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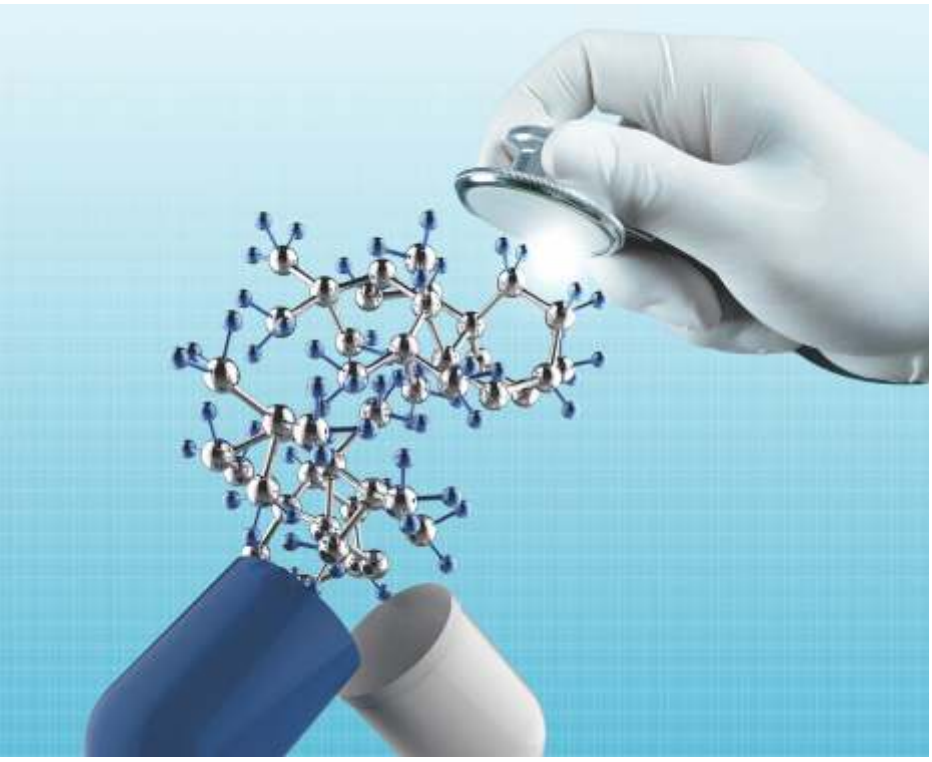
CANCER NEWS



PRECISION MEDICINE

Highlights:

Biosimilars

Precision Oncology

IBM Watson for Oncology

Rajiv Gandhi Cancer Institute and Research Centre
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EDITORIAL

Cancer is a disease of the genome. As more is learned about cancer tumors, it is being found that each tumor has its own set of genetic profile. Understanding the genetic profiles that are in cancer cells is leading to more effective treatment strategies that are tailored to the genetic profile of each patient's cancer. Precision medicine is about matching the right drugs to the right patients. Although this approach is technology agnostic, in cancer there is a tendency to make precision medicine synonymous with genomics. Precision medicine in oncology is focused on identifying which therapies will be most effective for each patient based on genetic characterization of their cancer, albeit at minimum morbidity to the patient.

The foundation of precision medicine is targeted therapies, first established in the late 1990s. Targeted therapies inhibit specific molecules involved in tumor growth and dissemination of cancer cells. Studies have also been performed to discover targets that predict effectiveness in radiation and chemotherapy. The proportion of clinical trials requiring a genetic alteration for enrollment has increased dramatically over the past several years, and many studies have demonstrated benefits of targeted therapies over cytotoxic therapies in both progression-free survival and overall survival.

However, genome-based cancer therapy is limited by incomplete biological understanding of the relationship between phenotype and cancer genotype. This limitation can be addressed by functional testing of live patient tumor cells exposed to potential therapies. Recently, several 'next-generation' functional diagnostic technologies have been reported, including novel methods for tumor manipulation, molecularly precise assays of tumor responses and devicebased in situ approaches. These address the limitations of the older generation of chemosensitivity tests. The promise of these new technologies suggests a future diagnostic strategy that integrates functional testing with next-generation sequencing and immunoprofiling to precisely match combination therapies to individual cancer patients.

Questions that must be addressed include whether precision oncology is just a theory or whether it realistically assures a better future, and if truly promising how can the application of precision oncology be improved and effectively implemented. Several lines of evidence strongly support the idea that precision oncology could benefit more patients compared with traditional chemotherapies. In spite of some early setbacks, precision oncology still has a great deal of promise and should not be abandoned hastily. The challenge of tumor heterogeneity should not discourage or intimidate efforts to overcome cancer but should push the field forward. As practice makes perfect, precision mends patients.

The present issue of the Cancer News highlights the newer advances in the field of 'Precison Medicine' and features the regular articles, such as Special Feature, Perspective, Guest Article, Outlook and In Focus. We are grateful to Dr Amit Verma, Consultant Molecular Oncology and Cancer Genetics, Max Cancer Centre, Gurugram, Haryana for contributing the Guest Article.

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SPECIAL FEATURE

IMMUNOTHERAPY IN ONCOLOGY

Based on mechanism of action, immunotherapies can be broadly divided into two categories. The first strategy is to boost already existing immunity significantly to eliminate tumors cells, which can be either by use of cytokines, such as Interleukin-2 and Interferon- Gamma or cell-based therapies, such as use of vaccinations and the introduction of oncolytic viruses for initiation of systemic immunity against cancer [1,2,3,4,5,6]. The second and most useful strategy is to counteract the inhibitory and suppressor mechanisms. The latter strategy includes antibodies against the T regulatory cells which is still in clinical trials and approved antibodies against immune checkpoint molecules mainly CTLA-4, PD1 and PDL-1, while many other inhibitory molecules are yet to be deciphered. In this review, we have tried to summarize the strategies in immunotherapy and approved therapies that are now being used in various types of cancers and some of the future drugs in the pipeline of immunotherapy.

Oncolytic Viruses in Immunotherapy

Oncolytic viruses are a novel technology of employing genetically modified viruses to kill cancer cells, specifically without affecting normal cells. The effect of these viruses occurs in two ways. The first effect is tumor specific infection of viruses and intratumoral replication and lysis leading to tumor debulking. The second effect is production of specific cytokines from the infected tumoral tissue and release of intratumoral antigens resulting in induction of sustained T cell immune response against remaining cancer cells [7,8].

These viruses are genetically modified, with insertion of promoters that restrict the virulence genes to be expressed only in tumor cells and genes that are pathogenic to the normal cells are deleted. Genes to express specific cytokines to favor recruitment and activation of T cell costimulatory molecules on cancer cells facilitating their recognition by tumor infiltrating lymphocytes are inserted [9,10,11,12]. However, one of the biggest challenge for successful production of oncolytic viruses is the host innate immunity against the viruses which acts and destroys before reaching the destined tumor cells. This was overcome by chemical pegylation i.e., covalent conjugation of the viral capsid and polymer coat with polyethylene glycol, which prevented antibody binding and neutralization and insertion of genes that prevent antigen presentation [13,14].

Many of the viruses tested as oncolytic viruses are non-pathogenic to humans, such as Newcastle virus, reo virus and Seneca valley virus. Some of the pathogenic viruses, such as herpes simplex virus and vaccinia virus are genetically engineered to become nonpathogenic [15]. Up-to-date, the most advanced oncolytic virus agent approved by FDA is Talimogene laherparepvec (T-VEC), for the treatment of advanced melanoma. Modifications done in T-VEC virus are deletion of two ICP34.5 genes to prevent neuronal involvement and their replacement by coding sequence for the GM-CSF cytokine [16]. Deletion of ICP47 in T-VEC induces viral replication, enhances antigen presentation, and increases oncolytic therapeutic activity. The enhanced local production of GM-CSF favors recruitment of antigen presenting cells to the tumor microenvironment and promotes anti-tumor immunity [17,18].

Following preclinical phase 1 and phase 2 studies which confirmed the optimized virus dose, tolerability and objective response rate of 26%, phase 3 clinical trials followed which recruited 439 patients with unresectable melanoma [19,20,21,22]. T-VEC has reached the primary end point of durable response rate. It was well tolerated by the subjects with only mild side effects, such as fatigue, nausea and got FDA approval for the treatment of advanced stage melanoma in October 2015[23]. T-VEC is the first and only approved oncolytic virus till now in oncology, indicated for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery. Recommended starting dose is up to a maximum of 4 ml of virus at a concentration of 1 million plaque-forming units (PFU) per ml. Subsequent doses should be administered up to 4 ml of T-Vec at a concentration of 100 million PFU per ml. It is contraindicated in immunocompromised patients and in pregnancy. Apart from local injection site reactions, development of herpes infection and local plasmacytoma has been reported in some patients.

