Clinics in Oncology

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BMS-CTMC-2024-32: Personalized Oncology, Platforms and Selection

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Abstract

Cancer is a complex and high-mortality disease caused by different kinds of risk-factors, hallmarks and pathogenesis stages. Personalized Oncology (PO) or Precision Medicine (PM) is adapted for drugs elections against various oncogenic pathways and hallmarks.

After six-decade development, personalized oncology has been evolving into various platforms in the clinic. However, greater therapeutic benefits should be based on correct selection of platforms and technique advances.

Next generation of PO will simultaneously contain information of pharmacology (drug sensitivity or drug combination), oncology (genomic sequencing, multi-omics profiling, computation, biomarkers and response scores) and toxicology (adverse side-effects and human mortality). Unlimited technical advances can greatly increase therapeutic benefits of cancer treatments.

Integration and balances of different techniques might take a leading-position in the future. A reliable, safe, effective and integrative platform will be accomplished by different scientific and technical approaches.

Keywords: Personalized oncology; Precision medicine; Drug selection; Artificial intelligence; Diagnostic platforms; Computational network; Single-cell multi-omics; Cancer metastasis

Cancer Treatment

Cancer epidemics

Cancer is an increasing epidemic disease worldwide (approximately 12% of all human mortality). In the near future, half number of adult human being will suffer cancer in their life-time, like UK [1]. Approximately, 7 to 10 million annual global human mortalities occurred in the past decade [2]. As a result, cancer treatment study and progress is desperately needed. Great sum of money and funds have been allocated into clinical cancer treatment study, especially in cancer diagnosis, prognosis and drug selection.

Treatment challenge for anticancer medicine

As cancer is a series of different disease (>200 cancer sub-types and thousands of related genes or molecules), cancer treatment will continue to be a leading area for medical science formation and drug development. Since cancer pathogenic traits and drug responses vary greatly in stages of somatic mutation, DNA methylation, translocation, copy number alteration, gene express, molecular profiling, cellular aberrations and multi-stage of metastatic cascade in the clinic [3,4], several types of individualized cancer therapy (personalized oncology or precision medicine PO/PM) were developed for achieving maximum drug responses in the clinic [5-8].

Personalized Oncology

Historical overviews

Cancer treatment has been experiencing massive changes in the past 6 decades. In the earliest (before 1970s), Paracea (one-size-fit-all modality, generally regarding as anti-proliferative agents) was the earliest treating goal. However, it was lately found that drug response greatly differs from patients and patients. To face with this dilemma, ideological and technical changes had been emerged in decade of 1970s. Figure 1 represents major personalized platform progress step by step; (Figure 1).

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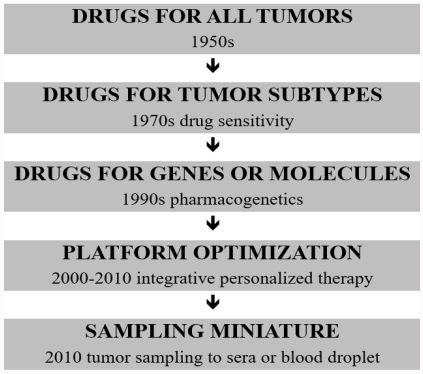

Figure 1: Drug and treatment progress timeline.

Figure 2: Progress of personalized oncology.

Table 1: Classification of current therapeutics.

Diagnostic classifications			
Genetics	Molecular	Multi-omics	Phenotypic features
Human mortality & therapeutic challenge			
Heterogeneity	Immune-regulatory	Drug resistance	Metastasis
Personalized oncology			
Biology	Drug sensitivity	Pharmacogenetics	Drug combination
Drug related problems			
Side-effects	Off-targets	Dose-related	Selection

The pathway of cancer treatment evolution is very long. At the beginning, anticancer drugs were expected to treat and cure all cancer patients. However, therapeutic benefits and outcomes were very limited by this way of therapeutic convention. Lately, it was generally accepted that anticancer drugs were active to different tumor subtypes, or even different patients with same tumor subtype. Entering into 1970s, drug sensitivity testing was translated into clinical trials (optimized drug selection and decision-making) [9].

