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An agenda for *Clinical Trials*: clinical trials in the genomic era*

Richard M Simon

The mantra of many clinical trialists has been to do randomized clinical trials with broad eligibility and avoid subset analysis. Developments in cancer research, however, have raised some questions about this approach in the genomic era of molecularly targeted therapeutics.

A large body of evidence indicates that cancers of most primary sites are heterogeneous with regard to molecular pathogenesis, genomic signatures and phenotypic properties. Consequently, it is not necessarily reasonable to expect such tumors to have equal sensitivities to a drug that inhibits a particular protein target. The protein target may be driving tumor growth in only a subset of the tumors.

As an example, two large randomized clinical trials were recently reported comparing standard therapy to standard therapy plus a new drug, Iressa, for patients with lung cancer [1,2]. Both trials were convincingly negative. Nevertheless, the US Food and Drug Administration approved the drug based on the recommendation of an advisory committee. The approval resulted from evidence of durable partial tumor response in about 10% of patients with advanced lung cancer in an uncontrolled phase II study. Subsequent publications indicated that patients who responded in the phase II trial were those whose tumors had a mutation in the kinase domain of their EGFR gene, rendering those tumors highly sensitive to treatment with an epidermal growth factor receptor inhibitor such as Iressa [3,4]. This result, indicating that Iressa was highly effective for a small subset of cases and that large randomized clinical trials of unselected patients failed to identify the value of the drug, has provided a stimulus to think about clinical trial methodology for the evaluation of molecularly targeted drugs in oncology.

Clinical trials in which eligibility is restricted to those patients whose tumors are sensitive to the drug can be substantially more efficient than traditional clinical trials with broad eligibility. Some of the dramatic improvements in the possible efficiency have been indicated by Simon and Maitournam [5]. The improvement in efficiency results because the treatment effect is substantially larger in the focused clinical trial if there is a good assay available for selecting patients likely to respond to the new treatment. Such focused treatment can provide a more favorable benefit to complication ratio and result in a greater proportion of the treated patients benefiting from the treatment. This can also have important economic benefits for society. Currently, for some indications such as stage I estrogen receptor positive breast cancer, fewer than 10% of the patients treated with cytotoxic chemotherapy actually derive benefit from the drugs. The proportion may be even lower for prevention settings of cancer and other diseases.

It is important, therefore, to develop predictors of whether an individual is likely to benefit from a given drug. For some cancer treatments, predictors can be based on assays for the expression of the drug target. This is the case for tamoxifen and herceptin. In these cases, focused clinical trials with patients selected based on assay results greatly enhanced the efficiency of clinical development. For Iressa, expression of the epidermal growth factor receptor did not correlate with response during phase II development. In such cases, it is important to use the phase II development period to develop response predictors using other data. This may involve performing RNA expression profiling of tumors for patients in phase II trials or sequencing candidate genes looking for mutations that correlate with response.

RNA transcript expression profiling is a powerful approach for developing classifiers of tumor sensitivity to a particular drug [6–9]. There is

National Cancer Institute, Bethesda, MD, USA

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Author for correspondence: Richard Simon, Chief of the Biometric Research Branch, Division of Cancer Treatment and Diagnosis, National Cancer Institute, 9000 Rockville Pike, MSC #7434, Bethesda, MD 20892-7434, USA. E-mail: rsimon@nih.gov

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a misconception among some clinical trialists that the multiple comparison issues involved with gene expression profiles preclude their effective use for tailoring therapy. The misunderstanding arises partly from the failure to distinguish between prediction and inference and partly from a concern that gene expression data will be used as a basis for data dredging in phase III clinical trials. In fact, useful predictors can often be developed with quite limited numbers of cases [10,11] and used as completely specified classifiers in the design of confirmator phase III trials.

Most statistical methods were developed for inference. The development of a multigene expression profile based predictor of outcome with an experimental treatment based on phase II data is a prediction problem. The objective should be accurate prediction. The objective is not to ensure that all the genes included in the predictor function are necessary. In general, many genes are correlated and the genes selected for inclusion in the model may not be stable under replication or resampling even if the predictions are excellent. The objectives of developing such a predictor is different from the objective of identifying what genes are correlated with outcome. Although the development of outcome predictors generally involves a "feature selection" component, the multiple comparison issues involving controlling the number of false positive features included in the model is not of direct concern. We do not really care about the false discovery rate of genes, what we care about is predictive accuracy.

Ideally, pharmacogenomic predictors are developed using phase II data so that they can be utilized to increase the efficiency of phase III trials. At the time the phase III trial is designed, a fully specified predictor should be available. This predictor can be used to select patients for the phase III trial [5], or as the basis of a single completely predefined subset analysis in a phase III trial not limited by preselection of patients. In either case, the phase III trial is free from the problems of data dredging.

Randomized clinical trials have been one of the most important developments in modern medicine and they will continue to be important. Whole genome technologies make it more feasible to develop disease classifiers which can make randomized clinical trials much more efficient, and treatments more effective. Such classifiers are direly needed in fields such as cancer, where the proportion of patients who actually benefit from most treatments is quite low, and the economic costs of treating the many for the benefit of the few are enormous. The change from our current approach to therapeutics development to a more personalized approach is not likely to occur rapidly, however. Technologically, the use of RNA transcript profiling data is limited by the availability of tumor tissue with preserved RNA. There are also many other obstacles that must be overcome. The development of traditional single protein biomarkers has been ineffective in oncology [12–15]. There is a lack of understanding among academic, industry, and government scientists of effective paths and appropriate requirements for development and validation of therapeutically relevant biomarkers. The development of profile biomarkers based on high dimensional assays offer additional challenges [16,17]. There are also important disincentives that must be overcome on the part of drug sponsors and clinicians. Pharmaceutical companies naturally prefer products with broad labeling indications. Development strategies, such as use of the predefined subset approach described above, must be identified that enable companies to invest in the development of pharmacogenomic signatures without the risk of losing broad labeling indications where supported by the results of phase III trials.

The randomized clinical trial remains a generally indispensable tool for the final evaluation of interventions. But genomic technology provides the opportunity to tailor treatments to those patients most likely to benefit. This is important for individual patients and essential for our societal health care budget. Biostatisticians and clinical trialists have made enormous contributions to medicine and should be proactive in addressing the important challenges involved in effectively combining these two areas.

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