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Biomarkers for personalized oncology: recent advances and future challenges

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ABSTRACT

Cancer is a group of diseases characterized by the uncontrolled growth and spread of abnormal cells and oncology is a branch of medicine that deals with tumors. The last decade has seen significant advances in the development of biomarkers in oncology that play a critical role in understanding molecular and cellular mechanisms which drive tumor initiation, maintenance and progression. Clinical molecular diagnostics and biomarker discoveries in oncology are advancing rapidly as we begin to understand the complex mechanisms that transform a normal cell into an abnormal one. These discoveries have fueled the development of novel drug targets and new treatment strategies. The standard of care for patients with advanced-stage cancers has shifted away from an empirical treatment strategy based on the clinical–pathological profile to one where a biomarker driven treatment algorithm based on the molecular profile of the tumor is used. Recent advances in multiplex genotyping technologies and high-throughput genomic profiling by next-generation sequencing make possible the rapid and comprehensive analysis of the cancer genome of individual patients even from very little tumor biopsy material. Predictive (diagnostic) biomarkers are helpful in matching targeted therapies with patients and in preventing toxicity of standard (systemic) therapies. Prognostic biomarkers identify somatic germ line mutations, changes in DNA methylation, elevated levels of microRNA (miRNA) and circulating tumor cells (CTC) in blood. Predictive biomarkers using molecular diagnostics are currently in use in clinical practice of personalized oncotherapy for the treatment of five diseases: chronic myeloid leukemia, colon, breast, lung cancer and melanoma and these biomarkers are being used successfully to evaluate benefits that can be achieved through targeted therapy. Examples of these molecularly targeted biomarker therapies are: tyrosine kinase inhibitors in chronic myeloid leukemia and gastrointestinal tumors; anaplastic lymphoma kinase (ALK) inhibitors in lung cancer with EML4-ALk fusion; *HER2*/neu blockage in *HER2*/neu-positive breast cancer; and epidermal growth factor receptors (EGFR) inhibition in EGFR-mutated lung cancer. This review presents the current state of our knowledge of biomarkers in five selected cancers: chronic myeloid leukemia, colorectal cancer, breast cancer, non-small cell lung cancer and melanoma.

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1. Introduction

Cancer is a group of diseases characterized by the uncontrolled growth and spread of abnormal cells. About 1,665,540 new cancer cases are expected to be diagnosed in 2014 with about 585,720 Americans expected to die of cancer (almost 1600 people per day) [1]. The National Cancer Institute (NCI) has defined personalized medicine …"as a form of medicine that uses information about a person's genes, proteins and environment to prevent, diagnose and treat disease" [1–3]. Compared with protein biomarkers, cancer genetic markers are more reproducible and less subject to intrinsic and extrinsic stimuli [2]). Personalized medicine has changed the paradigms in oncology (the branch of medicine that deals with tumors), because it is now based on understanding molecular carcinogenesis, pharmacogenomics, and individual genetic differences that determine the response to chemotherapeutics [4,5]. Even though this transition from empiric to mechanism-based, molecular biomarker-driven therapeutic decision process is still evolving, new classes of drugs and companion diagnostics are already beginning to emerge. These are changing the landscape for the management of many advanced-stage cancers [2]. Biomarkers in oncology that provide information use tools of molecular biology to characterize cancer signatures are crucial to personalized treatment and can be divided into: (a) diagnostic, (b) prognostic, (c) treatment and (d) prevention subgroups [5]. (a) Diagnostic biomarkers, also called predictive biomarkers, (targets for diagnostic intervention) are identified by characterizing key mutations and molecular pathways involved in tumor development and proliferation. These predictive biomarkers help optimize therapy decisions by providing information about the likelihood of a response to a chemotherapeutic intervention [5]. (b) Prognostic biomarkers identify somatic germline mutations, changes in DNA methylation, elevated levels of microRNA (miRNA) and circulating tumor cells (CTC) in blood. (c and d) Treatment and prevention biomarkers require more accurate molecular analysis to guide individual therapy by identifying patients with different outcome risks (such as recurrence of the disease) [5].

