Moving Toward Individualized Cancer Therapies

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Abstract In vivo analysis of the gene expression profiles of cancer cells before and after treatment in patients may define mechanisms of sensitivity and resistance to specific drugs and ultimately allow for the selection of optimal individualized therapy to improve outcome in cancer.

The ultimate goal of cancer therapeutics is to identify which drug regimen will benefit an individual patient. Advanced knowledge of the genetic lesion present in tumors already allows clinicians to choose the most effective drug, i.e., the kinase inhibitor Imatinib in chronic myelocytic leukemia or epidermal growth factor receptor inhibitors in a subset of lung cancer patients. These targeted therapies inhibit one or only few proteins and show a bimodal response pattern (only those patients with the genetic lesion respond to the therapy). In most cases, however, response to drugs shows a continuous spectrum (1). Defining the causes of this variability is essential for designing more effective and individualized therapies. So, which are the causes of this variability? A major component is linked to the local, anatomic tumor microenvironment, including matrix proteins, stromal cells, and angiogenesis. Second, patient’s age, sex, diet, concomitant conditions, and performance status also increase interpatient variability. Third, intertumor and intratumor heterogeneity due to variations in cell kinetics, apoptotic index, proliferation rate, and fraction of cells in S phase also effects response (1). Finally, this variability can be due both to genetic variation in the tumor and host factors affecting drug pharmacokinetics and pharmacodynamics (2).

Although the above three causes of variability are largely stochastic and difficult to ascertain, current technologies allow for precise definition of the genetic predisposition of the patient and of the specific genomic makeup of tumors in vivo. In this context, multiple studies have attempted to define whole-genome responses to drugs; however, most studies have used tumor cell lines in vitro or xenograft models in vivo, which may not reflect mechanisms underlying drug action and resistance in patients (3). To bypass these limitations, the analysis of gene expression profiling (GEP) of tumor cells before and after treatment has been proposed in hematologic malignancies, where samples can be easily obtained. Moreover, these tumors often present specific molecular signatures linked to clearly defined chromosomal translocations and to clinical outcome. For example, Evans and coworkers have for the first time studied tumor cell GEP before and after treatment in acute lymphoblastic leukemia (3). GEP of acute lymphoblastic leukemia cells done before and 24 hours after treatment with drugs commonly used in the treatment of this disease allowed for identification of genes and pathways involved in response, whereas additional studies highlighted genes and pathways associated with resistance (4).

In the current issue of CCR, Burington et al. (5) have extended these studies to multiple myeloma (MM). This cancer is characterized by clonal proliferation of neoplastic plasma cells in the bone marrow in association with elevated serum and/or urine monoclonal immunoglobulin (6, 7), and accounts for 10% of all hematologic malignancies. Despite high-dose chemotherapy with stem cell support and advances in novel treatments including thalidomide, bortezomib, and lenalidomide, it remains incurable, with a median survival of 6 years (6). Multiple studies have used genomics to define subgroups of MM patients based on specific genetic lesions including specific chromosome gains or losses, as well as immunoglobulin-related chromosomal translocations (8, 9), which have distinct prognosis and outcome when treated with conventional, high-dose, and novel therapies. Importantly, MM also represents a model of the importance of the tumor microenvironment in tumor pathogenesis because both direct adherence of MM cells to bone marrow and related induction of cytokines trigger tumor cell growth, survival, and cell adhesion–mediated drug resistance to conventional therapies.

Burington et al. (5) have done GEP on tumor samples in 87 newly diagnosed patients with MM, both before and 48 hours after treatment with either dexamethasone or thalidomide (Fig. 1). Most genes whose expression was significantly altered after therapy showed similar fold change after either thalidomide or dexamethasone treatment, suggesting that both drugs effect similar genes and pathways to elicit their therapeutic action. However, there were also a sizable number of genes that exhibited a differential response, with one drug inducing upregulation and the other having an opposite effect. Unlike a prior study by Holleman and colleagues (4) who used a subset of genes to evaluate event-free survival, the current study did a gene-by-gene Cox regression analysis to identify genes associated with event-free survival (6). Of 1,225 genes significantly differentially expressed before and after therapy, 95 showed a significant association with event-free survival. Importantly, those 87 patients included in the experimental group receiving either dexamethasone or thalidomide were also subsequently treated with two cycles of high-dose therapy, each followed by...
autologous stem cell transplantation (Total Therapy 2; ref. 10). The event-free survival and overall survival data used to identify those genes linked to survival were based on a treatment which therefore included several drugs and treatments in addition to thalidomide or dexamethasone. To obviate this limitation and strengthen their conclusions, the authors examined an independent cohort of 36 relapsed patients treated with the single agent lenalidomide, a thalidomide analogue, and found that those 95 genes emerging from the survival analysis of the 87 patients treated with thalidomide or dexamethasone were also significantly associated with event-free survival and overall survival in this group of relapsed patients treated with lenalidomide. Moreover, in 19 patients with available pretreatment and 48-hour posttreatment samples, GEP changes induced by lenalidomide were similar to those triggered by its analogue thalidomide. These findings suggest that this set of 95 genes may both allow for stratification of patients and provide insights into genes and pathways critical for drug response.

Several issues remain open. The timing of follow-up GEP is critical to define and distinguish between early, drug-specific versus late, nonspecific responses, such as apoptosis. This choice is heavily dependent on the drug tested, given the wide pharmacokinetic and pharmacodynamic variations between compounds. Given the role of the host microenvironment not only in tumor pathogenesis but also in pharmacokinetics and pharmacodynamics, in vivo studies using genetically engineered mice or severe combined immunodeficient-hu models in which human MM cells are injected directly into human bone within severe combined immunodeficient mice will likely be needed to predict the appropriate time for follow-up GEP in clinical trials. The reliance solely on treatment-induced variation in gene expression profile in tumor cells is another limitation of these studies. Specifically, recent reports show extensive modification of kinases after treatment with different drugs (11), highlighting the importance of posttranslational modification. This essential component of drug response and resistance must be integrated with GEP analyses in the future.

A final important focus will be to integrate data examining drug response in individual patients with currently available and ongoing data collection of GEP before therapy, which is directed to identify patient subgroups responding to novel

**Fig. 1.** Schematic representation of the experiments done in Burington et al. (5). Network analysis and comparison of the data obtained from an individual patient with comprehensive databases of patients treated with the same drugs may both provide insights into the mechanism of action and resistance of drugs in vivo and allow for refined personalized therapies.
therapies, i.e., bortezomib (12), and with genomic analyses that have identified different genetic subgroups of disease. Remarkably, in both acute lymphoblastic leukemia (3) and MM (5), GEP changes after treatment were independent of genetic subgroups, with common networks altered after similar treatments irrespective of molecular subtype of disease. This finding is surprising, given the different prognosis between different genetic subgroups in MM and acute lymphoblastic leukemia. Indeed, one would expect different GEP profiles after exposure of patients with distinct genetic subtypes to single agent or combination therapies. In the future, such genomic and proteomic studies after a “test dose” with a single or combination therapy of drugs may define mechanisms of sensitivity versus resistance between different subgroups and ultimately allow for selection of optimal individualized therapy to improve outcome in MM and other malignancies.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

References