Same period of Human Genome Project (HGP), US in 1990s, the pharmacogenetic or pharmacogenomic system was partly maturity in clinical drug selection and dosing in industry countries. The clinical pharmacogenetics utility means the popularity of personalized strategies clinically and worldwide.

Lately, the integrative strategy of personalized oncology was proposed before 2010s [5]. During 2010s and 2020s, different personalized cancer therapies, PO or PM were flourishing in clinical settings (Figure 2).

Scenario of current cancer treatment

Cancer treatment to date has a great number of limitations (Table 1). 70% to 90% human cancer mortality rate happens in patients with metastatic cancer. Advance-stage of cancer pathogenesis and internal/external risk factors are attributed for heterogeneity of cancer cells. Thus, the generation of personalized strategies or drug combination to overcome these limitations is a promising decision.

Table 2: The different terms from similarity and timelines.

Prefix evolution	Main context
Individualized (70s)	Cancer therapy, chemotherapy, drug therapy
Personalized (90s)	Cancer therapy, medicine, oncology
Precision (2000s)	Medicine, oncology

Current “well-known” clinical strategies

To make a great difference for PO or PM in clinical cancer trials, well adapted techniques supporting personalized strategies (powerful, multi-functional and computerized system) are required. Several popular disciplines and platforms are introduced.

Drug Sensitivity Test (DST) [9-14], tumor biomarker or multi-omics profiling [15-22], Pharmacogenetics (PG) [23-25], genomic, or RNA sequencing (precision oncology) [26,27]. Individualized metastatic therapy [28], cancer assistant therapy [29], patient’s decision aids [30,31] and others [32-34] were emerged from past applications. Some of them, like DST exist more than six decades worldwide.

Terminology similarity, overlapping and evolution

Due to long duration of technology and disciplinary evolution, the terminology for clinical disciplines experienced general changes. Many new researchers think ‘precision oncology’ is a brand-new approach announced by American President (approximately one decade) that is associated with congress bill allotment in US. However, the terminology is a character and disciplines from same medical meaning lasted for 50 years. In current research and review articles, you may see a lot of different terminologies. Indeed, they come from same medical meaning and pharmaceutical system. Different terminology in articles by different authors derives from medical customs, personal favorability and interests of politics. Table 2 shows part of their relations (Table 2).

Medical relation

Until now, no single drug or therapy can fit for all cancer (one-size-fit-all). Drug selections and combinations are therapeutic strategies for different medical approaches all over the world. From this point of view, personalized strategies shall have greater potentiality in the future. To accomplish this therapeutic modality, technology and knowledge updating should be attempted and performed continually in clinical trials. Detail information will be given in the followings.

Different Systems

Drug sensitivity testing

DST is to testify drug response to tumor by *in vivo* or *in vitro* methodology [11]. However, only less than 25% to 30% clinical therapeutic data reported any survival benefits in a statistically significant manner by tumor mass observation. In most clinical cases, patients’ survival is almost the same as without DST [9]. Moreover, this kind of survival elongations (the positive groups) is only several week or month benefits. Long-term disease control in cancer patients (achieving 80% to 90% of cancer patient’s survival elongation) for more than 5 years is not achieved successfully. Seeking solution from new technology and pharmaceutical areas is the main options in future [11-14]. To do that, technique innovation for drug sensitivity testing should be promoted.

Biomarkers or multi-omics profiling

Bioinformatics is a well-known diagnostic approach that

provides a variety of information for oncogenic progress in DNA, RNA, protein and glycol-ligand profiling and levels (multi-omics) in human plasma or tumor tissues and drug responses [15-22].

Past, the best example of cancer biomarkers in practical uses was the escalation of cancer biomarkers or antigens in human blood. Diagnostic routines for approximately 10 biomarkers are available in a lot of high-tier hospitals worldwide. However, it is not necessity to drug selection in the past. Anticancer drug activity is not parallel with oncology progress in algebra ways. Exponential, statistics, iterative, data regression, toxicological correlation must be studied for treatment benefits [19]. Since the pharmacological potency of anticancer drug is more complicated than current formats of precision oncology, new techniques or mathematical tools should be invented. Only through collective analysis and knowledge from Patho-therapeutic relation, beneficial and undesired side-effect ratio can be controlled. In depth diagnostic and therapeutic system is correlated worldwide.

