Translating Clinical Trials into Meaningful Outcomes

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Abstract

Efforts to unravel the complex biology that is necessary to develop new therapies best suited for an individual with cancer are at a crossroads with a strained health care system and an insufficient clinical trial apparatus. The resulting failures have been described as the “valley of death.” Progress into the future will require new considerations and the engagement of a broad band of stakeholders. To identify novel therapeutics that are likely to succeed in late development and to be meaningful for clinical practice, investigators will need to make a paradigm shift in designing clinical trials and endpoints while adhering to scientific rigor when interpreting results and making informed decisions. Large phase III trials that show a modest incremental benefit will continue to diminish in value for patients, clinicians, payers, and industry. Outcomes that are robust in both magnitude and application to the real world will take on increasing importance. Ensuring active participation by patients, lowering barriers to health care access, and protecting patients through health care reform are requirements for the future success of the cancer clinical research enterprise. The challenge today is to develop new approaches to translate scientific discovery into cost-effective and meaningful improvements in cancer outcomes.

Cancer is now the major killer of Americans under the age of 85 (1). Death rates are falling only slowly, and the number of cases is expected to increase steadily as the population ages. Juxtaposed against this modest decline in mortality rates has been unprecedented progress in understanding the process of oncogenesis and tumor progression, with increasingly detailed insight into the genetic alterations that predispose to cancer, identification of structural alterations in DNA that are acquired in the setting of cancer, and demonstration of pathways that are activated or suppressed in this disease. These discoveries have permitted the development of novel therapies directed at the molecular underpinnings of cancer, which in turn has facilitated the development of individualized cancer medicine. Personalization of therapy will also be facilitated in the future by increasing insights into the effect on therapy of normal host genotype (pharmacogenetics) and host physiological factors (potentially assessable by noninvasive imaging and other means).

Efforts to identify the unique features of a patient’s cancer and employ this information to define individualized treatment regimens have had limited success. Nonetheless, a well-reasoned approach to cancer therapy supports the concept that administering specific drugs to patients with specific molecular characteristics may yield major dividends. Consistent with this approach to individualized cancer care is the maturation of comparative effectiveness research coupled with cost-effectiveness research to ensure that both patients and society at large will benefit from high-value clinical interventions.

The failure to translate basic research into a product that can change clinical practice and public health was recently described as the “valley of death” (2). Contributory factors to this valley of death with respect to clinical cancer research and care include a strained system that is ill-equipped to address novel drug development, and clinical trials that yield modest gains for which the general public must sometimes pay exorbitant prices.

A new set of metrics is needed to make judgments about which new findings are clinically valuable or unimportant, and whether they represent good value to the patient in terms of both survival and quality of life. In addition to these objective considerations, we must also consider the ethical implications of the health system. To that end, we should encourage debate about how to optimize cancer research and cancer care in order to make high-quality screening, diagnosis, and therapy available to the greatest...
number. In this CCR Focus series, we address many controversial issues regarding drug development and the identification and dissemination of beneficial therapeutics.

The articles included in this series discuss issues that will be of critical importance as we strive to develop novel approaches to cancer prevention, diagnostics, and therapy that meet the high bar of clinical efficacy and cost-effectiveness. These issues and the studies that address them can be briefly summarized as follows:

