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Advancements and Challenges in Precision Oncology: A Comprehensive Review

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ABSTRACT:

Precision oncology, characterized by personalized cancer treatment based on individual genetic profiles, has transformed the landscape of cancer therapy. This review article examines the latest developments and challenges in precision oncology, focusing on biomarkers, targeted therapies, and adoptive cell therapy. Insights from clinical trials and collaborative research efforts provide a comprehensive overview of the field's progress. Despite notable advancements, obstacles such as interpreting complex genomic data and ensuring equitable access to targeted therapies persist. Future perspectives highlight the potential of precision oncology to continue improving patient outcomes through innovative approaches and collaborative initiatives.

Keywords: Precision oncology, biomarkers, targeted therapy, adoptive cell therapy, clinical trials, genomic profiling, personalized medicine

Introduction:

Precision medicine in oncology represents a paradigm shift in cancer treatment, moving away from traditional one-size-fits-all approaches towards tailored therapies based on individual genetic profiles. Biomarkers such as tumor mutational burden (TMB), mismatch repair gene defects, and microsatellite instability (MSI) have emerged as crucial predictors of response to treatment, particularly checkpoint inhibitors. By understanding the genetic makeup of tumors, clinicians can select therapies that are more likely to be effective, leading to improved outcomes and better patient care.

The use of precision oncology began with the introduction of imatinib as a treatment for newly diagnosed Philadelphia-chromosome-positive chronic myeloid leukemia. , since then, it has evolved to include the development of novel therapeutic agents that target biological abnormalities associated with cancer growth, and more recently, immunotherapy.

Over the past fifteen years, there has been notable advancement in the field, resulting in a variety of drugs being developed through molecular profiling. As of February 2023, the FDA has approved 155 companion diagnostic devices for targeted drugs intended for patients with solid tumors and hematologic malignancies.

There have been many clinical trials in precision oncology that resulted in a better treatment for cancer patients. Developments in molecular technologies and targeted therapeutics have accelerated the implementation of precision oncology, leading to better clinical outcomes in selected patients.

The clinical trials in precision oncology continue to expand. For instance, the NCI is launching new studies that include ComboMATCH, MyeloMATCH, and iMATCH. The ComboMATCH study is a phase II trial that focuses on the investigation of targeted drug combinations, based on the gene signatures of specific cancers, in order to overcome drug resistance to single-agent therapy [76]. The primary objective of ComboMATCH is to overcome the drug resistance to single-agent therapy and to enhance the effectiveness by developing genomically directed combination therapies.

Although there is evidence indicating that precision oncology yields better results for certain types of tumors and diverse cancers, there are still some challenges. These include the lack of universal use of molecular testing and modern technological advances to thoroughly understand the evolution of carcinogenesis in individual patients, and the lack of patient access to therapeutic strategies that would lead to the regression of this process and the elimination of cancer.

Even though many therapies with biomarker selection are available (either FDA-approved or investigational through clinical trials), precision oncology is not accessible to all patients with cancer, and some patients' tumors do not respond to these treatments. This lack of response can be attributed to the biological complexity of some tumors, which cannot be targeted with a single therapy, the absence of an effective targeted therapy, or an unknown mechanism of tumor resistance to treatment.

Methodology:

A comprehensive research was conducted using Pubmed and Frontier, focusing on publications related to the evolving Precision medicine in cancer treatement . The research was limited to English-language publications. To ensure a thorough analysis, the list of references from all identified complete publications were also reviewed.

A total of 10 studies were included in the review , encompassing research conducted within the last 10 years

Findings:

Precision medicine in cancer aims for individualized, patient-centered trials based on biomarkers such as tumor mutational burden (TMB), mismatch repair gene defects, microsatellite instability. These biomarkers predict checkpoint inhibitor responsiveness and offer insights into a tumor's biological history, guiding therapy selection. Advances in precision medicine have identified biomarkers, traced biological pathways, and developed targeted therapies, driving progress in precision oncology. This systematic review explores basket trials, umbrella trials, platform trials, and clinical studies to demonstrate the intricacies and challenges of targeted therapy, alongside recent advances in precision medicine.

