

SOUNDING BOARD

Limits to Personalized Cancer Medicine

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Rapid advances in the molecular characterization of tumors, including complete gene sequencing of multiple cancers in the Cancer Genome Project, have led to an increased understanding of the molecular pathways that underlie cancer. These genomic changes differentiate tumors from normal tissues, permitting targeted treatments for several types of tumor and thereby extending survival and improving patients' quality of life. Examples include trastuzumab for human epidermal growth factor receptor type 2 (HER2)-expressing breast cancer¹ and vemurafenib for melanomas that express mutated *BRAF*.² These drugs have become standards of care and are important components of cancer treatment. The genomic changes define groups of patients with cancer who can benefit from treatment, although for most patients with metastatic cancer, the duration of benefit is limited and is followed by drug resistance and cancer progression.

Progress in molecular pathology studies and their decreasing cost, increasing speed, and more comprehensive evaluation (from gene sequencing to expression profiles and proteomics) have encouraged investment by funding bodies and cancer centers in personalized (or precision) cancer medicine. The concept underlying this research is that molecular analysis of a tumor in an individual patient will allow the selection of effective drugs to control that tumor and thereby prolong survival. This concept is appealing to patients and to foundations that support cancer research, and the molecular characterization of tumors is being marketed directly to patients, despite a lack of evidence of benefit.³ Here we critically review the problems that have been associated with personalized medicine in patients with cancer; we suggest that the clinical benefit of personalized medicine as it is currently practiced will be limited.

RESEARCH PROGRAMS

There is a strong focus on personalized medicine by large cancer centers and those who fund research. In his State of the Union address, President Barack Obama announced that he had allocated \$215 million in the 2016 U.S. budget for precision medicine, of which \$70 million is allocated to the National Cancer Institute (NCI) to support research and clinical trials of personalized cancer medicine as part of the Cancer Moonshot Initiative.⁴ Almost all the 69 NCI-supported cancer centers have websites that emphasize programs in personalized medicine, although many centers advise patients that personalized medicine cannot yet be applied in the selection of treatments. Large, international cancer centers also have dedicated programs.

Most institutions are pursuing independent research and clinical programs. Inevitably, different programs will document similar successes, limitations, and problems, which wastes resources, including patients to participate in well-designed trials, clinicians' and scientists' time, and money. Some groups have formed consortia, such as the Lung Cancer Mutation Consortium,^{5,6} which consists of 16 sites in the United States that are testing for driver mutations in multiple genes in metastatic adenocarcinoma of the lung, and the Stratification in Colorectal Cancer program in the United Kingdom,⁷ which has funding of £5 million (approximately \$6.6 million U.S.) to provide genomic analysis for 2000 patients with colorectal cancer, but such collaborations are rare. The Cancer Moonshot Initiative from the U.S. government provides opportunities to boost collaboration.⁴

Ideally (and historically), different cancer institutions emphasize different avenues of research, so resources are applied to investigate multiple promising areas. Funding for research

is finite, and the concentration of research on personalized medicine might deprive other promising avenues of research of appropriate resources (immunotherapy is an exception). A few large coordinated efforts are appropriate to determine whether personalized medicine might lead to substantial improvements in outcome, but it would be wasteful for 30 to 40 independent programs to study the same approach.

CLINICAL STUDIES

We are aware of one randomized trial that compared outcomes in patients who were treated with targeted drugs that had been selected to match the genetic sequence of their tumor with outcomes in patients who received standard care.⁸ We also know of three large series that evaluated feasibility and tumor response in persons with advanced adenocarcinoma of the lung or in women with breast cancer, whose treatment was selected on the basis of limited gene sequencing,^{5,6,9} and three large series that evaluated the feasibility of inclusion in trials or outcomes in large series of patients undergoing genetic testing at three cancer centers.¹⁰⁻¹²

The outcomes of these investigations are discouraging (Table 1). Although 30 to 50% of the patients who were referred for genetic analysis of their tumors had driver mutations that were thought to stimulate tumor progression (see below), only 3 to 13% had treatments that had been selected by individual genomic analysis. There was no between-group difference in outcome in the randomized trial,⁸ and a low proportion of the referred patients could be included in prospective trials or had any signal of benefit (<5%) in the single-group studies.

Multiple factors may contribute to the limited success of the current clinical evaluation of personalized medicine, including limited access to targeted agents both within and outside clinical trials, as well as technical issues such as inadequate tumor specimens for analysis. Proponents point out correctly that molecular characterization will improve and that new and better drugs are likely to contribute to better results in future trials. However, we suggest that inherent limitations of molecular targeted agents, as well as the Darwinian evolution of tumors leading to intratumor heterogeneity, will limit this improvement.

