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Opinion

Challenging Standard-of-Care Paradigms in the Precision Oncology Era

Vivek Subbiah[1],* and Razelle Kurzrock[2]

The pace of genomic and immunological breakthroughs in oncology is accelerating, making it likely that large randomized trials will increasingly become outdated before their completion. Traditional clinical research/practice paradigms must adapt to the reality unveiled by genomics, especially the need for customized drug combinations, rather than one-size-fits-all monotherapy. The *raison-d'être* of precision oncology is to offer 'the right drug for the right patient at the right time', a process enabled by transformative tissue and blood-based genomic technologies. Genomically targeted therapies are most suitable in early disease, when molecular heterogeneity is less pronounced, while immunotherapy is most effective against tumors with unstable genomes. Next-generation cancer research/practice models will need to overcome the tyranny of tradition and emphasize an innovative, precise and personalized patient-centric approach.

Clinical Trial Paradigms in the Era of Targeted Therapies and Immunotherapies

"Victorious warriors win first and then go to war, while defeated warriors go to war first and then seek to win" — Sun Tzu, The Art of War

Between 2003 and 2013, new cancer drugs approved by the European Medicines Agency (EMA) or the United States Food and Drug Administration (US FDA) produced a total mean improvement in overall survival of only 3.4 months relative to the treatments that were available in 2003 [1]. Routinely, new medicines that confer an additional survival of mere weeks with statistical *P* value victories are hailed as major breakthroughs in oncology. The randomized controlled trial (RCT), considered the gold standard for cancer clinical trials, has failed to render cures or long-term survival for the majority of patients suffering from advanced malignancies. In diseases such as metastatic pancreatic cancer, >90% of patients are dead at 2 years, despite a multitude of traditional trials [2]. The high costs of conventional trials, the large number of patients receiving futile therapy on control arms, and the lack of **biomarker** (see Glossary) selection hampers progress. In this Opinion, we critically appraise the state of standard-of-care therapies, and present an overview of current clinical trial design paradigms in the era of genomically **targeted therapies** and **immunotherapy**.

Targeted Therapies

Over 100 years ago, Paul Ehrlich introduced the concept of 'magic bullet cures' in oncology [3]. Realization of this idea remained elusive until the last decade, with the advent of drugs such as imatinib targeting the altered Bcr-Abl tyrosine kinase, which is pathognomonic of chronic myelogenous leukemia (CML). CML became a poster-child for **precision oncology**. Before the imatinib era, median survival was ~4 years; today, life expectancy for patients with CML

Highlights

The central tenet of the precision oncology paradigm requires the delivery of the right drug at the right time to the right patient.

The current model for precision oncology usually matches single agents to patients with late-stage, refractory, molecularly complex disease. This is suboptimal.

Optimizing targeted therapy requires a departure from traditional paradigms: (i) deploying gene-targeted agents early in the disease course when the tumor is less complicated at the genomic level; (ii) administration of immune-targeted therapies to patients with complex cancers harboring high tumor mutational burden; and (iii) moving from monotherapy to customized combinations.

Genomics represents the tip of the iceberg. In the future, panomic testing that includes transcriptomics, proteomics, metabolomics, and immunogenomics will paint a more complete portrait of each tumor.

[1]Department of Investigational Cancer Therapeutics, Division of Cancer Medicine, Unit 0455, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA
[2]Division of Hematology & Oncology, Center for Personalized Therapy & Clinical Trials Office, UC San Diego – Moores Cancer Center, 3855 Health Sciences Drive, MC #0658, La Jolla, CA 92093-0658, USA

*Correspondence:
vsubbiah@mdanderson.org
(V. Subbiah).

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approaches normal, provided that treatment is started at the time of diagnosis [4]. Delaying treatment until late-stage disease (as is standard in solid tumors) renders even the breakthrough targeted therapies for CML ineffective. Other early examples of precision oncology efforts included the success of trastuzumab in Her2-positive breast cancer, and epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) inhibitors in *EGFR*- and *ALK*-aberrant lung cancers [5–7]; all of which have significantly impacted outcome, albeit not to the extent seen in CML.