Body: trials/types of medicine, benefits, challenges

Biomarkers:

The field of oncology is based on the identifying and targetting biomarkers. The bulk of precision medicine is directed towards the target therapy, which is not possible without biomarker identification. Some of the numerous biomarkers used to predict checkpoint inhibitor responsiveness are tumor mutational burden (TMB), mismatch repair gene defects, microsatellite instability (MSI), PBRM1 molecular alterations, and PD-L1 amplification are among the biomarkers that are . Along with mismatch repair gene defects and high microsatellite instability, high TMB, in particular ≥20 mutations/mb, has shown promise in accurately predicting the benefit from checkpoint inhibitors. Patients who received immunotherapy had an improved overall survival rate when their TMB levels were elevated. Nevertheless, some research calls into question the precision of TMB as a biomarker as MSI-H is taking its place.

In clinical trials, longitudinal genomic sequencing aids in the identification of lineage-specific evolutionary processes that direct subsequent trials. Tumor mutations produce neo-antigens that improve immune system recognition and connect immune checkpoint inhibitor response to cancer mutability. The response to immune checkpoint inhibitors and the infiltration of lymphocytic tumors are correlated with phenotypic measures such as MSI and DNA mismatch repair efficiency.Together with genome-scale CRISPR-Cas9 screens, collaborative efforts employ data from the International Cancer Genome Consortium (ICGC) and the Cancer Genome Atlas (TCGA) to find novel genomic alterations that could be targets for combination therapies and drugs.

Targeted therapy:

Over the past fifteen years, there has been notable advancement in the field, resulting in a variety of drugs being developed through molecular profiling. Previous researches demonstrated that targeted therapies tailored to tumor molecular alterations improved outcomes and survival rate, hence making them the heart of research in precision oncology today. Patients receiving matched therapy showed higher overall response rates compared to those without matching, especially in patients with one molecular alteration. To validate these findings, a clinical trial was conducted with two-month landmark analyses that assessed survival or progression-free survival(PFS) correlation with response by therapy type (matched vs. unmatched therapy). Therapy was labeled "matched" if a drug in the trial could inhibit at least one of the patient's tumor aberrations; otherwise, it was "unmatched". The study utilized data from the current validation analysis and previously published series to enhance statistical power. These were phase I clinical trials that enrolled patients who had exhausted current therapies or had advanced cancers .

A study was conducted amongst a total of 1,276 patients. Among these, 534 patients with 1 targetable alteration out of which 143 patients were treated with matched therapy and 20 of them were also given cytotoxic agents. The remaining 236 patients were treated with non-matched therapy out of which 87 were also given cytotoxic agents.

Out of 318 patients receiving matched therapy, 219 were included in the 2-month PFS analysis. Patients with an objective response had a median PFS of 38.7 months, while those without had a median PFS of 5.9 months. On the other hand, 352 patients on non-matched therapy, 176 were in the 2-month PFS analysis. Patients with an objective response had a median PFS of 8.5 months, while those without had a median PFS of 4.2 months (P=0.18).

When matched therapy was administered to patients with one molecular abnormality instead of treatment without matching, the patients had longer life times, longer time-to-treatment failure(TTF) , and higher overall response rates. Comparing matched targeted therapy to earlier systemic therapy, longer TTF was also linked to it.

Furthermore, reductions in LDH levels were one of the independent variables associated with prolonged longevity, according to multivariate survival analysis. Two or fewer metastatic locations, normal albumin levels, and normal platelet counts were additional independent variables associated with prolonged life.

Furthermore, advances in matched therapy in precision medicine has helped in the production and approval of several therapeutic agents that specifically target a single biomarker which is the potential cause of any specific cancer. A variety of treatments all targetting various biomarkers are still undergoing clinical trials, but targeted therapy for two biomarkers have gained more traction in the two past decades:

- **Neurotrophic tyrosine receptor kinase** (**NTRK) fusion gene**:

