Precision and Personalized Medicine in Oncology

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Q. Please generally describe the definition of precision therapy and describe your opinion on precision therapy in cancer according to what you have learnt this semester or before

Definition: Precision medicine is "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person." [1] This method would make it easier for physicians and experts to more reliably assess which care and preventive methods will function with which classes of individuals with a specific illness. In comparison to a one-size-fits-all strategy, infectious management and prevention methods are designed for the average person, with the variations between people less taken into account.

Precision Medicine in Cancer: According to Cancer National Institute Data The **rate** of new cases of **cancer (cancer incidence)** is 442.4 per 100,000 men and women per year (based on 2013–2017 cases). The **cancer death rate (cancer mortality)** is 158.3 per 100,000 men and women per year (based on 2013–2017 deaths). Standard therapies, such as chemotherapy, Surgery or radiation, are successful with only a fraction of the patient population regardless tumor heterogeneity. Tumors may have common genetic factors, and in one patient versus another, they may express different proteins. It is clear that therapies of cancer will result in tremendous patient benefits, and this has started to be understood by corporations and regulatory agencies. However, if PPM is to become part of routine cancer treatment, larger improvements to the healthcare and insurance processes must be discussed. [2]

Introduction: Most work is underway to better understand this community of diseases and treat them. Accumulated cell mutations, which manifest as tumours with unregulated proliferation, are the general distinguishing characteristic of cancer. Cancer is, however, a difficult, highly heterogeneous disease. There are over 100 varieties of cancers that are present in multiple organs that sub tissues and originate from different types of cells. [3] Many tumours have different classifications also.

Precision medicine has increasingly altered the diagnosis and treatment scope of oncology in recent years.[4] Technological advancements in characterising the genetic, proteomic, metabolomic, and cellular profiles of patients, together with the creation of broad biological databases and computerised research methods, have allowed clinicians to customise therapy techniques to specifically address the molecular modification causing the condition of particular patients. [5] Oncology has been designated as the near-term focus of the Precision Medicine Initiative, guided by new knowledge of the oncogenic mechanisms of cancer that has already influenced risk assessment and therapeutic strategies. The development and expanding use of targeted therapies to counter specific molecular drivers have already yielded compelling results, further supporting molecular signatures as representatives of a promising treatment decision tool.

Traditional Model V/S Personalized Precision Medicine Model (PPM) in Oncology

Traditional Model to PPM Model

Fig 1: A comparison of the major discrepancies between the conventional cancer care model and the new model of specificity and customised medicine (PPM). Cancer has historically been treated with general "one size fits all" approaches, such as chemotherapy, radiation, and tumour surgical excision. These therapies differ greatly among individuals in effectiveness and also frequently inflict damage to healthy organs and tissues that are not cancerous. The path to PPM is characterised by individualised therapies personalised to particular tissues, mutations in the genes, and personal factors related to each specific cancer patient. Companion diagnostics (CDx) help determine which medications for the tumour in a single patient would be more efficient, and experimental cell therapies are used to target cancer with negligible disruption to healthy tissues, rendering the PPM model more effective and better.

Development in Diagnosis:

Although recent findings in precision medicine have led to major strides forward in oncology diagnosis and care, precision medicine is still a relatively new idea and procedure in the area. Sanger sequencing was used prior to 2005 to sequence a few genes at a time. [6] **Sanger sequencing** had low throughput, and it also could not detect structural rearrangements. [6] For selective drugs, early companion diagnostics were mainly single-gene assays, but increased understanding of tumour molecular biology has culminated in patient monitoring for a larger range of genes.[7] **Next-generation sequencing (NGS)** overcame the limitations of Sanger sequencing. NGS can detect genetic alterations, such as rearrangements, copy number alterations, insertions, and deletions; it also comes at a lower cost. [7] NGS approaches are high-throughput and can evaluate several sequences of DNA in parallel. Their multigene panels reflect a focused method for concurrently decoding a variety of genes. [8] These panels can be individualized to the tumor types, and they differ according to the genes being tested. For example, targeted breast/ovarian panels may test for 6 or more genes, whereas a comprehensive panel that tests for numerous cancer susceptibility genes may test for 70 or more.

