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Review Article

Pharmacology Section

Precision Medicine: Emerging Trends in Cancer Therapy

RAHUL BADWAIK

ABSTRACT

Every individual has a different genetic make-up; even the genetic alterations are different in the same type of cancer. This demands specific and personalised treatment for the individual. Thus, studying the patient's genetic and clinical profile is the foundation for precision medicine. With the developing technologies and newer molecular tools, it has become easy to select a target-specific treatment based on the genetic makeup of an individual. More individualised approach through precision medicines will not only help in treating cancer but shall negate the scope of early detection with the advanced screening techniques and might also aid in preventing them. In this review, author discuss different aspects of precision medicine in cancer therapy.

Keywords: Personalised medicine, Pharmacogenetics, Pharmacogenomics, Precision health

INTRODUCTION

There have been major developments and newer discoveries in the present healthcare system. One such breakthrough is the discovery of precision medicine or personalised medicine. As the name suggests, it is used to deliver precise and personalised treatment to patients based on the genetic changes brought due to the disease. The President's Council of Advisors on Science and Technology in 2008 has defined precision medicine as, "The tailoring of medical treatment to the individual characteristics of each patient is required to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Preventative or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not" [1].

PRECISION MEDICINE IN CANCER

In today's era, the incidence of cancer is drastically increasing day by day making it the most challenging field for research. One in every three people develops cancer in their entire lifetime [2]. Cancer is one of the leading causes of deaths worldwide and still remains a challenge owing to its progress and unfavourable and discomforting treatments. The existing treatment options offer chemotherapy and radiation therapy that are toxic to both cancer and healthy cells, thus causing serious side effects to the patient.

In cancer, the bodily cells undergo genetic changes or mutations due to environmental, genetic, or epigenetic factors. Since each individual's genetic make-up is different, even the genetic alterations are different in the same type of cancer. This demands specific and personalised treatment for the individual. Thus, studying the patient's genetic and clinical profile is the foundation for precision medicine.

Some of these mutations occur gradually over a period of time, while some are hereditary. Several genetic changes, such as mutations, gene amplification, translocation, structural deletion, etc., cause different types of cancers. For example, the amplification of *cMyc* oncogene with translocation of chromosome 9 and 22 manifests BCR-ABL fusion, which is responsible for malignant changes. These genetic mutations bring about changes in the cancer cell physiology, such as deranged growth signals, insensitivity to growth inhibitory signals, apoptosis, and tissue invasion [3]. With the ever-improving medical standards, now the physician does not have to follow the one-size-fits-all method anymore. Currently, even the physicians try to collect data that might favour better understanding and better treatment options based on genetics. For identifying a suitable medicine for treatment, an array of DNA tests is done on the patient's tumour to identify the genetic changes or mutations responsible for the tumour. This is followed by the selection of the best available treatment that would target the mutated tumour DNA is selected. More individualised approach through precision medicines will not only help in treating cancer but shall negate the scope of early detection with the advanced screening techniques and might also aid in preventing them.

HISTORY OF PRECISION MEDICINE

The evolution of personalised medicine is linked to the Human Genome Project in 1997, in which discussions were made on a personalised and individualised form of treatment based on unique genetic data [4]. In 2015, President Barrack Obama had discussed launching a new precision medicine initiative that would aid in curing several diseases, such as cancers and diabetes, and which would give the necessary personal information to keep one healthy [5]. He had proposed to carry out a government funded research project enrolling over 1 million people of the US. The participants had to share their complete genetic data generated after sequencing for a period of 10 years. The main aim was to analyse the entire process of pathogenesis of any disease to design and select the best possible or targeted treatment for that particular patient.

The concept of precision medicine is not new, for instance, culture and sensitivity testing to identify the best available medicine for a specific causative organism and blood typing before blood transfusion are all examples of the use of precision medicine. However, it is after the development of the human genome sequencing, proteomics, and genomics that the research on precision medicine has gained momentum.

