy and spare patients unnecessary toxicity, but more broadly, it is critical for a renewed war on cancer: Without a robust mechanism for selecting the right treatment for the right patient at the right time, we will continue to see only incremental improvements and have little hope for substantial survival gains. We suggest that it is now imperative that future clinical trials be designed with a plan to incorporate biomarker development.

The realization that breast cancer, lung cancer, and colon cancer, for example, actually represent multiple distinct disease entities that vary in natural history and molecular pathogenesis must force us to rethink the current process of drug development. It is unrealistic to set goals of developing “blockbuster” cancer drugs that are effective in all patients with a given disease.

On the other hand, the development of imatinib for the treatment of chronic myeloid leukemia (CML) demonstrates the promise of targeted therapy. Studies have shown that the properties of CML depend on one altered signaling activity, that of the BCR-ABL kinase, an oncogenic fusion protein (5). The importance of BCR-ABL, which is present in virtually all CML cases, in the pathogenesis of the disease is also attested to by the fact that imatinib, which targets the altered kinase, effectively controls the disease in more than 90% of patients with CML.

On the other hand, there is the example of trastuzumab for the treatment of breast cancer. Trastuzumab’s target, the HER2 growth factor receptor, is over-expressed in only about 20% of breast cancers, and of these, only about 30% respond to the drug. Thus, if trastuzumab had been developed in an unselected population of patients with breast cancer, its effectiveness would probably not have been detectable. It was only because of the ability to identify a subpopulation of patients with breast cancer who are likely to benefit from the drug, those whose tumors overexpress HER2, that the drug’s effectiveness could be demonstrated.

Unfortunately, the imatinib experience is probably the exception, and the trastuzumab experience the rule. Given the heterogeneity

Fig. 1. Beginning the war on cancer. President Richard Nixon signed the National Cancer Act on 23 December 1971.
and complexity of most human cancers, we must expect that most drugs will have activity and efficacy in only a fraction of cases, like the example of trastuzumab. Indeed, it would be illogical, given what we now know of the complexity of most cancers, to expect otherwise. Further, we must also recognize that even the ability to identify the subpopulation with the active target (such as HER2) does not ensure success, reflecting the complexity of additional interacting events.

The reality of drugs working in only a small fraction of any given population of patients presents a major challenge for effective drug development, because the extent of clinical benefit from such a drug in an unselected population hovers near the threshold for statistical significance, necessitating many phase II studies conducted with the hope of sufficient success to justify a large, expensive, phase III trial, which then often fails to demonstrate meaningful clinical benefit. The importance of identifying the target population is further exemplified by the recent experience with gefitinib, an inhibitor of epidermal growth factor receptor (EGFR) tyrosine kinase. Gefitinib was removed from clinical practice in the United States and Europe because of lack of benefit, but it has been brought back into use in Europe as a result of studies demonstrating benefit in non–small-cell lung cancers with activating EGFR mutations (6).

An effective biomarker-development strategy, pursued in parallel with drug development, can enrich a study population in likely responders and permit the demonstration of meaningful clinical benefit, reducing both the number of exploratory phase II studies needed and the requisite size of the definitive phase III trial. The improved efficiency should drastically reduce the cost of drug development and, potentially, the price of drugs. In addition, it should allow more successful drugs to be developed more quickly. Several recent studies emphasize this opportunity. A phase I/II trial that included only those patients with a translocation of the EML4/ALK gene, seen in less than 5% of patients with advanced non–small-cell lung cancer, demonstrated remarkable responses (greater than 50%) to treatment with PF-02341066, a targeted oral drug that inhibits ALK receptor kinase (7). This result has now led to a larger trial in an enriched cohort of patients that would be predicted to benefit from the drug. A similar trend is seen in early studies with another targeted oral drug, PLX4032, in melanoma. More than 80% of patients with the BRAF V600E mutation had tumor regression (8).