Pharmacogenetics (PG) for cancer therapy

PG in cancer treatment has been entering into bottleneck. Present PG in cancer therapy mostly predicts the fraction of active or inactive metabolites by referring enzymes of human beings (single nucleotide polymorphism or Single Nucleotide Variation–SNP or SNV–same meaning) [23-25]. Currently, PG platform is advantageous in drug dosing rather than drug selection from a large number of different anticancer drugs [24].

Overall, PG application (microarray or SNPs) at this stage is an effort to optimize drug doses in individual patients. Yet, the data or application of narrow-range or wide-range of human key genes is also changed from patient to patient. The ratio of activity and toxicity for drug combinations can be superseded further, including broaden technique into drug selection or combination in the future.

Genome and RNA sequence

Gene expression and transcript sequencing changes are the main driving forces of oncogenic progress, metastasis and drug resistance in cancers. Novel and advanced systems at this discipline should be aimed to unveil these abnormalities and aberrations. These platforms of personalized medicine are widely named as precision oncology. The techniques of genomic or RNA sequencing developed quickly over the past two decades. It was based on the emergency and maturity of Next Generation Sequencing (NGS) [35,36]. The speed of gene sequencing increases 10,000 to 500,000 times than sequencing techniques of 1990-2000 (Human Genome Project). This discipline of drug selection is one of the fastest developing areas in personalized strategies nowadays.

Individualized metastatic therapy

A large proportion of cancer mortality (90%) is caused by neoplasm metastasis in the clinic [36-39]. Neoplasm metastasis is a complex and evolving course in the clinic (metastatic cascade). Pathways and stages are clarified for therapeutic benefiting. Certainly, some tumor spread modes and biology (seed and soil hypothesis, metastatic cascades and lymphatic metastasis) may be targeted by different types of anticancer drugs. However, DST, PG, biomarkers and precision oncology are commonly deficit in knowledge of metastasis treatment [40]. Current antimetastatic treatment is greatly unsatisfied in the clinic. New techniques and personalized strategies can improve therapeutics against metastatic tumors.

Since cancer metastasis plays a key role for cancer patient deaths,

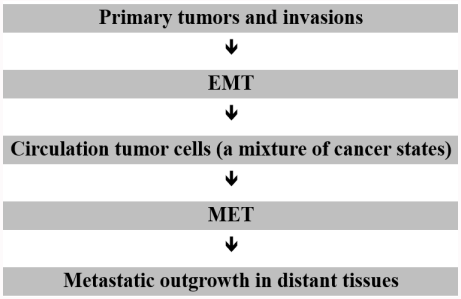

Figure 3: Key processes of metastatic cascade at pathological stage.

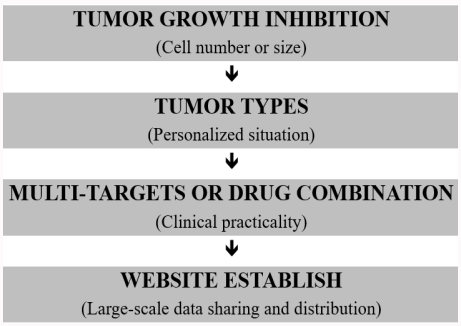

Figure 4: Flowchart of anticancer drug and treatment progress.

it is reasonable to focus on metastatic treatment study. Individualized metastatic therapy should be designed for therapeutic progression and save the life of millions every year [28]. Figure 3 show cancer biology in different stages of metastatic cascade. The stage of metastatic cascade should be personally targeted (Figure 3).

There is an opposite biological pathways and mechanisms between primary tumor and metastatic lodging at secondary sites [39,41]. How to counteract this neoplasm plasticity should to be worked out. As a result, effective antimetastatic drug and diagnostic variability should be promoted. By the discoveries of new drugs and diagnostics, cancer patients with noticeable metastatic tumors can be successfully treated.

New Frontiers

Useful avenues

In our point of view, current personalized disciplines are at early stage. Novel personalized systems should be promoted. We introduce them as below.

