Review Article DOI: 10.18203/issn.2456-3994.IntJMolImmunoOncol20180468

Precision medicine in oncology – On a journey from dreams to reality

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ABSTRACT

Precision medicine is defined as treatments targeted to the needs of individual patients on the basis of genetic, biomarker, phenotypic, or psychosocial characteristics that distinguish a given patient from another patient with similar clinical presentation. Precision Oncology is an innovation at the cusp of blooming. We reviewed the status of precision oncology today, and discuss the flaws, mainly in next-generation sequencing (NGS) and the design of clinical trials thus far. Precision oncology although paints a glossy imagery, the reality is laden with inherent flaws, lack of guided research and a generalisability for the clinical market. The scenario in India is similar. It remains to be seen, if Precision Oncology is able to withstand the scrutiny likely to come its way, and if it can appeal largely to a complex socioeconomic market as India. We conclude that precision oncology is not far from an exponential boom, provided the right questions are asked, and answers derived.

Key words: Precision oncology, Next Generation Sequencing, Methods of Next Generation Sequencing

Slowly the medical fog was clearing –at least now I had enough information to dive in to the literature. While numbers were fuzzy having EGFR mutation seemed to add around a year of life on average, with potential for long term survival; not having it suggested an 80% chance of death within two years. Clarifying the rest of my life would be a process.

Like my own patients, I had to face my mortality and try to understand what made my life worth living—and I needed Emma's help to do so. Torn between being a doctor and being a patient, delving into medical science and turning back to literature for answers, I struggled, while facing my own death, to rebuild my old life—or perhaps to find new one. An Excerpt from "When Breath becomes Air" by Paul Kalanidhi

The author describes his feeling when he was presented with the diagnosis of adenocarcinoma of lung. There is a hint of melancholic faith, in his mention of possibly having an epidermal growth factor receptor (EGFR) mutation, which is amenable to treatment.

Precision Medicine in Oncology

Precision medicine is defined as treatments targeted to the needs of individual patients on the basis of genetic, biomarker, phenotypic, or psychosocial characteristics that distinguish a given patient from another patient with similar clinical presentation.[1]

Examples of precision medicine would include identification of bacteria in culture and starting appropriate antibiotics according to sensitivity reports. Another example would be recombinant factor VIII and IX, which virtually revolutionized efficacy and safety of treating patient with hemophilia.[1]

Cancer is an ancient disease, the origins, of which can be traced all the way to the Egyptian civilization.[2] The first clues to the presence of cancer were found from the fossilized mummies, which showed the evidence of bone cancers. It is an uncontrolled growth of clonal cells driven by genetic aberrations, influenced by environmental factors.[3] The pathogenesis of cancer involves a multi-step dynamic process that includes clonal expansion, genetic diversification, and clonal selection.[4] At the heart of tumorigenesis lies the driver mutation (the genetic aberration necessary for progression), i.e., loss of function mutations in tumor suppressor genes (EG) or gain-of-function mutations in oncogenes.[4,5] Although it is an ancient disease, the treatment of cancers is an ever-evolving paradigm. From the initiation of chemotherapy, which was largely empiric to therapy targeted against a specific molecular aberration, medical oncology is a steadily progressing field. The world cancer burden is likely to increase from 12 million new cases in 2012, to 24 million new cases, in 2035. A majority of this increase would arise from developing nations, including India.[6]

Precision oncology takes into account the variation inherent in the tumor evolution. It advocates an individualistic approach, rather than a one sock fits all points of view. Targeted therapy

for chronic myeloid leukemia (CML) in patients with BCR-ABL fusion with tyrosine kinase inhibitors (TKIs), in fact, personalized medicine at its inception.[7] It is built on the concept of individualistic treatment approach, specifically targeting the aberrancy that results in phenotypic disease and/or is responsible for its progression. Precision oncology is the use of patient's genomic data for "informed diagnosis, prognosis, treatment and prevention of cancer for that patient."[8,9]

We have reviewed the status of precision oncology today, and discuss the flaws, mainly in next-generation sequencing (NGS) and the design of clinical trials thus far.

The Presence of Precision Oncology Today

CML was the first human malignancy found to be associated with a recurrent chromosomal abnormality. TKIs such as imatinib, dasatinib, and nilotinib have successfully improved the lifespan of patients with CML.[3] This compound improved the overall survival rates of CML patients to 90% over 5 years and 88% over 8 years.[2] Use of trastuzumab in breast cancer patients with her2-neu overexpression is another example of precision medicine. Other important examples are included in Table 1.

