ISSN 0974-3618 (Print)
0974-360X (Online)

www.rjptonline.org

REVIEW ARTICLE

Personalized Medicine - A Novel approach in Cancer Therapy

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ABSTRACT:
The word"personalized medicine" wasregularlylabelled as providing patient withtheright drug at the right dose at the right time.Personalized medicine was being advanced through data from the Human Genome Project. Cancer was a disease of the genome. In cancer, different tumours may have the same DNA, but the gene expression pattern was different in different tumour types.Genomic variations in EGFR and ERCC1 have been correlated with drug response in small cell lung cancer patients, HER2, BRCA1 in breast cancer.The isolation and analysis of CTCs may be a useful method for tracking how cancers evolve during therapy.Personalized medicine was receiving a large amount of growing attention for its tremendous potential with new opportunities.

KEYWORDS: Personalized medicine, Cancer, Human genome project, Personal 'omics' profile, Circulating tumour cells, Precision oncology

1. INTRODUCTION:
The term "personalized medicine" was often described as providing patient with "the right drug at the right dose at the right time." More broadly, personalized medicine (likewise known as precision medicine) might be thought of as the adapting of medical treatment to the individual needs, and preferences of a patient during all stages of care, including prevention, diagnosis, treatment, and follow-up.[1]

Personalized medicine was an emerging practice of medicine that uses anperson's genetic profile to guide decisions made in regard to the prevention, diagnosis, and treatment of disease. Knowledge of a patient's genetic profile can help physicians select the proper medication or therapy and administer it using the appropriate dose or regimen. Personalized medicine was being cutting-edge through data from the Human Genome Project.[2]

Received on 16.08.2016 Modified on 08.09.2016
Accepted on 12.09.2016
Research J. Pharm. and Tech. 2017; 10(1): 341-345.
DOI: 10.5958/0974-360X.2017.00069.5

Thus, both the course of disease and our response to treatments are intimately tied to our genome sequence. Beyond our genomes, person-to-person variation likewise manifests at the RNA, protein and metabolite levels. Each person had a unique variation of the human genome. Although most of the variation between individuals had no effect on health, an individual's health stems from genetic variation with behaviors and influences from the environment.[3]

Contemporary advances in personalized medicine trust on technology that authorizes a patient's fundamental biology,DNA, RNA, or protein, which ultimately leads to confirming disease. For example, personalized medicine techniques such as genome sequencing can reveal mutations in DNA that influence diseases ranging from cystic fibrosis to cancer. Another method, called RNA-seq, can show which RNA's are involved with specific diseases. Unlike DNA, levels of RNA change in response to the environment. Therefore, sequencing RNA can reveal a broader understanding of a person's state of health. Methods of RNA-seq are very similar to genome sequencing.[4]

2.Personalized Medicine and Cancer:
Cancer was one of the foremost causes of demise in the United States, and more than 1.5 million new cases and more than 0.5 million deaths were reported during 2010 in the United States alone. Following completion of the

sequencing of the human genome, substantial progress had been made in symbolising the human epigenome, proteome, and metabolome; a better understanding of pharmacogenomics had been developed, and the potential for customizing health care for the individual had grown tremendously.[5] Recently, personalized medicine had mainly complex the systematic use of hereditary or other information around an individual patient to select or improve that patient's anticipatory and beneficial care. Molecular sketching in vigorous and cancer patient samples might allow for a greater degree of personalized medicine than was currently available. Evidence about a patient's proteinaceous, hereditary, and metabolic profile could be used to tailor medical care to that individual's needs.[6] A key attribute of This medical model was the development of acquaintance diagnostics, whereby molecular assays that measure levels of proteins, genes, or specific transmutations are used to provide a precise therapy for an individual's ailment by stratifying disease status, selecting the proper medication, and adapting dosages to that patient's specific needs. Additionally, such devices can be used to assess a patient's risk factors for a number of conditions and to tailor individual preventative conducts.[7]

Although DNA from different cells was the same, genes coding in one organ (and their cells) behave differently than genes in other organs. In cancer, different tumors might have the same DNA, but the gene expression pattern was different in different tumour types. Technologies such as gene-expression microarray allow us to examine the gene expression profile of hundreds of genes at a time and cancer-associated gene expression profile from normal profiling. For decades, standard medical care had been guided by cohort-based epidemiological studies in which the genetic variability of individuals was not accounted for and most of the conclusions are based at the population level. Modern personalized medicine takes into account an individual's genetic makeup and disease history before a treatment regimen was generated. Thiswas in contrast to traditional personalized medicine, in which care was based on a patient's family history, social circumstances, environment, and lifestyle.[7]