Vaccines in Immunotherapy

The success of preventive cancer vaccines, such as Hepatitis B, Human papilloma virus, is well known. Vaccination against the cancer neoantigens is one of the earliest attempts for the immunotherapy in oncology, with the basic understanding that all of us harbor CD8+ and CD4+ T cells capable of recognizing tumor antigens. The main difference between prophylactic and tumor vaccines is that active immunity is required for the former, whereas the tumor vaccines requires the breakage of immune tolerance induced by tumor [24]. For this to happen, dendritic cells must be targeted with high quantities of antigens, expanded, activated with appropriate agents. There have been several reasons, some known and some unknown, for the failure of production of anti-cancer cancer vaccine with significant efficacy and reliable and reproducible effects. The deeper knowledge and pathways of antigenic stimulation, presentation, particularly regarding dendritic cells, which are far more important antigen presenting cells (APC) than other cells, such as macrophages, are still elusive [25,26].

The most important step in the development of successful cancer vaccine is identification of specific antigens. The first-generation vaccin'es clinical trials used short peptides, but it was seen that they are ineffective in stimulating dendritic cells. Later, it was identified that it is better to use full length proteins harboring wide range of epitopes and that therapeutic efficacy can be further increased when immune stimulants like interleukin-2 are co-administered [27]. Another aspect to consider is tumor heterogenicity. In trials using fusion melanoma antigen family A3 protein (MAGE-A3) in HLA-A2 positive non-small cell lung cancer, there was no statistically significant benefit. Although patients were tested for expression of MAGE-A3, it was later seen that there is no homogeneity in MAGE 3 expression. Similarly, GVAX, one of the most promising vaccine products based on preclinical studies, failed to show benefit in Phase III trials due to a lack of clinical efficacy because of inadequate immunogenicity [28].

In dendritic cell based vaccines, dendritic cells are isolated from the patient's peripheral blood, and incubated with tumor antigens ex-vivo, and when activated, reinfused into patient, expecting to stimulate T cell immunity against cancer cells [29,30]. Sipuleucel-T, a dendritic cell vaccine, cultured with a fusion protein consisting of prostatic acid phosphatase linked to the DC growth and differentiation factor GM-CSF (granulocyte macrophage colony-stimulating factor), showed approximately 4-month improvement in median survival [31], which led to US-FDA approval in 2010 for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer [31]. Despite this increase in survival, sipuleucel-T have failed to show meaningful decreases in tumor volumes in randomized clinical trials. This therapy is available in only few centers across the globe, as it is a very cumbersome technique.

Adoptive Cell Therapy (ACT)

Tumors consists of lymphocytes and macrophages which infiltrate them, primed against the antigens of tumor but unable to attack due to immunosuppressive environmental milieu. This immunotolerant environment is created by tumor cells by secreting cytokines which recruits T regulatory cells (T regs) and Myeloid Derived Suppressor Cells (MDSCs) in its own microenvironment [32]. This adoptive T cell transfer technique attempts to reverse the functional impairment of tumor specific T cells that reside within the tumor, often referred to as tumor infiltrating lymphocytes (TILs). These T cells are isolated from peripheral blood, draining lymph nodes or resected tumor tissue, and grown and cultured ex-vivo, replicated in sufficiently large numbers and then reinfused along with cytokine cocktail [33].

This ACT technique, theoretically, should overcome the baffling task of breaking tolerance and replication to produce sufficiently large quantities of high avidity effector T cells in vivo [34]. Lymphodepletion conditioning regimens are administered to patients prior to administration of TILs, speculated to eliminate immunosuppressive T-regs and MDSCs from tumor environment and also by increasing homeostatic cytokines IL-7 and IL-15 [35]. 93 patients of advanced stage melanoma were infused with autologous TILs in conjunction with IL-2. The response rates ranged from 49 to 72% with 22 % patients showing complete regression of tumor with durable responses up to 82 months [36]. The disadvantages of ACT therapy are that lymphodepletion conditioning regimens can be life threatening to the patients with advanced cancer. The best patient population suitable for this therapy is not yet defined [35]. This therapy till now has shown efficacy only in melanoma, and is thought due to high mutagenicity and heightened immunogenicity of melanoma [34].

Improvement in genetic engineering techniques has explored two strategies to broaden the use of TILs. The first strategy is engineered expression of alpha and beta chains of T cell receptor with antigen specificity of the transferred receptor. This is accessible to any patient whose tumor expresses the HLA peptide complex and expresses the target antigen that can be recognized by TCR [37]. The second strategy is development of chimeric antigen receptors (CARs), consisting of immunoglobin variable domain fused to TCR constant domain. These CAR T cells virtually can recognize any specific antigen that is expressed on cell surface, omitting the need for MHC expression and antigen processing in the target tumor cell. These strategies are being actively evaluated in B cell malignancies, melanoma, synovial sarcoma and several other cancers [38].

Immune Check Point Blockade

The multitude of somatic gene mutations confers potential antigenicity to human cancers, but this immune response is inhibited by cell mediated and cytokine mediated responses by tumors as already described previously. One of the very important mechanism is induction of tolerance among tumor specific T cells by expression of inhibitory ligands that bind the inhibitory receptors that are naturally present over T cells. This inhibition of T cells also occurs naturally to control total amount of immune response and it is referred to as checkpoint. The most exciting part of immunotherapy was ensued with the success of this checkpoint inhibitors causing "checkpoint blockade" to trigger antitumor immune response and it strikes in a new era in the treatment approach to advanced cancers [39]. Because this is the most important part of the immunotherapy, let us discuss these mechanisms and drugs more clearly.

Sato et al., reported an improved survival in patients with ovarian tumors having more CD8+ tumor infiltrating lymphocytes (TILs) and a high CD8+/regulatory T cell ratio. It was observed that the presence of CD8+ infiltrating lymphocytes predicted a good prognosis, while the presence of CD4+CD25+FoxP3+ T regulatory cells (Tregs) and B cell infiltration seems to confer worse prognosis [40]. During physiological immune response, after tumor associated antigens (TAAs) or tumor specific antigens (TSAs) recognition by CD4+ and CD8+ T cells, these antigens are processed into small peptide and presented by antigen-presenting cells (APCs) through MHC class II, two positive signals are required for activation. The first one being connection between the T cell receptor (TCR) and MHC molecules; the second necessary step is the interaction between B7 on APCs and CD28 on T cells. This CD28 has a competitive receptor for B7 ligand, the cytotoxic T lymphocyte antigen-4 (CTLA-4), which is responsible for delivering an inhibitory signal. This negative feedback is mainly used against autoimmune response in secondary lymphoid organ, several other inhibitory pathways are present within the tumor microenvironment [41]. The most well recognized and important peripheral regulatory pathway is the interaction between the programmed cell death-1 (PD-1) receptor, expressed on T cells, and the corresponding ligands programmed cell death ligand-1 and 2 (PD-L1 and PD-L2) on the tumor cells surface [42]. The binding between PD-1 and PD-L1 and PD-L2 causes the inhibition of T-cells proliferation, the cytokine's secretion, and the increase of Tregs, ensuring the maintenance of self-tolerance. This mechanism is naturally utilized by epithelial cells and leukocytes to prevent autoimmune damage and tumors use this as a masquerading mechanism.

It was observed in several clinical studies that high expression of PD-L1 is correlated with a worse prognosis in several types of tumors, such as non-small cell lung cancer (NSCLC) [43,44], kidney cancer [45], and bladder cancer [46], and more importantly, independent of the prognostic significance of PD-L1 expression, B7/CTLA-4 and PD-L1/PD-1 receptor interactions are important immune escape mechanisms, allowing tumor progression. Currently, various antibodies targeting PD1, PD-L1 and CTLA-4 have shown activity in several cancers, such as melanoma, lung cancer, head and neck cancer, renal cell carcinoma and bladder cancer.