[9] Clinicians can tailor a multigene panel to the genes of interest. Panel options are also updated frequently as new genes are discovered.

The Process of Precision Medicine

Getting Data

Genomics, Meta Genomics, Transcriptomics,
Physiological Data, Proteomics, Physiological Data
and data storage

Developing Personalized Medicine

Data Processing

Outlook for the treatment

Companion diagnostics, Lab sequencing, Lab
developed test

Regulating Treatment

Economical Maintenance and Cost Deprivation

Including in the Guidelines

Maintaining Ethics

Fig 2: The Process of PPM

Precision Medicine in Lung Cancer Treatment:

Fig 3: Chemo Sensitivity with different types of genetic mutations in Non Small Cell Lung Cancer [10]

Fig 4: Mechanism of

T cell inactivation, Mab like Prembolizumab Nivolumab [10]

Lung Cancer Gene Based Drug Sensitivity:

Drug name	Drug class	Metabolic pathway (major)	Genetic target	Resistance
Gefitinib	Tyrosine kinase inhibitor: Gen. I	CYP3A4	EGFR	EGFR (T790M gatekeeper), KRAS, MET amplification, HGF over-expression
Erlotinib	Tyrosine kinase inhibitor: Gen. I	CYP3A4, CYP1A1	EGFR	EGFR (T790M gatekeeper), KRAS, MET amplification, HGF over-expression, BRCA1 expression
Neratinib	Tyrosine kinase inhibitor: Gen. II	CYP3A4	EGFR, HER2	EGFR (T790M gatekeeper), KRAS, MET amplification, HGF over-expression, HER2 (T798I gatekeeper)
Afatinib	Tyrosine kinase	Minimal	EGFR, HER2	EGFR (Partial to T790M gatekeeper), KRAS, HGF over-expression, HER2 (T798I

	inhibitor: Gen. II			gatekeeper), SRC/ERBB3/c-KIT/c- MET, FGFR1
Osimertinib	Tyrosine kinase inhibitor: Gen. III	CYP3A4	EGFR	EGFR (mutations around gatekeeper but effective against T790M), BRAF V600E, MET amplification, more to be seen...
Crizotinib	Anaplastic lymphoma kinase inhibitor: Gen. I	CYP3A4, CYP3A5	ELM4- ALK, ROS1, c- Met	ALK (L1196M gatekeeper), EGFR, KRAS
Alectinib	Anaplastic lymphoma kinase inhibitor: Gen. II	CYP3A4	ALK, RET	ALK (effective against L1196M)
Ceritinib	Anaplastic lymphoma kinase inhibitor: Gen. II	CYP3A4	ALK, ROS1	ALK (effective against L1196M)

Brigatinib	Anaplastic lymphoma kinase inhibitor: Gen. II	CYP2C8, CYP3A4	ALK, EGFR, ROS1	ALK (effective against L1196M), EGFR (effective against T790M)
Atezolizumab	Monoclonal antibody		PD-L1	(Prospective) Immune deficiency, JAK1, JAK2, B2M, CD8 hypoexpression
Nivolumab	Monoclonal antibody	N/A	PD-L1	Immune deficiency, JAK1, JAK2, B2M, CD8 hypoexpression
Pembrolizumab	Monoclonal antibody	N/A	PD-L1	Immune deficiency, JAK1, JAK2, B2M, CD8 hypoexpression
Atezolizumab	Mab	N/A	PD-L1	JAK1,2,B2M
Nivolumab	Mab	N/A	PD1	JAK 1,2

Precision Medicine in Breast Cancer Treatment:

Breast cancer continues to be the most commonly diagnosed malignancy among women in the United States.[11] The identification of human epidermal growth factor receptor 2 (HER2) overexpression as another molecular therapeutic target was accompanied by the discovery and confirmation of oestrogen receptor (ER) expression as a therapeutic target. In 15% to 30 percent of patients with metastatic breast cancer, HER2 overexpression is observed and brings a bad prognosis. A important therapeutic advance was the introduction of HER2-targeted agents, such as trastuzumab, trastuzumab emtansine, pertuzumab, lapatinib, neratinib and afatinib. [12] Advances in high-throughput genomic technology, in addition to ER and HER2, have made it possible to better understand the molecular mechanisms leading to tumour development.