The study of genetics has been more accessible owing to the reduction in the cost of the sequencing techniques. However, extraction of useful and relevant data from the vast information that is generated is a challenge and requires expertise. In 2003, the human genome project was successfully completed, which paved the way to research in the field of genetics and also produced a vast pool of molecular data [6]. Nowadays physicians of various faculties of medicine are considering the genetic basis of the medical condition for better understanding and deciding the best treatment options for the patient. This approach will not only improve the treatment options but also target at reducing the unfavourable side effects and drug interactions. Precision medicine and pharmacogenomics go hand in hand. Pharmacogenomics helps decide whether a particular modality will be beneficial, cause side effects, or might not help the patient at all taking their genetic makeup into consideration [7]. The

success of precision medicines largely depends on the availability of the exact biomarker. Thus, extensive research is being carried out across the world to identify the biomarkers for a particular disease and to invent a specific medicine that targets them.

Though there are a few known biomarkers for different types of cancers, the response to the cancer therapies varies, where some patients are benefitted, some show no response, and few have major side effects. Huge amount of data is available to prove that the origin and progress of cancer is related to changes at the genetic level [8]. With the advancement in molecular diagnosis, it has become easy to detect these genetic changes and design treatment drugs targeting them. Few successful treatments with targeted biomarkers have already been identified, such as the human epidermal growth factor receptor 2 antibody [9], targeted therapy for HER2 positive breast cancer [10], BCR-ABL inhibitor imatinib in chronic myelogenous leukaemia [11,12], and BRAF inhibitors vemurafenib and dabrafenib in melanoma [13,14].

CURRENT SCENARIO IN CANCER TREATMENT

At present, a cancer patient has to undergo several tests to identify the type, the stage, and the extent of spread of cancer. This could be because they are not aware which treatment would work best for the particular type of cancer. Nevertheless, with several researches being carried out, it is expected that in near future physicians would be able to decide which treatment would suit best for the patient based on the genetic changes observed.

CHALLENGES IN CANCER TREATMENT

Cancer treatment is the most crucial and challenging task for the physician as it determines the morbidity and mortality rate in cancer patients [15].

- Cancer stem cells: Researchers have found that the characteristics of cancer cells resemble that of stem cells. However, the traditional cancer treatments lack this targeted action causing lack of response or recurrence once the treatment is stopped.
- Drug resistance: The cancer stem cells are known to have certain proteins that cause efflux of drugs. For example, Breast Cancer Resistance Protein (BCRP) that causes drug efflux in breast cancer.
- Delay in early detection: Since the cancer is asymptomatic in the initial stage, it seems to be neglected, and once the patient develops symptoms, metastasis would already have occurred.
- Metastasis: This is one of the major problems in treating cancer. Metastasis usually occurs by local spread, through blood circulation, or through lymphatic drainage. There are certain cancer marker proteins that indicate the presence of cancer spread.

TYPES OF PRECISION MEDICINE IN DIFFERENT TYPES OF CANCERS

Breast Cancer Treatment

Several successful clinical trials of personalised medicines have been conducted in breast cancer treatment [16]. The treatment is made personalised if the breast cancer cells are HER2-positive or oestrogen and progesterone positive. For example, if the patient has HER2-positive breast cancer, she would receive the targeted treatment using the drug trastuzimab, which has been proven to be effective and also known to reduce the risk of recurrence. Also, if a patient possesses hormone receptors for oestrogen or progesterone, she is most likely to benefit from hormonal therapy that involves binding of the drug to the receptor site, thus blocking the binding of cancer cells to that site. Certain drugs, such as ADP ribose, polymerase inhibitor, and tyrosine kinase inhibitors, are already used effectively in the treatment of metastatic breast cancers [17].

Lung Cancer Treatment

There are several targeted therapy trials, such as BATTLE, where the drug erlotinib has been tested for advanced stage non-small cell lung cancer [18]. In another study, patients' tumour carrying mutations in the EGFR gene has been tested for improvement by adding erlotinib or crizotinib to the standard therapy [19].