ESMO clinical practice guidelines incorporated guidelines of precision cancer medicine in colorectal cancer, in 2014, and non-small cell lung cancer, in 2016.[10,11]

NGS-targeted Panels, Whole Exome, Whole Genome/ Transcriptome Assays

The sequencing of the first cancer genome laid the path for the application of NGS to better understand tumor genomics. NGS led to a better understanding and characterization of many cancers, resulting in definition of new subtypes, development of biomarkers and establishment of novel therapeutic targets, and culminating in the completion of The Cancer Genome Atlas project.[12] A large database consisting of whole genome sequencing of approximately 25,000 adult and pediatric tumors is underway.[12] These NGS endeavors include Therapeutically Applicable Research to Generate Effective Treatments for pediatric and International Cancer Genomics Consortium for adult cancers. Testing for both DNA and RNA aberrations through NGS has found its way to the clinical scenario.[12]

The Table 2 summarizes the salient features, pros and cons of NGS.

With the availability of NGS, the complexity of tumor genomics is recognizable. Considering the broad range of large-scale chromosomal aberrations, the identification of driver mutations (i.e., those responsible for the proliferation of the cancer) and passenger mutations (i.e., those which are not responsible for the growth of the tumor) is a major challenge.[12-14] As mentioned in a review by Horak *et al.*, it is worthwhile to consider other genetic aberrations that may have developed during tumor evolution. These may eventually become driver mutations in the setting of a drug therapy targeted against the original driver mutation.[12]

A tumor continues to evolve with time, which makes it challenging to find drug therapy which is largely applicable and predictable. Given the dynamic nature of the tumor, and its heterogeneity the challenge to develop a clinical trial to address these issues persists. As the genomic testing is possible only once at most times, considering the cost, the availability of tissue, and the need for invasive techniques to procure additional tissue, it is a static marker. The manner in which the genomic instability identified may exist, function, and evolve is unique to an individual.[7,14] A novel concept consists of an initial genomic study, followed by repeat studies of the body fluids to obtain circulating tumor cells (CTCs) or circulating tumor DNA (ctDNA).[7]

Liquid Biopsy

It is the periodic sampling of body fluids (blood, urine, etc.) of patients for direct assay and quantification of driver genomic alterations identified through NGS.[7] This may help in avoiding multiple invasive biopsies, which may be required to better appreciate the evolution of tumor genomics. For example, in lung cancer liquid biopsies, blood samples are mainly used as a sample source for analyzing CTCs or ctDNA, in addition to other biomarkers of interest, such as circulating microRNAs, circulating RNA, platelets, plasma/serum metabolites, or exosomes.[15] The use of CTC as a prognostic biomarker is already well established in cancers of the breast, colon, and prostate. The potential clinical benefits of a liquid biopsy may be seen in early detection of cancers, real-time response to therapy, detection of developing resistance, prognosis, and tumor heterogeneity analysis. Various technologies available for liquid biopsies are NGS, fluorescence *in situ* hybridization, reverse transcriptase polymerase chain reaction, *in vivo* culture, and flow cytometry. Its limitations include the absence of robust studies and guidelines, lack of standardization across laboratories, and lack of incorporation into phase III trials to enable guideline formulation.[7] Liquid biopsies, are set to play a major role in understanding tumor evolution, and are set to have an established role in clinical practice guidelines. It is an efficient, feasible, and easily reproducible answer to the problem of constantly growing intratumor heterogeneity.[7,12]

Tumor Only versus Tumor/Normal Assessments for Clinical NGS Assays

In today's clinical practice, the tumor tissue is tested for already established abnormal genetic variations, which are "actionable," i.e., are important in guiding treatment, prognosis and are the basis of the pathogenesis, against which molecular therapy is likely to produce benefit. However, it is likely that in this process, probability of mischaracterization

of known mutations as drivers, may lead to overlooking of other genetic variations which may be important in better understanding tumorigenesis and evolution.[14] As mentioned in the review by Borad *et al*., Jones *et al.* compared tumor-only approaches with tumor/germline sequencing approaches and found a 31% false-positive rate in NGS approaches and a 65% false-positive rate in tumor-only exome approach, highlighting the importance of transitioning to tumor/normal assays as the field moves forward. In contrast to these NGS tumor-only assays, whole exome sequencing/whole genome sequencing pipelines typically use tumor/normal comparisons and as such are able to overcome this false-positive variant call issue. However, the major advantage of the tumor only approach, i.e., the ease of clinical application cannot be discounted.[14]

Use of NGS as Biomarkers for Prognosis and Sensitivity

It was observed, during a basket trial, that therapy against BRAF mutation in colorectal cancer was not effective, as opposed to the high efficacy of vemurafenib in advanced melanoma. The presence of EGFR feedback loop, KRAS mutation in patients with colorectal cancer, made it resistant to therapy with anti-BRAF agents. Once, a specific driver alteration has been identified and validated, it is important to study its relevance as a biomarker of sensitivity or resistance.[7]

