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Review

Hurdles on the road to personalized medicine

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ABSTRACT

Cancer treatment is slowly shifting from an approach in which the tissue of origin and the histology were the guiding principles for the choice of chemotherapy towards a genotype-centric approach in which the changes in the cancer genome are used to select patients for treatment with highly selective and targeted drugs. This transition has all the hallmarks of a disruptive innovation and requires major adjustments in the way that cancer is diagnosed and treated. We discuss here the hurdles on the road ahead to a more personalized treatment of cancer.

1. Introduction

In the past decade, we have witnessed the development of a number of highly effective cancer therapies. These new therapies rely on the notion that the genetic aberrations that lie at the heart of the cancerous process create a dependency on this aberration, a situation referred to as "oncogene addiction" (Weinstein, 2002). Inhibition of this signal, to which the cancer cells are addicted, leads (at least initially) to massive responses to drugs that selectively inhibit these so called "driver" pathways. A direct consequence of this new treatment paradigm is that the precise nature of the genetic aberration becomes a key factor in treatment. This represents a departure from the more conventional "organ centric" approach to cancer treatment, in which the organ of origin and classical pathology had major parts in guiding the first line of drug treatment. This new approach necessitates a new type of molecular diagnostics to identify the genetic aberrations in each individual tumor. At present there are about a dozen relationships between genetic aberrations in the cancer genome (mutations, amplifications, translocations) and "targeted" cancer drugs that selectively inhibit the products of these altered genes (Table 1).

Moreover, it becomes increasingly evident that many cancers consist of multiple "intrinsic" or molecular subtypes, as first described over a decade ago for breast cancer (Perou et al., 2000). For instance, it is now evident that colorectal cancer also has multiple subtypes having different prognosis and

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Table 1 – Overview of relationships between cancer genotypes and their predicted responses to targeted therapy.

Cancer type	Genotype	Therapy
Colorectal cancer	Mutant KRAS	Cetuximab/ Panitumimab (no response)
Chronic Eosinophilic Leukemia (CEL)	PDGFR translocations	Imatinib
Chronic Myeloid Leukemia (CML)	BCR-ABL translocation	Imatinib
Resistant CML	Mutant BCR-ABL translocation	Dasatinib Ponatinib Bosutinib
Gastro-Intestinal Stromal Tumor (GIST)	Mutant KIT	Imatinib
Breast cancer	HER2 amplification	Trastuzumab[a] Pertuzumab[a] ado-trastuzumab emtansine[a]
Melanoma	Mutant BRAF	Vemurafenib Dabrafenib Trametinib Dabrafenib/Trametinib
Myelofibrosis	Mutant JAK2	Ruxolitinib
Non Small Cell Lung Cancer	Mutant EGFR	Erlotinib Gefitinib Afatinib
Non Small Cell Lung Cancer	ALK translocation	Crizotinib Ceritinib
Non Small Cell Lung Cancer	ROS1 translocation	Crizotinib

a Eligibility is not strictly on genomic amplification of *HER2*, as strong HER2-positivity by immunohistochemistry is also an eligibility criterion for treatment.

responses to therapy and similar stratification based on gene expression is also seen in pancreatic cancer and glioblastoma (Budinska et al., 2013; De Sousa et al., 2013; Perou et al., 2000; Roepman et al., 2013; Sadanandam et al., 2013; Sorlie et al., 2001; Verhaak et al., 2010). Such molecular subtypes often do not have distinctive mutations and can only be identified through analysis of the complex gene expression patterns that characterize them. The tools to identify such subtypes are complex and require sophisticated computer algorithms to calculate the subtype score, which is well beyond the capabilities of the average pathology department in a community hospital.

The transformation described above has all the hallmarks of a "disruptive innovation", a radically new approach in the way we diagnose and treat cancer. As with other disruptive innovations, this change requires an overhaul of established structures. We describe here three areas that require a major restructuring to enable precision medicine, guided by the genomic aberrations that drive the oncogenic process, for the majority of cancer patients.

2. Centers of excellence for diagnosis and treatment

Now that DNA and RNA increasingly take center stage to guide the treatment of individual cancer patients, it will become critical to collect high-quality biopsies from all tumors. Currently, formalin-fixed paraffin embedded (FFPE) tumor tissue is the standard in cancer pathology because the ease of storage and the faithful preservation of tissue architecture, which is critical to the current morphology-based diagnosis. A first disruptive innovation will be the standardized preservation of nucleic acids of the tumor in the best possible way. While some information can be retrieved from the highly degraded, depurinated and cross-liked nucleic acids extracted from FFPE tissues, frozen tumor biopsies will have to become mandatory to get the maximum benefit from our increased insights into the relationship between the cancer genome and course of the disease. Patients will soon no longer accept that convenience rather than accuracy drives the format of tissue preservation for vital decisions regarding their treatment. If professional bodies do not take the initiative to change practice guidelines, we may soon see that in the litigation-rich US society patients will go to court to claim malpractice because of "willful destruction of evidence" (a felony crime under US law) when cancer tissue is only stored as FFPE material.

