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Role of Biomarkers in Prognosis of Cancer and Prediction of Response by Chemotherapy: A Comprehensive Review

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Abstract:*-Biomarkers may play important roles in many aspects of cancer management: they may be utilized as tools for drug discovery, as pharmacological markers for drug efficacy both preclinically and in early-phase trials,and as surrogate endpoints for disease progression in late-phase trials. Biomarkers may likely have a role in the development of future treatments, as well. The adoption of personalized medicine has led to increased efforts to identify new biomarkers across tumor types. In addition to well-established biomarkers such as KRAS and EGFR in colorectal and lung cancer and HER-2 and ER/PR in breast cancer, many emerging biomarkers are being investigated in multiple tumor types. Some have started showing promising data, but they will have to go through many steps in the validation process, which might take many years of research.*

Key words: *Biomarker,Colorectal;selectivity;FDA*

1. DEFINITION

The National Cancer Institute definition of biomarker is: "A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a conditions or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition. Also, called molecular marker and signature molecule.[1]Naturally, a cancer biomarker pertains to any biomarker that fits the aforementioned definition but only for cancer, and no other disease.

2. TYPES OF CANCER BIOMARKERS [2-11]

There are a no. of molecular cancer biomarkers such as-

Type of tumor	Biomarker
Breast	ER, HER-2/Neu
Colorectal	EGFR, KRAS, UGT1A1
Gastric	HER-2/Neu
Leukemia/Lymphoma	CD20 Antigen, CD30, TPMT, PDGFR
Lung	ALK, EGFR, KRAS
Melanoma	BRAF

Other Examples of Biomarkers:
Tumor Suppressors Lost in Cancer -Examples: BRCA1, BRCA2.
RNA -Examples: mRNA, microRNA.
Proteins found in body fluids or tissue-Examples: Prostate-specific antigen, and CA-125. [12]

3. PROPERTIES OF AN IDEAL BIOMARKERS

The ideal biomarker mark out the events between exposure and disease, perform establishment of dose response, and identifies early events in the natural history, also identifies mechanisms by which exposure and disease are related, reduces misclassification of exposures or risk factors and disease, established variability and effect modification, enhanced individual and group risk assessments. Desirable characteristics of biomarker for cancer are shown in Table 1.

In medicine; a biomarker is a term often used to refer to a protein measured in blood whose concentration reflects the severity or presence of some disease state. More generally a biomarker is anything that can be used as an indicator of a particular disease state or some other physiological state of an organism.[13-15]

A biomarker can be a substance that is introduced into an organism as a means to examine organ functions or other aspects of health. Example, rubidium chloride is used as a radioactive isotope to evaluate perfusion of heart muscles. It can also be a substance whose detection indicates a particular disease state, example, the presence of an antibodies may indicate an infections.

There are some proteins which play role in signaling process, as their concentration level may show reflection during uneven function of any organ or constituents of body. It indicates a change in expression or state of a protein that correlates with the risk or progression of a disease, or with the susceptibility of the disease to a given treatment. Biomarkers are characterized biological properties that can be detected and measured in parts of the body like the blood or tissue.[16,17]According to Food and Drug Administration (FDA) an ideal biomarker should be specific, sensitive, predictive, robust, simple, accurate, and inexpensive. It should be used in standard biological sources such as serum,urine as the basis of measurement .

Table 1. Desirable Characteristics of Biomarker for Cancer

Purpose	**Non-invasive**	**Low cost**	**Simple to perform**	**Accurate**	**Informative (discriminatory)**
Screening	+++	+++	+++	+++	+++
Predisposition	+++	+++	+++	+++	+++
Early detection	++	++	++	+++	+++
Prognosis	+	+	+	++	++
Drug response	+++	++	++	+++	+++

Table 2. Currently Used Biomarkers in Different Fields

Classification of Cancer Biomarker	**Biomarker**
Genetic biomarker	Biomarker of PTEN tumor suppressor gene status Gene mutation Oncogene
DNA biomarker	Gene amplification Microsatellite instability Mitochondrial DNA Viral DNA
RNA biomarkers	microRNAs Protein biomarker B7 co-regulatory ligands Raised serum lactate dehydrogenase High-motility group protein A2
Metabolic biomarker	Hypoxia-induced factor-1
Epigenic biomarker	DNA methylation Immunological biomarker: T-cell and cytokine response Biomarker in cancer stem cells: crpto-1