Modern personalized medicine was based on targeted therapy. In targeted therapy, it was essential that information about the altered pathway and the components leading to cancer are available. For example, Herceptin was used in female breast cancer patients who express higher levels of HER-2. Gleevec was prescribed in chronic myleloidleukaemias to inhibit tyrosine kinase. In these patients, reciprocal translocation between chromosome 9 and chromosome 20 occurs, resulting in hyperactivation of abl-driven protein signaling.[8]

The International Human Epigenome Consortium (IHEC) coordinates the production of reference plots of the human epigenome for key cellular states relevant to health and disease, including cancer . To achieve substantial coverage of the human epigenome, the IHEC set the ambitious goal of deciphering at least 1,000 epigenomes within the next 7–10 years. The plan was to produce high-resolution maps of informative histone modifications, high-resolution DNA methylation maps, landmark maps for the transcription start sites of all protein-coding genes, the entire catalogue and expression patterns of non-coding and small RNAs, and comparative analysis of epigenome maps of model organisms relevant to human health and disease. Surveys of individuals, pedigrees, and genetically identical twins will be used to determine the relationship between genetic and epigenetic variation worldwide. NIH Roadmap Epigenomicswas another program that provides epigenomic maps as reference standards.[9]

Metabolomics, a new addition to the field of personalized medicine, was the study of low molecular weight molecules or metabolites found within cells and biological systems. The metabolomewas a measure of the output of biological pathways and, as such, was often considered more representative of the functional state of a cell than other "omics" measures such as genomics or proteomics. As an example, acetoamide (paracetamol)-treated patients are followed for treatment response via metabolic profiling of their urine and blood. Pre- and post-dose analysis shows high p-cresol sulfate before treatment and low acetoamidesulfate to acetylamino glucuronide after treatment. Common technologies for measuring the metabolome include mass spectrometry (MS) and nuclear magnetic resonance (NMR) spectroscopy , which can measure hundreds to thousands of unique chemical entities. Despite early promise, challenges remain before the full potential of metabolomics can be realized. Existing metabolomics facilities are at capacity, with relatively few scientists who possess in-depth expertise in metabolomics and a dearth of training opportunities to provide that expertise. Some companies provide metabolomics services and limited standards; however, issues concerning cost, intellectual property rights, and limited profit incentives minimize their use in basic, clinical, and translational research.[10]

The design of personalized health care was based on prevention or therapeutic approaches in conjunction with current knowledge of the cancer type. Although personalized medicine had been used in a number of cancers, we have selected few cancers below where incidence and prevalence of cancer was high in US and more data was available compared to other cancers.[11]

Screening for *BRCA1* and *BRCA2* mutations like wise was a common practice in clinics for women in different age groups and parity status. Because of differences in individuals' genetic backgrounds and personal susceptibility to environmental and modifiable factors, interventions do not always succeed. Increasing evidence supports personal genomic susceptibility as the major factor in responding to intervention and prevention. The approach provided by these investigators includes behavior modification for high-risk subjects (primary prevention), early detection and extensive monitoring of genetically susceptible subjects and non-invasive treatment of early stage cancer cases (secondary prevention), and finally prophylactic and therapeutic intervention to slow disease progression (tertiary prevention). Based on the molecular characterization of breast cancer, individualized preventive strategies for personalized health care might be designed and implemented.CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) genotyping and its influence on breast cancer treatment by tamoxifen indicate the importance of personalized medicine in treating patients. Tamoxifenwas a standard treatment (endocrine therapy) for steroid receptor positive breast cancer patients. Cytochrome P450 activates tamoxifen and forms active metabolites 4-hydroxytamoxifen and endoxifen.[12] These metaboloites have two order of magnitude affinity towards the steroid receptor compared to tamoxifen. These compounds inhibit proliferation of cells. CYP2D6 had different variants and poor metabolizers and severely impaired CYP2D6 are suggested to be associated with high recurrence of breast cancer. Thus genotyping of CYP2D6 before treatment might predict response to treatment. Intelligent clinical dissuasion can be made about the option of choosing strong CYP2D6 inhibitors which might inactivate active metabolites. Because the pharmacogenomics based approaches use CYP2D6 genotyping to have an idea about personal metabolizer phenotype, ethical concerns must be addressed in advance.Raloxifene becomes an alternative choice of treatment in CYP2D6 poor metabolizer patients. Erb-B2 expression based therapy of breast cancer hadshown results in the field of personalized medicine. Recent report, however, indicates that routine assessment of CYP2D6 should not be used as a guide for tamoxifen treatment and other factors should likewise be considered. These investigators have suggested that aromatase inhibitors should not be administered to those patients who are pre- or permenopausal. Norendoxifen, a metabolite of tamoxifenwas considered a potential lead compound in therapeutics due to its inhibition properties of aromatase. Other reports suggest that Mamm Print and Oncotype DX are current diagnostic tools which are based on expression profiling and have promising results in personalized medicine. Metabolomics, interactomics, brings powerful ability to screen cancer cells at different stages of disease development leading to novel therapeutic target identification and validation of known targets.[13]