In parallel, massive sequencing efforts have mapped the genome. The sequencing costs of a single human genome have dropped in a breathtaking manner, from 3 billion US dollars over a decade ago to about one thousand US dollars today. Hundreds of actionable genes have been discovered and thousands of new drugs with novel mechanisms of action, including gene-targeted agents and immunotherapy, are being identified. Yet, although we have witnessed a few remarkable triumphs by utilizing genomics, other high-throughput omics technologies such as **proteomics, transciptomics,** and **metabolomics** are in nascent stages.

Immunotherapies

Immunotherapy may be the ultimate example of a precision treatment. **Checkpoint inhibitors**, for instance, activate the immune machinery, enabling its innate ability to recognize and destroy tumors [8,9]. The immune system is both personalized and precise. Furthermore, we now realize that the immune apparatus distinguishes malignant cells from their normal counterparts because the cancer cells present neoantigens, which are produced as a result of the mutanome [10]. Additionally, specific genomic alterations, such as *PD-L1* amplification (associated with almost a 90% response rate in refractory Hodgkin's disease treated with anti-PD-1 checkpoint inhibitors) and high tumor mutational burden are greatly predictive or response [9,11–13]. Most striking is the ability of immunotherapy to induce durable complete remissions, even in patients with advanced metastatic cancer. The recent US FDA approval of **pembrolizumab**, an immune checkpoint inhibitor for **microsatellite instability** high (MSI-H) cancers across all solid tumor types (histology-agnostic approval) in pediatric and adult patients is an attestation to the power of precision medicine[i] [14–16]. This approval also demonstrates that genomics and immunotherapy are wedded to each other, and their successes epitomize the power and potential of this marriage.

Conventional Clinical Trial Paradigms

Unfortunately, conventional clinical trial strategies may not be the best way to evaluate the new generation of genomically or immune-targeted agents. Indeed, genomics has unveiled a reality that is incompatible with canonical trial design – every metastatic tumor is both unique and complex at the molecular level [17–20] (Figure 1, Key Figure, Table 1). Furthermore, drugs that are highly effective in small subpopulations of patients are not amenable to randomized trials in unselected patient populations. Under such circumstances, trials must first identify response biomarkers and then individualized combination therapy needs to be given.

The central premise of precision oncology is to offer 'the right drug for the right patient at the right time' Ironically, traditional models for clinical research are almost diametrically opposed to those needed based on the science of precision medicine: (i) in conventional models, commonalities are found between patients in order for them to receive the same drug regimen, instead of individualizing therapy; and (ii) targeted monotherapies are matched to one specific molecular alteration in a patient's tumor, rather than giving combination treatment optimally tailored to the entirety of the tumor genomic portrait. Regarding timing of therapy, genomically targeted agents are often applied to heavily pretreated patients, rather than early in the course

Glossary

Precision medicine: 'an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person' (definition of the National Institutes of Health, NIH); 'a form of medicine that uses information about a person's genes, proteins, and environment to prevent, diagnose, and treat disease' (definition of the National Cancer Institute, NCI).

Precision oncology: field in oncology defined by customizing treatment to an individual's molecular profile.

Biomarker: characteristic that is objectively measured or evaluated as an indicator of abnormal biological processes or pharmacological/biological responses to a therapeutic intervention.

Randomized controlled trial: trial in which two treatment groups (an experimental group versus control group; sometimes given a placebo or a traditional therapy regimen) are compared. The only expected difference between the control and experimental groups in RCTs is the treatment effect of the experimental therapy being studied.

Genomics: study of genes.

Targeted therapy: drugs that either target molecular alterations specific to cancer cells (e.g., mutated, amplified or epigenetically up- and/or downregulated signaling proteins), or target immune cells to increase anticancer immunity.

Immunotherapy: prevention or treatment of disease with agents that stimulate the immune response of the host.

Tumor mutational burden: number of mutations in a tumor.

Vemurafenib and dabrafenib: tyrosine kinase inhibitor of aberrant BRAF.