Approved Immunotherapies in Clinical Use

Name of Immunotherapy	Type of Immunotherapy	Indication	Approved Year
PEMBROZULIMAB	Anti PD-1 antibody	NSCLC, SCCHN, Melanoma	2014
NIVOLUMAB	Anti PD-1 antibody	NSCLC, Bladder cancer, RCC, SCCHN, Melanoma, Hodgkin's lymphoma	2014
ATEZOLIZMAB	Anti-PDL1 antibody	NSCLC, Bladder cancer	2016
IPILIMUMAB	Anti-CTLA4 antibody	Melanoma	2011
DARATUMUMAB	Anti-CD38 antibody	Multiple myeloma	2015
ELOTUZUMAB	SLAMF-7 directed antibody	Multiple Myeloma	2015
SIPILEUCEL-T	Dendritic cell vaccine	Prostate cancer	2010
BLINATUMOMAB	Bispecific CD19-directed CD3 T-cell engager	Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL	2014
TALIMOGENE LAHERPAREPVEC (T-VEC)	Genetically modified oncolytic viral therapy	Unresectable cutaneous, subcutaneous, and nodal lesions in melanoma recurrent after surgery	2015

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PERSPECTIVE

IBM WATSON FOR ONCOLOGY – A PRIMER

Today the medical science has advanced to such an extent that keeping up with the latest advances in one's chosen field has become a hopeless task. The data explosion and acceleration in knowledge acquisition in the field of oncology is probably the greatest. Every year nearly 45,000 research papers are published in oncology alone. Computer technology has made the access of this somewhat easier with availability of all such global knowledge on the internet. However, what we get on the net is data, a huge amount of it – the Big Data! To sift through all of this to actually find a solution to current clinical problem is a very daunting, sometimes a very confusing task and nearly impossible for a single individual to do. Technology systems that can process huge volumes of disparate information and provide evidence based insights to support challenging medical decisions is required for this task. There was a need to somehow collate the available data and derive meaningful and practical conclusions from it.

Earliest attempt at this was tried at Stanford University in 1970s. MYCIN, an early backward chaining expert system that used artificial intelligence to identify bacteria causing severe infections and to recommend antibiotics with the dosage adjusted for patient's body weight, was never actually used in practice but research indicated that it proposed an acceptable therapy in about 69% of cases, and was better than the performance of infectious disease experts who were judged using the same criteria. It outperformed members of the Stanford medical school faculty. Some of the observers raised ethical and legal issues related to the use of computers in medicine – if a program gives a wrong diagnosis or recommends a wrong therapy, who should be held responsible? However, the computer hardware then was not powerful enough and the networks were not fast/secure enough to be used in a commercially viable system.

Recent advances in artificial intelligence, artificial neural networks, cheaper heavy duty computer hardware and superfast secure networking have made it easier to crunch this big data into knowledge. What is artificial intelligence (AI) and artificial neural networks (ANNs)? AI in healthcare means using algorithms and software to approximate human cognition in the analysis of complex medical data. The primary aim of health related AI applications is to analyze relationships between prevention or treatment techniques and patient outcomes. ANNs are a computational model based on a large collection of simple neural units (artificial neurons), loosely analogous to the observed behaviour of biological cerebral axons. Each neural unit is connected with many others and the links can enhance or inhibit the activation state of adjoining neural units.

This is dynamic and cumulative – as more datasets are processed, the number and quality (enhance/inhibit) of links between neural units can increase reflecting the acquired knowledge. Thus the system learns and becomes more efficient and knowledgeable to deal with the next case, exactly like a physician becoming better with experience.

IBM Watson was the first commercially available cognitive computing platform which analyzes high volumes of data, understands complex questions posed in natural language and proposes evidence-based answers. The beauty of the system is that it continuously learns, gaining in value and knowledge over time, from previous interactions. The Watson platform is best known for its appearance on the American television quiz show 'Jeopardy', where it beat human contestants. Watson for Oncology was developed by IBM in concert with Memorial Sloan Kettering Cancer Centre (MSKCC) starting in 2012.

Key points of the system are:

- It can understand natural language. So a loosely structured or even unstructured electronic medical record (EMR) or clinician inputs can be queried.
- It is powerful enough to handle humongous amounts of patient data from varied sources - all the different hospitals and the clinicians which the patient had visited in past, insurance acquired data, imaging reports, laboratory reports and even the sensors in monitoring equipments, mobile phones and fitness bands.
- It has a huge tabulated and indexed database of all the evidence generated from randomized control trial (RCT), expert panels, peer reviewed papers, expert guidelines and meta-analyses.
- It can crunch numbers big time. All the available statistics, flow charts and algorithms are implemented and displayed without any bias.
- Lastly, it learns. Each new case analysis, treatment and follow up are absorbed in the network and are used in relevant future cases. This approximates what a human expert does - learn and incorporate.

How does it work? The computer interface is interactive, initially collecting patient demographics and presenting complaints from the treating physician. Then once proper security/access clearances are obtained, the system will collect all the available medical data about the given case from EMR, physician inputs, past records, PACS and lab reports. It will then consolidate and sift through it, trying to eliminate duplications and inconsistencies, becoming interactive if it is unable to resolve it. With this summarized dataset the software will then identify, evaluate and compare treatment options with Watson's ability to understand the longitudinal medical record, available expert guidelines, flowcharts, RCTs and apply its oncology training to each unique patient case. It will quickly generate a list of potential treatment options and expected outcomes ranked by applicability:

- Recommended
- For consideration
- Not recommended

It will then go into interactive mode facilitating the physician to review treatment options and supporting evidence side by side to understand Watson's rationale and quickly access the relevant articles and clinical data at a click of button. The system can also be opened up to patients to help understand specific care options available to them.

Trained at MSKCC, Watson for Oncology is now being used at more than 30 hospitals and health systems around the globe and the results are compelling. Watson for Oncology uses more than 300 medical journals, more than 200 textbooks, and nearly 15 million pages of text to identify and rank evidence-based treatment options, including specific drugs and related administration instructions. Watson also links to peer-reviewed studies and clinical guidelines. Its "machine-learning" capability allows for continuous updating as new data accumulate. Currently, Watson for Oncology can assist clinicians with treatment plans for breast, lung, colorectal, cervical, ovarian, and gastric cancers. IBM plans to train Watson on at least 10 additional cancer types in 2017.

How definite is the evidence that this technology has improved patient outcomes, lowered costs, or provided some other benefit? At this point, there isn't much. In a double-blinded study of 638 breast cancer cases, the doctors at Manipal found Watson was concordant with the tumor board recommendations in 90 percent of cases. However, this impressive result came in the latter stages of the 3-year study after 175 "discordant cases" were reviewed a second time, adjusted by the oncologists, and were then once more passed through Watson. While IBM has entered into numerous deals to use its artificial intelligence system in healthcare, there is no published study yet linking the technology to improved outcomes for patients.

So as of now, it is more of a hype generated due to the novel nature and use of technology. However, it is definitely a useful as a tool to harness and tame the knowledge explosion. One thing is beyond debate: Watson is a complement to an oncologist, not a replacement. It can be a trusted, qualified resource for the multidisciplinary collaborative care team. As the technology improves, matures and goes through rigorous trials, we can probably expect a more 'intelligent' system which can be used by lay persons too. However, it is always going to be the decision of the treating oncologist and the patient to determine what is truly the best option for the patient.

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GUEST ARTICLE

PRECISION ONCOLOGY: AN OVERVIEW

What is Precision Oncology?

The emerging discipline, often called Personalized Cancer Medicine, or Precision Oncology or Genomics-driven Cancer Medicine, seeks to determine patient's specific tumor-driving genomic networks, and then design a rational combination therapy, selected from the rapidly growing arsenal of targeted drugs aiming to ameliorate the effect of the genomic aberrations in that particular patient's tumor. The word "personalized" expresses that cancer genomic data may facilitate rational treatment choices that are tailored to individual patients and on the other hand "precision" refers to enhance molecular depth, mechanistic intelligibility, and therapeutic clarity for clinical implementation. The advantages of this approach are that the targeted therapies are identified more precisely with a fewer side effects, and may be more effective than broad cytotoxic therapies.

Evolutionary Phases of Precision Oncology

1st Generation Precision Oncology involves testing for key known molecular abnormalities that are establised with drug response in particular tumor types (like EGFR mutation analysis for TKI in lung cancer). It is disease specific and constrained by the tissue-of-origin, andother non-molecular characteristics such as histopathology.

2nd Generation Precision Oncology involves testing of a few to hundreds of possible mutational hotspots simultaneously, or sequencing the exomes of several hundred cancer-associated genes, and this approach might sometimes disregard non-molecular characteristics. It requires specialized equipment, including next-generation sequencing.

Next Generation Technology

Next generation sequencing (NGS), is a massively parallel sequencing, also called deep sequencing, describes an advanced DNA sequencing technology, which has revolutionized genomic research and has become integral to various clinical applications. In contrast, the conventional Sanger sequencing technology, of used to decode the human genome in over a decade's time, but using NGS an entire human genome can be sequenced within a single day. The next-generation sequencing (NGS) and associated target sequence enrichment technologies are robust platforms that can detect these "actionable" cancer molecular alterations in a large number of genes in a single multiplexed assay. Thus, precision medicine has shifted from a 1-gene–1-drug paradigm to a multigene-many drugs model. With the rapidly developing of molecularly targeted cancer therapeutics, the utility of multigene sequencing panels for detecting tumor-specific mutations and identification of the corresponding drugs, the role of NGS-based companion diagnostics has become more relevant in the near past.