Table 1: Examples of molecular targeted therapy[2]

Mutation	Cancer	Therapy
BRAF	Melanoma	Vemurafenib, Dabrafenib
EGFR, ALK, K-ras	NSCLC	Gefitinib, Erlotinib
ER/PR Gene Expression	Breast	Tamoxifen, Aromatase inhibitor
EGFR, K-ras G13D	Colorectal	Panitumumab, Cetuximab, Imatinib
HER2/neu	Breast	Olaparib, Trastuzumab

EGFR: Epidermal growth factor receptor

Trials: Basket versus Umbrella Design and its Pitfalls

With new emerging evidence and technology that may aid in guiding precision oncology, new age trial designs (Figure 1) are being tried out that address the complexities involved in this ever-changing arena of medical oncology.

The "Umbrella" trials include patients with one particular histology (which forms the stem of the umbrella) but evaluate multiple predictive biomarker groups with the same protocol (spokes). Examples include I-SPY2, SAFIR-01 in breast cancer, ALCHEMIST, Master Protocol in lung cancer, and FOCUS04 in colorectal cancer.[7]

The "Basket" trials study the effect of targeted drug therapy against one molecular aberration with different tumor types. Examples include NCI MATCH trials and other institutional trials. The WINTHER trial is a prototype of this trial.[7]

Although these trial designs are able to incorporate large populations, and study effects of treating actionable targets across a variety of different cancers, they are only able to address interpatient heterogeneity.[7]

SHIVA trial, a randomized controlled trial evaluated the role of targeted drug therapy versus conventional chemotherapy and found no significant difference in the period of disease-

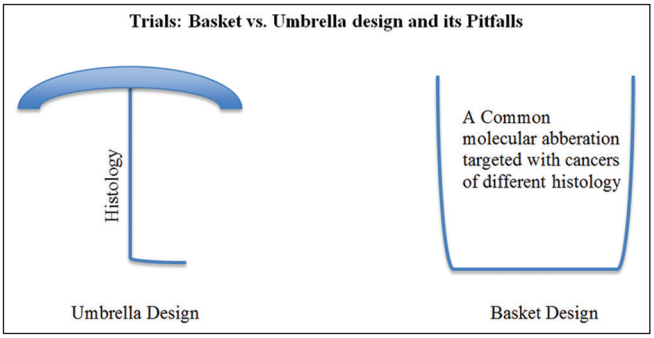

Figure 1: Schematic diagram representing Umbrella and Basket design of trials

Table 2: Pros and cons of different methods of next-generation sequencing[5,12-14]

	Targeted Panels	Whole Exome	Whole Genome
Coverage	Identifies known aberrations in a range of 20–500 genes; better depth of coverage	Targets 1% of the genomes; mainly the protein coding regions, successfully identifying 85% of cancer mutations; screens 22,000 genes	Whole genome study; able to uncover alterations in promoters and enhancers
Pros	Low cost Easy for clinical application Detects single nucleotide variants with higher accuracy Rapidly standardizable	Useful for research but may be used in a clinical setting as well Identifies unknown mutations Cheaper with higher value	Detailed assessment of genomes Excellent for new studies Highest resolution Possible to provide information about germline variants, hence, guide family counseling and screening of genetically susceptible family members
Cons	No use in research Limited observations	Time consuming takes around 4 weeks Complex workflow required Complex for clinical consumption Lower resolution for complex nucleotide variants	Most expensive

free progression. The poor results of this trial were attributed to the limited knowledge of molecular characterization, the flaws in the administration of drug therapy, or poor handling of tissues.[5]

All of these trials rely on molecular characterization of tumor tissue from a single location and at a single time point, whether it is obtained through an archived diagnostic specimen or a freshly procured biopsy. Genomic profiling is typically carried out on only one such sample due to reasons such as cost, challenges in tissue access, and sufficiency in DNA quality and quantity.[7]

Despite these limitations, novel new generation clinical trials for precision oncology are on its way. They are collaborative, large and take into account the most important biological hallmark, i.e., intratumor heterogeneity. TRACERX for lung cancer and BEAUTY in breast cancer are a few such powered trials. Additional information about the evolution of tumor with the help of NGS on metastatic lesions, and constant surveillance reassessment of tumor genomics on therapy, with the help of repeated blood sampling for ctDNA or CTC will be made available.[4,7,14]

Limitations

Precision cancer medicine, like every fresh initiative, is not free from its limitations and challenges. The biggest challenge, perhaps, is the task of implementation of the data gained from the clinical trials to a community setting.

