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Precision oncology for patients with advanced cancer: the challenges of malignant snowflakes

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Precision oncology implies customizing treatment to the unique molecular and biologic characteristics of each individual and their cancer. Its implementation is being facilitated by remarkable technological advances in genomic sequencing, as well as the increasing availability of targeted and immunotherapeutic drugs. Yet, next generation sequencing may be a disruptive technology in that its results suggest that classic paradigms for clinical research and practice are a poor fit with the complex reality encountered in metastatic malignancies. Indeed, it is evident that advanced tumors have heterogeneous molecular landscapes that mostly differ between patients. Traditional modes of clinical research/practice are drug centered, with a strategy of finding commonalities between patients so that they can be grouped together and treated similarly. However, if each patient with metastatic cancer has a unique molecular portfolio, a new patient-centered, N-of-one approach that utilizes individually tailored treatment is needed.

Precision oncology (personalized cancer therapy) entails tailoring treatment to the unique molecular/biologic makeup of each tumor. The basis for its implementation is decades of preclinical work that identified specific molecular/biologic aberrations that promote tumor growth and/or evasion of host immune-surveillance, and the development of targeted treatments to prosecute these anomalies. Technological tools that enable interrogation of genomic profiles have advanced at a startling pace, with the first human genome sequenced just over a decade ago (costing approximately 3 billion dollars) and taking years to accomplish, while today full genomic next generation sequencing (NGS) can be completed in days for less than 5 thousand dollars.

Reclassification of Cancer

The reality unveiled by NGS fits poorly with traditional oncology trials and practice. Indeed, NGS represents a disruptive technology whose findings dictate the necessity of new approaches, including a need for the reclassification of cancer. Cancers are currently categorized according to anatomical site of origin (e.g., breast, lung or colon cancer), yet oncologists have long recognized that tumors originating in a particular organ respond differently to the same agents and, furthermore, that drugs may be effective in cancers originating from different organs. NGS provides a possible explanation, since most molecular aberrations do not segregate by organ of origin, and tumors from different organs may have similar mutations.[2]

Malignant Snowflakes

NGS has revealed a complicated picture—i.e., patients with metastatic cancers have unique genomic landscapes; their tumors may be "malignant snowflakes" in that no 2 are identical.[1] For instance, in 57 patients with metastatic breast cancer, we observed 216 somatic aberrations (131 being distinct) in 70 different genes, (NGS, 182 or 236 gene panel; median = 4 aberrations/patient).[1] As technologies

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improve to full genomic sequencing of tumor and germ-line, additionally enabling assessment of host variations influencing drug metabolism/toxicity, it seems inevitable that tumors will be defined by their unique molecular signatures.

Innovative Approaches to Clinical Research/Treatment

The reality that most tumors are distinct and driven by specific molecular aberrations demands novel approaches. The following have been proposed: (i) use traditional clinical trial paradigms that group patients together, but base therapy on the molecular drivers, rather than just tumor histology; or (ii) replace traditional paradigms, and treat patients with customized, individualized combinations of drugs.[3]

The first approach has already emerged, with the advent of genomically-driven trials, either within histologies (e.g., BRAF inhibitors for *BRAF*-mutant melanoma) or so-called "bucket" or "basket" trials that are histology-agnostic (a BRAF inhibitor for any *BRAF*-mutant cancer). (In many ways, the latter strategy is analogous to classic organ-specific trials (e.g., a colon cancer trial) that could be viewed as a molecularly-agnostic "bucket" trial for a particular histology).

The strategy of molecularly driven trials has yielded remarkable responses in several malignancies.[4,5] However, few patients with advanced solid tumors achieve complete remission and almost all relapse, probably because of the presence/ emergence of additional aberrations that mostly differ between patients. Computer algorithms that identify convergence pathways for multiple aberrations may enable the continued grouping of individuals with distinct molecular portfolios together for the sake of treatment.[6] However, even if there is some convergence of genomic paths, additional technologies such as transcriptomics and proteomics, as well as probing host polymorphisms, are likely to reveal yet more complexity/individuality. Distilling these myriad anomalies down to a few signals that can be prosecuted with a limited number of drugs appears unlikely. For instance, the optimal drug (e.g., small molecule inhibitor versus antibody) may vary with the host proclivity to toxicity as well as the specific part of the pathway rendered abnormal, which in turn may depend on the precise mutation.