So why has this strategy been so difficult to pursue? First, there is the challenge of collecting tissue samples for these assays—samples that must be obtained at the time of treatment, not at diagnosis, because the biology of the disease often changes substantially during the course of treatment. Too often, an additional requirement for sample collection in a clinical trial is viewed as too onerous and will negatively affect patient accrual. Recognizing the importance of the information that can emerge from such trials, we must facilitate the implementation of the most promising assays. Of course, it is also true that as data that demonstrate the power of the assay to guide therapy more effectively accumulate, there will be incentives for going the extra step, to collect the tissue for analysis. Doing so will be necessary to improve outcomes for patients.

Second, in our experience, biologists and physicians gravitate toward “simple” assays, believing that a complex genetic or genomic assay cannot be a routine clinical assay but rather is just a discovery tool. But in most instances, simple biomarker tests, such as immunohistochemical assays or gene-amplification tests, may not reliably distinguish the feature of the tumor that determines the response to a given drug. The trastuzumab example cited above illustrates the challenge posed by using simple assays for the target. The fact that only 30% of those patients with the target (HER2-positive) actually benefit from the drug highlights the fact that simply having a knowledge of the presence of the target is not sufficient to optimize the use of the drug. Similar examples exist for cetuximab and histone deacetylase inhibitors in solid tumors, and probably reflect the complexity of the pathways and the impact of other cooperating mutations. These observations emphasize the importance of not simply relying on the target as the biomarker but rather developing more complex biomarkers that can assess these contextual effects.

The advances made in genetics and genomic technologies provide the tools to address this underlying biological complexity. The effect of K-Ras mutations on resistance to cetuximab in colon cancer patients is one such example (9, 10). Other work has demonstrated a role for PI 3-kinase activation in determining the response to trastuzumab in HER2-positive patients (11). These examples illustrate the complexity of cancer phenotypes and the fact that the simple assay of the target may only be a starting point in identifying who is likely to benefit from a drug.

It is also true that tests for single genetic abnormalities, such as screening for K-Ras mutations in colorectal cancer, are unlikely to be sufficient to fully dissect the complexity of cancer phenotypes. For instance, although patients with K-Ras mutant colorectal cancer are uniformly resistant to cetuximab, only a fraction of K-Ras wild-type patients benefit from the drug. Further work suggests that BRAF status, EGFR amplification, and cytoplasmic expression of PTEN might influence cetuximab efficacy (12), emphasizing the importance of further dissection of these complex signaling events.

The power of genomic measurements, and in particular of gene expression profiles that capture subtle variations in biological phenotypes, offers great promise in going beyond the assays for drug targets or even downstream genetic alterations. Some have argued that complex genomic assays cannot be translated into routine clinical practice, but in reality, these genomic tests are often no more difficult to use than many standard clinical assays. The test results can often be reduced to a simple overall score, and several have already been shown to be applicable in day-to-day clinical practice. As two examples, complex expression profiles that are prognostic for breast cancer, assayed by either reverse transcription polymerase chain reaction (OncoType Dx) or DNA microarray (Mammaprint), are already in routine clinical use and have formed the basis for two large phase III trials (TAILORx and MINDACT, respectively) that are evaluating the extent to which these tests do indeed help to classify patients with respect to risk and the need for chemotherapy (13, 14).

A further example of using complex assays in prospective clinical studies, in this case to match patients with the most appropriate therapy, can be seen in a breast cancer neoadjuvant trial (testing drugs to shrink the tumor preoperatively) under the sponsorship of the Department of Defense Breast Cancer Program (15). In this case, gene expression signatures previously shown to predict response to either doxorubicin or docetaxel (16) are being used to select a chemotherapy regimen. This prospective randomized phase II trial, comparing response rates when drugs are selected randomly versus guided by the genomic signature, provides a paradigm for implementing these assays in day-to-day clinical practice in a manner that is still compatible with the standard of care. Such studies
demonstrate the feasibility of collecting fresh tissue in a prospective trial and the capacity of a complex gene expression assay to be implemented in a real-time fashion. The further important opportunity deriving from such a study is the ability to identify patients who are likely to be resistant to therapy so as to set the stage for follow-on studies that could then evaluate more experimental treatments.