Genomic Application	Molecular Targets	Targeted Event	Examples of FDA-Approved Therapy	Optimal Technology
Oncogenic drivers (detected by DNA)	ERBB2 amplification (HER)	Malignant transformation and progression	Trastuzumab, pertuzumab, trastuzumab emtansine, lapatinib, neratinib	NGS if multiple genes have been validated
	PIK3CA mutations		Alpelisib	
	AKT1 mutations		--	
	ERBB2 mutations		--	
Oncogenic drivers (detected by RNA or protein expression)	Estrogen receptor genes expression	Malignant transformation and progression	Tamoxifen, anastrozole	Gene expression, phosphoprotein assay
	mTOR activation		--	
	CDK4/6 activation		Abemaciclib, ^a palbociclib, ^a ribociclib ^a	
Lethal subclone	ESR1 mutations	Resistance to aromatase inhibitors	--	Ultradeep sequencing, circulating DNA
DNA repair	BRCA1/2 mutations	Mutational processes	PARP1 inhibitors (olaparib, talazoparib)	Targeted sequencing, whole-exome sequencing, SNP arrays
Immune system	PD-L1 overexpression	Detection of immune resistance (eg, immune checkpoints)	Anti-PD-1 antibody (atezolizumab)	Whole-exome sequencing, RNA sequencing
	Neoantigen			

CDK4/6 indicates cyclin-dependent kinases 4 and 6; HER, human epidermal growth factor receptor; mTOR, mammalian target of rapamycin; NGS, next-generation sequencing; PARP1, poly-(ADP-ribose) polymerase-1; PD-1, programmed death 1; PD-L1, programmed death ligand 1; SNP, single nucleotide polymorphism.

^aCDK4/6 determination not required prior to treatment.

Fig 5: Chemo Drug Sensitivity in Gene based Personalized Medicine [12-21]

Different technologies can diagnose molecular changes leading to tumour growth and/or drug tolerance, and some can be targeted by currently accepted treatments.

Precision Medicine in Melanoma

Another malignancy that has seen a dramatic improvement in the understanding of its molecular biology and the growth of selective therapies is melanoma. Compared with other tumour types, melanoma has a relatively high prevalence of acquired mutations, including the epidermal growth factor receptor, insulin-like growth factor receptor, and mitogen-activated protein kinase pathways. In the pathophysiology of melanoma, immune dysregulation also plays a major position. The presence on the T-cell surface of the cytotoxic T-lymphocyte-associated protein 4 and programmed cell death protein 1 receptors promotes the inactivation of T cells, thereby avoiding the killing of cancer cells by the immune system. [23] So the FDA approved drugs against the genetic mutations are important and most important to detect the sensitivity of the drugs.

My Opinion in Precision Medicine

Precision Medicine is a new concept and present in the oncology since 2012. it's the most important part and the future of the Oncology. The Cancer treatment should be gene and molecular based. (Genomics and Proteomics). Knowing Tumor Heterogeneity and Tumor Microenvironment is important and the detail genetic analysis will give the clear picture of the tumor heterogeneity and tumor microenvironment.

Cancer is a genetic evolution through genetic mutations .Detecting the genetic mutations are very important through different Gene sequencing Techniques. Precision medicine and personalized medicine technique is useful to detect the genetic mutation by knowing the molecular level of that tumor. Now, that molecular analysis is done by couple of methods but next generation sequencing technique is currently most widely used. The detail analysis tells us about the systemic therapy which are sensitive towards that tumor. In the traditional one, we give the systemic therapy to the patients blindly and sometimes it works and

sometime it doesn't that means it's a case of refractory. Now each systemic therapy has its own severe adverse effect on the patient's body. In the case of personalized medicine the adverse effect is limited. The drug sensitivity is really a great achievement. Problem is cost, these techniques are highly costly. Most of the people can't afford. My opinion is this should be included in the treatment guidelines and the cost should be affordable.

