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Personalized Medicine in Oncology and Companion Diagnostics: Development and Challenges

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Abstract

The core of the whole concept of personalized medicine is to tailor medical practice, from prevention, diagnosis, treatment to prognosis, based on the underlying pathophysiological changes of the disease and the patient. More specifically, this approach may include new diagnostic tools to determine genetic alterations and expression, including the noncoding genetic elements, in order to more precisely screen and diagnose diseases and their subtypes, select the most effective and/or the least toxic therapeutic agents including dosage personalization, and stratify patients into different prognostic groups. This review will focus on the molecular biomarkers in medical oncology that help achieve the above mentioned applications, the selected molecular companion diagnostics, as well as the challenges around the aspects of development of these tests.

Keywords: Companion diagnostics; Molecular diagnostics; Personalized medicine; Biomarkers; Personalized oncology

Introduction

Currently, oncologists select therapeutic regimens based on the results of previous clinical trials performed on a population of patients with the "same" cancer. For example, until recently, platinum-based doublets are usually prescribed as a first-line therapy for patients with the "same" diagnosis of nonsmall cell lung cancer (NSCLC), with a response rate of less than 30% [1-3].

However, NSCLC encompasses a mixture of malignancies originated from lung. They not only have different histological types, but also dramatically different oncopathogeneses. Similar findings are also observed in other types of cancers with the same histological type, but with different pathophysiological changes. As we learn more about the molecular variations, medical oncology is evolving into a more personalized medicine where molecular diagnostics could increasingly determine precisely the subtype and genetic features of the disease and a particular patient, and predict whether that individual and/or cancer will be susceptible to a drug or drug toxicities [4]. This leads to the emergence of companion diagnostics, which are important tools to predict how a particular patient will react to a particular treatment. Companion diagnostic is defined as a particular diagnostic test that is specifically linked to a therapeutic drug [5]. This linkage is important in the therapeutic application and clinical outcome of a drug. Much of the activity in companion diagnostics has been focused in the area of oncology.

The Diagnostics

The introduction of targeted therapies into clinical oncology practice involves the development of cancer biomarkers. The use of molecular profiling is an essential companion for these targeted therapies, a process known as "companion diagnostics" (Table 1) [6]. Even though it is a recent concept, its clinical applications have been adopted for many years. For example, the expression of estrogen receptor is associated with response to endocrinal therapy in breast cancer. For patients with NSCLC, genetic alterations and matched drugs have been developed that target specific receptors and signaling pathways. It has been shown that epidermal growth factor receptor (EGFR) overexpression/mutation results in activation of signaling pathways that affect cell proliferation, including antiapoptotic signaling pathways, which contributes to oncogenesis. Cancer cells with EGFR mutations are largely dependent on this specific signaling pathways stimulated by activated EGFR [1]. The demographics of patients who harbor this mutation are more likely to be never smokers, female, and of East Asian descent [7,8].

EGFR

Until recently, the first-line chemotherapy for NSCLC was usually platinum-based doublet regardless of the histological type. However, studies show unique benefit of pemetrexed in nonsquamous histology while paclitaxel might be more effective in squamous cell carcinoma of the lung [1]. Adenocarcinomas may also respond to bevacizumab therapy. Patients with squamous cell carcinoma who receive bevacizumab are at risk of developing severe, even life-threatening, hemorrhage [9]. In addition, other mutations such as mutations at EGFR are preferentially associated with certain histological types, such as bronchioalveolar type adenocarcinoma (lepidic predominant adenocarcinoma) [10]. Therefore, it is necessary to determine the histological type before ordering the molecular test.