3rd Generation Precision Oncology is an upcoming architecture of precision oncology overcoming the limitations of the complexity of multiple genomic alterations in given tumor at cross-sectional time point. It uses broad-spectrum panomics (genomic, transcriptomics, proteomics, metabolomics) and sophisticated network-based statistical reverse engineering methods to identify the putative driver networks for a given patient's tumor.

Table 2: Companion Diagnostic (Theragnostics)

Cancer Type	Biomarker
Breast	ER/PR and HER-2/neu
Colorectal	EGFR, KRAS and UGTIAI
Gastric	HER-2/neu
GIST	c-KIT
Head and Neck	p53 and LOH /microsatellite instability
Leukemia/Lymphoma	Cd20 Antigen, CD30, FIP1L1-PDGRFalpha, PDGFR, BCR/ABL, PML/RAR alpha, TPMT and UGT1A1
Lung	ALK, EGFR and KRAS
Melanoma	BRAF
Uterine and Cervical	HPV infection and oncogene E6 and E7 expression

Table 1: Molecular Profiling Approches

Hotspot mutation analysis	5- 50 genes
Comprehensive genomic profiling	300-500 genes including CNV, FUSIONS,
Whole Exome sequencing	1% of the Genome (6000 - 22000 Genes)
Whole Genome sequencing	Complete coding and non-coding region of the genome
RNA sequencing	Complete transcriptome profiling
miRNA sequencing	Tissue/Disease specific small RNA sequencing
Methylation sequencing	Cysteine methylation patterns across various genes
ChiP sequencing	All transcription factor binding sites and histone modification status

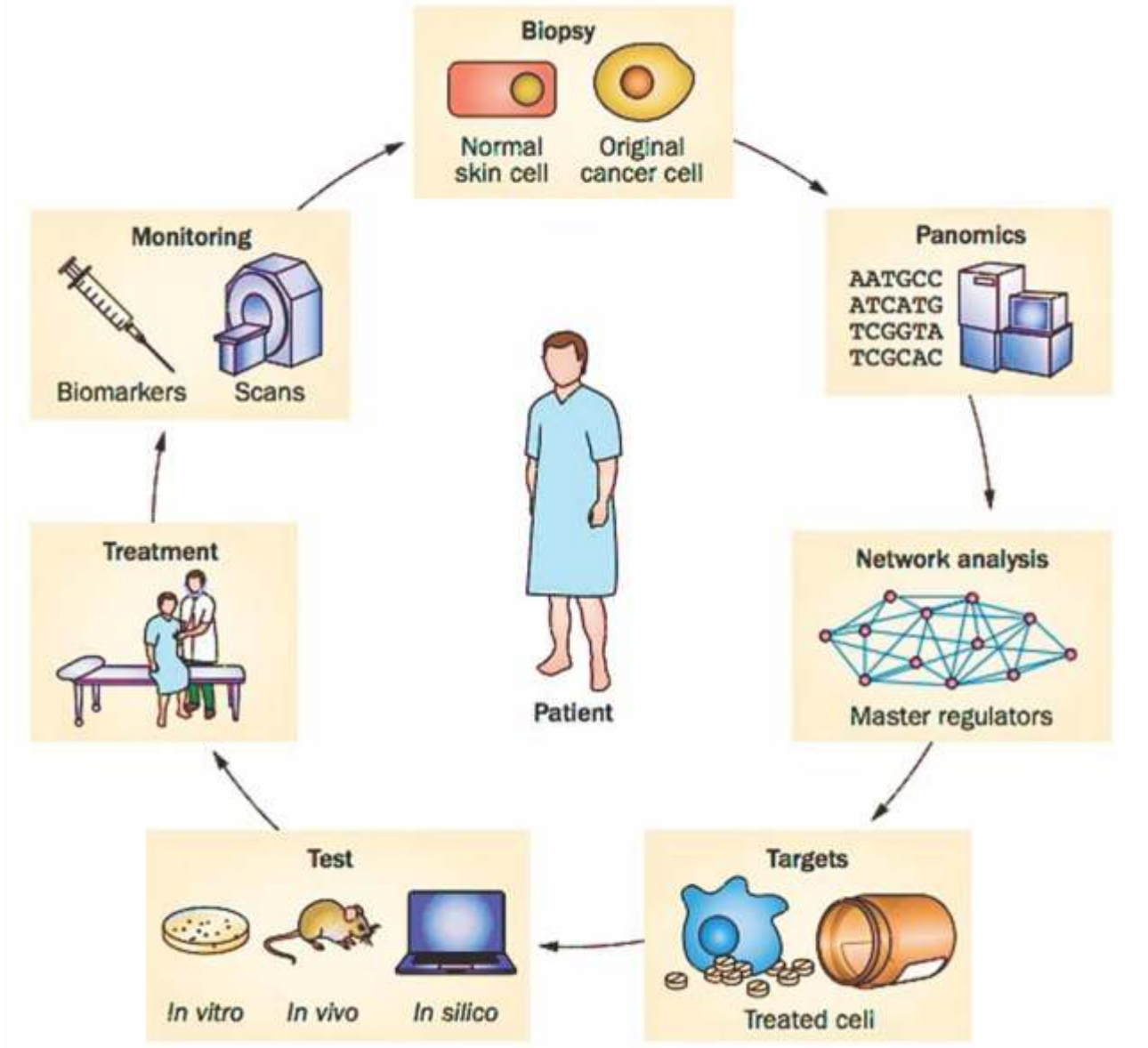

Fig. 1 (Adapted from Shrager, J. & Tenenbaum, J. M. Nat. Rev. Clin. Oncol. 21 January 2014)

Once these are computed, they are combined with important related clinical features (such as the patient's treatment history, availability of drugs and drug-drug interactions) to come-up with a treatment plan that attacks these tumor drivers with cocktails of appropriate targeted therapies (Fig. 1).

Challenges in Practicing Precision Oncology

Conceptually, the implementation of genomics-driven cancer medicine might seem straightforward. First, characterize the genomes of patients' tumors using state-of-the-art technologies; second, filter the genomic data through a knowledge base of existing and emerging anticancer drugs; and third, present an annotated list to the treating oncologist that can be incorporated into clinical decision making. However, multiple challenges must be addressed to bring this ambitious goal to fruition:

1. High-quality genomic information must be obtained consistently in the diagnostic setting, often from sparse amounts of archival tumor tissue.
2. Large-scale genomic data generation feasibility in a clinical setting.
3. Extent of genomic data needed for clinical decision making.
4. The cost-effectiveness of various platforms, and how rapidly clinical genomic data can be delivered.
5. The precision, accuracy, reproducibility and repeatability are the key analytical challenges that accompany comprehensive genomic alterations, thus need of identifying these alterations with high accuracy.
6. Access to tumor tissue for profiling is complicated, subject to sampling bias, and can be limiting for certain types of cancers.

7. Clinically actionable so-called driver events must be distinguished from the much larger set of passenger alterations that are present in tumor DNA.
8. Rigorous analysis and astute clinical interpretation of comprehensive genomic data with the assistance of computational algorithms.
9. Detection of multiple actionable mutations and the dilemma of choosing the drugs or drug combinations.
10. Applying the genomic information in clinical settings with limited evidence (lack of level 1 or 2 evidence). Ethical issues arising from the identification of novel germline mutations.

A framework for genomically guided personalized therapy was recently proposed. Four major criteria for use of this methodology have been outlined for incorporation into routine decision making. First, there must be confidence in NGS to accurately call genetic alterations and determine the patient's tumor genomic profile. Second, the clinical implications of the patient's genomic profile must be determined, with primary focus on current prognosis and identification of potential predictive biomarkers. Third, relevant FDA-approved drugs must be identified in addition to relevant clinical trials that outline the potential of the indicated treatment. Finally, an assessment of scientific evidence of each of the indicated agents in the context of the patient's specific genomic alterations should yield an appropriate clinical decision.