NTRK fusion gene acts as an oncogenic trigger by initiating the proliferative pathway, which make them potential therapeutic targets NTRK fusion-positive cancers. Imatinib was one of the very first tyrosine kinase inhibitors (TKI) that underwent several clinical trials and recieved FDA approval in 2001.It was used to treat Philadelphia chromosome–positive chronic myeloid leukemia. Additionally in 2007, results were seen in the BATTLE program for lung cancer treatment with the use of TKI . Since then an increasing number of small-molecule targeted drugs have been developed for the treatment of malignancies. Larotrectinib is another TKI that provides positive outcomes in both adult and pediatric patients with advanced or metastatic solid tumors known to harbor NTRK gene fusions across a wide range of tumor types. A pivotal study of 55 patients with NTRK fusions treated with larotrectinib demonstrated a 75% overall response rate across various ages and tissue types. Data showed a 57% overall response rate with a median response duration of 10 months.

- **Checkoint inhibitor/ blockade:**

The checkpoint mutations are a method of weakening the immune response against the tumor cells, and preventing the T cells form destroying the tumor cell. The mechanism of checkpoint blockade leads to the activation of innate antitumor activity by enabling T cell mediated tumor destruction. This breakthorugh led to the first FDA approved immune checkpoint inhibitor therapy (ICI), CTLA-4 inhibitor (Ipilimumab), followed by PDL-1 inhibitors (Atezolimumab, Durvalumab and Avelumab), and PD-1 targeting agents(Nivolumab, Pembrolizumab, and Cemiplimab). Pembrolizumab and nivolumab were approved for advanced melanoma and later gained approval for multiple cancer types. Pembrolizumab received FDA approval for the treatment of adult and pediatric patients with unresectable or metastatic, MSI-High (MSI-H) or dMMR solid tumors , with tissue tumor mutation burden-high status, defined as ≥ 10 mutations/megabase, based on pooled analysis from five independent clinical trials. Unfortunately, the results vary between different individuals as some might not respond to the treatment. Since the promising results from the use of ICI several other approaches to innate antitumor activation have been explored: *adoptive cell therapy , cell-based products , modified cytokines , CD3-bispecific antibodies and oncolytic viruses. This approach still has a long way to go in the field of cancer therapy.*

A Multicenter Retrospective Real-World Cohort Study that was published in February 2023 , evaluated the efficacy and safety of immune checkpoint inhibitors (ICIs) and tyrosine kinase inhibitors (TKI) (ICI+TKI) in 51 patients with advanced or metastatic renal cell carcinoma (mRCC) who received ICI+TKI therapy at 9 Japanese institutions. The overall survival rates at 6, 12, and 18 months were 93.1, 82.5, and 68.8%, respectively. The median PFS for patients who received ICI+TKI was 19.0 months, objective response rate was 68.6%, and disease control rate was 88.2%. ICI+TKI-related adverse events occurred in 84.3% with any grade and in 43.1% with grade ≥3. Treatment selection with poor prognostic factors may be prudent, even though ICI+TKI is an efficacious and safe first-line treatment in patients with mRCC.

- **Adoptive cell therapy**:

These therapeutic agents lead to the stimulation of the immune system which intiates tumor cell killing. Various types of ACT include: chimeric antigen receptor (CAR) , tumor infiltrating lymphocyte (TIL) , T-cell therapy , engineered T-cell receptor (TCR) , and natural killer cell thrapy. (NK). An approach still in its early stages of clinical trials, but shows significant potential in the furture of precision medicine

As of February 2023, the FDA has approved 155 companion diagnostic devices for targeted drugs intended for patients with solid tumors and hematologic malignancies. The clinical trials in precision oncology continue to expand. For instance, the NCI is launching new studies that include ComboMATCH, MyeloMATCH, and iMATCH. The ComboMATCH study is a phase II trial that focuses on the investigation of targeted drug combinations, based on the gene signatures of specific cancers, in order to overcome drug resistance to single-agent therapy The primary objective of ComboMATCH is to overcome the drug resistance to single-agent therapy and to enhance the effectiveness by developing genomically directed combination therapies.

• The emerging “master protocol” frameworks have been proposed to provide a means of comprehensively and adaptively evaluating treatments from the field of oncology

Master protocols are often classified into “basket trials”, “umbrella trials”, and “platform trials”

Basket trials refer to trying a single drug in multiple types of cancer which are defined by: histology , diseases stage , number of prior therapies , genetic/ demographic data.