Two main mutations in exon 19 and exon 21 of the EGFR gene account for up to 90% of EGFR mutations and predict response to EGFR tyrosine kinase inhibitor (TKI) therapy in lung cancer. EGFR TKIs such as erlotinib have been approved for lung adenocarcinomas harboring these EGFR mutations [7]. There are three approaches to determine EGFR alterations: DNA sequencing for EGFR mutation status, fluorescence in situ hybridization (FISH) for gene copy number, and immunohistochemistry (IHC) for protein expression (Table 1). Identification of specific activating mutations in EGFR requires DNA sequencing, which is the gold standard. PCR-based testing is more sensitive. Testing for EGFR protein expression can be done by IHC;

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Relevant Histological Subtypes	Pathway	Molecular Diagnostics	Potentially relevant Therapies
Lung adenocarcinoma	EGFR	Cobas® EGFR Mutation Test (Roche, Indianapolis, IN) Therascreen EGFR PCR Kit (Qiagen, Valencia, CA)	TKIs
Colorectal cancer	KRAS	Therascreen KRAS RGQ PCR Kit (Qiagen)	MEK1/MEK2 inhibitors, EGFR inhibitors
Lung adenocarcinoma	EML4-ALK	Vysis ALK Break Apart FISH Probe Kit (Abbott Laboratories, Abbott Park, IL, USA)	ALK inhibitors, e.g. critzotinib
Lung adenocarcinoma*	ROS1	Vysis FISH for ROS1 rearrangement (Abbott)	Crizotinib
Melanoma*	BRAF V600E	Cobas® 4800 BRAF V600 Mutation Test (Roche, Indianapolis, IN)	Vemurafenib
Breast Cancer**	HER2	HER2 FISH pharmDx Kit (Dako, Carpinteria, CA) HercepTest immunocytochemical assay (Dako)	Trastuzumab

*Tumors at advanced stage should be tested at time of diagnosis, or at time of recurrence of progression in patients who originally presented with lower stage disease but were not previously tested.
**Tumors should be tested in when trastuzumab treatment is being considered

Table 1: Molecular diagnostics in selected cancer types.

it is readily available in many labs and may be used as a prescreening tool [11]. While FISH is an established modality for assessing gene amplification in the case of EGFR in NSCLC, it is expensive, time-consuming and requires special protocol, materials, and fluorescent microscope [12]. Clinical utility of testing for EGFR gene amplification is uncertain [1].

Resistance to EGFR targeted therapy is a major clinical concern [1]. Some mutations, such as insertion mutations of exon 20 of EGFR gene and KRAS mutations, confer primary resistance [13]. Acquired resistance after 6–12 months of TKI therapy is associated with the T790M substitution in exon 20 of EGFR gene in about 50% of patients and amplification of MET gene in about 20% [7].

Anaplastic large cell lymphoma kinase gene

Anaplastic large cell lymphoma kinase gene (ALK) rearrangement within NSCLCs results from an interstitial deletion and inversion in chromosome 2p that leads to the EML4-ALK fusion gene products even though other rarer fusion partners of ALK have also been identified [1,7]. This mutation in lung adenocarcinomas is not common and accounts for about 3–8% of adenocarcinomas [14]. Patients with this mutation can have a significant response to inhibitors of ALK kinase like crizotinib [1]. The overall response rate was 57% [15]. A recently developed US Food and Drug Administration (FDA)-approved companion diagnostic, the Vysis ALK Break Apart FISH Probe Kit, is commercially available to identify patients with this mutation.

ROS1

Another recently observed mutation identified in a subset of NSCLC is ROS1 rearrangement [16]. ROS1 is a proto-oncogene receptor tyrosine kinase of the insulin receptor family and signals down the MAPK (mitogen-activated protein kinase) signaling cascade through phosphorylation of RAS (an abbreviation of "rat sarcoma") and previously identified in glioblastoma [17]. ROS1 rearrangements have been shown to be present in about 1–2% NSCLCs, mostly identified by FISH. This subset of patients appears to demonstrate similar clinical characteristics as in patients with ALK rearrangements with positive response to ALK inhibitors (such as crizotinib) in limited clinical studies [18]. It is predominantly seen in younger, never smokers with adenocarcinomas [19].

