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Herceptin- A Revolutionary Tool among Personalized or Customized Medicines

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Abstract

Our current medicinal practices are based on population averages. Medicines discovered in one research centre of a particular country and tested on animals and a broad population available there, are used for the treatment of worldwide population. Medicines are applying based on statistical averages gained from their randomized clinical trials. The drugs available in the world markets are only effective in 50% of the total population. Rest of them are taking medicines like placebo, means they do not produce any effects actually. It is due to the genetic differences. We all are different in every aspect. Our choices of food, our cloths, our dreams, ambitions, rituals, and cultures everything is different. But medical system prescribes drugs based on "one size fits to all". How can that be sensible? Here comes the importance of personalized medicine. Personalized medicine or precise medicine (PM) is a newer approach of pharmacogenomics under progression. It is actually a customized kind of medicine meant for individual patients according to their genetic makeup. For that we thoroughly understand the patient details not only age and sex but in a detailed way including their genetical variations. So we can understand their drug responsiveness as early as possible. That's why precise or personalised medicines are also called as genomic medicines. And it will also eliminate the time, cost and failures in the clinical trials which are serious issues that developing countries currently facing.

Keywords: Personalised Medicine; Genomics; Customized

Introduction

Why a medicine needed to be personalised. The trial and error process in drug making also demands a lot of pressure to the manufactures. One size fits to all is not any more a successful formula regarding a wide range of population. A particular drug dose may be effective for some of the population, but for the rest the prescribed dose may be toxic due to their poor metabolic nature or may be in effective due their high metabolic rate. In such cases there are chances for generating adverse reactions as well as ineffectiveness. If the practitioner is known with the metabolic activeness of an individual patient towards that particular drug prior prescribing, he could design a safe dose regimen according to that [1].

'Theranostics' a combination of diagnostics and therapeutics is new method in pharmacogenomics. It will allow practitioners to touch with the detailed information about patient's genotype and to monitor individual's therapeutic regimen and assess patient's response. For example, when we consider a woman having atrial fibrillation and she receives anticoagulant drug warfarin. A genetic test is performed to find out for variations in two specific genes that affect her body's metabolism and response to the drug. Combined with other factors, the test shows a proper dosage range for this patient. That's how we are supposed to generate personalised medicine or PM. As a result, the patient avoids

experiencing uncontrolled bleeding, life-threatening blood clots and risk of stroke with this powerful drug [1,2].

Along with all these advantages like every innovations PM also have some disadvantages. Finding all kinds of genetic variations and response patterns towards a drug is expensive and time consuming process. It might take years to make such a data base and has to face a lot of legal problems also. So for making this innovation or making PM possible and at a faster pace of growth, we need some more key factors: [3,4].

- New tools to decode the human genome more rapidly and accurately using physically smaller yet more powerful machines.
- Large-scale studies and sample repositories that help link genetic variations to disease across multiple countries and continents.
- Health information technology (HIT) that fosters the integration of research and clinical data, which is already growing faster in developed countries like U.S as a result of aggressive government incentives for adoption.

The major goal of personalized medicines is the prevention and recovery of a diseased state without any adverse effects. According to PMC in Washington 13 drugs and its combinations were found to be effective as PM in 2003. Within 5 years the number increased 5 times and 72 showed their admittance to be a personalized medicine and it is still going on. Let's look out for some examples.

- The best known example is warfarin/coumarin therapy associated with CYP450 enzyme [5].
- Herceptin (Trastuzumab) used to treat breast cancer with overexpression of HER2 receptors.
- Gleevec (Imatinib mesylate) used to treat chronic myeloid leukemia.
- Zelboraf (Vemurafenib) used to treat melanoma, which is effective in patients with V600E.
- Erbitux (EFGR) used in colon cancer.
- Xalkori (ALK) used in lung cancer.

Here in this article we are focusing more on Herceptin (Trastuzumab) a drug for cancer and how researchers are going to recommend this drug as a personalized drug [1,4].