Trametinib and cobimetinib: MEK inhibitor.

Panomics: informal name for technological fields in biology that end in omics, such as genomics, proteomics, and metabolomics.

Proteomics: study of proteins.

Transcriptomics: study of transcripts.

Metabolomics: study of metabolism.

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Key Figure

The Snowflake Theory and Changing Drug Development Paradigms

Metastatic cancer = Snowflakes at molecular level

Current paradigm
One treatment for all

Future paradigm
Customized therapy

Drug-centric trial (traditional)

Patient 2
Patient 1   Patient 3

Drug
Regimen
A

Strategy: Find common feature between patients (e.g. type of cancer or type of molecular aberration) and place all on same drugs

Patient-centric therapy
We already customize treatment

Metformin   Metformin
          Fluoxetine

Patient 1   Patient 2
Diabetes, CHF, RA   Diabetes, infection, depression

β-blocker
     Tofacitinib   Clarithromycin
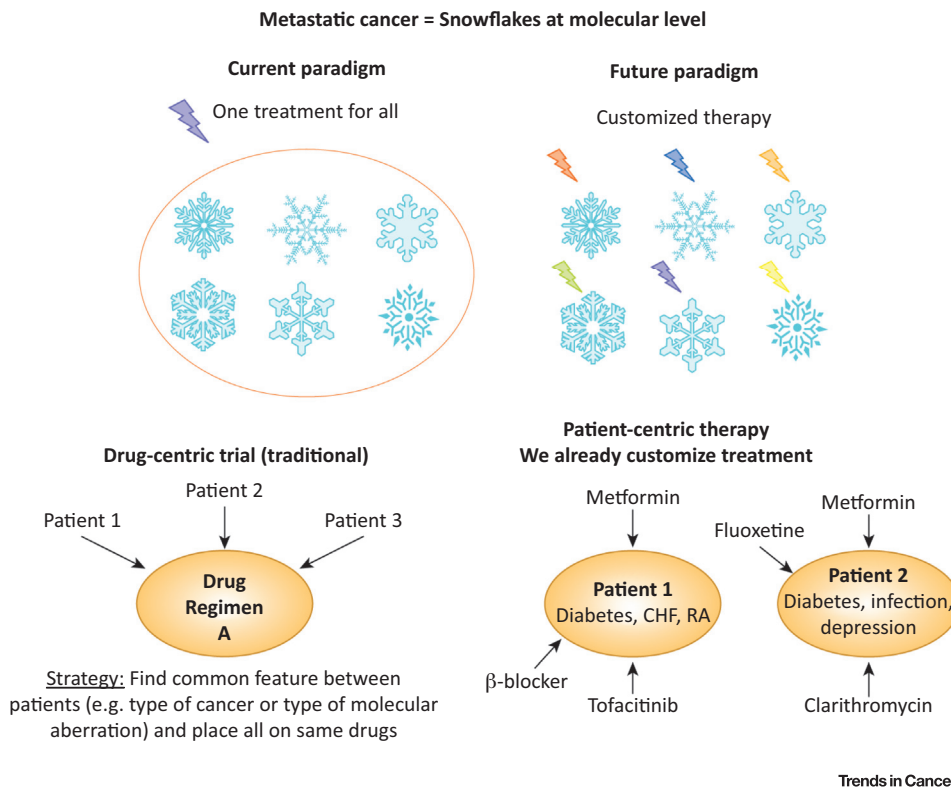
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Figure 1. Top panel: cancers are akin to malignant snowflakes. No two snowflakes are identical, and it seems that it is also extremely unusual for two metastatic tumors to have the same genomic fingerprint. As it turns out, if metastatic tumors are akin to malignant snowflakes in their distinctiveness, individual tumors become the ultimate extrapolation of rare and ultra-rare tumors — n-of-one malignancies. Bottom panel: moving from drug-centric to patient-centric trials and care. If each cancer is unique and complex, precisely targeting it requires personalized combination therapy regimens. Bottom panel shows that personalized therapy is already routine in patient care outside the oncology setting. Abbreviations: CHF, congestive heart failure; RA, rheumatoid arthritis.