Intratumor heterogeneity

Intratumor heterogeneity refers to the variation in the genetic character of a tumor as it evolves. Molecular characterization of a tumor and a metastasis may also show substantial heterogeneity.[5,14] It was observed that the molecular characteristics of the metastatic lesions were similar to subclones from the primary site. This suggests that the metastatic lesions, also probably contain the key to developing resistance to drug therapy. The use of liquid biopsies may help mitigate this problem, as serial testing noninvasively would become possible.[5] Tumors are seen to have a branched evolutionary pattern, i.e., the presence of multiple subclonal driver populations that lead to a constantly variable, evolving tumor.[5] With treatment against the driving mutation, the drug-sensitive tumor cells are killed. This leads to the emergence of drug resistance subclones, leading to cancer progression. This poses a serious question: Whether, any therapeutic strategy could provide cure or long-term remission despite the presence of intratumor heterogeneity. The failure to recognize the complexities of disease, of which intratumor heterogeneity is a prime example, is a key factor that is responsible for therapeutic failures (<10% of anticancer drugs that enter phase 1 clinical trials are approved for marketing) and the disparity between the level of investment in biomedicine and its output to improve human health.[5]

For the success of targeted therapy, the cancer oncogenics should be such that the major "driver" aberrancy (i.e., the one that is necessary for progression) should be present on all tumor cells and when suppressed will lead to cessation of further progression. However, as a cancer will have many subclones that may proliferate after suppression of the "driver" aberrancy, there is a risk of progression despite targeted therapy costing several thousand dollars.[5] The development and proliferation of genetic variations may be induced either *de novo*, or during treatment targeted against a known treatable, supposed actionable target.

Highly complex for clinical practice

Establishment of guidelines, treatment algorithms incorporating specific molecular therapy, is underway. With the number of randomized controlled trials, with improved study designs that are ongoing, it may become possible to have more answers, to the benefits of precision medicine. Training needs to be provided for healthcare personnel to interpret the large data that will become available from whole exome studies. The gap from the laboratory to the clinician's office is a large one, and efforts will be required for bridging. Simplified algorithms, specific nuclear sequencing, incorporation into medical training, and simplified reportage of the genetic sequencing will be necessary for guiding therapy.[7,13]

Cost

The cost of treatment needs to be weighed against the margin of benefit it provides. The terrific response to imatinib in CML makes it logical to market. However, the development, marketing, and research directed into therapeutics with questionable, marginable benefit are taking away from resources that could be directed toward more effective therapy.[5] It is likely that the cost of NGS is likely to drop, but even then would be quite unrealistic to hope for the dissemination of the technology to the roots of India.

Indian Scenario

As a nation who spends only about 1% of gross domestic product for health care, considerable advances have been noticed in the healthcare sector. However, as an academic teaching institute located in a rural area, our main objective is focused on management of common infectious diseases and treatment of common non-communicable diseases such as hypertension and Type 2 diabetes mellitus. We have come a long way from a resource-limited setting to one with resources that are able to provide state-of-the-art therapeutic options for those who can afford it. However, the field of cancer genomics is not high on the list of avenues, as the focus is mainly on non-communicable disease prevention and treatment.

To the best of our knowledge, no papers have been published that studies the effects of specific molecular therapy in cancers in Indians, so far. Most of the experience with precision medicine in India is based on recommendations, as part of standard guidelines. Since the cost of therapy is too high, the

beneficiaries are either those who can afford it or those who are enrolled under an ongoing international trial.

Several institutes across the country are enrolled in collaborative partnerships and ongoing large-scale studies. However, it would be interesting to see the evolution of tumors considering the race, and the histology common in a specific geographical location.

Lack of literature in Indian population, along with lack of laboratory support and finances to carry out research in developing cheaper variants for NGS, makes it difficult for a general application of precision oncology in India.

Conclusion

Although several targetable molecular aberrations are identified with proven beneficial role in some cancers, further research into drug resistance to those is pending. A lot more work needs to be done to solidify the argument for precision medicine, along with the establishment of algorithms and guideline formation. More research into making precision medicine cost-effective and the technology simpler to disseminate is the need of the hour, considering the Indian scenario. Encouragement of government sponsorship of newer advances and targeted drug therapy is the big hope. Precision oncology is at the cusp of an exponential boom, provided the right questions are asked, and answers derived.

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How to cite this article: Patel AN, Shah M. Precision medicine in oncology – On a journey from dreams to reality. Int J Mol ImmunoOncol 2018;3:15-19.

Source of Support: Nil. **Conflict of Interest:** None declared.