1. Merge the advantageous characters of different personalized strategies and techniques (such as biomarkers + DST–both oncology and pharmacology);

2. Popularize cancer diagnostic or therapeutic decision-making through computers or Artificial Intelligence (AI).

3. Anticancer drugs or therapeutics commonly have a lot of adverse side-effects, drug resistance and stem states. Negative side of therapy (therapeutic toxicity, resistance and stem states) should be revealed in personalized medicine [42,43].

4. Cooperate and dialogue with cancer patients [29,30].

Drug combinations

Most cancers have multitude of genetic alterations and molecular

Table 3: The associations between techniques and biological suitability.

Major strategy	DNA+RNA	Macromolecules	Drug Response
Microfluidics	√	√	+++
Microarray	++	+	√
SNP or SNV	++	++	+
Next-generation sequencing	+++	+	√
Single-cell	++	+++	√
Liquid biomarkers	+	+++	√
RNA-sequence	++	+	√
Metastasis	√	++	++
Immune repertoire	++	+	++
Drug combinations	+	+	++
Hormonal/assistant	√	++	++

Symbolic meaning: +: Some suitability; ++: Good suitability; +++: Excellent suitability; √: Needs future improvement

abnormalities, especially for late-stage cancer patients. Drug combination can more or less improve this matter [44-47]. However, it also needs to be specifically tailored for different cancer patients. How to combine and select anticancer drugs is an emerging problem and knowledge for anticancer drug therapy study and application in different clinical situations.

Several approaches can be used to optimize drug combination;

1. Randomized testing and comparisons of anticancer drug combination efficacy in experiments and clinics [45-47]

2. Combination of drugs of different targets and mechanisms of action

3. Combination of chemotherapeutic drugs and bioagents [48]

Due to a great number of anticancer drugs (180-200 worldwide, anticancer drug combination could have huge number of possibilities of drug selection [45]. Personalized medicine can provide such drug selection techniques and matched drug therapeutic to different patients. This project of drug selection study has a bright future.

Patient's decision

Therapeutic decision in the future will not only come from doctors, patient's desires are also important. In order to comfort cancer patients and improve therapeutic outcomes, decision aids systems will be helpful in clinical cancer trials [30,31]. By providing decision aids service, cancer patients are able to decide drugs or therapeutics from their own-desire and financial conditions. Future personalized paradigms and strategies need feedbacks from patients.

Therapeutic activity and toxicology balancing

Patient's survival benefits are not only determined by drug response to cancer, but also influenced by drug toxicity. Drug toxicology (metabolism enzymes, immune-suppression, cardiovascular and others) plays key roles for patient's treatment (survival benefits). Pharmacological tests of therapeutic complication and toxicity is the key for patient's health and mortality. Drug underlying mechanisms (genetic- or molecular loops, circuits, axis or cascades) in patients lead to different therapeutic machinery and toxicology. Novel PO or PM systems of personalized paradigms will target this complexity of cancer pathophysiology and drug selection in clinical treatment. New technology is waiting for assisting therapeutic breakthroughs. Advanced techniques matter a lot in this area.

Technical advances

Among different types of therapeutic strategies, which type of personalized strategy is the best? This is a difficult question to answer. Each of them has its own advantages and disadvantage. At present no one type of personalized strategies is obviously advantageous over the rest of clinical strategies. In addition, no available personalized strategy is well enough to significantly increase the patient's survivals based on larger human population. So, we desperately need some dramatic moves to create reliable, matured, safe, affordable, multi-functional personalized strategies–integrating the advantages of most personalized types and techniques [5]. There isa long way to go, yet main obstacles (low survival benefits for advanced-staged cancer patients) should be finally overcome.

Current state of cancer treatments is far from our requirements–greatly elongation of cancer patient's survivals (high rate of 5-year survivals for advanced-stage of cancer patients). Facing with this difficult, improvement of personalized disciple or techniques is inevitable. To attain this goal, comparison and merge of existent discipline is the top priority.