Herceptin (Trastuzumab) as an Antineoplastic Agent

Herceptin is a monoclonal antibody used in the treatment of breast cancer and stomach cancer which are HER2 receptor positive. Axel Ullrich and his coworkers developed clones of human HER2/neu mutant gene at Genetech lab. Later Dennis slamon and his collegues at UCAA showed HER2 over expresson in 20% of patient with aggressive breast cancer. HER2 is an oncogene protein and a member of epidermal growth factor receptor family like EERB (Erythroblastic oncogene B). The over expression of this oncogene has been shown to play an important role in the development and progression of certain aggressive types of breast cancer cells. Normally it is given as an Iv infusion and as a SC injection (Herceptin hylecta). [10] The different treatment patterns Herceptin follows are;

- Used alone to treat breast cancer in its metastatic stage by preventing the growth of cells.
- Used alone to treat early stages of cancer and also to prevent recurrence.
- Used in combination with Pertuzumab and Taxotere before surgery to prevent HER2 progression
- Used along with Pertuzumab to prevent the recurrence after surgery.

Mechanism of Action of Herceptin

As we know genes are the instructing modules of all cells. They give different signals to cells regarding their growth and repair. If the gene goes abnormal it would be sending wrong signals to the cells. Some cells may possess many more copies of a gene. If all these copies become abnormal the cell will receive multiple wrong signals and show abnormal activities like over growth. This situation is called "over expression" of a gene which leads to the formation of cancerous cells. HER2 receptors are such kind of over expressive genes found on the surface of breast cells which make them cancerous. Herceptin has been found to be effective against this particular gene. Herceptin can block the HER 2 receptors from receiving wrong signals there by it can prevent the overgrowth of breast cancer cells [6].

There are 2 methods currently available for the detection of HER2 receptor over expression in breast cells. IHC (Immunohistochemistry) and FISH (Fluorescence in situ hybridization). Among them we prefer IHC as a common detection method over FISH because of it high prize even though it is the most accurate one. Like every chemotherapeutical agents Herceptin also have a lot of side effects. But it shows major Side effects in patients with heart and lung problems. Many biosimilars are also available for Herceptin Eg; Herzuma (trastuzumab- pkrb), Kanjinti (trastuzumab - anns), Ogivri (trastuzumab –dkst),Ontruzant (trastuzumab-dttb), Frazimera (trastuzumab-9xyp) [7].

Herceptin as A Personalized Medicine

Herceptin (Trastuzumab) was approved by FDA in 1998. Since then it was hitting the markets as a major single drug and as combinations for patients with metastatic breast cancer who had not respond for other chemotherapeutic agents. After the introduction, the sale of this drug was reported as $188 million in U.S and became a best drug among top 20 bestselling biotech drugs with increasing

demand year by year. So it is relevant to select Herceptin for researchers to make it as personalized medicine for future applications [6,7].

Cells with over expressed HER2/neu genes are said to be HER2 positive that means cancerous. Physicians must prescribe Herceptin only to patients with test result HER2 positive. Otherwise it will have harmful effects. In women with HER2 negative or normal HER 2receptor genes Herceptin increases the risk of heart problems. So the regulatory organizations like FDA should be more careful before approving drugs to multiple uses among large population. They should be able to tell the correct patient on which the dug will exert its correct action. Then we can say whole heartedly a drug is successful. The genetic variations and mutation on the HER2/ neu genes will also causes the same situation. Proper detection mechanisms are needed to determine the correct drug response in every patient. Currently available tests like IHC and FISH are not sufficient to provide clear cut genetic information. More sophisticated technologies are needed. And a regular data base should be maintained for each patient as a profile with detailing of drug dosing and consequent drug response. It should be a common accessible data base to all physicians, technicians and researchers. Then only they could analyse the results and make a control over the drug use. But a hidden problem is also there. Since we are providing all personal information about the patient in a common medium accessible to many people. We cannot assure the safety and privacy of those details further. There may be chances of misusing those data. So there are many ethical as well as non-ethical issues to be solved behind each step [7,8].