Information provided concurrently by predictive (diagnostic) and prognostic biomarkers makes possible quicker diagnoses and more accurate treatment choices. Predictive biomarkers using molecular diagnostics are currently in use in clinical practice of personalized oncology for the treatment of following five diseases: chronic myeloid leukemia, colon, breast and lung cancer and melanoma (Table 1). In these diseases, biomarkers are being successfully used to evaluate benefits that can be achieved through targeted therapy and in evaluating the toxic side effects of chemotherapy [5]. Examples of these molecularly targeted therapies are: tyrosine kinase inhibitors in chronic myeloid leukemia (CLM) and gastrointestinal tumors; anaplastic lymphoma kinase (ALK) inhibitors in lung cancer with EML4-ALk fusion; *HER*2/neu blockage in HER2/neu-positive breast cancer; and epidermal growth factor receptors (EGFR) inhibition in EGFR-mutated lung cancer [5]. Predictive biomarkers are also helpful in matching targeted therapies with patients, thereby avoiding the side effects of "one size fits all" standard (systemic) therapies [5].

In oncology biomarkers have been identified for the most common types of tumors: breast, lung and prostate cancers. The poor prognosis of several these metastatic tumors, has prevented some of these new technological advances from significantly impacting survival rates [5]. The choice of targeted therapies relies on previous genetic analysis which is being used as a basis for detecting abnormalities. This requires that populations of patients carrying genetic abnormalities be first identified so that the given therapy can be used with a positive outcome [6]. New technologies such as microarrays, new generation sequencing methods, and mass spectrometry focused on nucleic acids have the potential of expanding the range of DNA biomarker analyses such as Onco DEEP and Onco TRACE [7].

1.1. *Biomarkers in selected cancers*

1.1.1. *Chronic myeloid leukemia*

Leukemia is a cancer of the bone marrow which is characterized by the presence of recurring chromosomal and genetic abnormalities that result in losses, amplifications, translocations and inversions of DNA and blood fragments or whole chromosomal aneuploidies [8]. From 2006 to 2010, the overall leukemia incidence rates have increased slightly (by 0.5% per year) with an estimated 52,380 new cases of leukemia expected in 2014.

Chronic myeloid leukemia (CML) was the first human malignancy found to be associated with a recurrent chromosomal abnormality [9,10]. CML is genetically characterized by the presence of the reciprocal translocation t(9;22)(q34;q11) resulting in a BCR-A1 gene fusion on the derivative chromosome 22. CML is caused by the fusion protein BCR/ABL1, which exhibits constitutive tyrosine kinase (TK) activity [11–13]. Even though TK inhibitor therapy for CML has been shown to be generally successful [10], the disease is still detectable in spite of treatment [14] and CML leukemic stem cells have been shown to be resistant to TK inhibitor therapy [15].

CML is characterized by three phases: an early or chronic phase (CP), an advanced disease stage consisting of an accelerated phase (AP) and a blast phase (BP) which is rapidly fatal [16]. The National Comprehensive Cancer Network (NCCN) guidelines and the European Leukemia Net (ELN) recommendation specify that the first line therapy for Philadelphia chromosome (Ph+) CML is a BCR-ABL tyrosine kinase inhibitor [16]. Five BCR-ABL inhibitors are approved by the US Food and Drug Administration (FDA) for the treatment of Ph+ CML (CP): imatinib, dasatinib, and nilotinib approved for first-line therapy; bosutinib and ponatinib approved for second line therapy. At present in the United Stated no BCR-ABL inhibitor is available for CML-AP/BP [16]. Ph+ CML patients who have been treated with BCR-ABL inhibitors are presumed to have achieved long-term survival based on surrogate endpoints (biomarkers that are intended to substitute for a clinical end point) [17]. As patients respond to treatment the Ph+ clonal population progressively decreases [16]. Surrogate endpoints used in CML have become more sensitive now that they are able to detect residual disease.

With the success of imatinib therapy in achieving a complete and long term cytogenic response (CCyR) in CML patients, attention is now being focused on molecular responses (MRs) as measured by reductions (below the threshold of major MRs) in *BCL-ABL* transcript levels [18]. Molecular monitoring in CML has 2 components: 1) the measurement of *BCR-ABL1* mRNA levels to access response to therapy and