The Conundrum of Combination Therapy

Complicating the situation further is the fact that most advanced neoplasms harbor multiple molecular aberrations. The strategy of grouping patients for mono-therapy has been feasible, though complicated. The need for combinations of drugs to optimize response/circumvent resistance is however clear, as few patients with advanced disease achieve long-term survival with mono-therapy. Yet, even tumors that have an aberration in common often differ in the rest of their molecular fingerprint.[1] This fact makes grouping patients for combination therapy a herculean task. Indeed, the very definition of "personalized" treatment is not consistent with canonical trial and practice paradigms, where patients are treated in the same way based on some biologic commonality. Rather, the data indicate that, even if patients have an aberration in common, the rest of their molecular backdrop is distinct,[1-3] and hence customized individualized therapy—the N-of-one approach—is required for optimal results.

Individualized Treatment Outside of the Cancer Field

There are several challenges that present themselves when a strategy of individualized combination therapy is broached. The most pronounced are related to concerns about the safety of combinations of anti-cancer drugs, when such combinations have not undergone formal early-phase testing. In this context, it is important to examine the lessons learned from the practice of medicine outside the cancer field.

The typical patient with cancer is already receiving 5 to 10 drugs for their co-morbidities, which frequently include heart disease, diabetes, depression, etc. The appropriate drugs are routinely prescribed (without phase I safety testing of the combinations) based on patients' "individual" co-morbidities and well-known algorithms regarding metabolism/organ function that dictate safety. Why is cancer an exception? The historic prohibition against combining anti-cancer drugs without formal phase I testing is likely a legacy of the cytotoxic era. Cytotoxics have considerable side effects resulting in the legitimate concern that *de novo* combinations would result in dangerous toxicities. Targeted agents, however, often have fewer side effects. Furthermore, there is a wealth of information that has been gleaned from years of practice in non-cancer fields on the routine, safe use of combinations tailored to an individual's condition, and this information could be applied to anti-cancer drugs. Algorithms/simulations that incorporate multiple factors (e.g., toxicity, metabolism, targets, drug class, need for initial dose reductions) could be deployed to permit *de novo* combinations of cancer drugs similar to what is routinely done for patients with multiple non-cancer illnesses

In summary, the following major points emerge from discoveries in clinical cancer genomics.

1. Cancer should to be reclassified based on its molecular/biologic characteristics, rather than just organ of origin.
2. Metastatic cancers appear to be "malignant snowflakes," each having unique genomic portfolios.
3. If tumors are defined by their molecular makeup, advanced molecular tests should be considered a standard diagnostic tool for patients with cancer.
4. Mono-therapy is unlikely to cure patients with advanced/complex malignancies. Customized combination therapy will be required.
5. Customized combinations of drugs are routinely prescribed outside the cancer field, and tailored to the patient's co-morbidities. Algorithms based in part on lessons learned from years of such practice should be developed in order to predict safe

starting doses for *de novo* anticancer combinations.

6. The definition of "personalized" treatment is inconsistent with canonical trial/practice paradigms, where patients are grouped together based on a biologic commonality. A patient-centered, N-of-one approach is needed to optimize therapy.

7. Profound changes in many aspects of current developmental therapeutics practice in oncology will be required to take maximal advantage of the knowledge being generated by molecular science. These changes will require new consensus among the patient, scientific, medical, industrial, and regulatory stakeholders.

Disclosure of Potential Conflicts of Interest

Dr. Kurzrock receives consultant fees from Sequenom and has an ownership interest in RScueRx Inc.

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