4. ROLE OF BIOMARKER IN TREATMENT SELECTION

Classification of Tumour subtype with biomarkers

Classification of a malignancy by tissue of origin is the first step towards predicting survival and choosing therapy. Because a tumour's anatomical location usually indicates its tissue of origin, molecular markers are rarely required. Histological examination generally confirms the diagnosis and identifies the tumour subtype. However, new molecular markers might sometimes be helpful in the differential diagnosis.[18]A combination of high-throughput RNA, protein and tissue microarray technologies is recently being used to identify markers potentially useful for distinguishing colon and ovarian abdominal carcinomas from an unknown primary location. Similarly, biomarkers have been reported to distinguish primary head and neck squamous cell carcinoma (HNSCC) from metastatic lung squamous cell carcinoma (SCC), to determine the site of origin for HNSCC of unknown primary location and to track genetic mutations that occur with the progression of that tumour.[19]

Strategy of treatment guided by biomarkers

Tumour classification, stage and sometimes grade are used to assess prognosis. However, as noted above, there would be a cost if formal cancer staging incorporated every other parameter able to improve prognosis. Furthermore, stratification in clinical trials using all possible TNM combinations would be

impractical, given limitations in patient participation and resources. Addition of markers could similarly fragment the staging process, thereby limiting its utility. More information is generally better than less information, but the advantages must be weighed against those of a stable classification with relatively few categories.

Biomarker expression often supplants or complements tumour classification, stage and grade when biologically targeted therapeutics are under consideration.[20]

Prominent examples include CD_{20} positivity for treatment of lymphomas with rituximab, HER2/NEU positivity for treatment of breast cancer with trastuzumab, BCR-ABL translocation for treatment of chronic myelogenous leukaemia (CML) with imatinib, and KIT or platelet-derived growth factor receptor-α (PDGFRA) positivity for treatment of Gastrointestinal stromal tumours (GIST) with imatinib.

ER positivity or PR positivity is a prerequisite for treatment with tamoxifen or aromatase inhibitors. Similarly, somatic mutations in the tyrosine-kinase domain of the epidermal growth factor receptor (EGFR) have recently been shown to predict a greater efficacy of gefitinib in patients with non-small-cell lung cancer (NSCLC).

Some of those markers are FDA-approved and in widespread clinical use,others have been assessed only in the research setting. For example, ER, PR and HER2/NEU status are routinely determined for breast cancer, whereas EGFR mutations are usually assessed only in clinical trials. Outside of such trials, patients with NSCLC are often given EGFR-antagonists, such as gefitinib, as salvage therapy on an empirical basis without marker studies, especially if they are more likely to have the mutation (that is, patients who are female, never-smokers, diagnosed with adenocarcinoma.

Both prognosis and prediction of response are necessary for the selection of neo-adjuvant or adjuvant chemotherapy. Tissue classification, TNM staging, molecular biomarkers, grade and other factors might be used in combination for that purpose. The combinations of variables might not be easy to analyse manually, but computer Decision support systems (DSS) can make the automatically assessments. For example, Adjuvant Online, a DSS used for breast cancer, estimates 10-year cancer recurrence and survival for women, taking into account their predicted response to adjuvant chemotherapy.Markers can also be used to avoid idiosyncratic drug toxicity such as the sustained, life-threatening leukocyte suppression seen when mercaptopurine is given to leukaemia patients with homozygous mutations of the thiopurine methyl-transferase (TPMT) gene.

5. SPECIFICITY OF BIOMARKER

It should be noted that characteristics that suit a molecular marker for one application might not do so for another. For example, A markers are used in screening the general population must have an extremely high specificity to minimize false positives that necessitate the costly or invasive follow-up studies and scare patients and their families needlessly. The same marker need not be so specific if used for high- risk populations and can be even less so once a cancer has been detected. The arguments about use of PSA for screening continue, but its value monitoring diagnosed prostate cancer or its treatment would be hard to dispute.[21-23]

The TNM staging system (based on a combination of tumor size or depth (T), lymph node spread (N), and presence or absence of metastases (M)) provides a basis for prediction of survival and choice of initial treatment, patients stratification in clinical trials, accurate communication among the healthcare providers, and uniform reporting of the end result of cancer management.