1. The view that the current system of oncology drug development is not serving us well from the standpoint of providing useful therapies or prevention strategies at manageable costs is now widely accepted. Specific suggestions for changes that should be introduced, and why, are presented in several of these articles. In particular, LoRusso and co-authors (3) argue for a different paradigm in the development of targeted anticancer therapies. Specifically, the authors speak of a paradigm shift in which the clinical development of a targeted agent would be tightly linked to interaction with the planned target. Thus, they argue that “if investigators do not see target effects, they should declare a ‘no-go’ rather than spending critical resources pursuing a lower chance of success.” The combination of the diverse drugs we have in the pipeline today and our increasing ability to characterize tumors molecularly gives us the luxury to pursue smarter cancer drug development. We should move away from a “lottery” approach in which we hope for surprises and unanticipated off-target effects. For example, although sorafenib has been heralded as an example of successful targeted development, it actually failed to inhibit its anticipated target. LoRusso and colleagues argue that the main goal of phase I trials should be broadened from just defining the recommended phase II dose to also identifying, whenever possible, subpopulations in which there is potential for activity, and to begin investigating, as early as possible, biomarkers to define the use of the novel agents relative to specific targets. In some instances, the important biomarker or target will be the one that was initially predicted to be important, whereas in other cases we will find that the truly important targets were unanticipated. The essential factor is that we have tissue samples available from patients in early trials that will allow us to assess the characteristics of tumors prove to be particularly sensitive. LoRusso and colleagues argue for more rational early clinical trial designs. This could include a shift to a narrower patient population, i.e., patients for whom a particular drug is being developed. This could also include “window of opportunity” studies in which patients who have good standard options are enrolled for only one or two cycles of a phase I therapy and are then moved on to the standard option of choice. This type of design will become more critical as the pipeline of drugs available in the community continues to grow. Conducting multiple phase II trials with the goal of empirically seeking a signal for further development is difficult to justify in the modern era unless that signal is both molecularly defined and compelling. Current approaches should be replaced with selective, hypothesis-driven, adequately designed phase III enabling studies, with patients selected based on the presence of targets that are found in phase I and II trials to predict major drug benefit.

2. The complexities of phase III trial designs are reviewed by Booth (4), who details improvements that have been made in the clinical trial system since the 1970s, but also notes areas in which there has been little change. Biostatistical input and design has, in part, helped to define incremental benefits in phase III trials. Such trials have steadily grown larger as it has become clear that some incremental benefits can only be demonstrated in a large trial cohort. This has the net effect of decreasing the number of trials that can be carried out, and brings with it the need for an ever-larger cadre of data managers, contract research organizations, and monitoring organizations. The need to gather data in very large trials also brings with it the need to open more clinical trial sites and require more data integrity documentation, all at greater cost, despite the fact that some sites enroll few patients. However, the most important aspect of trial size is that if it takes a large trial to demonstrate drug efficacy, either the impact of the new therapy must be very modest (and hence may well not be worth the associated costs) or the therapy must only be benefiting a small subpopulation. In the latter case, resources could perhaps be put to better use in the translational quest to define who will benefit rather than to determine whether a small benefit can be detected in a large population of unselected patients. For example, if the drug target is present in only 10% of patients, then selecting patients with the target of interest can decrease the number of patients required to demonstrate by up to 99%, and can cut phase III costs by up to 95% compared with conducting the trial in unselected patients (5). Booth notes that studies are also needed to confirm whether clinical trial results translate to the real world and the tested drug actually provides the expected benefit.

3. Fojo and Parkinson (6) discuss the limited clinical utility of current targeted therapies, as well as their exaggerated importance when reported at scientific meetings, and an approach to performing smarter clinical trials by identifying subjects with the target(s) at which therapy is directed. They also note that clinical trials reporting marginal improvement likely include not only patients who received benefit or no benefit, but also patients who were harmed. Several recent examples of this (e.g., addition of erlotinib to chemotherapy in the frontline therapy of non-small-cell lung cancer (NSCLC) (7)) reinforce the notion
that our clinical-trial approach must be rigorously scientific.

4. It is important to ensure that patients understand the benefits, especially if marginal, of the therapies being offered to them. Oncologists and health care providers must become more proactive in discussing options, potential toxicities, and benefits with patients, and should discuss the therapy’s potential costs. Smith and Hillner (8) remind us that we must be candid with our patients, and that patients have a far greater ability to understand the value of marginal therapies when cure is not a goal. Temel and colleagues (9), in introducing early palliative care for NSCLC, confirmed in a clinical trial the arguments of Smith and Hillner, and further showed an almost 3-month survival benefit simply by adding palliative care to standard cytotoxic therapy.