Drug-centric approach: approach to treatment centered on a drug or drug regimen.
Patient centric approach: approach to treatment centered on the patient.
Checkpoint inhibitor: agent that inhibits an immune checkpoint and hence can reactivate the immune system.
Pembrolizumab: antibody that works as a checkpoint inhibitor.
Microsatellite instability: microsatellites represent repeated sequences of DNA that are one to six base pairs in length. Microsatellite instability is a condition of genetic predisposition to mutation in microsatellites that results from an impaired DNA mismatch repair gene.

of the disease, when tumors are less heterogeneous, and the targeted drugs are more likely to be effective [21,22]. **Tumor mutational burden** and complexity, on the other hand, may be an advantage for immunotherapy. Importantly, standard-of-care therapies deny and/or delay evaluation of new drugs in patients with lethal cancers by making the tumors more drug resistant, impairing the immune system, and/or rendering the patients too sick to be eligible for innovative treatment.

In order to unlock the potential of precision oncology, profound changes in our traditional approaches need to occur. These changes start with universal genomic testing at the time of diagnosis of cancer [23] (Table 2) and include customizing drug combinations, with genomically targeted treatments given early in a patient's disease course, and immunotherapy using

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Table 1. Redefining Clinical Trial Paradigms and Standard of Care

Subject matter	Solution	Challenge
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.	Current treatment paradigms, including precision oncology trials, are drug centered rather than patient centered.
Monotherapy is unlikely to cure patients with advanced/complex malignancies	Combination therapies needed	Matched customized combinations for n-of-one tumors require evaluation of the strategy of personalization or an algorithm for matching, rather than the drug regimens themselves
The inimitability of tumors means that each cancer is akin to a malignant snowflake – both unique and complex in its genomic portrait	Unique/complex tumors require individualized combination regimens	With 300 drugs, there are ~4.5 million three-drug regimens
Dosing of combinations of anticancer drugs has traditionally required a phase I study	Outside of oncology, patients regularly receive *de novo* combinations of drugs based on understanding impact on metabolic enzymes etc. The average oncology patient is already on eight medications, which have not been assessed together in a phase I study, but are given safely together. Dosing algorithms for anticancer drug combinations can be similarly derived from a variety of sources including the literature [57–60].	The pathway to approval and payer acceptance of drug combinations is unclear
If tumors are defined by their molecular makeup, advanced molecular tests should be considered a standard diagnostic tool for patients with cancer	Universal genomic testing of cancers	Points and counterpoints in Table 2

checkpoint inhibitors administered to patients with evolved cancers harboring high mutational burdens or microsatellite instability.

Standard of Care, Standard of Proof, and Proof of Standards

Evidenced-based, standard-of-care guidelines/pathways are promulgated by a variety of organizations and emphasize consistency[ii] [24,25]. Departure from these guidelines may leave the physician legally liable and justify insurers' refusal to pay. Yet, the standard-of-care oncology treatments are associated with >90% mortality at 2 years for some metastatic cancers.

Importantly, in their present rendition, standard-of-care pathways, by virtue of their emphasis on uniformity of management, are antithetical to precision oncology, which requires personalization of therapy. Indeed, if each patient's tumor is complex and unique, then, in order to precisely target that tumor, one must apply medicines that affect the distinct alterations of the tumor, and this requires customized treatment.

Moving Precision Oncology Forward

Precision oncology trials test feasibility of matching drugs to targeted therapy [26–29]. The evidence for this matching strategy is rapidly accumulating, both from these trials and from literature data mining [30,31]. Indeed, large meta-analyses of ~85 000 participants in phase 1, 2, and 3 studies demonstrated that biomarker selection was the single most significant independent factor predicting improvement in all outcome parameters. Of equal importance, the use of genomically targeted therapy without a biomarker produced negligible response rates, which were also worse than the results with cytotoxic agents [32–35].