KRAS

Mutations of KRAS, also known as Kirsten rat sarcoma virus oncogene homologue, are more common in smokers and account for about 20–30% of lung adenocarcinomas. The most common mutations in KRAS are activating missense mutations in codons 12 and 13 [20]. Patients who have KRAS mutation in their tumors do not respond as well to standard chemotherapy and EGFR TKI [21,22]. However, results of agents targeting MEK1/MEK2 kinases downstream of RAS have been promising [23]. In July 2012, the FDA approved Qiagen therascreen® KRAS RGQ PCR Kit to determine whether a patient's tumor contains a KRAS genetic mutation [24]. In colorectal cancer (CRC), KRAS mutations indicate poor response to EGFR inhibitors [25,26]. Approximately 30–40% of colon cancers harbor KRAS mutations with the majority of KRAS mutations also present at codons 12 and 13, similar to NSCLC.

BRAF V600E

BRAF V600E mutation is found in about 50% of melanoma patients [27,28]. In August 2011, the FDA approved vemurafenib and its companion diagnostic Cobas BRAF Mutation Test to detect BRAF mutations in melanoma. This test is reproducible, more sensitive, and accurate than direct sequencing in detecting BRAF V600E [29,30]. In patients with BRAF V600E mutation, the response rate is around 48% (95% confident interval of 42 to 55%) [31].

HER2

The presence of HER2 status in solid tumors, such as breast and gastric tumors is important as it serves as a predictive marker for the treatment involving the monoclonal antibody trastuzumab. About 20% of patients with breast and gastric cancers have HER2-positive tumors. The HER2 gene resides on chromosome 17 and carries the blueprint for the cell to manufacture the HER2 protein [32]. Treatment using monoclonal antibody trastuzumab in breast and gastric cancer patients is associated with an improvement in disease progression and response rates [33,34]. There are two methods of testing for HER2 tumor status, IHC and FISH. The HercepTest is an IHC-based assay to measure the amount of HER2 protein receptors. It is readily available in many labs and is often the first method considered for a companion diagnostic for identifying HER2 status in these patients. HER2 FISH PharmDx Kit measures the frequency of HER2 gene amplification and the concordance with IHC is high (~95%) [35,36].

Gene profiling

The abovementioned companion diagnostics are tests for single genes and their associated targeted therapy. As the array technologies and next generation sequencing (NGS) develop, other companion diagnostics may cover a group of genes or the whole genome. Oncotype DX determines the gene expression profile of 21 genes [37]. It does not predict the response to certain drugs, but rather predicts the disease recurrence rate of breast cancer at the intermediate risk after mastectomy. This will guide the selection of adjuvant therapy. NGS can determine the whole genome of patients and their cancer, and therefore, identify druggable mutations. Lipson et al showed that 71%

of NSCLC and 52% of CRC cases harbor druggable mutations [38]. In the future, personalized oncology will need to integrate the genetic alterations into drug selection.

The Challenges

While dramatic progress has been made, development of companion diagnostics faces challenges common to any medical advancement including reimbursement issues, development timelines, and navigating FDA pathways to approval.

Development of a biomarker might actually be more difficult than that of the drug it is linked to [39,40]. It should have proven clinical utility, robust analytics, reproducibility, standardization, and reliable systems [41]. The question of clinical utility must first be answered to determine if it is meaningful and can change clinical practice [42]. In addition, robust measurement must be established that can be reproduced in other patients; data be normalized across different platforms and different datasets. Furthermore, there are challenges of adapting research tool to the level of standardization and reproducibility [43].

There are also difficult regulatory and reimbursement issues in translating companion diagnostics into clinical practice. In the United States, the FDA is the leading regulatory agency in providing concrete and specific guidance for industry on the regulatory process for companion diagnostic and therapeutic pairs [44,45]. However, there are separate processes and responsibilities within the FDA for drugs and diagnostics, with little coordination. This can pose additional administrative and logistical challenges for sponsors.