A second issue is that the primary tumor and its metastases are often not synonymous in genotype, requiring a re-biopsy of the tumor upon relapse (Dupont Jensen et al., 2011). However, no general guidelines for taking of sequential biopsies exist to date. As one example, how many biopsies should one take to probe the heterogeneity of the tumor? Moreover, a large diversity exists among centers with respect to the imaging facilities and competences, including interventional radiology. In this respect it is noteworthy that more than 50% of cancer patients are currently being diagnosed and treated in non-academic local centers, both in the US and in many European countries. Such centers are often lack the modern imaging facilities needed to undertake a rigorous sequential biopsy program.

Another compelling argument to concentrate cancer diagnosis is that the molecular diagnostic tests will quickly become more complex. At present, molecular cancer diagnostics is limited to the survey of a handful of "actionable" mutations in genes (Table 1). These can be identified through

relatively simple genotyping kits. However, a cumulative analysis of over 5000 cancer genomes teaches us that each cancer type has rare actionable mutations that each occur at a frequency of between 1 and 5% (Lawrence et al., 2014). To test for all these rare mutations one-by-one is not cost effective. In addition, there is often not enough tissue from a single biopsy to perform multiple diagnostic tests. The obvious solution to this problem is to survey the cancer genome for possible actionable mutations in a single massive parallel sequencing experiment, using both DNA and RNA to identify the alterations that can form the basis of a rational therapy. We realize that reimbursement of such testing panels by insurance companies is an issue in the near term, given that the clinical utility of the use of these panels is currently lacking. Together, these trends will lead to a shift of the complex molecular cancer diagnostics from community hospitals to regional centers of excellence as patients increasingly demand more sophisticated treatments for their disease. Scientific societies and professional bodies will need to design accreditation systems to help patients select in which centers they may best undergo these complex treatments. The influence of the patient internet forums may make this transition more rapid than most of us expect.

3. Innovation in drug development and clinical testing

The conventional way of drug development is through three subsequent phases of clinical studies, with increasing numbers of patients being enrolled. If such a novel agent turns out to be superior to standard of care, it is approved for use on a large and often unselected patient population. This process has a high attrition rate, with on average 9 out of 10 drugs failing along the way. With the new generation of targeted cancer drugs, patients can often be stratified upfront to increase response rates. This leads to smaller registration trials with a higher success rate. While such strategies often yield seemingly impressive results, the gain is seen primarily in progression free survival (PFS) rather than in overall survival (OS). This should not come as a surprise to any clinician, as AIDS can also not be controlled effectively with a single anti-viral agent. What the initial responses to targeted agents tell us is that we are hitting the tumor in a critical survival pathway, but at the same time the escape routes are wide-open, providing ample avenues for resistance development. As with AIDS, the obvious answer is the use of combination therapies. But which of the many possible combinations of the hundreds of available cancer drugs is most effective in fighting resistance?

Genetic tools that enable the identification *of synthetic lethal* interactions between signaling pathways facilitate the identification of particularly powerful drug combinations. Synthetic lethality refers to a situation in which inactivation of two genes or pathways individually is not lethal, but the combination of the two is. This technology has been used to identify a potent drug combination for the treatment of *BRAF* mutant colon cancer and found that combining BRAF and EGFR inhibitors is required to induce cell death in *BRAF* mutant colon cancers (Prahallad et al., 2012). Three clinical trials are currently ongoing based on this concept (NCT01719380; NCT01750918; NCT01791309). This approach has the potential to go far beyond the "trial and error" approach that is currently used to test combination therapies for cancer.

An inevitable consequence of the development of rational combinations of targeted therapies based on insights into the genetic vulnerabilities of individual cancers is that large phase III trials with single agents will become a thing of the past. At first glance, one would think that "blockbuster" drugs should also be history soon, as each drug will find a use in a smaller niche indication. However, this may not be the case. As one example, amplification of the *HER2* gene is not only seen in some 15–20% of breast cancer, but also in some 10% of gastric cancer (Gravalos and Jimeno, 2008), 2% of non small cell lung cancer (Heinmoller et al., 2003) and 3% of colon cancer (Bertotti et al., 2011). It is plausible that all these cancers also benefit from HER2-targeted therapies. However, direct proof of this may be challenging, given the low frequency of these events. "Reimbursement with evidence collection" could help address the utility of specific drugs in these small patient groups. Moreover, due to the introduction of highly effective targeted therapy for chronic myeloid leukemia (CML), the prevalence of CML is expected to increase to 35 times the annual incidence, greatly expanding the eligible patient population for these drugs (Huang et al., 2012). Consequently, the market for targeted agents could in some instances become quite sizeable.

