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Unique Molecular Landscapes in Cancer: Implications for Individualized, Curated Drug Combinations

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Abstract

With increasing lysophisticated technologies in molecular biology and ‘omic’ platforms to analyze patients’ tumors, more molecular diversity and complexity in cancer are being observed. Recently, we noted unique genomic profiles in a group of patients with metastatic breast cancer based on an analysis with next generation sequencing (NGS); amongst 57 consecutive patients, no two had the same molecular portfolio (1). Applied genomics therefore appears to represent a disruptive innovation in that it unveils a heterogeneity to metastatic cancer that may be ill suited to canonical clinical trials and practice paradigms. Upon recognizing that patients have unique tumor landscapes, it is possible that there may be a ‘mismatch’ between our traditional clinical trials system that selects patients based on common characteristics in order to evaluate a drug (drug-centric approach), and optimal treatment based on curated, individualized drug combinations for each patient (patient-centric approach).

Keywords

Clinical trials; Genomics; Personalized medicine

The canonical approach to cancer research and treatment is a drug-centric one. Specifically, for the most part, new therapeutics have been developed in large groups of patients who share a common histology based on the organ of origin of the cancer. The success of this strategy for patients with metastatic cancer has been modest. Recently, a more refined tactic has been instituted. Instead of grounding the classification system on the organ of origin or histology alone, new nosologies based on underlying molecular drivers or pathways, mostly as subsets of classic histologies, are being tested (2–4). The latter strategy combines a companion diagnostic that selects a subgroup of patients with a specific cancer by virtue of their harboring a specific biomarker which can be targeted by the agent under study. For example, a clinical trial may select patients with melanoma who have a *BRAF* mutation to

enroll on a trial of a BRAF inhibitor (4, 5). This is a rational approach to drug development conceptually and has also resulted in impressive response rates in clinical testing (5, 6). Beyond this first generation advance of combining companion diagnostics and drugs within histologies, are even more novel studies, known as “basket” or “bucket” or “histology-agnostic” trials, that select patients by the presence of the biomarker (e.g. *BRAF* mutations), regardless of the organ of origin of the cancer, for treatment with cognate inhibitors (e.g., BRAF inhibitors).

Although genomic selection has shown remarkably high response rates in metastatic cancer (3, 4, 7), inevitably most patients relapse, often within months, and succumb to their disease. The foundation of these approaches (both the canonical histology-based approach and the new genomic one) is finding a commonality amongst patients in order to test a drug or combination of drugs. Ultimately, therefore, these are drug-centric strategies. Yet, the new reality unveiled by genomics –that each patient with metastatic disease has a complex and, often, unique set of genomic aberrations--suggests that ideal management of metastatic cancer may require a new model (8, 9). Several approaches to this problem have been suggested (10). The classic one entails finding common pathway themes, even amongst the diversity of cancer aberrations (11, 12). Indeed, several investigators have shown that, even though patients may have diverse genomic aberrations, the pathways activated may converge (11, 12). Finding crucial oncogenic hubs that are held in common between patients therefore might be critical. However, it is possible that despite the convergence of pathways, as full genomic sequencing is supplemented by transcriptomics, proteomics and more, amplified diversity may be identified. Furthermore, it is increasingly clear that, even when a single pathway is activated, the precise aberration may have crucial implications for therapy. For instance, different epidermal growth factor receptor (EGFR) abnormalities, while all activating the EGFR machinery, may respond to distinct therapeutic molecules. In general, the exon 19 aberrations such as L747_A750del that delete the four amino acids LREA, as well as the L834R exon 21 mutation, are sensitive to the reversible epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors, including erlotinib and gefitinib (13, 14). In contrast, in-frame insertions and/or duplications of 3 to 21 base pairs clustered between codons 767 and 774 in EGFR exon 20 are resistant to both reversible and irreversible TKIs; T790M exon 20 mutations are also resistant to some irreversible TKIs such as afatinib in the clinic (15–17). The precise effects of these diverse aberrations on protein structure/function and, hence, therapeutic actionability may require a precise understanding of three-dimensional protein crystal structure and function.