Other technical limitations associated with specimen process that may affect companion diagnostics include specimen age, tumor content, degree of necrosis, presence of endogenous and exogenous inhibitors, and damaging effects of formalin fixation that can limit DNA amplification. All of these factors can affect the accuracy of a test. In melanomas, melanin itself may inhibit DNA polymerases, producing invalid test results [12]. Several key technical features associated with the test itself must also be addressed such as reproducibility, rapid turnaround time, requirement for a minimal amount of specimen, comprehensive understanding of the influence of potential endogenous and exogenous interfering substances, and little cross-reactivity with the mutations on assay performance. To maximize the clinical applicability, diagnostic tests should use available clinical samples (ie, formalin-fixed paraffin-embedded samples) [24]. Another potential issue is whether or not there is enough tissue to perform the tests. Immunohistochemistry using antibody measures only one or a few proteins (genes) at a time and reading is often subjective. There is a need for standardization of immunostaining and rigorous validation of performance for targeted therapy [45].

The reimbursement/payment situation associated with companion diagnostics is a big challenge. The emergence of new tests that determine whether or not certain patients should take specific drugs means that the insurers must pay for actually works [46]. However, payers may not pay every single molecular test that has been ordered [28]. So far, there are few guidelines regarding the reimbursement of companion diagnostics. Most payers have their own guidelines to determine the reimbursement.

The Pathway to Approval

Applying for a companion diagnostic device must go through rigorous regulatory requirements and approval by the Federal Food, Drug, and Cosmetic Act and relevant medical device regulations. To support a companion diagnostic device, a potential new therapeutic agent in co-development must be validated and meet standards for safety and effectiveness. If the new therapeutic agent is being used to treat serious or life-threatening conditions, the FDA may decide to approve this therapy even if its companion diagnostic device is not yet approved. In general, the FDA uses a risk-based approach to determine whether a companion diagnostic device is safe for patients. A premarket submission for companion diagnostic device approval is recommended as this can facilitate concurrent approval of both the therapeutic drug and its companion diagnostic device. Labeling of the companion diagnostic device must also be specific in regards to the intended use of the device in accordance to the *Code of Federal Regulations*, title 21, sec 809.10(A)(2). It should name the class of drugs that the device is intended. Once this process has been cleared for one disease, additional premarket approval (PMA or 510(k)) must be obtained to use for another disease to ensure the use of the companion diagnostic device is safe and effective in this new setting. Devices that are being considered for use in clinical trials of a potential therapeutic drug is considered risky under *Code of Federal Regulations*, title 21, sec 812.3(m)(3) due to potential risk of patient safety [47]. In such cases, trials must be conducted in full compliance with the investigation device exemption (IDE) regulations. Presubmission IDE to get feedback from the FDA should be filed early in order to incorporate their advice into the design and development of the device [48]. When a device and therapeutic drug are being studied together in a clinical trial, investigation submission should be obtained for both the diagnostic device and the therapeutic drug.

Conclusion

The concept of personalized medicine is steadily evolving from a theoretical concept into an integral part of modern medicine. Development of personalized medicine will lead to better outcomes for patients and lower costs for the healthcare system––offering patients the promise of medicines best suited for their specific type of disease. Ultimately, this means more effective treatments and patients will be less likely to take drugs that provide little or no benefit. Genomics has played a big role in personalized medicine as this not only reduces side effects for patients but also cuts down on the trial and error approach to prescribing medicine. There are still challenges to overcome in biomarker discovery, validation, and commercialization.

Having diagnostic capabilities intertwined throughout all stages of drug development would be a significant advantage. Personalized medicine involving the use of pathogenetic information of disease and patients to personalize the healthcare is going to be the future of medicine, allowing clinicians to give more effective and less toxic drugs to patients. The technology is incredibly fast but understanding how they connect to diseases takes a lot more work and time.

Competing interests

Dr. Pan is a cofounder and shareholder of the Accelerated Medical Diagnostics, Inc.

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