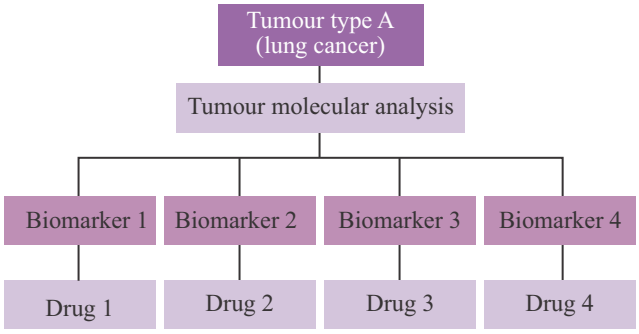

Fig. 2: Umbrella Study Design

Precision Oncology Driven Clinical Trials

Initially, targeted therapeutic agents followed the same clinical development pathway as cytotoxic chemotherapy, that is, based on tumor location and histopathology, driven by the notion that molecular aberrations were tumor specific. Efforts to advance this approach stalled because of the lack of efficacy data in patients with different cancer types that shared a molecular aberration, coupled with early observations that the functional importance of some aberrations varied between tumor types. However, the emergence of programmes that identified molecular targets and matched treatments to molecular subtypes led to several reports that directly linked this approach to improvements in clinical outcome, irrespective of the organ in which the tumor originated.

Table 3: Few Important Clinical Trials Based on the Principles of Precision Oncology

Study	Tumor	Phase / Design	Location
Bisgrove	All	Phase II. non-randomized	United States
IMPACT	All	Phase I	United States
MOSCATO01	All	Phase I	France
Lung-MAP	Squamous lung	Phase II/III. randomized	United States
BATTLE	NSCLC Umbrella	route to four phase II randomized	United States
BATTLE - 2	NSCLC	Phase II randomized	United States
BATTLE - FL	NSCLC	Phase II randomized	United States
I-SPY 2	Breast cancer	Phase II	United States
NCI-MPACT	All	Phase II stratified. Non-randomized	United States
NCI-MPACH	Solid	Phase II stratified. Non-randomized	United States
V-BASKET	All	Phase II stratified	Global
CREATE	Selected	Phase II stratified	European Union
WINTHER	All	Stratified. Non-randomized	European Union
SHIVA	All	Phase II stratified, controlled	France
MOST	All	Phase II stratified, controlled	France
SAFIR 02 Lung	NSCLC	Phase II stratified, controlled	France
SAFIR 02 Breast	Breast cancer	Phase II stratified, controlled	France
Lung MATRIX	NSCLC	Phase II stratified, controlled	United Kingdom
FOCUS 4	Colorectal cancer	Phase II/III randomized	United Kingdom
IMPaCT	Pancreatic cancer	Phase II stratified, randomized	Australia

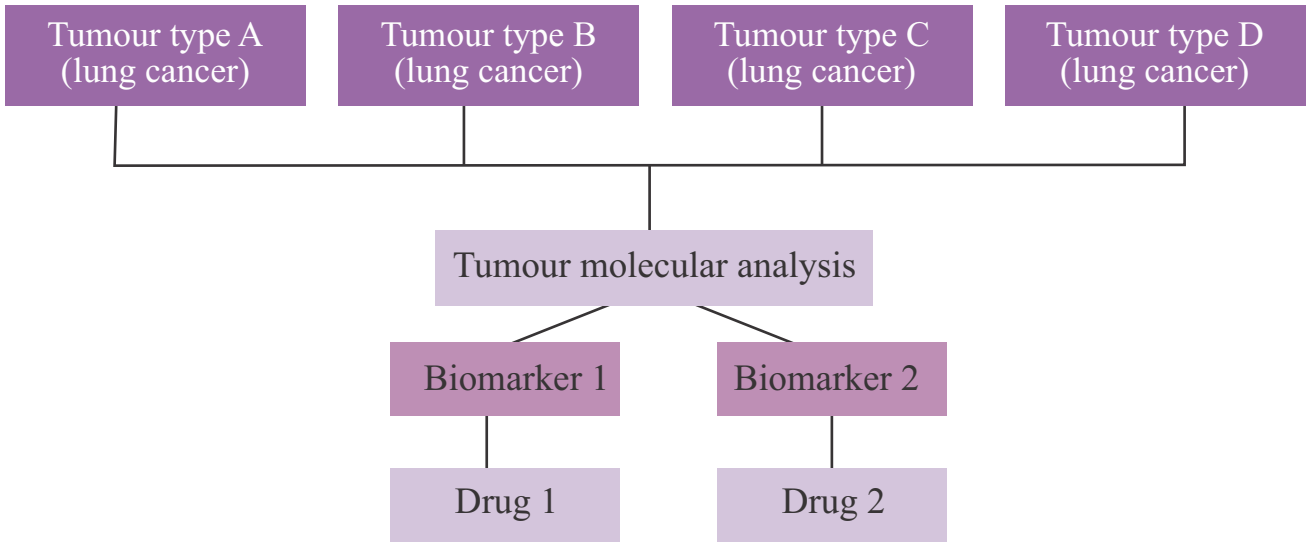

Fig. 3: Basket studies - recruit patients on the basis of their molecular characteristics irrespective of the organ in which their tumour originated

To meet emerging requirements, and enticed by the promise of clinical benefit, it is recognized that the established pathways of therapeutic development would need to change. Novel study design principles that generate efficiencies in clinical trials of targeted therapies in Precision Oncology are following-

Umbrella Studies: Patients with the same type of cancer are screened for a series of hypothesized predictive biomarkers. They are then allocated to appropriate therapies within the trial architecture. (The biomarker status for each tumor in the study is determined by tumor molecular analysis).

Future of Precision Oncology

Precision medicine's more individualized, molecular approach to cancer will enrich and modify, but not replace, the successful staples of oncology — prevention, diagnostics, some screening methods, and effective treatments. From the perspective of patients and their oncologists who struggle daily with advanced cancer, the promise of precision cancer medicine and delivering personalized care comes with many obstacles that must be circumvented before. The confluence of science, technology, and drug discovery has produced a tractable investigative path with a reasonable chance to improve the outcomes of many patients with cancer. Despite the challenges, one should keep hope that genomics-driven medicine will win the day across all cancers.

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OUTLOOK

A THERAGNOSTIC APPROACH TO PERSONALIZED AND PRECISION MEDICINE IN CANCER

Personalized medicine enables the use of diagnostic and screening methods to better manage the individual patient's disease or predisposition towards a disease. Personalized medicine enables risk assessment, diagnosis, prevention and therapy specifically tailored to the unique characteristics of the individual, thus enhancing the quality of life and public health.

Mutations introduced during primary tumor cell growth result in clonal heterogeneity which is represented by cells with a large fraction of the total mutation (founder cells) from which sub-clones are derived. In case of solid tumors, extensive heterogeneity within individuals is well known along with extensive heterogeneity between individuals. This is one of the reasons why genomic analysis from single tumor biopsy specimens under estimates the mutational burden in such heterogeneous tumors. This further contributes to treatment failures and drug resistance. There are many challenges in the execution of targeted therapy in cancer. A typical example of this challenge is the presence of two individual phenotypes in the same patient with one disease. Molecular genetics deciphers severe frequent cancers into specific rare cancers with the need of specific treatment strategies. Molecular characteristics redefine tumor classification for molecular targeted therapies, ensuring equity of access to innovation thereby offering the best treatment to patients considering the cost-effectiveness ratio.

Many technologies have evolved over time for understanding cancer. Functional imaging has gradually moved on to targeted imaging techniques which is capable of tumor characterization, microenvironment, metabolism, angiogenesis, proliferation, apoptosis, receptor expression, hypoxia and few others. Emerging from the investigations of the genomic & proteomic signatures of cancer cells, increasing number of promising targets have evolved and few specific imaging probes have come to the bed-side which is termed the nuclear fuel for molecular imaging by SPECT or PET. This helps in the non invasive depiction & quantification of biochemical processes and functional characterization of tumor biology. There are a few key steps in developing a probe for nuclear imaging. Finding a specific target for the disease like enzyme, receptor ligand, peptide or antibody with relevant target affinity is the first step.