How the reports Come and Shows the treatment drug sensitivity:

CHOICE ONE

No	Drug	Indication	Dose/Schedule/Notes ²
1	Afatinib + Cetuximab	EGFR p.G719A mutation, EGFR overexpression, EGFR ICC positive	Standard dose

CHOICE TWO

No	Drug	Indication	Dose/Schedule/Notes ²
1	Pemetrexed + Cisplatin + Bevacizumab	Chemosensitivity, PALB2 mutation, VEGFA overexpression, VEGFA ICC positive	Standard dose

Other Potentiating Drugs³:

No	Drug	Indication	Dose/Schedule/Notes
1	Doxycycline	MMP11 overexpression	100 mg 1 BD
2	Vitamin C	SLC2A1 (GLUT1) overexpression	High dose intravenous administration

1. Recommendations for cytotoxic and targeted therapy options, based on observed cellular and molecular indications, are as per existing information and literature in public domain.
2. The Treating Oncologist may consider appropriate dosage, as well as suitable dose reduction, based on a real-time clinical evaluation of the patient, as well as the reported and/or expected toxicity profile(s) of the drug(s).
3. Potentiating drugs are to be administered simultaneously with Targeted and Chemotherapy drugs.

Fig6: A 76 years old Lung Adenocarcinoma IVA patient goes for Personalized Medicine in Chittaranjan National Cancer Institute, Kolkata and the Drug Sensitivity showed like this. So we will give those drugs to the patients. [24]

Things are checked in the Personalized Medicine: [24]

1. Patient and Specimen Details
2. Report Highlights
3. Cancer Pathways in Tumor
4. Therapeutic Implications (Tumor Tissue mRNA)
5. Global Gene Expression Highlights
6. Somatic Genome Alterations (Tumor Tissue)
7. Somatic Genome Alterations (Cell Free Nucleic Acids)
8. Disease Relevant Negative Findings
9. Fusion Analysis
10. Microsatellite Instability Analysis
11. Histopathological Analysis
12. Immunohistochemistry Analysis
13. Pharmacogenetics
14. Circulating Tumor Cells Enumeration
15. Immunocytochemistry Analysis
16. Chemosensitivity Analysis
17. Variant Allele Fraction and Coverage
18. Criteria for Classification
19. Genes Analyzed
20. Methods and Limitations

So, The main thing is to check the sensitivity of the chemo drugs towards the tumor microenvironment and through this the best treatment protocol comes out which is specific to that tumor of that specific patient. In another patient the treatment will be completely different because each person has a different types of tumor genetic and tumor micro environment.

Conclusions: Our knowledge of and therapies for cancer is being revolutionised by developments in genomic medicine. In oncology, molecular-guided therapy is a pragmatic approach to care that has the ability to minimise the time and financial expenditure of inadequate interventions, thus increasing the length and quality of life of the patient. There are well-validated molecular targets for both breast cancer and melanoma that are actionable for FDA-approved therapies. The diagnostic and care platforms in other types of cancer are also being modified by these developments. Looking ahead, clinical studies such as the National Cancer Institute Molecular Analysis for Therapy Choice and the American Society of Clinical Oncology Targeted Agent and Profiling Utilization Registry will test the performance, including safety and efficacy, of using targeted agents based on genomic alterations in patients with advanced cancer, regardless of cancer type.[25-26] The findings of these studies are expected to lend credence to the wider use of high-throughput genomic analyses in oncology as a method for patient decision making. And, as NGS technology continues to advance, in order to identify patients at risk of relapse, the dynamic mutational landscape of a patient's cancer can also be longitudinally analysed by regular liquid and tissue biopsies before and during therapy. Preliminary initiatives are still ongoing to resolve application issues (e.g. workflow, introduction of EHR, economic assessments) so that precision medicine can be implemented more generally in clinical oncology practise.

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