Review article

EMERGING TRENDS IN USE AND ROLE OF BIOMARKERS IN ONCOLOGY TRIAL

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Date of submission: 15.07.2017; Date of Publication: 5th Sep 2017

ABSTRACT

In 21st century new era of – omics (pharmacogenomics, proteomics and metabolomics) paved way for revolutionary personalized medicine. and relies on valid biomarkers that pinpoint what drugs a patient should receive .Tumor biomarkers represent an effective tool for tumor diagnosis, treatment, prognosis, and therapeutic monitoringIdeally, the use of biomarkers in early trials would help predict the likelihood of success or failure of a drug in efficacy trials, guide selection of patients more likely to respond to the agent, and provide meaningful correlations with toxicity and response.Biomarkers can predict drug efficacy more quickly than conventional clinical endpoints, they hold the potential to substantially accelerate product development in certain disease.In the present articlerole and use of the genomic marker in oncology trials has been analyzed from the period of past 10 years. Translating new knowledge about Pharmacogenomicbiomarkers into routine clinical practice has become a reality rather than a futuristic vision.

INTRODUCTION:

Although basic research on tumor biology has broadened the understanding of factors such as occurrence, metastasis, and drug resistance, care of cancer patients is generally by indiscriminate treatment, that is, patients are given the same treatment without fully considering their individual biological characteristics. In 21st century new era of – omics (pharmacogenomics, proteomics and metabolomics) paved way for revolutionary personalized medicine. Personalized medicine or pharmacogenomics, is the prescribing of drugs based on a patient's individual biological profile and relies on valid biomarkers that pinpoint what drugs a patient should receive .Tumor biomarkers represent an effective tool for tumor diagnosis, treatment, prognosis, and therapeutic monitoring[1]. Today you "would not even conceive" of developing a new drug without simultaneously looking for biomarkers for efficacy, safety, and to measure the pharmacodynamics of the drug. The NIH Working Group has defined biomarkers as characteristics used to measure and evaluate objectively normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic interventio[2] differentiating an affected person from a person without disease. In cancer research and detection, a biomarker refers to a substance or process that is indicative of the presence of cancer in the body. It might be either a molecule secreted by malignancy itself or a specific response of the body to the presence of cancer [2].

There is tremendous variety of biomarkers, which can include proteins (e.g., an enzyme or receptor), nucleic acids (e.g., microRNA or other non-coding RNA), antibodies, and peptides, among other categories. A biomarker can also be a collection of alterations, such as gene expression, proteomic, and metabolomics signatures. Biomarkers detected in the circulation (whole blood, serum, or plasma) or excretions or secretions (stool, urine, sputum, or nipple discharge), and thus easily assessed non-invasively and serially, or can be tissue-derived, and require either biopsy or special imaging for evaluation.

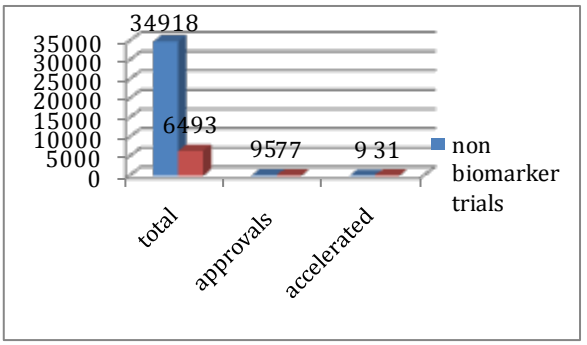
There are two major types of biomarkers: biomarkers of exposure, which are used in risk prediction, and biomarkers of disease, which are used in screening and diagnosis and monitoring of disease progression[3]. Predictive biomarkers predict response to specific therapeutic interventions such as positivity/activation of HER2 that predicts response to trastuzumab in breast cancer.Prognostic biomarker, on the other hand, may not be directly linked to or trigger specific therapeutic decisions, but aim to inform physicians regarding the risk of clinical outcomes such as cancer recurrence or disease progression in the future. An example of a prognostic

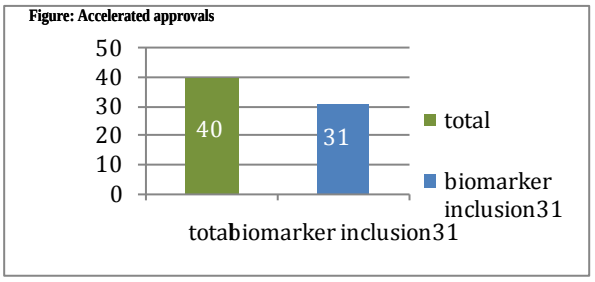
cancer biomarker is the 21-gene recurrence score which was predictive of breast cancer recurrence and overall survival in node-negative, tamoxifene treated breast cancer[4]