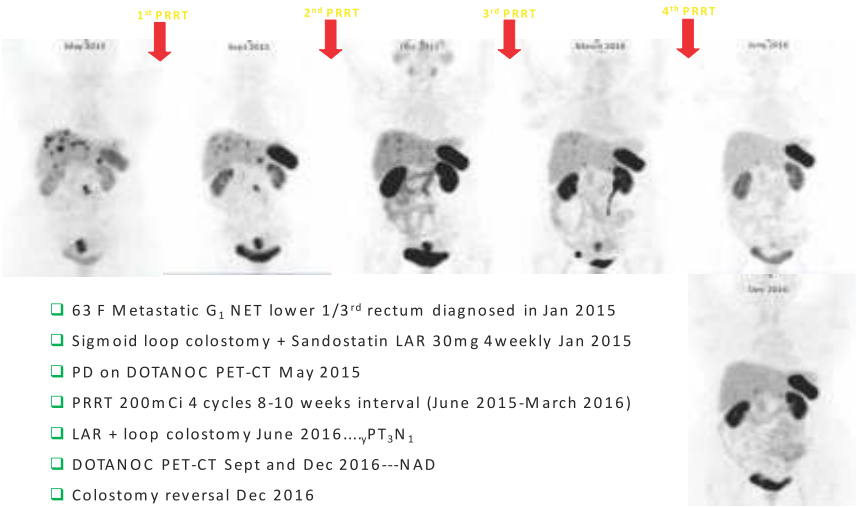
This is followed by physico-chemical behavior in vivo corresponding to the T1/2 of isotope, optimizing the lead molecule for creating a favorable bio-distribution and co-relating with the biochemical process. One of such targets is 16-α (18F)-fluoro-17-β-Estradiol, commonly known as FES. This is a synthetic estrogen with good co-relation between FES uptake and ER expression in tumors and good in-vivo stability. To use FES in the evaluation of breast cancer, it is essential to understand the principle of treatment of breast cancer and thereby optimiz the indications. It is crucial to correlate the threshold level of receptor expression by conventional techniques with quantification of tracer uptake as just demonstrating uptake of FES is not enough: how to use this information in the treatment paradigm is important and aids in personalized care. Co-relation between molecular markers of breast cancer and the outcome has also been recognized. The receptor status plays an important role in predicting outcome and has a significant role in personalizing treatment protocols. In vivo receptor imaging has made an inroad from the bench to the bed-side now. Hormone positivity has an impact on both treatment planning and prognosis and therefore imaging the ER receptor plays an important role. In this context, 16-α-(18F)-fluoro-17-β-estradiol positron emission tomography 18F-FES PET CT is supposed to play a crucial role in resolving diagnostic dilemma and also planning further management. Measurement of ER expression is by biopsy at the time of primary diagnosis. Estrogen is involved in the growth of both normal and cancerous breast tissues. Its activity is mediated by ER receptor and its positivity in breast cancer cells has a profound impact on treatment and patient outcome. With the background knowledge of tumor heterogeneity, a uniform expression of receptor is an exception rather than a rule. At the same time the expression in primary tumor and the metastatic sites may be different which may further prompt the need for imaging. FES PET-CT scan in combination with FDG PET-CT scan can be used as a problem solving modality in deciding the regimen. Our initial results point to this and highlight the spectrum of metastatic sites which can be resolved by this radiopharmaceutical. A common rule of thumb could be well differentiated hormone positive tumor with FDG uptake less than FES uptake which is unlikely to benefit from cytotoxic chemotherapy and would be an ideal candidate to be treated with hormone or vice versa where a poorly differentiated tumor with higher FDG uptake in comparison to FES will need cytotoxic chemotherapeutic regimen. In the coming years and in future, we hope that the treatment of breast cancer has a very

high potential to be personalized based on PET scan (both FDG and FES) and other molecular biomarkers giving early and clear indications to the treating oncologist as to where the disease is heading and how the treatment regimen needs to be modified.

Moving on from diagnosis to therapy and combining the diagnosis and therapy using the same vector, the term theragnostic is the combination tool that helps to define the right therapeutic tool for specific disease. "We treat what we see and see what we treat" signifies that at first a diagnostic radionuclide is labelled with the target and once expression is documented, the same target is labelled with a therapeutic radionuclide and treatment is executed. This term was used first by John Funkhauser/pharma industry at the beginning of the 90's when at the same time the concept of personalized medicine appeared. This helps in maximizing tumor dose and sparing normal tissue having high specific and rapid uptake in metastasis with high effective T1/2 and high absorbed tumor dose, expecting the response to be proportional to high dose delivered.

In nuclear medicine theragnostics is easy to apply and understand because of an easy switch from diagnosis to therapy on the same vector. Most prominent and oldest application is radioiodine.

Imaging and treatment of neuroendocrine tumors and prostate cancer are examples of successful implementation of the theragnostic concept and valid examples of personalized medicine. Biologically NET's are functioning or non-functioning. The functioning ones are associated with clinical syndrome and increased bio-markers. Non-functioning tumors have histopathological (HP) features of NET but no clinical syndromes. These have high expression of somatostatin receptors which have five different G–protein coupled somatostatin receptor sub-types (SSTR 1-5) cloned and pharmacologically characterized. SSTR 2 is expressed in approx. 90% of GI NET and 80% of pancreatic NET. In insulinomas, however, < 50% express SSTR-2. Histopathological grading also contributes to treatment selection. Well differentiated NET G-1 , mitotic count < 2/10 HPF with Ki 67 < 2% and G2 : mitotic count 2-20 / 10 HPF with Ki 67 2-20%, show good expression of somatostation receptor and are candidates for receptor based therapy. 177-Lu DOTATATE therapy can be successfully applied to these patients with excellent results and can even lead to cure in metastatic NET which has failed conventional therapy. In selected cases it has also been used to downstage the tumor, in a neoadjuvant setting, followed by curative surgery. Poorly differentiated neuroendocrine carcinomas, G 3 with mitotic count > 20/10 HPF with Ki-67 >20%, however, show poor expression of somatostatin receptor and require, conventional cytotoxic drugs.These methods of classification also dictate the type of tracer which would be optimum for diagnosis. High grade or poorly differentiated NET metabolizes glucose much more than the well differentiated ones, has less receptor expression and vice versa. It is due to this tumor heterogeneity that even many of the well differentiated NETs may require imaging with both 68-Ga DOTA and conventional 18F FDG to predict treatment outcome. Due to great variability in cellular differentiation FDG provides prognostic information. The FDG positivity is seen more in Ki67 >15% and there is a significant co-relation between uptake of DOTA and FDG and histological tumor grade. FDG is also very useful in receptor imaging negative cases. As a rule of thumb, poorly differentiated NET will show high glucose metabolism and low receptor expression. FDG also has a high prognostic value irrespective of tumor grade and is useful in predicting treatment response in low grade and low proliferative tumors. In a G2 NET patients with -ve FDG PET will have a better outcome. In case of +veFDG PET, a more aggressive disease course, is expected and avid uptake predicts survival.



- 63 F Metastatic G_1 NET lower 1/3rd rectum diagnosed in Jan 2015
- Sigmoid loop colostomy + Sandostatin LAR 30mg 4weekly Jan 2015
- PD on DOTANOC PET-CT May 2015
- PRRT 200mCi 4 cycles 8-10 weeks interval (June 2015-March 2016)
- LAR + loop colostomy June 2016....$_{y}PT_3N_1$
- DOTANOC PET-CT Sept and Dec 2016---NAD
- Colostomy reversal Dec 2016

In-vivo depiction of the overall tumor phenotype which is a result of multiple putative and unknown interactions at the cellular level, is advantageous in a heterogeneous tumor where pathology is subject to sampling error. Functional targeting in-vivo with appropriate tracer targets have the power of demonstrating inter-lesional heterogeneity between the primary and metastatic sites and is helpful in assessing the biology at the intermediate grading indices. All these will hopefully aid in fine-tuning treatment on an individual basis in this widely heterogeneous group of tumors.

In prostate cancer, biochemical relapse is common and occurs in 20-30% in radical prostatectomy and upto 60% after primary EBRT. Generally, local failure is predicted with 80% probability when biochemical relapse occurs >3 yrs after treatment and systemic failure is predicted if its < 1 year. In such cases PSA doubling time is an important factor and detecting sites of relapse is crucial. Prostate specific membrane antigen (PSMA) is the specific prostate epithelial cell membrane antigen. In-vitro studies have indicated that virtually all prostate cancer cells express PSMA. PSMA is also expressed in normal prostate, benign prostatic hypertrophy, small intestine, proximal renal tubular and salivary glands cells. Fortunately, PSMA expression in these cells is 100-1000 times less than prostate cancer cell. Moreover, its expression increases with higher grade and hormone resistance in prostate cancer cells. Due to non-secreting nature and internalization after ligand binding endocytosis (via clathrin coated pits), PSMA has received worthy attention for theragnostics. Radiolablled anti-PSMA antibody (Capromabpendetide, ProstaScint) is Food and Drug Administration (FDA) approved for detection of soft tissue metastasis and recurrence in prostate cancer patients. Due to low accuracy and technical challenge it is not utilized in most places. Small molecules which can be labeled with better radionuclide and clear fast is the current necessity.

One novel promising PSMA specific pharmacophore is Glutamate-Urea-Lysine. It binds with extracellular domain of PSMA, followed by internalization. Experience with Glu-NH-CO-NH-Lys-(Axe)-[68Ga(HBED-CC)] (68Ga-PSMA) is promising with better and early detectability. We have reported excellent sensitivity and detection capability for sub-centimeter sized lymphnodes during staging. Besides evaluation of recurrence, 68Ga-PSMA PET can be utilized in advanced prostate cancer for detection of nodal and distant metastasis. Role in guiding biopsy and radiotherapy planning is being looked into and expected to become a reality in near future. 68Ga-PSMA also serves the basis of treatment of CRPC with 177Lu labelled PSMA.