MOLECULAR TARGETED AGENTS

An increasing number of anticancer drugs are available that target different signaling pathways. They have two major limitations: most molecular targeted agents provide only partial inhibition of signaling pathways, and many are too toxic to be used in combination. Pathways that signal cell proliferation or cell survival in cancer cells are highly plastic and adaptable,¹³ whereas pathways that stimulate cell death may be suppressed.¹⁴ Normal cells depend on related signaling pathways, and their inhibition by molecular targeted agents leads to toxic effects. There have been major inconsistencies between preclinical studies seeking to validate molecular targets and the inhibition of these targets by candidate molecules,¹⁵ and the few references to achievable clinical levels of inhibition of the molecular target by these agents suggest that doses with an acceptable safety profile provide incomplete target inhibition.^{16,17} This situation contrasts with almost complete target inhibition by effective therapies such as aromatase inhibitors for the treatment of breast cancer.¹⁸

The importance of molecular pathways is often specific to the cancer type. Several “basket” trials that are not based on histologic findings are ongoing in which patients with multiple types of cancer are recruited on the basis of an activated or mutated pathway. For example, vemurafenib was associated with a higher rate of survival than dacarbazine among patients with melanoma that expresses the *BRAF* V600E mutation² but had only modest activity against other biomarker-selected cancers that express this mutation sporadically.¹⁹

With the possible exception of immune-checkpoint inhibitors, cancer cells have an almost universal capacity to develop resistance to a single molecular targeted agent by means of up-regulation of the partially inhibited pathway, mutation of the target, or activation of alternative pathways. A combination of molecular targeted agents may inhibit alternative pathways, but the extent of signaling plasticity could render this approach impractical, because adaptive responses involve multiple other potential targets.¹³ Combinations of molecular targeted agents that target different pathways have often resulted in dose reduction because of toxic effects, thereby further reducing the inhibition of indi-

Table 1. Clinical Studies That Have Evaluated Personalized Cancer Medicine.*

Clinical Study	Design	Screened Sample	Patients with Genetic Profile	Patients with Mutation That Might Be Targeted by Drugs	Patients Receiving Matched Drug	Main Outcome Result
SHIVA trial ⁸	Randomized, controlled trial of matched molecular targeted agent or physician's choice	741 patients with metastatic solid tumors who were amenable to biopsy	496 (67%)	293 (40%), of whom 195 underwent randomization	96 (100% of experimental-therapy group)	No significant difference in progression-free survival (primary end point); hazard ratio for death or disease progression, 0.88 (95% CI, 0.65–1.19)
Lung Cancer Mutation Consortium	Testing for driver mutations in metastatic lung adenocarcinomas at multiple centers				Many treated as per guidelines for an approved biomarker	Longer overall survival in the subgroups with a mutation treated with directed therapy than in those without the mutation or those that do not receive directed therapy
Study I ⁵		1007 patients	733 (73%) tested for ≥10 genes	466 (46%)	260 (26%)	
Study II ⁶		1315 patients	919 (70%) tested for ≥8 genes	529 (40%) had mutations, with 187 (14%) of them that could be targeted by drugs and had follow-up	127 (10%)	
SAFIR-01 ⁹	Treatment chosen after genetic profiling by comparative genomic hybridization and gene sequencing	423 women with metastatic breast cancer	299 (71%)	195 (46%)	55 (13%)	4 patients had a partial response and 9 had stable disease for >16 wk (3% of screened sample)
M.D. Anderson Study ¹⁰	Treatment chosen after gene sequencing of patients with advanced cancer	2601 patients	2000 (77%)	789 (30%)	83 (3%) in genotype-matched trials; 116 (4%) with common mutations not in trial	Not stated
Princess Margaret IMPACT–COMPACT study ¹¹	Treatment chosen after gene sequencing of archival tissue	1893 patients with advanced solid tumors	1640 (87%)	938 (50%) had mutations, approximately 20% of which could be targeted by drugs	84 (4%) treated in genotype-matched trials	Response rate of 20% in genotype-matched trial vs. 11% in unmatched trials
Cleveland Clinic Study ¹²	Treatment chosen after gene sequencing	250 patients	223 (89%)	109 (44%)	24 (10%)	Not stated

* CI denotes confidence interval, COMPACT Community Oncology Molecular Profiling in Advanced Cancers Trial, and IMPACT Integrated Molecular Profiling in Advanced Cancers Trial.

vidual targets, and some combinations have been associated with unacceptable levels of side effects. In a review of 95 doublet combinations in 144 trials, approximately 50% of the combinations could use the full doses that were recommended for use as single agents, whereas other doublets required substantial dose reductions.²⁰ There are few examples of successful combination of more than two molecular targeted agents, so even if cost were not a consideration, the use of multiple such agents in combination is usually not feasible.