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Table 2. Case for Universal Genomic Testing of Tumors: Points and Counterpoints

Points	Counterpoints	Refs
Obtaining knowledge of genetic aberrations is not worthwhile if no action can be taken in terms of treatment	Genomics is the diagnosis. Every patient with cancer deserves a diagnosis. Genetic abnormalities also predict prognosis. Genomics can also predict contraindicated drugs, e.g., EGFR therapy in *KRAS*-mutant colorectal cancer	[23]
Prohibitive cost precludes universal genomic testing	Cost of testing has decreased precipitously Financial burden of cancer therapy is massive Cost of testing for a complete diagnosis and to select appropriate therapy is tiny compared with the money squandered on ill-chosen treatments	
Genomic testing has not been validated in prospective trials	In comprehensive meta-analyses of ~85 000 patients treated on clinical trials, genomic biomarkers were an independent factor associated with improvement of all outcome variables	[33–35]
Genomic testing may benefit only a subgroup of patients or may be germane to only rare diseases	Virtually impossible to know in advance of testing who will benefit Options that may not exist at the time of a patient's initial diagnosis may become available before the patient's disease progresses Universal genomic testing of malignancies will enable curating clinically relevant data in large databases	

The Right Drug at the Right Time for the Right Patient

The Right Drug

The discovery of $BRAF^{V600E}$ mutations as a *bona fide* oncogenic driver in 50% of melanomas led to a drug development race in order to target the product of this gene. Treatment with the potent BRAF inhibitor **vemurafenib** showed high response rates leading to FDA approval in 2011 [36,37]. Since then, the BRAF inhibitor **dabrafenib** and two MEK inhibitors (**trametinib** and **cobimetinib**) have also been approved [38–40]. Yet, most patients fail to achieve complete or long-term partial remission. This is likely due to the fact that the majority of metastatic melanomas harbor several genomic alterations [41]. Hence, patients require combination therapy tailored to the biomarker portfolio of their tumor. Indeed, a recent study demonstrates that higher matching scores (number of matches divided by number of alterations) independently correlates with better outcomes [26].

The Right Time

Timing is vital in cancer therapy. Tumor complexity increases with time and under the pressure of therapy. CML epitomizes this evolution with three well-defined stages: chronic phase, accelerated phase, and blast crisis. Other cancers almost certainly undergo a similar evolution, but it is not as well delineated clinically [42]. In recent years, the clinical outcome of CML has been transformed. Three major steps enabled this transformation: (i) discovery of the underlying genetic defect (*BCR-ABL*); (ii) identification of a targeted agent (imatinib) that obviated the aberrant enzymatic activity of Bcr-Abl; and (iii) administration of imatinib to patients with newly diagnosed disease. The third step, that is treating early disease, is the one that is most frequently not addressed in solid tumors.

As an example, BRAF inhibitors in patients with *BRAF*-mutant melanoma can result in responses so remarkable that they have been designated as the oncological equivalent of the Lazarus syndrome [43]. This syndrome refers to the spontaneous return of circulation after failed attempts at resuscitation. Patients near death from melanoma can experience

dramatic tumor reduction. Unfortunately, these patients are not usually cured, and the disease almost inevitably returns after a few months and results in the patient's demise. If the experience with CML holds true, durable responses in solid tumors will require either administration of targeted agents such as BRAF inhibitors to newly diagnosed disease and/or giving customized combinations of drugs to patients with advanced disease in order to block resistance pathways.

The Right Patient (and the Right Cancer)

Most novel drugs are tested in patients who have exhausted standard-of-care therapies. At this time, not only is the cancer refractory, but the patient's performance status and biological/immune reserve may also be too poor to realistically expect the best outcomes. For these reasons, patients should be treated with novel therapies earlier in their disease course.