Skin Cancer Treatment

Patients with KIT mutated melanoma have been shown to have 20%-25% more effective response to dacarbazine [20]. Almost 45%-50% melanomas show BRAF mutations. Vemurafenib is approved as a first-line treatment option for BRAF-mutated melanoma, since it shows significant survival benefit [13].

MERITS OF PRECISION MEDICINE

With the current scenario of treatment available with its fatal side effects, precision medicine seems to be a boon by its several merits such as [21]:

- It provides the ability to choose the best treatment that might work for a particular patient.
- Prevents the use of unnecessary treatment options, which are less likely to benefit the patient.
- It also minimises the undesirable side effects the patients have to face while taking the therapy that might not work for them.
- The genetic profiling gives a better understanding of the prognosis and pathogenesis of the disease.
- As compared to the standard trial-and-error options, it reduces the cost of treatment.
- It promises to improve the quality of life and chances of better survival.
- The pool of genetic information collected shall be useful to carry out research in various fields of medicine, even for future scientists.
- It gives better scope of deciding and predicting the best treatment based on the genetic pathogenesis of the disease.
- It promises improved techniques for early detection, treatment, and prevention of a large number of diseases.
- In diseases like cancer where the treatment modalities offer survival for only few months with disfiguring treatment options, precision medicine is a ray of hope assuring longer survival rate with improved quality of life.

Precision medicine is the future for cancer care and treatment.

COST OF PRECISION MEDICINE

Cost associated with precision medicines is a topic of concern. Since, it is a developing field; several million dollars would be required for multiple years. To identify the target DNA, several techniques such as sequencing tests are required which again are quite costly. Designing and developing drugs that would target the concerned genetic makeup shall also be expensive. This makes the overall cost of treatment high, which might be a concern for reimbursement from the insurance companies. However, the launch of precision medicine initiative has reduced the cost of DNA sequencing and other genome-based technologies [18] to identify and classify the disease and to predict the clinical outcome.

IMPACT ON EXISTING HEALTHCARE

Though there is enough information based on genetic discoveries, which might be of use to several patients, its use is still limited owing to the traditional ways of literature-based treatments available. This makes the use of available precision medicines very limited [22].

To use the discovered therapies on precise genetic variants, better models for preclinical trials and better designs of clinical trials are required.

The amalgamation of precision medicines with approaches like RNA interference (RNAi) and nanomedicine shall pave ways for newer discoveries in the field of medicine. RNAi can be incorporated in specifically designed nanoparticles towards the targeted genetic mutation site [23]. Nanotechnology can also be used for the development of molecular diagnosis for identifying the various biomarkers. Thus, its utility in the field of cancer medicine can be of great use as it can be used for early detection and designing and delivering a safe and effective treatment with lesser side effects and better chances of cure [24]. To design a precision medicine, depending on the disease, the patient's entire system is studied at genetic, phenotypic, and molecular level, and a treatment drug is selected targeting these variations. The response to the treatment is tested with the help of biomarkers [25]. Till date, cancer patients with similar type or grade of cancer are treated with similar approach. Despite this, different patients respond differently or some do not respond at all and succumb to this dreadful disease or its disfiguring treatments [5].

Several commercial, government aided and academic clinical trials are being conducted to study the genetic alterations responsible for tumour formation [26]. There has being an increase in the clinical trials being conducted in adults in the United States [27]. These trials are based on molecular profiling of the tumour tissue to detect the exact location and pathogenesis of genetic mutations. This helps in designing patient-specific drug or a combination of drugs to provide greater benefit and lesser side effects. The genomic alteration information gives future researchers the required data to conduct further studies.