Umbrella trials, evaluate multiple targeted therapies for a single disease that is stratified into subgroups by molecular alternation.

Platform trials, also referred to as multi-arm, multi-stage (MAMS) design trials , are trials that evaluate several interventions against a common control group and can be perpetual . This design has pre-specified adaptation rules to allow dropping of ineffective intervention(s) and flexibility of adding new intervention(s) during the trial.

The ultimate goal of precision medicine is to have an individualized , patient-centered trial based on the best available biomarkers , rather than .

Activation of innate antitumor activity has evolved in treating tumors. Several approached have been explored: checkpoint blockade, adoptive cell therapy , cell-based products , modified cytokines , CD3-bispecific antibodies and oncolytic viruses.

a. The checkpoint are a method of weakening the immune response against the tumor cells , and preventing the t cells form destroying the tumor cell; thus blockage of these checkpoints renders the T cells stronger and damages the tumor cells.

These include: PD-1 inhibitors (Nivolumab, Pembrolizumab, and Cemiplimab), PDL-1 inhibitors (Atezolimumab, Durvalumab and Avelumab), and CTLA-4 inhibitor (Ipilimumab). Unfortunately, the results vary between different individuals as some might not respond to the treatment.

Several biomarkers are targeted towards predicting checkpoint inhibitor responsiveness such as tumor mutational burden (TMB) , mismatch repair gene defects , microsatellite instability , PBRM1 molecular alterations , PD-L1 amplification.

More specifically high TMB has shown accurate prediction in of the benefit from checkpoint inhibitors , thus resulting in mismatch repair gene defect and high microsatellite instability.

This was evidenced in the analysis of 151 of 1.638 patients being treated with immunotherapy , had a high TMB values (≥ 20mutations/mb).

The improvement of overall survival was evidenced in patients with elevated TMB in relation to other patients with low or intermediates TMB levels (reduced clinical responsiveness). However TMB accuracy as a biomarker is still questioned by other studies, and is replaced by microsatellite instability (MSI-H).

b. Adoptive cell therapy is an approach that stimulates the immune system leading to tumor cell killing. Various types of ACT include: chimeric antigen receptor (CAR) , tumor imfiltrating lymphocyte (TIL) , T-cell therapy , engineered T-cell receptor (TCR) , and natural killer cell thrapy. (NK)

The major challenges in precision medicine:

Failure to match patients is attributed to (i) enrollment of individuals with end-stage disease, who deteriorate or die early; (ii) use of small gene panels that yield limited actionable alterations; (iii) delays in receiving and interpreting genomic results; and (iv) difficulty accessing targeted therapy drugs and/or limited drug availability.

Moreover , implementation of precision medicine is often encountered by many challenges, the most common being: the need to screen large number of patients in order to find rare genomic defects , incomplete biologic / molecular profiles to select therapy , difference in the metabolism and adverse effects of study drugs in various ethnic groups , constant evolution in genomic landscapes , and lastly the lack of access to drugs for patients with limited resources.

Possible solutions:

Several initiatives might help overcome the challenges introduced by our emerging understanding of cancer biology: (i) molecular profiling (tissue, blood) should be used at the time of diagnosis and during the course of the disease, the latter to monitor response and resistance; (ii) completion of molecular profiling should be expedited; and (iii) bioinformatic analysis should be optimized to include the key drivers of carcinogenesis.

Chefaa :

When matched therapy was administered to patients with one molecular abnormality instead of treatment without matching, the patients had longer life times, longer time-to-treatment failure, and higher overall response rates. Comparing matched targeted therapy to earlier systemic therapy, longer TTF was also linked to it.

Reductions in LDH levels were one of the independent variables associated with prolonged longevity, according to multivariate survival analysis. Two or fewer metastatic locations, normal albumin levels, and normal platelet counts were additional independent variables associated with prolonged life.

Certain tumor types have fewer "targetable" abnormalities than others, such as colorectal cancer. Mutations were recognized to exist in thyroid cancer patients. The most prevalent modifiable molecular abnormalities were loss of PTEN, mutations in KRAS and PIK3CA, and BRAF.