There is a dilemma in TNM staging: frequent revisions to include new biomarkers would undermine the value of conferred by the stability and universality of TNM stage, but a static formulation of TNM risks falling behind the state of the art in diagnostic techniques and biological concepts and biomarkers. Biomarkers initially considered for screening of cancer or risk assessment might also prove the useful for cancer staging or grading. A biomarker for use in staging or grading need not be as specific as it must be for screening, early detection or risk assessment.[24]

A minute centered cancer therapeutic cost are extra common, assessing the intended goal will extra frequently be deemed essential for prediction of clinical components and impartial of TNM stage.Targeted therapies and their associated biomarkers will often 'co-evolve'. The ideal biomarker assay for staging should be sensitive and specific and cost-effective, fast and robust against inter-operator, inter-institutional variability. It must also demonstrate clinical value beyond that of the other types of information that are already available at the time of diagnosis.[25]

Biomarker candidates must undergo clinical validation before receiving the US Food and Drug Administration approval. Most of the candidate markers, which process is just beginning.

Despite all of the potentially useful biomarkers. Example, those identified from microarray or mass spectrometry studies and almost none have been incorporated into formal TNM staging.

6. BIOMARKERS FOR CANCER DIAGNOSIS AND PROGNOSIS

Biomarkers play a crucial position in medicine as they give an concept approximately the severity of a sickness close to the presence of the traits of any disease. Which can be identifiable and measurable. It surely indicates the physiological state of an organism by using acting as a hallmark of a specific country of disease. They help in the evaluation of diverse biological, pathogenic approaches inside an organism in addition to the pharmacological reaction to therapeutics by means of objective of objective degree consisting of diagnostics and other imaging technology. They deliver an concept about the drug motion and drug metabolism and its efficacy as well as safety.

The improvement of most cancers includes multiple ranges which includes genetic changes, epigenetic, cytogenetic in addition to cellular cycle modifications. Hence, the advancement of different technologies that can help in the detection of the development of different stages may help in getting an in-depth understanding of the progression of cancer that may help in the development of possible therapeutics for different types of cancer. Therefore, biomarkers play a very essential role in the detection and diagnosis and prognosis of patient as well as the selection of personalized treatment for cancer.

The understanding the pathways of the disease, the gene,protein targets of the disease have helped in the use of biomarkers in the different imaging technologies such as genomics and proteomics as well as genetics that are non-invasive in nature. The establishment of the exact relationship between the clinical pathology of cancer progression. The biomarkers can help in its early diagnosis and the prognosis of the patients by the clinical oncologists, which may further help in the development of patient specific treatment.[26-29] The Human genome project has helped in the advancement of sequencing studies with the development of microarrays, mass spectrometry, etc. that has helped in the expansion of the number of biomarkers available for different types of cancers. Some of the biomarkers are presently used in the diagnostic.

7. CYTOGENETIC MARKERS

One of the markers for most cancers is the extraordinary structural modifications delivered in the chromosomes together with chromosomal aberrations. Somatic mutations in the reporter genes and oncogenes as well as the tumor suppressor genes have also proved to be a potent marker for cancer. apart from them, precise modifications in the transcriptomes are also being advanced as biomarkers. E.g. the transcriptome marker primarily based on the degrees of exon-three deleted version isoform of proghrelin, the

precursor of ghrelin, which is a boom element associated with proliferation of prostate cancer cells is being developed as a biomarker.

8. GENETIC MARKERS:

The transformation of the genes leading to gain or loss of function is associated with the formation of oncogenes. The random mutations that occur due to different factors in the regulatory region of the genes are responsible for this oncogenic transformation. In most of the cancers and genes act as potent biomarkers that help in the diagnosis as well as gene-based therapy of the disease. Gene deletions may also help in the development of the disease. These changes within the genes can be identified using PCR techniques as well as Microsatellite probes as microsatellite instability and alterations is one of the changes evident in preneoplastic stage of tumor cells. The Adenomatous polyposis gene (APC) is associated with the suppression of cancer, which is altered in the carcinoma patients by somatic mutation and hypermethylation or production of short and non-functional APC protein.