Various studies have been conducting to reveal the relation between genotyping and drug dosing. As we said earlier warfarin dosing related to CYP 450 and CYP 2C9 gene polymorphism is quite relevant to be discussed here. A major cause of variability in warfarin response is due to mutations in the genes of these particular enzymes. The development of FDA approved Amplichip R CYP450 test is a mile stone in personalized medicine. This gene test can give a valid result on variations of these 2 metabolic enzymes CYP450 and CYP 2C19. But the adoption of this test to clinical practice is still doubtful due to the lack of evidences about their clinical utility. And it is not applicable for HER2 gene testing for Herceptin like drug [9,10].

For proving a drug as a personalised medicines various aspects have to be checked like the identification and screening of the candidate gene on which the drug is going to produce a response, possible polymorphisms, correlation of polymorphism with therapeutic targets, prediction of drug response and clinical outcomes, selection of therapeutic dosages on the basis of genotypes etc. A wide array of genomic technologies is also to be included such as high throughput technologies, global gene expression analysis, genome wide functional analysis, gene expression monitoring etc [11-13].

Pharmacogenomics Approaches on Herceptin

It has been already proven that treatment with Herceptin shows good improvement and overall survival in metastatic cancer. Despite the effectiveness it has also developed some primary and secondary resistance due to reasons such as incomplete HER2 blockage when we use Herceptin alone, hetrero dynamic signalling from other growth factors like HER 3 biomarkers, oncogene mutation in PK12 pathway and loss of HER2 extracellular domain for action. In order to solve these issues Trastuzumab is given as combination with Pertuzumab and Lapatinib. And it is also given as an antibody drug conjugate like Trastuzumab emtansine. In 2012 FDA has approved Trastuzumab and Pertuzumab combination for the first line treatment of breast cancer because they have synergistic activity and reduced side effects on immune genesis and cardiovascular toxicity as combinations. Regardless of the targeted therapy combinations employed based on tumour genomic profile, these 2 drugs will likely to continue to form a backbone of the personalized regimen for HER 2 positive breast cancer [3,13].

The oncogene mutation in PK12 pathway and over expression of HER3 biomarker receptors can be subject to poor prognosis and lower response to HER2 therapies. So before implementing the therapy these things have to investigate and validated which is possible by pharmacogenomic indulgence. Neoadjuvant trial is also an attractive platform for rapid triage of drug efficacy, biomarker identification and validation. The utilization of neoadjuvant trials in breast clinics can also be used to approve novel drugs, to compare different combinations, to identify predictive markers and also to determine optimal HER2 sequencing. In the current times one size fits to all is increasingly become obsolete. Since the success of Herceptin for HER 2 breast cancer, there have been strides in the development of personalized therapeutics. Allowing Herceptin as a personalized medicine we can claim that when a patient with HER 2 positive breast cancer come to the clinic, the routine use of gene sequencing, chances of gene mutation, identify gene biomarkers and accordingly select patient who will optimally benefit from particular HER 2 blockers and their combinations [10,14,15].

Conclusion

Personalised medicines are having lots of advantages over our conventional prescribing methods which make them an incredibly safer option, like

- Predictability
- Preciseness to individual patient

- More powerfulness
- Disease prevention capacity
- Accurate diagnosis
- Safer drug with less side effects
- Effective outcomes etc.

Discovery of a drug is a long term process which takes almost 10 to 12 years minimum and it's a million dollar needed business. After all hurdles when a drug come to the market if it could not be able to make a position, there it is considered as a failure drug. And they get completely vanished from the market or medical field. The arrival of concept of personalized medicine will have a solution for this too. Failure drugs might be generating adverse effects or showing ineffectiveness only to a certain category of people. It might be effective to other categories. By testing their genetic variations and drug response, if we found it is safe to the other category then we can bring back those drugs as well. When we think about the various possibilities of this concept, its seems to be extremely revolutionary and as a promising one. Individualizing the drug therapy will be arising issues related to its practical consequences. But PM will be a best choice for redesigning the current treatment system.

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