The genetics and epigenetics of colon cancer are well characterized, and biomarkers for the early detection of colon cancer are known. A number of common treatments for colon cancer are available (chemotherapy, radiation, and surgery). Furthermore, colonoscopy screening had helped in detecting This cancer when polyps are just beginning to form. A correlation of mutations, microsatellite instability, and hyper methylation in tumours from individual patients was being completed. The information from such experiments will help to identify subgroups that are likely and not likely to respond to a particular treatment regimen. This will allow patients who are likely to benefit to receive optimal care and allow those who are unlikely to benefit to avoid unnecessary toxicity and costs. In general, when colon cancer was treated at an early stage, many patients survive at least 5 years after their diagnosis. If the colon cancer does not recur within 5 years, the diseasewas considered to be cured. Stage I, II, and III cancers are considered potentially curable. In most cases, stage IV cancer was not considered curable, although there are exceptions.[14-16]

Abnormal genetic and epigenetic events contribute to the development of myeloid neoplasia. Most of these alterations have been localized in hematopoietic differentiation and cellular proliferation pathways. A number of therapeutic agents have been developed to treat myeloid dysplasia. Attempts are being made to integrate pathological information with genomic information so that future directions in personalized genomics can be explored.Lymphomas are closely related to lymphoid leukaemias, which likewise originate in lymphocytes but typically involve only circulating blood and the bone marrow (where blood cells are generated by haematopoiesis) and usually do not form static tumours. There are many types of lymphomas and, in turn, lymphomas are a part of the broad group of diseases known as haematological neoplasms.[17,18]

Lymphoma was a cancer in the lymphatic cells of the immune system. It was present as a solid tumour of lymphoid cells. Lymphoma mainly Hodgkin lymphoma and non-Hodgkin lymphoma, although at least 60 subtypes of lymphoma have been reported to date. This cancer originates from lymph nodes but can affect other organs such as the bowel, bone, brain, and skin. Risk-stratification for all clinically identified subtypes had not been completed yet. Approaches for the stratification of lymphoma subtypes include refining clinical prognostic models for better Risk-stratification, use of high-throughput technology to identify biologic subtypes

within pathologically similar diseases, "response-adapted" changes in therapy via imaging with [(18) F] fluoro-2-deoxy-d-glucose positron emission tomography (FDG-PET), and anti-idiotype vaccines. Lymphoma treatment was accomplished by chemotherapy, radiation therapy, and bone marrow transplantation.[19]

An effective treatment for acute promyelocyticleukaemia of identifying and developing the PML-RARA fusion gene and applying all-trans retinoic acid (ATRA). This investigation had led to the discovery of the bcr-abl fusion gene in chronic myelogenousleukaemia and development of imatinib.[20]

Genetics-based drug therapy does not always work efficiently. Erlotinib and crizotinib are other genetics-based drugs with minimum efficacy in different cancers. The mechanism of action of these medications was based on apoptosis. The reason for developing apoptosis-based therapies was the advantage of killing cancer cells specifically with low or minimal toxicity. These drugs were not effective because the differentiation and proliferation pathways were not affected by these drugs. In an ideal situation, the drug should inhibit all of these pathways and stop the signaling steps.[21]

CONCLUSION:

Personalized medicine was receiving a large amount of growing attention for its tremendous potential with new opportunities. The ultimate prowess of personalized medicine depends on the discovery of the personal genetic causes of disease. The remarkable advent of current high-through put technologies in combination with improved knowledge of the molecular basis of malignancy provides a solid base for identifying novel molecular targets. Genomic sequencing and its interpretation will have to be further developed and standardized for routine clinical practice to develop efficient and effective methods for discovering and verifying new biomarkers and enabling personalized medicine technologies. Medical educational institutions should prepare the next generation of physicians to use and interpret personal genetic information appropriately and responsibly. Though for a developing country like Bangladesh it will not be easy to adopt a higher and expensive technology, but for the sake of cancer patients and better outcome we will have to run in parallel with the developed countries.

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