It is known that metastatic prostate cancer responds to well established innovative anti androgen treatment. In addition to other conventional treatment methods the recently approved androgen receptor antagonist enzalutamide and CYP17A1 inhibitor abiraterone has been reported to have 3.9 and 4.8 months survival benefit respectively. Progression to androgen independence is the main cause of morbidity and death in these patients. Based on the theragnostic concept, the main aims of treatment are to improve outcomes by early interventions in suboptimal responders sparing low risk patients from over treatment, to reduce acute and late treatment related side effects, achieve best possible therapeutic gain, ensure effective palliation and improve quality of life.Tumor targeting with 177Lu PSMA has the potential advantage of saving the normal tissue while delivering high dose to tumor, easy radiopharmaceutical labelling and high expression in all cancer cells, thus making it an optimal target for radionuclide therapy. It is safe with a low toxicity profile achieving good therapeutic benefit. We have seen objective regression in lesions and symptomatic relief. In our experience at RGCI & RC, we have found it to be a safe and effective method for treating end stage androgen independent, progressive CRPC where achievable tumor dose is demonstrated by Ga-68 PSMA scan before therapy. We believe that treatment of recurrent prostate cancer is feasible with 177Lu PSMA with a positive objective response and a low side effect profile. Molecular Imaging has high potential to link target identification with treatment and thus to personalize it. It also has very high potential for in-vivo tissue characterization to improve prediction, prognostication, road map for biopsy and monitoring and validate the “Treat what you see & see what you treat" concept.

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IN FOCUS

BIOSIMILARS - CURRENT AND FUTURE PERSPECTIVES

Abstract

Biological agents are utilized in oncology practice for cancer therapy and in supportive management of treatment-related side effects. A biosimilar is a biological product that is shown to be highly similar to a licensed biological product (the reference product) with no clinically meaningful differences from the reference product in terms of purity, safety, or potency. It is important for oncology practitioners to be knowledgeable about current biosimilars and those in development for cancer treatment in order to provide guidance and make an informed decision when incorporating these drugs into clinical practice.

Introduction

The treatment of cancer continues to place a significant burden on healthcare systems, with the number of cancer cases continuing to rise due to an aging population. Improvements in cancer diagnosis and disease management are now extending survival and consequently, increasing the length of time patients remain on treatment. As a result, there is a need to control current levels of expenditure, which are unsustainable.

Biologics for the treatment and supportive care of cancer have enhanced the therapeutic options for clinicians in the management of oncologic therapy. Monoclonal antibodies (mAbs) are employed as targeted treatment in cancer pathogenesis and in growth factors utilized to resolve therapy-related hematologic deficiencies. With the patents set to expire for a number of medications, interest related to the development of biosimilar agents has expanded for cost-saving benefits and global access[1].

Biosimilars are defined as biological products that are shown to be highly similar to a licensed biological product (the reference product) with no clinically meaningful differences from the reference product in terms of purity, safety, or potency[2]. The recent approval of several biosimilars in the United States has the potential to offer cost savings and health gains for patients with rheumatic diseases and cancers through highly similar efficacy.

Biologics and generic drugs are not classified as the same. Generic drugs are small molecules that are easy to replicate, while biologics are complex molecules that are produced through living cells. Because biosimilars are produced in living cells, variation may occur by reason of post-translational modifications, such as glycosylation, which may impact drug efficacy or safety. Hence, the reason the approval process for biosimilars is so rigorous[2]. The approval of any biosimilar is based on robust analytics and nonclinical and clinical studies depicting that the biosimilars and the reference products are highly similar with no clinically meaningful differences in relation to purity, safety, and efficacy[2].

Regulatory Requirements for Approval of Biosimilars in Oncology

Regulatory requirements for the approval of biosimilars in guidelines of the European Medicines Agency (EMA), the FDA, and the World Health Organization (WHO) are science-based and similar[2]. The approval of "biosimilarity" is based on the comparison of the proposed biosimilar to the reference product with respect to structure, function, animal toxicity, human pharmacokinetics and pharmacodynamics, clinical immunogenicity, clinical safety, and efficacy. Overall, biosimilarity is confirmed when "the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components. Furthermore, there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product."

The objective of a biosimilar development program is not to reestablish benefit but rather to demonstrate that there are no clinically meaningful differences based on the robust evidence. A stepwise process is conducted that begins with an analytical and nonclinical comparison of structural and in vitro functional characteristics followed by nonclinical in vivo animal studies and clinical studies[2]. The set and amount of data that are considered to be sufficient to demonstrate biosimilarity are determined on a product-specific basis.

The structural and in vitro functional characteristics are the foundation of biosimilar development and consist of the analysis of primary, secondary, tertiary, and quaternary structures that include aggregation, post-translational modification (i.e., glycosylation, phosphorylation, and deamidation), intentional chemical modification (i.e., pegylation), and biologic activity. The necessary extent of the nonclinical in vivo animal studies and clinical studies is dependent on the evidence from the preceding step[2].

Final approval is based on one or more comparative clinical studies within a suitable clinical setting with at least one study that assesses immunogenicity, pharmacokinetics, or pharmacodynamics that demonstrate safety, purity, and clinical efficacy of the biosimilar[3].

For example, in the case of Filgrastim Hexal in Europe, the comparison of efficacy to the reference product filgrastim (Neupogen) was based on a pharmacodynamics study in healthy volunteers that was considered acceptable by the EMA. In the case of filgrastim-sndz (Zarxio) in the US, the comparison of efficacy to the reference product Neupogen was considered acceptable by the FDA.

Overall, during the evaluation of the biosimilarity of a proposed biosimilar compared to the reference product, regulatory agencies factor in the entire scope of the research and development program from the analytics to the clinical trial data, which vary on a case-by-case basis[2].

Extrapolation of Indications

Once the similarity with the reference product has been established in terms of structure, function, pharmacokinetics, pharmacodynamics, efficacy, safety, and immunogenicity, the biosimilar is acknowledged as similar to the reference product. In the event that the reference product is licensed for multiple therapeutic indications, extrapolation of indications may be possible with scientific justification. Extrapolation is defined as the approval of a biosimilar for use in an indication held by the reference product that has not been directly studied in a comparative clinical trial with the biosimilar[4]. Regulatory agencies such as the EMA, FDA, and WHO require comprehensive comparability that focuses on efficacy, safety, and immunogenicity with a clinically relevant mechanism of action and receptors in the indication for an extrapolation to be considered[2]. Additional information may be required if the mechanism of action or receptors involved are different in order to justify the extrapolation of indication[2].

The utilization of extrapolation is critical to the concept of biosimilarity. The EMA perspective is that "the primary rationale for data extrapolation is to avoid unnecessary studies in the target population for ethical reasons, for efficiency and to allocate resources to areas where studies are the most needed." Weise et al identified replicating the efficacy and safety data of the reference product as scientifically not necessary and even unethical in some cases.

Within a true biosimilar to the reference product, it is expected that therapeutic effects such as efficacy, safety, and immunogenicity are similar. When extrapolation of clinical data is expected, the therapeutic indication of the clinical studies should be sensitive enough to detect clinically meaningful differences between the proposed biosimilar and the reference product[2].

Biosimilars approved for cancer therapy have been granted approval for indications that are held by the reference product based on the extrapolation of efficacy and safety data. The following case identifies the scientific data needed to demonstrate a biosimilarity and extrapolation of indication.

Filgrastim (Neupogen): This agent is a granulocyte-colony stimulating factor (G-CSF) used in oncology for supportive care to prevent chemotherapy-induced neutropenia. Filgrastim is also utilized in patients with acute myeloid leukemia or severe chronic neutropenia, or who are undergoing bone marrow transplantation and engraftment. In the European Union (EU), several biosimilars to filgrastim have been approved, including biograstim, filgrastim ratiopharm, ratiograstim, and tevagrastim from Teva Ltd (Castleford, UK); zarzio from Sandoz GmbH (Kundl, Austria); and nivestim from hospira (Lake Forest, IL). More recently, zarxio (filgrastim-sndz) from sandoz (Princeton, NJ) was approved in the US for all indications of the reference product, neupogen.