Advanced Cancers Are Akin to Malignant Snowflakes – Complex and Unique

No two snowflakes are identical, and it seems that it is also extremely unusual for two metastatic tumors to have the same genomic fingerprint [17–20,44] (Figure 1). For example, in 57 patients with advanced breast cancer, 216 somatic aberrations were observed (131 being distinct) in 70 different genes; no two patients had the same molecular signature [17]. A study in advanced osteosarcoma with multiple molecular profiling technologies showed similar results [20]. Furthermore, we may be viewing only the tip of the iceberg. As new technologies emerge beyond limited panel genomic sequencing, both the complexity and the individuality of tumors are likely to be amplified (Figure 2).

Customized Combination Therapy: From Drug-Centric to Patient-Centric Research and Care

One of the major stumbling blocks in precision oncology is that there are intrinsic and acquired resistance mechanisms to targeted therapy. One drug matched to a driver aberration may not realistically be expected to cure patients or achieve remissions if each tumor has distinct and complex alterations [31,41]. Other drugs must be added to overcome resistance [31,45,46]

A paradigm of individualized therapy means that the traditional way that drugs/drug regimens become standard of care no longer works. Canonical drug development paradigms are drug-centered (Figure 1). The drugs are the focus of the trial and each patient enrolled receives the same regimen, regardless of their genomic and phenotypic heterogeneity. However, if each tumor is different, we may need to test thousands of regimens in increasingly small subsets of patients. Indeed, if there are ~300 drugs in oncology, there are ~45 000 two-drug regimens and ~4.5 million three-drug regimens. The traditional clinical trial design model breaks down. However, the conundrum is solvable. Precision medicine implies patient-centered trials and care. The patient is the focus and the drugs can therefore vary from patient to patient. In this model, it is not the drug regimen that is evaluated, but rather the strategy of individualization. The question then becomes what is the standard of proof for this strategy? In the era of precision oncology, new clinical trial designs need to evaluate personalized care performance so that standard-of-care guidelines can include, emphasize, or even mandate individualized treatment.

The One-Size-Fits All Treatment Model in Oncology Is an Anomaly

In daily medical practice, physicians already use customized combinations to treat nonmalignant conditions. A patient with diabetes, congestive heart failure, and rheumatoid arthritis
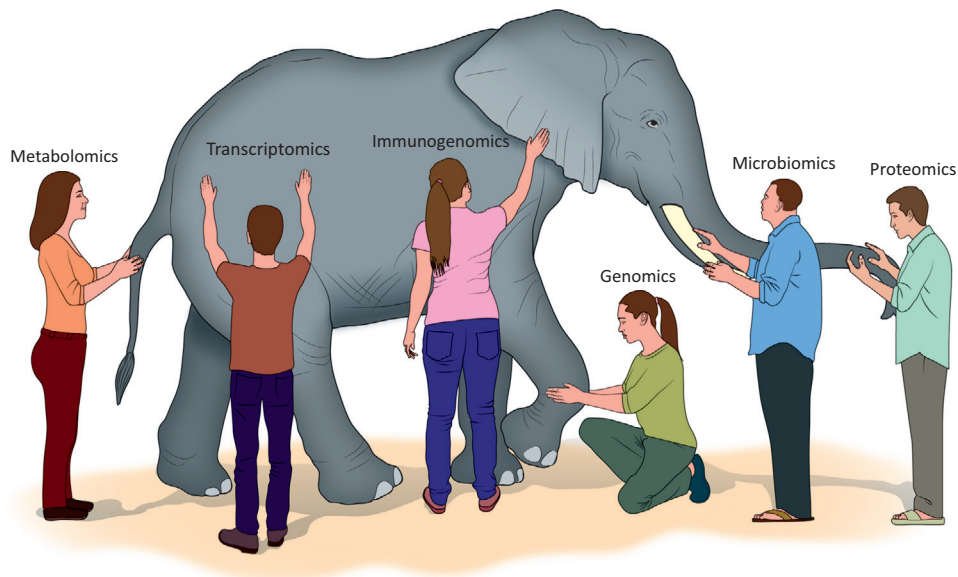
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Figure 2. Six Blind Men and Elephants
Beyond genomics – transcriptomics, proteomics, and more. The comprehensive molecular profile of the not-too-distant future may include genomics, transcriptomics, proteomics, metabolomics, microbiomics, epigenomics, mutanomics, lipidomics, and immunogenotyping, and may hence predict response to multiple modalities including immunotherapy and chemotherapy [47–56]. Each of these modalities gives us a piece of the puzzle, akin to the parable of the six blind men who each touch a different part of the elephant, such as the tusk versus the trunk, and therefore have vastly different views of the elephant. Panomics testing is a requisite of comprehensive analysis and may require complex computer algorithms for data integration and computation.