In order to improve available personalized strategies, new round of experimental/clinical campaign for future personalized approaches will be carried out. Presently, anticancer drug development is more suitable for human leukemia treatment and less effective to solid human tumors, especially to late-staged cancer patients. In the future, more complex forms of PO will be developed for cancer patients with solid tumors (Figure 4).

Technical Challenge

Idea and technique novelty

The most obvious drawback of current personalized strategies is that almost no survival benefits in patients with noticeable metastatic nodules in spite of DST, PG and other item utilities [35-40]. But it can be a future paradigm if we adhere ideology of technical merge [48-50]. Let's review the key issue of technical merge, analysis and invention (Table 3, 4).

In the earliest, we proposed that integrated personalized systems would be a future trend [5]. After more than decade reflection, we reiterate our past argument with new twist and turn in detail information analysis and statistics among different personalized medicine platforms and strategies.

Cellular or genetic diagnostic modality

Cancer is a disease of a great diversity of tumor genotypic or phenotypic properties [4]. Now cancer can be categorized into 13 distinct hallmarks [4]. The different types of anticancer drugs

Table 4: Technical cores of different personalized strategies.

ICT strategies	Core techniques
Drug sensitivity testing	Cell number, viability, miniature or organoids
Pharmacogenomics & sequencing	SNP, microarray, sequencing
Metastasis condition	Tomography, circulatory tumors
Bioinformatics	High-throughput techniques (multi-omics)
Immune	Genes, molecules, bioassay
Drug combinations	Pharmacological principle and existing theory
Hormonal/assistant therapy	Drug characters, cytokines

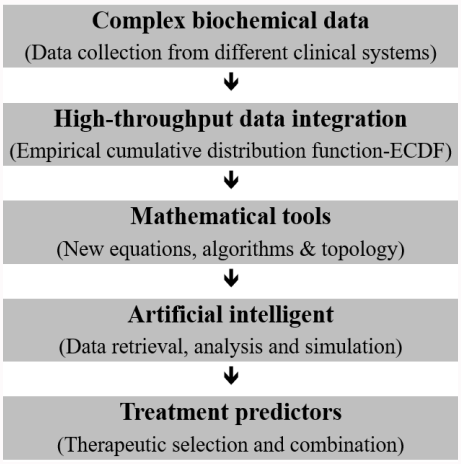

Figure 5: Computational systems for personalized therapeutic progresses.

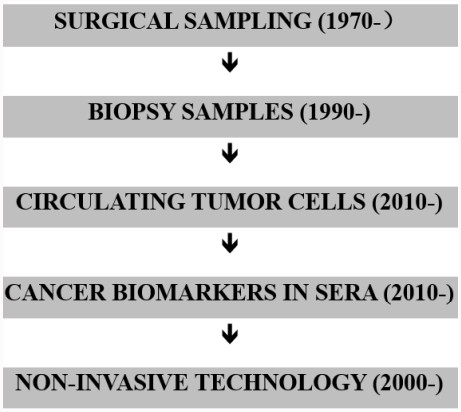

Figure 6: General utility of tumor samples for clinical uses.

or personalized modalities are selected or combined for targeting these different cancer phenotypes and hallmarks. It is proposed that different cancer hallmarks are suitable for different diagnostic modalities and therapeutic targets.

Table 3 & 4 show the cores of different types of diagnostic profiles for cancer in the clinic. From our early suggestion, integrated personalized strategy will be popular and can improve the responses and outcomes of clinical cancer treatment. Diverse biomedical techniques and biomarker profiles in personalized manner will be integrated and associated by computational or mathematical tools in long period of times. Groundbreaking medical discovery and clinical diagnosis will be led by clinical evidence and exploitation [48-50]. More than one decade ago, we proposed that integrated personalized strategies would be the key issue of personalized medicine advances [5], after more than one decade, we happy to see a sign of integrative prosperity worldwide [20,25,26].

Computational assistance

Future personalized strategies will be more complicated than ever before. Clinicians or mathematician can work together to assist personalized treatments [51,52]. The sharing and cooperation between biomedical scientists and mathematicians may improve clinical computational network easier to reach. To attain this goal, we can see the layout of computational tools and progress step by step worldwide [53-57] (Table 5 & Figure 5) This will be a global heating topic in the future.