With rare exceptions, patients with advanced disease will fail to achieved urable responses with even targeted drug regimens. Resistance emerges through a variety of mechanisms (2, 18, 19), as clones of tumor cells (either with *de novo* or acquired resistance) evolve. Rational combination approaches selected based on current bioinformatic and molecular analytic approaches, tailored for each individual based on their unique molecular profiles, and curated to prevent the development of resistance, represent a solution that warrants exploration. However, logistically, this approach represents several challenges, since it fails to conform to the historic framework created for clinical trials and practice. Most importantly, if the complexity revealed by genomics suggests that patients with metastatic

tumors need customized therapy, it is a patient-centric, rather than drug-centric approach that might provide the highest yield. A patient-centric approach would require tailoring combinations of agents to the precise portfolio of abnormalities seen in an individual patient's cancer. Indeed, as our computing and bioinformatics powers grow, it may be also feasible to take into consideration host genomic and other characteristics, and perform *in silico* prediction of which drugs would not only maximize response but also minimize toxicity for a particular patient.

Current approaches to combination therapy in oncology are based on lessons learned from the cytotoxic era. Classic chemotherapy has serious toxicity, and therefore each time two or more drugs were combined, they needed to be tested in the controlled environment of a clinical trial. However, applying this approach to targeted individualized combinations presents significant obstacles. For instance, if there are about 300 drugs available to oncologists (about 150 that are approved by the FDA (20) and another 150 that are in advanced investigational use or could be repurposed from other fields), the number of two drug combinations is 44,850; the number of three drug combinations 4,455,100. If we continue to evaluate drugs on a combination-by-combination basis – the drug-centric approach – would require over 1,000 years to test possible combinations based on currently available targeted agents. Not only is the timeline for evaluating these combinations untenable, but the cost of conducting the needed number of clinical trials to evaluate each possible combination of drugs would be astronomical. Therefore, the risk: benefit ratio of *de novo* tailored combinations need to be weighed against the risk:benefit ratio of continuing our current paradigms. Can new drug combinations be given safely without extensive testing? In this regard, a few other factors should be considered. First, non-oncology drugs are routinely combined, with an excellent safety record, without *a priori* testing in a clinical trial. For instance, the average cancer patient is already on a median of 8 drugs (21) (perhaps including an antidiabetic, antidepressant, antibiotic, etc.) when they are treated, and anti-neoplastics are added, without formal safety testing for the combinations. Our understanding of molecular pathways, CYP metabolic enzymes and so forth help inform our safe use of these combinations. These and additional parameters gleaned from assessing hundreds or thousands of drug combinations already performed could form the basis of guidelines for *de novo* new combinations. Although this approach may not be risk free, the risk:benefit ratio of moving forward would need to be weighed against that of continuing the current system of drug by drug, combination by combination testing. Finally, rules of thumb have been found for phase I drug testing (e.g., 1/10 of the lethal dose in 10% of animals (LD10) for mice for initial dosing) and have resulted in strong safety records (22, 23). The question that arises is could modern targeted agents therefore be safely combined in this way as well, that is with the use of a “rule of thumb,” since they are generally well tolerated, and considerable knowledge about their metabolism is available.

In conclusion, genomics has unveiled a new complexity to metastatic cancer. Despite emerging genomic-based clinical protocols, mainly focused on single companion diagnostics and drugs, we may still be trying to ‘retrofit’ new knowledge on an old clinical trials system (i.e., treating groups of patients by seeking common characteristics so that a drug or test can be validated). Suggested solutions have included finding convergence hubs

(24, 25) and/or moving to earlier disease that might be less complex (26). However, though convergence is attractive, it is plausible that complexity is considerably greater than a small number of pathways. Indeed, within a single pathway, individual mutations may result in gene product conformational changes that are amenable to treatment by vastly different drugs. Further, our current genomic platforms may be assessing just the tip of the iceberg of malignant complexity, which could be significantly amplified when we interrogate tumors by not only genomics, but also transcriptomics, proteomics, epigenetics, and more.