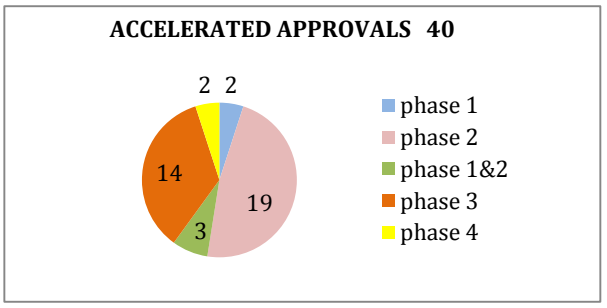
In 21st century new era of – omics (pharmacogenomics, proteomics and metabolomics) paved way for revolutionary personalized medicine. Personalized medicine or pharmacogenomics is the prescribing of drugs based on a patient's individual biological profile and relies on valid biomarkers that pinpoint what drugs a patient should receive. Personalized medicine generally involves the use of two medical products – typically, a diagnostic device to stratify patient population and a therapeutic product – to improve patient outcomes Volumes of information arising out of the human genome project combined with a dramatic decrease in costs of DNA sequencing, are giving way to an explosion of publications linking particular genetic markers to diseases or conditions and a rapid application of this information in the development of new molecular diagnostic tests. From FDA's vantage point, the era of personalized medicine has clearly arrived. Of the new drugs approved since 2011, approximately one-third had some type of genetic or other biomarker data included in the submission to characterize efficacy, safety, or pharmacokinetics. Estimates show the total number of biomarkers of interest at about 1, 133, 00020 — a potentially overwhelming number. However, many pharmaceutical companies have begun to invest in 'omics' — genomics, proteomics, metabonomics — to begin to sort through this mountain of molecules and characterize biomarkers based on a molecular understanding of disease.

In cases where a test is essential for the safe and effective use of a corresponding therapeutic product, it is termed a "companion diagnostic." Vemurafenib/BRAF V600E:In August 2011, FDA simultaneously approved the drug vemurafenib along with its companion diagnostic, the Cobas 4800 BRAF V600E mutation test, for use in treating metastatic or unresectable melanoma[5]. The aim of the present study is to evaluate the role and use of genomic biomarkers in cancer drug approvals.

The data of cancer drugs approved during past 10 years 01/01/2006 to 30/06/2016 was acquired from US FDA official website database which is available for public access. Retrospectively the trial data of the drug was collected from clinical trial.gov website and the role and use of the genomic marker has been analyzed from the period of past 10 years(01-01-2006 to 30-06-2016) the clinicaltrial.gov website has enrolled total of 41,411 oncology trials. Biomarker inclusion trials were only 6493, whereas non biomarker inclusion trials were 34,918.







Total no of oncological trail enrolled during past 10 years (2006 to 2016) is 41,411.only 15.6% of the enrolled trials include genomic markers as an integral part of the trial. These genomic markers are either used as surrogate end points or either had a major role in stratifying the patients in either inclusion or exclusion criteria. In the past decade the trials which have succeeded in getting approvals from US FDA are 172 among which 77(44.7%) are biomarker depended trail and the rest 95(55.3%) are non-biomarker inclusion trial.

The various trials which have been granted accelerated approval are 40(23%) of the total approvals. Among the accelerated approval trials 31(77.5%) are genomic marker depended, with phase2 trials (47.5%) playing a predominant role followed by phase 3 trials (35%). Ideally, the use of biomarkers in early trials would help predict the likelihood of success or failure of a drug in efficacy trials, guide selection of

patients more likely to respond to the agent, and provide meaningful correlations with toxicity and response[6]. Attrition rates for drugs in development process is high the percentage of tested products entering phase I trials that eventually gain regulatory approval has been estimated at a paltry 8%[7] .more than 90% of oncological drugs that enter clinical development will not reach market approval due to failure of clinical trials to demonstrate therapeutic benefit, contributing to costly and slow cancer drug development[7]. Because biomarkers can predict drug efficacy more quickly than conventional clinical endpoints, they hold the potential to substantially accelerate product development in certain disease. Utility of biomarkers should be measured against their effect on costs, accrual, and especially patient safety. Highly expensive biomarkers and/or Today, patients with breast, colorectal, and lung cancers, as well as melanoma and leukemia are routinely offered "molecular diagnosis," allowing their physicians to select treatments that are more likely to improve their chances of survival. These cancers are no longer considered single diseases, but instead sub-classified on the basis of their genetics. Translating new knowledge about pharmaco-genomic biomarkers into routine clinical practice has become a reality rather than a futuristic vision.

Development of cancer drugs is complicated in part by the fact that many cancers are heterogeneous, meaning that cancers in the same organ can have very different origins and characteristics, each with their own specific genetic makeup. How best to integrate rapidly evolving genomic information into clinical care while ensuring safety and efficacy is a topic of considerable public debate and discussion.

biomarkers requiring invasive procedures with potential for increased risks should not be included in clinical trials if the information provided by them will be unlikely to change decisions about further development of the experimental agent

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