5. The recently passed health care reform act is predicted to change the face of clinical medicine over the next 10 years. This legislation offers the possibility of expanding access to cancer and other health care arenas, creating information networks that transcend individual health care networks, and facilitating clinical research on a scale that was unprecedented in the past. How is that predicted to alter the outcome for all stakeholders, and what impact will it have on scientific advancements? Dalton and colleagues (10) itemize some of the implications of the Patient Protection and Affordable Care Act of 2010 for cancer researchers. Although we recognize that it does not solve every problem, ensuring that patients have access to insurance benefits while they are enrolled on a clinical trial is in itself a major advance.

6. The importance of supporting the clinical trial network by health care insurance is clearly laid out in the article by Klamerus and colleagues (11). Over a 5-year period at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, 628 (13.6%) of 4,617 patients who had signed informed consent documents to enroll in a clinical trial were denied enrollment due to lack of coverage by their insurers for their participation. Denial of access to therapeutic clinical trials, even among insured patients, is a significant barrier to clinical cancer research. This barrier spans racial, ethnic, and gender categories, and it therefore skews the outcome of such clinical trials, limiting our understanding of the potential impact of an investigational therapy across the entire population.

7. We must do a better job of defining what constitutes patient benefit rather than being swayed by marginal statistical considerations. The pivotal question is, How do we assign value to a specific antineoplastic therapy? The final article in this CCR Focus series, by Schnipper et al (12), grapples with this problem. They discuss how the U.S. health care system might define the value of a given cancer therapy, and suggest factors that should be considered when crafting a system that provides for equitable distribution of cancer care (health care) resources. The problem of rising health care costs in the United States, and its impact on society and individuals is discussed. They also direct our attention to potential alternatives, such as the algorithms used in the United Kingdom to assess the value of new therapies within the constraints of a fixed health care budget. The authors pose a number of ethical considerations that arise in the context of broad use of costly new cancer therapies of modest or little value. In particular, they note that the societal imperative to rescue those in urgent peril is often applied to the terminally ill cancer patient, and large amounts of money and effort are spent simply to prolong life by a few days or weeks. They argue that this “rule of rescue” should not be applied in most circumstances in oncology, and that

Table 1. Recent “Significant Advances” (P < 0.05) in Epithelial Malignancies in Patients Who Had Not Been Selected on the Basis of Molecular Characteristics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Tumor</th>
<th>Survival Gain (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine (15)</td>
<td>Pancreas</td>
<td>1.5</td>
</tr>
<tr>
<td>Bevacizumab (16)</td>
<td>Colon</td>
<td>2.2</td>
</tr>
<tr>
<td>Erlotinib (19)</td>
<td>Pancreas</td>
<td>0.4</td>
</tr>
<tr>
<td>Bevacizumab (17)</td>
<td>NSCLC</td>
<td>2</td>
</tr>
<tr>
<td>Sorafenib (20)</td>
<td>renal</td>
<td>2</td>
</tr>
<tr>
<td>Temozolamide (18)</td>
<td>GBM</td>
<td>2.5</td>
</tr>
<tr>
<td>Docetaxel (21)</td>
<td>Prostate</td>
<td>2.4</td>
</tr>
<tr>
<td>Topotecan (22)</td>
<td>Cervix</td>
<td>2.3</td>
</tr>
<tr>
<td>Cetuximab (23)</td>
<td>Colon</td>
<td>1.5</td>
</tr>
<tr>
<td>Erlotinib (24)</td>
<td>NSCLC</td>
<td>2</td>
</tr>
<tr>
<td>Cetuximab (26)</td>
<td>NSCLC</td>
<td>1.2</td>
</tr>
<tr>
<td>Bevacizumab (25)</td>
<td>Breast</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Data from Stewart and Kurzrock (27).
if patients and physicians were better prepared [as outlined by Smith and Hillner (8)], this tendency would be mitigated. Furthermore, the more we know about which patients are most likely to benefit from a therapy and which are least likely to do so, the more rationally we can direct these "rescue" attempts.