There are two issues that need to be resolved before the development of targeted agents in combination can become successful on a larger scale. First, pharmaceutical companies will increasingly have to collaborate, as it is not always the case that one company has both drugs that need to be combined in a clinical study. Second, and probably more importantly, we lack a coordinated global effort to map the genetic dependencies in cancers that form the basis for these combination therapies. This precludes the design of rational combination therapies for cancers of defined genotype and has been identified as a "missing link" in genotype-directed cancer therapy (Bernards, 2012).

4. Cost of drugs

As mentioned above, the historic attrition rate in drug development is very high, making for an average cost of over $800 million for every drug that reached the market (Rawlins, 2004). The pharmaceutical industry uses these numbers to justify the high cost of new cancer drugs, but this cost structure does not appear sustainable in the new era of drug development for two reasons. First, by selecting patients upfront, registration of a drug becomes possible in focused phase II studies with 100s rather than 1000s of patients, cutting both drug development time and cost. Second, the selection of patients upfront makes for a higher success rate in clinical development. Thus, it will no longer be the case that one "winner" has to help pay of 9 "losers", cutting down further the cost of drug development. Healthcare payers will soon realize this and will negotiate much lower prices for cancer drugs than the unsustainable pricing we have seen in the recent past.

Another major savings in terms of cancer drug expenditure lies in the fact that the current unfocussed administration of drugs is ineffective. It is estimated that cancer drugs are ineffective in 75% of the cases. With an annual expenditure of cancer drugs of $49 billion a year, that implies that some 37 billion dollar is spent to make patients sicker (due to side effects) rather than better (Spear et al., 2001). Another important aspect of the new treatment paradigm is "not to give the wrong treatment to the wrong patient". Therefore, substantial gains could be achieved through a more intelligent allocation of adjuvant chemotherapy, which is now systematically prescribed in a number of clinical situations. Robust data confirm that systematic adjuvant chemotherapy significantly diminish the risk of relapse and improve survival. However, it is also clear that a large number of these patients are already cured after loco-regional treatment and will receive toxic adjuvant treatment for no reason. However, it is difficult to identify the patients that require adjuvant therapy. Conventional criteria are imprecise and lead to overtreatment of a large proportion of patients (estimated between 50 and 60% of the women with local breast cancer). Recently, gene expression signatures have been reported, which allow for the identification of patient subgroups with an excellent prognosis, having practically no risk for relapse after loco-regional treatment (Drukker et al., 2013; Paik et al., 2004; van de Vijver et al., 2002). Trials are currently undertaken to demonstrate that sparing such women systematic adjuvant chemotherapy is not detrimental for their overall survival, whereas their quality of life after the initial treatment will be obviously much improved (Cardoso et al., 2008). That physicians are paid to administer chemotherapy does not help in reducing overtreatment. Taking these arguments together, we do not believe that personalized cancer care necessarily has to be more expensive, especially when the majority of the very effective targeted cancer drugs become available as more affordable "generics".

5. Outlook

It has been proposed that intra-tumor heterogeneity will limit the success of any targeted therapeutic approach, as resistant subclones of cancer cells most likely pre-exist in the population prior to treatment. Such resistant variants become dominant soon after drug exposure, as they have a selective advantage under these conditions. One reason that tumor size is almost always in independent variable in multivariate analysis of tumor characteristics is that a larger volume of tumor cells proportionally increases the chance that resistant variants are present in the tumor prior to treatment. This explains why smaller tumors are easier to cure than larger ones and makes the case for early detection of cancer through screening programs. A recent development that seems promising in this context is the finding that advanced tumors shed DNA in the bloodstream of the patient and this allows one to genotype the cancer from a "liquid biopsy" taken from the blood (Murtaza et al., 2013). Moreover, one can often detect resistant variants in cell free tumor DNA in blood during drug treatment long before these resistant variants become clinically manifest (Diaz Jr et al., 2012; Misale et al., 2012). When the sensitivity of this technology improves over the next few years and the cost of DNA sequencing continues to decline, it may become feasible to screen the entire population for the presence of incipient tumors through their release of mutant cancer-associated alleles in the blood. How such asymptomatic patients should be treated is currently uncertain. Studies involving sequential blood screening for circulating tumor DNA accompanied by intensified imaging will be required to establish this. When this population screening happens, far fewer patients may present with metastatic disease, with proportional increased chances of controlling the disease. How quickly the events outlined here will unfold is difficult to predict, but it is safe to say that cancer diagnosis and treatment will be very different a decade from now.

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