Artificial intelligence in PM

Artificial Intelligence (AI) techniques has been applied to a lot of global hospitals [58]. This important cancer treatment trend must be noticed as early as possible. Since repetitive therapeutic work or variability of doctor's prescriptions will be superseded by computers, robots and other artificial intelligence technology. Don't miss this opportunity in the future. However, no well-received system has been widely used in personalized medicine. Itis still a modern challenge and opportunity worldwide. With the awareness of more countries, these kinds technical popularity will be received.

Patient's participation

Cooperation and dialogues between doctors and patients are worthwhile. In the future, cancer patient decisions will be based on an increasing and maturity of medical knowledge for cancer patients in general and indispensable. The bond between doctors and patients may bring new hope for rapid medical development in cancer treatment.

System miniature

Tumor cells provide rich information for the therapeutics. The size of tumor samples will determine the quality of personalized medicine. In the earliest, surgical sample was the only source of tumor sampling and profiling. With the technical progress, biopsy tumor sample can also be used as tumor resources of personalized medicine. More recently, circulation tumor cells (liquid tumors) are frequently used in the clinic [59-64]. Figure 6 provides this progress and sample miniature; At the end, no tumor sample is needed *via* the advent of proper non-invasive tumor observation and diagnostic systems. This process will reduce the burden for cancer patients (Figure 6).

Future Approaches

System promotion

Tumor is a complex ecosystem that can evolve with heterogeneity and drug resistance [65,66]. Only more integrative personalized strategies can solve this drawback. The advance for PM is not well enough to counteract with them. A great deal of new progress will be pursuit. Thus, we may design some smarter strategies for the sake of cancer treatment promotion. Platform diversity and integration may be used to smaller tumor sampling in drug response prediction. Of course, cost burden is also considered.

Technical maturity and merge

The personalized strategies in the future will contain information of both oncology and pharmacology. Thus, the future strategy of personalized medicine must at least contain a process of drug response (pharmacology), tumor pathophysiologic feature (oncology), therapeutic toxicology (toxicity and resistance) and others (patient's desire and insurance status). In the future, cancer diagnosis and treatment will be faster and precision.

To conclude, more dramatic technical innovations or merge will be developed in the following study. Among these trends, computational network, patient's decision aids and artificial intelligence must be integrated into one system. Reliable, high-resolution, safer, versatility, multi-functional and lower cost personalized strategies will be developed. Integrations of oncology-pharmacologic-toxicology combined framework will be a reasonable way in the future (Figure 7).

Table 5: Layout for computational network and AI system in the future.

System buildup stages	Mathematical methodology
Descriptive statistics	Complex data stoichiometry
Inferential statistics and description	Iterative, matrix, logic & mechanistic
Mode building	Methods & equation
New equation and computations	Theorem setup & selection
Artificial intelligence	Association with computers

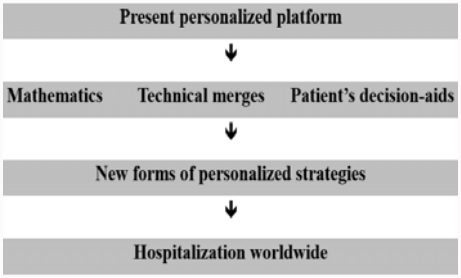

Figure 7: General outlooks of personalized strategy developments in the future.

Development of targeted drugs

Personalized medicine progress needs high effective anticancer and antimetastatic drugs. Drug targets and evaluative systems should be updated constantly [67-72]. Without effective drugs, the drug selection and treatment will be meaningless. Drug development and licensing also affect the quality of personalized medicine. A wider vision is important.

Conclusion

Anticancer treatment in the clinic is a difficult job for improving, especially survival benefits. By updating relevant technologies, it can certainly improve cancer therapy a great deal. Deep understand cancer pathophysiology, therapeutic modes and technical innovation will be the driving-force for treatment perfection.

In summary, we look forward to some powerful classes of personalized strategies from bench (laboratory) to the bedside (hospitals). From our perspective of personalized strategies, integration, mathematical and patient's participation is the worthwhile solution as we can see until now.

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