receives a different set of drugs than a patient with diabetes, infection, and depression (Figure 1). The drug doses are adjusted to prevent drug–drug interactions based on known factors such as impact on metabolic enzymes. The average patient enters the oncology clinic on approximately eight drugs tailored to their specific health problems. These individualized drug combinations have never been formally tested in phase I studies; yet physicians safely and effectively administer them on a regular basis to the benefit of their patients.

In oncology, however, there is a cultural precept that, if a new drug combination has not been tested in phase I studies, it should not be used because its safety is unknown. This precept may be a legacy of the cytotoxic era, since combining cytotoxics could have serious safety concerns. However, modern anticancer agents have fewer prohibitive adverse effects and our understanding of drug combinations has grown. One size fits all is not the norm in medicine, and, since advanced cancers are heterogeneous, it should cease to be the norm in oncology care.

Immunotherapy: Yet Another Paradigm Shift

One of the most important mechanisms by which cancer cells evade the immune system is exploitation of checkpoints by the tumor to disable T cells. The PD-1/PD-L1 axis is of particular interest because of rapidly emerging data suggesting that inhibition of this checkpoint can restore anticancer immunity. Impressively, clinical responses with checkpoint inhibitors have been observed in multiple different malignancies. Remarkably, some patients with advanced tumors can achieve durable complete remission.

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Marriage of Genomics and Immunotherapy

The major predictive markers for checkpoint inhibitor response include high tumor mutational burden, either associated with microsatellite instability or not, CD8 infiltrates, and PD-L1 over-expression or amplification [9,11,12]. These markers reflect the coupling of the immune system and genomics. Once the immune system is reactivated with the use of checkpoint inhibitors, T cells must still be able to differentiate tumor cells from normal elements. T cells distinguish tumor cells from normal self in large part through presentation of neoantigens created by the mutanome. The more neoantigens, the better the chance of immune recognition. Hence, high tumor mutational burden correlates with favorable outcome after checkpoint inhibitor treatment [13]. In contrast, patients with lower number of genomic alterations appear to respond better to gene-targeted therapy [26], presumably because, in malignancies with more genomic alterations, the presence of resistance mutations abrogate the effects of treatment.

Concluding Remarks

Breathtaking advances in our understanding of genomics and the immune system have brought us to the threshold of a tipping point in cancer treatment. It appears, however, that our established models for clinical research and practice are a suboptimal fit for the reality of tumor heterogeneity (see Outstanding Questions). In order to overcome the cancer problem, it is important to break free from the tyranny of tradition, and construct novel paradigms for the management of neoplastic disease.

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Resources

[i]https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm560167.htm

FDA (2017) FDA approves first cancer treatment for any solid tumor with a specific genetic feature

[ii]https://www.nccn.org/professionals/physician_gls/f_guidelines.asp

NCCN (2016) NCCN Guidelines

Outstanding Questions

Genomic sequencing is a basic diagnostic tool that delineates the underpinnings of malignancy and is therefore crucial for classifying disease, predicting prognosis, and directing therapy. If a basic precept of medicine is that each patient deserves an accurate diagnosis, should not universal genomic testing of tumors be necessary?

What adjustments to clinical trial design and regulatory and care structures are needed to move from a drug-centric approach to a patient-centric approach, wherein each tumor is prosecuted with a customized combination of drugs?

Would finding patients with identical or near-identical tumors treated in the same manner still be feasible with a new form of interrogation based on mining of large, well-annotated databases using computerized and artificial intelligence algorithms?

What is the optimal approach to identifying immunogenic, mutanome-derived neoantigens that induce a T-cell response?

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