We must also recognize that the challenge will only increase, because genome-scale DNA sequencing has shown that there can also be substantial complexity in the gene alterations within a single patient’s cancer. Most cancer genomes are peppered with mutations and alterations, and although not all of them define the cancer phenotype, estimates suggest that many cancers harbor more than 10 alterations of importance. Thus, it is probable that no single drug, even if used in a patient likely to have a response, will be highly effective. Although the concept of combination therapy is not new, the current process of developing combinations by trial and error is neither efficient nor feasible, given the enormous complexity of cancer. Hence, we need to develop a strategy to guide the use of drugs and drug combinations.

Although the theme of the 2009 annual meeting of the American Society of Clinical Oncology was “Personalizing Cancer Care,” most studies presented there were investigating drugs in unselected cohorts of patients. There must be a greater sense of urgency in the planning and execution of genomic-guided or biomarker-driven trials. Conducting trials that evaluate drugs in unselected populations of patients, knowing that only a very small fraction of these patients will actually benefit from the drug, is a practice that should stop. Although we can’t say that in each and every case the collection of biopsies will enable the development of effective biomarkers, we can say that in the absence of these tissue samples, biomarker development will be impossible. It’s challenging to change this paradigm, no question about it. But it can be done—witness the recently completed BATTLE trial at the University of Texas M.D. Anderson Cancer Center, which enrolled more than 200 advanced-stage lung cancer patients, with fresh tissue biopsy samples collected from each (17). Likewise, the ACOSOG Z1031 neoadjuvant breast cancer trial evaluating aromatase inhibitors accrued 377 patients, again with fresh tissue biopsies (18). It can be done.

We have reached a juncture where talking about personalized cancer medicine and the importance of incorporating these goals into clinical trials is no longer sufficient. Rather, we must address this challenge head on and develop mechanisms to ensure that new studies make the best use of the available technologies. Perhaps one component of the approval process for new clinical trials should be a viable and valid plan for biomarker discovery and development. It could be argued that it is unwise and perhaps unethical to continue the practice of treating large numbers of unselected patients knowing that only a fraction will benefit—and further knowing that there are technologies available that have the potential to match the right drug with the right patient. We owe it to the patients, and to all of us who potentially will be patients, to change this practice if we are to make meaningful gains in implementing effective cancer therapy and winning the war on cancer.

REFERENCES AND NOTES

10. A randomized phase II trial comparing 16 to 18 weeks of neoadjuvant chemotherapy to 25 mg daily, letrozole (2.5 mg), or anastrozole (1 mg) in postmenopausal women with clinical stage II and III estrogen receptor positive breast cancer (http://clinicaltrials.gov/ct2/show/NCT00698971).
11. Competing interests: A.P. is a member of the Scientific Advisory Boards of Eli Lilly and Company, GlaxoSmithKline, and CancerGuideDx. J.R.N. has been a member of the Scientific Advisory Boards of Johnson & Johnson, Millennium Pharmaceuticals, CancerGuideDx, and the Erbitux Biomarker Advisory Board of Bristol-Myers Squibb and holds equity in Expression Analysis, Inc. A.P. and J.R.N. are listed on Duke University patent applications that describe methods for using genomic signatures to predict oncogenic pathway activation and for predicting chemotherapy sensitivity.
14. A randomized phase III trial comparing 16 to 18 weeks of neoadjuvant exemestane (25 mg daily), letrozole (2.5 mg), or anastrozole (1 mg) in postmenopausal women with clinical stage II and III estrogen receptor positive breast cancer (http://clinicaltrials.gov/ct2/show/NCT00698971).
Refocusing the War on Cancer: The Critical Role of Personalized Treatment
Anil Potti, Richard L. Schilsky and Joseph R. Nevins (April 21, 2010)

Editor's Summary

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