The main conclusion we can draw from this collection of studies is that the system for supporting clinical cancer research and care in the United States needs to be reassessed. Fortunately, this issue is receiving a large amount of attention from leaders in the field, some of whom have contributed to this CCR Focus series. We anticipate a future in which trials will be streamlined to include subjects whose cancers are sufficiently well characterized and represent a plausible substrate for the targeted therapy(ies) under investigation, not only in traditional phase I–III studies but also in phase 0 and phase IV (postmarketing) trials. We must be open to new, more streamlined clinical trial designs; to "go/no-go" decisions; and to new approaches for collecting data. We must move beyond current rigid clinical trial paradigms and embrace the use of studies that move seamlessly from phase I to phase II and III without requiring additional time-consuming protocol writing and regulatory review, and we must increasingly use adaptive designs that permit us to use knowledge gained from patients treated earlier in a study to guide selection of subsequent study patients.

Furthermore, ultimate approval of the new agent should be based on the observation of clinically unequivocal benefit (such as the ability to lead to a high rate of marked tumor regression or substantial prolongation of survival in a molecularly defined population) rather than on simple statistical "proof" of a survival advantage in unselected patients. The use of high response rates in nonrandomized trials has proved to be a very reliable basis for approving agents (13). On the other hand, randomized trials has proved to be a very reliable basis for approving patients. The use of high response rates in nonrandomized studies but also in phase 0 and phase IV (postmarketing) trials. We must be open to new, more streamlined clinical trial designs; to "go/no-go" decisions; and to new approaches for collecting data. We must move beyond current rigid clinical trial paradigms and embrace the use of studies that move seamlessly from phase I to phase II and III without requiring additional time-consuming protocol writing and regulatory review, and we must increasingly use adaptive designs that permit us to use knowledge gained from patients treated earlier in a study to guide selection of subsequent study patients.

Furthermore, ultimate approval of the new agent should be based on the observation of clinically unequivocal benefit (such as the ability to lead to a high rate of marked tumor regression or substantial prolongation of survival in a molecularly defined population) rather than on simple statistical "proof" of a survival advantage in unselected patients. The use of high response rates in nonrandomized trials has proved to be a very reliable basis for approving anticaner agents (13). On the other hand, randomized survival comparisons (particularly in unselected patients) can be very misleading (14), and have led to the approval of a wide range of agents that yield statistically significant results but provide limited benefits for unselected patients (Table 1) (15–26). Such survival-based randomized studies in unselected patients may miss a marked benefit in defined subpopulations, or alternatively it may result in a drug being widely applied even though it benefits only a small minority of patients (27). It also may miss the fact that a drug is helping one subpopulation while potentially harming another (7). For example, in one study, the addition of erlotinib to frontline chemotherapy in NSCLC had no significant impact on the overall population (28) (Fig. 1), but was associated with prolongation of progression-free survival in patients with EGFR mutations and shortening of PFS in those with K-ras mutations (7) (Fig. 2). Phase II studies should be designed to provide a preliminary definition of the distinct subgroups of patients who will benefit, rather than simply reporting a response rate in the overall population. We should aim for large,
unambiguous gains in small studies rather than for small advances in large trials. Although studies aiming for incremental benefits have improved outcomes in hematological and germ cell tumors, in childhood malignancies, and in the adjuvant situation, they have had only a marginal effect on most metastatic epithelial malignancies (27), and we must reject the trend toward conducting ever larger studies aimed at detecting ever smaller incremental gains. The size of the gain, and not the impressiveness of the P-value, must drive our decisions.

Finally, it should be noted that our steadily increasing armamentarium has the potential to stifle new drug development, as patients may switch from one minimally beneficial standard option to another before they are referred to a clinical trial. Futility therapy must be discouraged, and patients must be fully incorporated into the decision-making process. Patients need to be provided with information that will permit them to choose rationally, rather than given choices based on a small and unpredictable possibility of benefit. We must direct energy and attention to understanding our collective responsibility to provide innovation and care to those who are most likely to benefit in the context of a health care system characterized by cost-effectiveness and equitable distribution of diagnostic and therapeutic approaches to cancer (5, 29).

Disclosure of Potential Conflicts of Interest


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