Even though there are specific or precise drugs available for a particular type of cancer, an individual suffering from that particular cancer still has to undergo a series of genetic tests to analyse whether the genetic changes, which the target drug solves, are similar. Thus, some say that precision medicines are not for everybody. As per the latest research statistics, presently there are more than 70,000 genetic testing products with around 10 new products added each day in the market [28] showing an annual growth rate of 28% [29].

The improved clinical trials, genetic testing, and tumour profiling has helped in designing drugs that will not only fight cancer but also prevent it. It promises physicians for improved knowledge and choose treatment options that would be best for their patients.

INDIA'S PERSPECTIVE ON PRECISION MEDICINE

Precision medicine is an emerging field that is based on studying the genetic makeup of an individual to identify the variations responsible for the disease. In a country like India, with diverse populations, a high percentage of consanguineous marriages pose a large risk of inherited genetic diseases. If these disorders are detected early and treated based on the genetic aberrations, they might reduce the health burden. With a population of 1.4 billion, a large number of patients are affected by diseases in which genetics plays a vital role.

It has been shown that Indians spend about $23 billion annually in testing or treating non-communicable diseases. Genetic testing and precision medicine are slowly getting recognition amongst Indian medical fraternity [30]. With the improvement in the economic strata, better medical facilities, and expert physicians, India seems to be a major emerging market for precision medicine industry.

Patients are being tested for genomic variations associated with several diseases and are prescribed treatment accordingly. Apart from other diseases like cardiac disorders and diabetes, cancer seems to be the most prominent cause of mortality and morbidity and also several genetic level tests are being routinely conducted for the detection and classification of cancer. Hence, it seems to be the most common disease where precision medicines can be tremendously successful. Precision medicine also promises to reduce the financial and physical burden, as it shall provide faster results and reduce the duration of hospital stay as compared to the time and money spent with the use of trial-and-error medicines, however, there may be limitation in developing countries.

In the western countries, there is greater awareness of the benefits of precision medicines along with easy availability of resources, technological aids, funds needed for its development as compared to India. However, India is also developing in the field of genetics with remarkable expertise in the fields of genetics and biotechnology.

In India, it is mostly the patients that are the payers, and due to lack of adequate awareness about precision medicines and the novel tests, it has miles to meet up the hype. Since the patient pool is large and the healthcare system is unorganised, it is a challenge to form a uniform platform. Patients should be made aware about the new tests and available treatment options. The private physicians, hospitals, insurance companies, and government should collaborate to facilitate the process. Further, genetic tests should be considered for inclusion under insurance coverage to reduce the financial burden of the patients.

LIMITATION

Testing for genetic mutations has become a standard procedure in cancer patients but not everyone benefits from these targeted therapies [31]. The precision medicines are less successful in patients with advanced cancers who have tried and tested all the standard treatment options. Usually the successful cases are highlighted, but the failure rate is even more. These failures highlight that there is a lot to explore and discover. Precision medicine is still a young budding field requiring time and advanced techniques. There is a need to design a huge database to store all the genetic data extracted as well as the expertise to identify the useful data.

CONCLUSION

Though precision medicine is a budding field, yet it has developed tremendously owing to the human genome project. Its application in the field of cancer seems to be the most promising due to the variable nature of the tumour and its response to treatment requiring a personalised approach. As per the above discussion regarding the current treatment scenario for cancer with its fatal side effects and not so promising outcomes, the promises hypothesised by precision medicine seem to be a boon. But still, the complete genetic changes are yet to be discovered which might aid in complete cure in cancer with minimum side effects. With the present newer discoveries and proving in larger sample size populations, the future seems to be fruitful for precision medicine in cancer.

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PARTICULARS OF CONTRIBUTORS:
1. Head, Department of Medical Affairs, RPG Life Sciences Limited, Mumbai, Maharashtra, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Rahul Badwaik,
RPG Life Sciences Limited, 463, 4th Floor, RPG House, Dr. Annie Besant Road, Worli, Mumbai, Maharashtra, India.
E-mail: drrahulbadwaik@yahoo.co.in

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