TUMOR EVOLUTION AND INTRATUMOR HETEROGENEITY

The molecular characterization of biopsy samples from different regions of multiple tumors in humans or from the primary tumor and metastases has shown substantial heterogeneity.²¹⁻²⁶ Likewise, sequential biopsy samples from tumor sites in the same patient show considerable genomic heterogeneity.²²⁻²⁵ These findings have led to a Darwinian model of tumor evolution, which can be represented by a branching tree²²: some mutations are present in all sampled cancer cells and are clonal markers of the cancer, whereas others are unique to subclones that are generated. Sensitive genetic characterization of individual cancer cells indicates that intratumor heterogeneity is present early in cancer development and that subclones are selected by cancer treatment.²⁷ Although many mutations may not influence proliferation or survival of the cancer cells (so-called passenger mutations), other acquired mutations (drivers) influence tumor progression and must be targeted in order for treatment to be effective.

The development of intratumor heterogeneity poses major limits to the potential targeting of mutated pathways on the basis of molecular analysis of a tumor sample (i.e., limits to the central concept of personalized medicine). Molecular analysis of a single biopsy sample from a tumor does not represent other parts of it, and treatment that is based on that analysis, even if there is an effective agent, is likely to have limited benefit because molecular pathways that are active in other parts of the tumor will lead to tumor growth from different clones of tumor cells. Although the analysis of circulating tumor DNA (ctDNA) might mitigate the challenges of

multiple biopsies, ctDNA may arise from subpopulations of a heterogeneous tumor, including dead cells, and the difficulty with regard to detecting minor, viable clones that are capable of repopulating a tumor after therapy remains. Treatment that leads to the death of drug-sensitive tumor cells might accelerate the emergence of resistant tumor cells, with tumor progression occurring largely by means of selection of preexisting tumor subclones.^{22,27} The failure to recognize the complexities of disease, of which intratumor heterogeneity is a prime example, is a key factor that is responsible for therapeutic failures²⁸ (<10% of anticancer drugs that enter phase 1 clinical trials are approved for marketing²⁹) and the disparity between the level of investment in biomedicine and its output to improve human health.³⁰

The essential question for personalized cancer medicine is whether any therapeutic strategy could provide cure or long-term remission despite the presence of intratumor heterogeneity. There are two possibilities. First, a clonal driver mutation might be present in all tumor cells and required for tumor progression despite other mutations in subclones, such that the inhibition of this pathway would lead to profound anti-tumor effects. Second, mutations that drive genomic instability and the development of intratumor heterogeneity could themselves be targeted. We think that successes from either approach are likely to be rare.

The successful treatment of chronic myeloid leukemia by imatinib is perhaps an example of such a clonal driver mutation,³¹ but it is an exception. The clonal BCR-ABL translocation is present in a high proportion of people with chronic myeloid leukemia and allows treatment of a group rather than an individual patient on the basis of the presence of a genetic biomarker. Responses of HER2-positive breast cancer to trastuzumab¹ and BRAF-mutated melanoma to vemurafenib² are probably due to driver mutations in all or almost all the tumor cells, but the emergence of drug resistance points to adaptation or selection of other driver mutations in subclones.

The targeting of clonal markers that are present in all tumor cells by immunotherapy, rather than the inhibition of the pathways associated with them, is a potential approach.³² The concept of targeting genes that control genomic

diversity is unlikely to succeed for the same reason that drugs that target the metastatic process are not useful: intratumor heterogeneity and micrometastases (in persons who will die from metastatic disease) will both be present by the time the tumor is diagnosed.²⁷ Although the targeting of a DNA-repair gene in patients whose tumors have an existing mutation in a second DNA-repair gene can lead to tumor response, this effect is transient and is most likely due to the requirement of DNA repair for tumor-cell survival rather than to the inhibition of clonal diversity.³³

COST

New drugs to treat cancer are marketed at ever-increasing prices, and unlike other commodities, price is unrelated to value (i.e., to clinical effectiveness).³⁴ Expensive medications can be cost-effective (e.g., imatinib and trastuzumab), but the development and marketing of expensive drugs with marginal effectiveness diverts resources from the development of more effective therapies.³⁵ The application of personalized medicine will involve substantial cost. Molecular analysis of tumor samples will become cheaper and more efficient, but the selection of multiple molecular targeted agents to treat tumors (concurrently or sequentially, depending on the presence of side effects) on the basis of aberrant pathways will be enormously expensive. This cost could be justified if the approach led to major gains in survival or its quality, but for the reasons we have expressed above, this situation is unlikely.

CONCLUSIONS

The concept of personalized medicine is so appealing (see reviews by Biankin et al.³⁶ and Swanton et al.³⁷) that seemingly only curmudgeons could criticize it. Learning more about the variability of the molecular characteristics of individual tumors and its relationship to the natural history and outcome of disease is important research but has not facilitated choice of treatment. We do not suggest abandoning personalized medicine but rather evaluating it in a small number of well-designed collaborative programs, with research programs that recognize and combat the limitations we have de-

scribed. There should also be a clear message to patients that personalized cancer medicine has not led to gains in survival or its quality and is an appropriate strategy only within well-designed clinical trials.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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