9. EPIGENETIC MARKERS:

Epigenetic changes are usually associated with modification in the gene expression patterns that result due to changes in the histone proteins associated with DNA by methylation and acetylation or phosphorylation. The hypomethylation of genomes is associated with instability of the genomes as well as stronger gene expression and while hyper methylation in the CpG island promoter is associated with the silencing of the functions of the tumor suppressor genes such as apoptotic genes, metastatic genes as well as biotransformation and signal transduction genes. Hypermethylation and aberrant methylation has been used as a biomarker in many carcinomas. The research in the field of epigenetics has helped in increasing the rate of survival with some form of leukaemias as well as lymphomas with the use of drugs that help in the alteration of DNA methylation and histone acetylation. However, the development of drugs and therapeutics that may help in the reversal of the epigenetic changes remain to be seen in near the future.

To obtain molecular imaging of sickness biomarkers the usage of MRI and focused MRI assessment retailers with high specificity, high relaxivity (sensitivity) are required.so far, many studies had been dedicated to growing centered-MRI contrast retailers to obtain molecular imaging by means of MRI. Commonly peptides, antibodies, or small ligands, small protein domains, such as HER-2 affibodies, have been applied to achieve targeting. To enhance the sensitivity of the contrast agents, these targeting moieties are usually linked to high payload MRI contrast agents or MRI contrast agents with high relaxivities.[31-34]

10. CONCLUSION

In the age of technology future is bright for biomarkers. As various institutes are working on early detection of cancer there is possibility that we can detect cancer before the tumor formation. The scale of this attempt preclinical studies and large clinical trials is considerable, making it expensive. Collaboration with the pharmaceutical industries is essential because experimental anticancer drugs are an essential reagent for biomarker discovery experiments. Many cancer biomarkers will be broadly applicable (for example, they will not be restricted to predicting the response to a single drug), so a collaborative, precompetitive partnership with industry is warranted. Similar to government-sponsored projects such as the Human Genome Project and The Cancer Genome Atlas, early results from collaborative biomarker discovery projects should be released into the public domain to encourage further study and to avoid

downstream intellectual property disputes that could delay commercialization efforts. It is time to establish an associative approach using a public-private partnership model to solve the cancer biomarker problem. All the stakeholders, patients, doctors, pharmaceutical and molecular diagnostic companies, regulatory agencies and health-care payers stand to benefit.Universal cross sectional imaging is impractical and would be associated with high cost and potential radiation related morbidity. There are two major approaches to molecular discovery of marker. In the high throughput "shotgun" strategies thousands of contenders are screened simultaneously.

In the traditional hypothesis driven approach, interactions between molecules known to be important to pancreas cancer development are studied to identify novel molecules and pathways.When we talk about specific type of cancer prostate cancer (CaP) continues to be the second leading cause of cancer-specific death in men in Western countries. The marker presently used for CaP detection is an boom in serum prostate particular antigen (PSA). but, the PSA take a look at might also deliver positive or negative statistics and does not allow the differentiation of benign prostate hyperplasia(BPH) and non-competitive CaP and competitive CaP. Tears are a unique source of body fluid and it contains proteins, peptides and mucins and lipids which is useful for studying clinical proteomics. Advances within the area of proteomics have substantially superior they have a look at of tears, with a greater quantity of proteins now being recognized in tears. Identification of novel biomarkers in tear is a new location of improvement. current advances in the field of proteomic strategies stay the promise of imparting the clinical oncologists with new tools to locate novel CaP biomarkers for early prognosis and analysis. Early diagnosis of cancer needs focus on biomarkers identification. One possible approach may be the study of signaling system of pathways related with cancer in our body, as study of signaling system is not easy in itself; focus on one factor at a time is not an easy task. Relative study with respective to each factor that is at a time study of effect on one factor into another one and on whole process can be effective. Beside all these problems related ultimate solution with early diagnosis of cancer, biomarker identification. We are in the age of technology and in future solution will be definitely found out. Many promising fields are growing day by day like nanotechnology and medical inventions, so we can hope for promising future ahead.

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