A new patient-centric model for clinical research and treatment may need consideration. This model would involve testing the “strategy” of N-of-one molecular matching with customized combinations. Each patient would be treated with a consistent strategy, that is molecular matching, but with a differing combination of tailored drugs selected by that strategy. Further, rather than locking down the knowledge base, specific information on molecular profiles, treatments, and outcomes for each patient would be collected in a database, and constantly updated as new information is obtained in real time. Statistical methods such as the Bayesian hierarchical modelling, individual patient data meta-analysis, and various regression and classification methods for analyzing heterogeneity of treatment effect could be applied to identify effective treatment/marker pairs (27–29). Consequently, the most currently updated information would be deployed to guide the treatment choice of subsequent patients. If the strategy proved successful and properly validated, it could then be extended to new patients and new combinations previously untested.

Genomics represent a disruptive technology that has revealed an underlying complexity to cancer that may not fit well with our current approach to clinical research and therapy. Our current models have yielded incremental steps forward, but most patients who develop metastatic cancer still die, treatments have considerable toxicities, and the costs of cancer care is substantial and soaring. Current omics technology suggests that patients with metastatic malignancies each or for the most part have unique tumors, and optimized therapy will require an individualized approach. This reality may require moving from a drug-centric to a patient-centric approach that validates an N-of-One strategy and then applies it to new patients (Table 1). To maximize benefit, a heuristic tactic for new individualized regimens will need to be created and rules established based on historic precedent, mathematical probabilities and known molecular pathways. Such a system represents a departure from old paradigms of clinical research and practice and is not risk free. However, the complexity of cancer may not be resolvable by adhering to traditional paradigms, and ultimately the risk:benefit ratio of the status quo versus new approaches will need to be ascertained.

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Table 1**Key Changes Needed to Implement Customized Combination Therapy**

	Current Model	Patient-centric model with customized combinations	Oversight areas that would be affected	Comment
Diagnosis	Patients are grouped together based on a histologic or molecular characteristic in order to be treated with a drug or combination of drugs	Combinations of drugs are tailored to each patient's molecular portfolio	Internal review boards, guidelines for practice, payors, Food and Drug Administration (FDA)	
Therapy Decisions/Molecular Tests	Histologic diagnosis and/or companion diagnostics of single genes are used to determine treatment	Panel of genes are interrogated in order to determine treatment	CLIA, FDA	
Molecular Tests	Tests are locked down and cannot be changed after approval	Tests are dynamic and incorporate new knowledge as it develops	CLIA, FDA	
Safety of Therapy	Safety of new combinations of cancer drugs are determined by Phase I testing	Safety of new combinations of drugs are determined by validated algorithms	Internal review boards, guidelines for practice, payors, FDA	Combinations of drugs without phase I are already routinely given to patients with multiple illnesses aside from cancer
Clinical Research	The safety and efficacy of drugs or combinations are tested. The drug or combination of drugs is the same for all patients on the trial	The safety and efficacy of a strategy is tested (strategy is molecular matching with customized combinations). While the strategy remains consistent between patients, the drugs may be different for the patients on the trial	Internal review boards, guidelines for practice, payors, FDA	Novel statistical methods will be needed
Drug approval	Safety and efficacy in large randomized trials needed in histologically defined disease	Safety data needed. Trials for efficacy may be small and approval may not be limited by histology	FDA	
Access to drugs	Patients can access drugs after approval based on large randomized trials	Patients will be able to access drugs if they meet requirement that strategy of matching has been used to choose the drugs	FDA, payors	