Matched targeted treatment was associated with greater rates of response, TTF, and survival.

A fraction of patients with advanced malignancies that have received extensive pretreatment and react well to therapeutic targeting with PI3K/AKT/mTOR pathway inhibitors can be found by screening for PIK3CA mutations, PTEN aberrations, and MAPK mutations. Individuals with mutations in H1047R fared very well.

Precision oncology involves targeting abnormal cancer-causing proteins in a patient's tumor with specific anticancer drugs. The utilization of advanced sequencing techniques and analysis of biomarkers such as immune markers assist in selecting the most effective treatment for the patient.

Challenges

Navigating the complex pathophisiology and genetics of cancers and generating individual targetted therapies has evolved with the progress in precision medicine in cancer treatment, nevertheless we still have many obstacles to overcome.

We also face challenges in terms of both the population and trials themselves. These include several factors: difficulty screening large groups in order to find rare genomic defects, incomplete biologic/molecular profiles to select therapy, difference in the metabolism and adverse effects of study drugs in various ethnic groups, and constant evolution in genomic landscapes.

Moreover, the lack of universal use of molecular testing and modern technological advances to thoroughly understand the evolution of carcinogenesis in individual patients, and the enhanced multi-omic tools shifting from microarrays to single cell technology necessitates providing researchers/clinicians with robust tools to allow integration of old and new data in the genomic field have been identified as challenges.

While matched therapy guided by next-generation sequencing (NGS) holds promise, its widespread efficacy remains uncertain due to limited randomized trials. Challenges include selecting samples and targets, interpreting results, and ensuring drug accessibility. NGS technologies offer unbiased genome analysis, revealing numerous mutations, yet only a fraction can be effectively treated, along with the countless biomarkers that still remain unidentified the complexity of treatment still remians high. Although molecular entry criteria in clinical trials raise costs and complexities, Integrating NGS-identified biomarkers into standard cancer care optimizes therapy recommendations, emphasizing the need to balance tissue requirements, clinical value, cost, and efficiency in testing and treatment pathways.

Optimal testing for NTRK fusions remains undetermined, with various methods like NGS and immunohistochemistry used in clinical trials. While these approvals offer hope for rare cancers lacking alternative therapies and high NTRK fusion prevalence, they underscore the significance of molecularly targeted therapies and regulatory collaboration in novel clinical settings.

Another unresolved issue with matched therapy is the the failure to match patients which is attributed to (i) enrollment of individuals with end-stage disease, who deteriorate or die early; (ii) use of small gene panels that yield limited actionable alterations; (iii) delays in receiving and interpreting genomic results; and (iv) difficulty accessing targeted therapy drugs and/or limited drug availability.

However, despite the availability of many therapies with biomarker selection (either FDA-approved or investigational through clinical trials), precision oncology is not accessible to all patients with cancer, and some patients' tumors do not respond to these treatments. This lack of response can be attributed to the biological complexity of some tumors, which cannot be targeted with a single therapy, the absence of an effective targeted therapy, or an unknown mechanism of tumor resistance to treatment.

Lastly, enthusiasm for novel targets must align with evidence from well-designed clinical trials and preclinical models. Molecular data backed up by robust data is crucial in forming clinical decisions and guiding future trials effectively.

Conclusion:

In conclusion, Cancer treatment is rapidly moving towards precision medicine based on genomic alterations. Matched therapy using next-generation sequencing (NGS) shows promise with potential benefits in progression-free survival (PFS) and overall survival (OS). Although early studies are positive, conclusive evidence is still awaited. Ongoing research and technological advancements are crucial for unlocking precision oncology's full potential in diverse cancer types and stages. Despite challenges, genomic-driven therapy marks a paradigm shift in cancer care, holding the potential to revolutionize treatment strategies in the future.

Future Perspectives:

The future of precision oncology holds promise for continued advancements in biomarker discovery, targeted therapy development, and immune-based approaches. With ongoing research and technological innovations, precision medicine has the potential to revolutionize cancer care and improve outcomes for patients worldwide. By addressing challenges such as drug accessibility and interpretation of genomic data, the field of precision oncology can continue to evolve and positively impact the lives of cancer patients.

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