The justification for the extrapolation of indications for all filgrastim biosimilars consisted of the following (1) the overall analytical data from a head-to-head comparison of the reference product that showed similar molecular structure and in vitro function, pharmacokinetic studies depicting similar exposure and pharmacodynamics studies depicting an effect on absolute neutrophil and CD34+ cell counts in healthy volunteers, and efficacy, safety, and immunogenicity in cancer patients; and (2) the mechanistic binding to the G-CSF receptor that mediates the same biologic activity (i.e., stimulating bone marrow cells). In the case of filgrastim biosimilars, the extrapolation of indications was based on the totality of evidence (i.e., quality, safety, efficacy, and the mechanism of action) of the similarity between filgrastim biosimilars and the reference product, which was further supported by post-approval studies.

Biosimilar mAbs in Development for Cancer Treatment

Considering the high structure complexity of mAbs, the EMA published additional guidelines for the development of mAb biosimilars. Essentially, the guideline states that extrapolation of clinical safety and efficacy data to other indications approved for the reference mAb is possible based on the comparability analyses with scientific justification. The request for an indication extrapolation must be scientifically supported in terms of the mechanism of action and the receptors involved in each indication.

Table 1: Biosimilars to Trastuzumab for Oncology with Registered Phase III Trials

Biosimilar Name	Company	Indication Tested	Estimated Study Completion Date	ClinicalTrials.gov Identifier
BCD-022	Biocad	HER2 + MBC	October 2016 (results available)	NCT01764022
PF-05280014	Pfizer	HER2 + MBC	February 2018	NCT01989676
ABP 980	Amgen	HER2 + MBC	February 2017	NCT01901146
CT-P6	Celltrion	HER2 + EBC	June 2019	NCT02162667
SB3-G31-BC	Samsung Bioepis	HER2 + EBC or LABC	November 2016 (no results available)	NCT02149524
Hercules/MyI1401O	Mylan GmbH	HER2 + MBC	December 2018	NCT02472964

EBC: early breast cancer; HER2: human epidermal growth factor receptor 2; LABC: locally advanced breast cancer; MBC: metastatic breast cancer. Source: Reference 21.

In cancer therapy, the typical preferred endpoints to anticancer activity consist of progression-free survival or overall survival, which may not always be sensitive enough to establish similar efficacy of the biosimilar mAbs and the reference products. Hence, the EMA recommends utilizing a clinical endpoint that measures activity as a primary endpoint (i.e., overall response rate or pathologic complete response). The EMA also recommends extrapolation of clinical data from a population that is potentially homogeneous and not immune-compromised versus a population that is less homogeneous and is immune-compromised.

Trastuzumab: Trastuzumab (Herceptin [Genentech and Roche]), a humanized recombinant mAb targeted at the human epidermal growth factor receptor 2 (HER2), is indicated for the treatment of HER2-positive breast cancer in the adjuvant and metastatic setting. It is also indicated for the treatment of HER2-positive metastatic gastric or gastroesophageal junction adenocarcinoma. The composition of matter patent covering trastuzumab marketed in Europe (Roche) expired in 2014, while the last composition of matter patent in the US (Genentech) will expire in 2019. Trastuzumab biosimilars in late-stage clinical development are focused on metastatic and early breast cancer (Table 1)[5].

A number of biosimilars to trastuzumab have been approved worldwide. For instance, Herzuma (Celltrion [Incheon City, Republic of Korea]) was approved by the Korean Ministry of Food and Drug Safety in South Korea. In addition, Hertraz (Mylan [Mumbai, India]) and CANMAb (Biocon [Bangalore, India]) were approved by the Drug Controller General of India. These worldwide biosimilars have been approved for all indications of the reference product Herceptin. Although these biosimilars are approved in Asia, they may not meet the stringent regulatory requirements for clinical justification of biosimilarity guidelines from the EMA, FDA, or WHO.

Bevacizumab: Bevacizumab (Avastin [Genentech and Roche]) is a humanized recombinant mAb targeted at the human vascular endothelial growth factor (VEGF). In the EU and US, bevacizumab is utilized as a constituent of combination therapy in the treatment of metastatic colorectal cancer, metastatic or recurrent nonsquamous non–small cell lung cancer (NSCLC), and metastatic renal cell carcinoma, in addition to cervical platinum-resistant, recurrent epithelial ovarian, fallopian tube, and primary peritoneal cancers. The composition of matter patent covering bevacizumab marketed in the US (Genentech) will expire in 2019, while the last composition of matter

Table 2: Biosimilars to Bevacizumab for Oncology with Registered Phase III Trials

Biosimilar Name	Company	Indication Tested	Estimated Study Completion Date	ClinicalTrials.gov Identifier
BCD-021	Biocad	NSCLC	December 2016 (results available)	NCT01764022
BCD-021	Biocad	NSCLC	December 2016 (results available)	NCT01764022

NSCLC: non-small-cell lung cancer. Source: Reference 26.

Table 3: Biosimilars to Rituximab for Oncology with Registered Phase III Trials

Biosimilar Name	Company	Indication Tested	Estimated Study Completion Date	ClinicalTrials.gov Identifier
BCD-020	Biocad	NHL	October 2016 (no results available)	NCT01701232
PF-05280586	Pfizer	FL	June 2018	NCT02213263
ABP 798	Amgen	NHL	March 2018	NCT02747043
Gp2013	Sandoz	FL	March 2018	NCT01419665
CT-P10	Celltrion	FL	March 2018	NCT02260804
RTXM83	mAbxience	DLBCL	July 2017	NCT02268045

DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; NHL: non-Hodgkin lymphoma.
Source: Reference 29.

Rituximab: Rituximab (Rituxan [Genentech and Biogen Idec, US]) and MabThera (Roche, EU) are chimeric murine human mAbs targeted at the CD20 antigen of B cells. Rituximab contains a dual therapeutic area of oncology and anti-inflammation. Rituximab is utilized as a constituent in combination with glucocorticoids for treatment of non-Hodgkin lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis, and granulomatosis with polyangiitis and microscopic polyangiitis. The composition of matter patent covering rituximab marketed in Europe (MabThera) expired in 2013, while the last composition of matter patent in the US (Rituxan) will expire in 2018.

A number of rituximab biosimilars are in late-stage clinical development (Table 3) and are focused on various indications such as rheumatoid arthritis, follicular lymphoma, and diffuse large B-cell lymphoma[7]. A biosimilar to rituximab has been approved by the Russian Ministry of Health (AcellBia [Biocad, St. Petersburg, Russia]).

Conclusion

As biosimilar mAbs begins to enter the field of oncology, it is increasingly important for cancer practitioners to understand the biosimilar development and evaluation process of data in order to make an informed decision and incorporate these medications into clinical practice. With a true biosimilar to the reference product, it is expected that therapeutic effects, such as efficacy, safety, and immunogenicity are similar. The approval of biosimilar mAbs for oncologic therapeutics is expected because patents for oncology biologic mAbs have already expired or will expire in coming years.

Biosimilarity is based on comparable analytics and functional, nonclinical, and clinical studies. The extrapolation of an indication is an important component of the biosimilar concept. The mAb biosimilar development program's utilization of extrapolation may address drug shortage issues (i.e., increased demand and manufacturing) within the stringent regulatory requirements of the EMA, FDA, and WHO. The European experiences with biosimilars have shown promise over the past few years with similarities to the reference biologic. Oncology pharmacists can play a pivotal role in the continued and increased use of biosimilars in cancer therapy.

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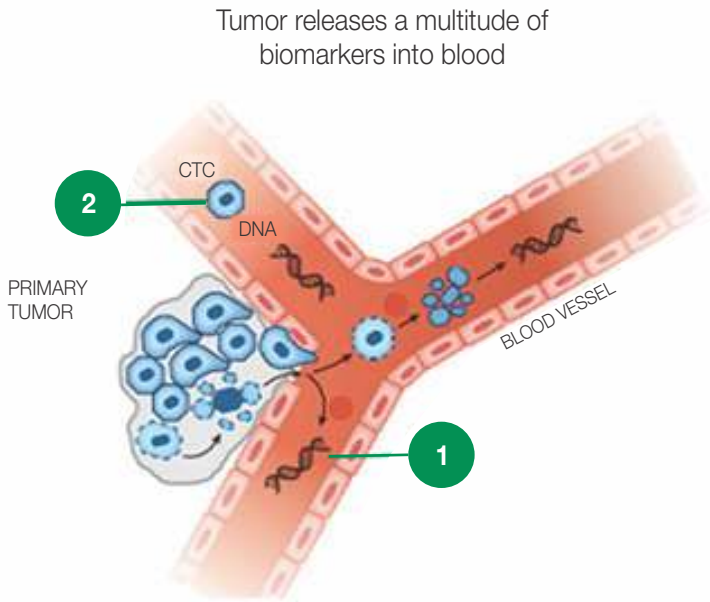

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