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Precision Oncology: Targeted Therapies for Cancer

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ABSTRACT

A paradigm change in cancer therapy, precision oncology tailors treatments to a patient's tumor's genetic features. Precision oncology tackles cancer-causing genetic abnormalities, unlike standard therapies. This review examines the history, biological foundation, and kinds of targeted medicines that have become strong alternatives to traditional treatments. Clinical uses have changed due to genetic profiling and medication development, including monoclonal antibodies and small molecule inhibitors. Although progress has been achieved, accessibility, medicine resistance, and data integration remain issues. Precision oncology would use AI, enhance immunotherapy choices, and address socioeconomic constraints.

Keywords: Precision oncology, Targeted therapies, Genetic mutations, Molecular profiling, Monoclonal antibodies.

INTRODUCTION

Precision oncology is a revolutionary approach to cancer care that offers personalized, effective, and less toxic treatments. Traditional methods have limitations, and increasing doses of therapies is often insufficient. However, targeted therapies have emerged as a promising solution, as they are able to address specific genetic mutations. Precision oncology tailors treatment options based on individual molecular alterations, including base substitutions, insertions/deletions, and gene fusions. This approach improves outcomes by selecting effective treatments or determining the non-suitability of certain therapies [1]. Early efforts in precision oncology can be traced back to the late 1970s, with two main approaches: the 'hormonal-targeted' approach for hormone-responsive breast and prostate cancer, and the 'biochemical-targeted' approach for high-dose methotrexate in tumors with impaired dihydrofolate reductases. These approaches were validated through tests and randomization. The success of hormonal treatments sparked interest in developing similar approaches for other tumor types. In the 1990s, precision oncology focused on oncodriver mutations and translocation events, leading to targeted therapies such as imatinib, gefitinib, lapatinib, and crizotinib. Two additional paradigms have emerged: exploring tumor molecular profiles for actionable alterations, and using immunotherapy to inhibit immune checkpoints across all tumor types [2].

DEFINITION AND CONCEPT

Precision oncology is a patient-centered approach to cancer therapy that targets specific characteristics of an individual patient's disease. It aims to discover actionable genetic alterations in a patient's tumor and provide medications or recommend clinical trials that would target or leverage that alteration. The term has been widely adopted by the scientific community and has raised issues beyond science, including the definition of key terms and the implications of commercialization. Precision oncology emphasizes disruption, innovation, and collaboration between scientists, bio-pharmaceutical corporations, venture capitalists, entrepreneurs, and patients. It relies on computational interpretation and data storage to inform behavioral responses, such as the uptake of precision medicine and DNA profiling risk-reduction. Precision oncology focuses on creating bio-data banks with tissue samples and clinical treatment data [3].

HISTORICAL DEVELOPMENT

Precision oncology has evolved from key discoveries, advancements in testing technologies, and significant milestones. The Philadelphia chromosome and the identification of the first oncogene, RAS,

were crucial breakthroughs. Imatinib, a targeted therapy for CML, paved the way for precision medicine in treating various cancers. The advent of detection technologies like next-generation sequencing led to the identification of TP53 and other cancer genes. This enabled the development of targeted therapies against mutant forms of RAS, BRAF, EGFR, and others. The molecular-guided paradigm was formed through validation of mutations as drug targets. Precision oncology is the result of collaborative efforts in basic research, pharmaceuticals, and clinical practice. Keeping up with the rapidly evolving field is challenging, but the focus will be on the historical first branch and its lessons for other branches [4].

MOLECULAR BASIS OF CANCER

Cancer is a genetic disease that arises from acquired mutations in somatic cells. In the human genome, there are 20,000-25,000 protein coding genes supported by a large transcriptional regulatory network comprised of other RNA genes and promoter regulatory elements. Owing to very high fidelity in DNA replication, the overall mutation rate is estimated as 1-2 mutations per cell division. This low germline mutation rate translates to ~70 new mutations in any progeny human lymphocytes, on average [5]. Cancer-causing somatic mutations can be acquired at high rates through mechanisms such as faulty DNA replication, error-checking, repair, cell death, and genome restructuring. Different cancer subtypes have unique mutation spectrums, with some mutations occurring at higher rates than expected. Alterations can be categorized as base substitutions, deletions, insertions, copy number variations, or chromosome structure aberrations. Activation of oncogenes, DNA repair abolishment, and aberrant signal transduction often converge on the Ras pathway. Additional mutations increase tumor aggressiveness. Telomerase activation occurs after supporting alterations. Drugs targeting Ras oncogenes are in clinical trials, and more may be developed for other common mutations in various cancer types [6].

GENETIC MUTATIONS IN CANCER

Cancer is a genetic disease caused by changes in cell genomes. These mutations can be inherited or occur after conception as somatic mutations. They can involve changes in DNA sequence, copy number alterations, or structural rearrangements of chromosomes. Mutations can range from small changes to large deletions or rearrangements. They occur through replicative errors or DNA damage with improper repair. Cells constantly face risks that can damage their genetic material from internal and environmental factors [7].

PRINCIPLES OF TARGETED THERAPIES

Practically all therapies developed for cancer are based on the understanding of the disease's fundamentals - either biology or genetics. Chemotherapies and similarly acting anti-cancer agents are developed to hinder DNA replication and/or to damage DNA itself by binding to it and/or metabolically controlling damage repair mechanisms. Old anti-cancer drugs were designed, for instance, to mimic nucleotides and thus interfere with the replication taking place on DNA. However, any unwanted damage to the genome can lead to defects eventually causing diseases, including but not limited to diabetes, heart diseases, and cancer. In turn, new drugs are developed based on understanding the signaling pathways leading to elevated proliferation and viability [8]. Drugs target proteins involved in aberrantly active signaling pathways. Monoclonal antibodies can target extracellular receptors activated on tumors, such as epidermal growth factor receptors or hyperactive FGFR2, mutant p53, and Ras proteins. Fusion proteins also target aberrantly activated growth factor receptors. Drugs can inhibit soluble extracellular signal molecules. Herceptin (Trastuzumab) is a monoclonal antibody designed to block extracellular signaling on Her2 positivity. Monoclonal antibodies can target invading tumor-promoting signals from the developing vasculature or proteolytic activity on the tumoral extracellular matrix. Antisense oligonucleotides or RNA interference can interfere with the expression of cancer-causing proteins. Targeted therapies for cancer mainly focus on kinases but can target any disease-causing proteins, especially when combined with cytotoxic drugs. Anti-cancer agents are being explored for newly detected cancers, and there is a search for histo-pathological tests to guide targeted therapy. "Cocktail therapies" against common mutated signaling pathways may become more prevalent [9].

TYPES OF TARGETED THERAPIES

Targeted therapies control cancer growth by specifically targeting and inhibiting the signals that promote cancer cell proliferation. This approach is facilitated through the utilization of small molecules such as BCR-ABL, which directly interact with and modulate genes involved in tumor development and progression. Additionally, monoclonal antibodies like trastuzumab have the capacity to selectively bind to specific proteins, thereby inhibiting their function and impeding the growth of cancer cells. These targeted therapies have presented notable advancements in the field of oncology, introducing groundbreaking treatment options for patients. Examples of these significant therapies include rituximab, bevacizumab, panitumumab, and cetuximab, each of which offer precise and exceptionally effective treatment opportunities in the fight against cancer. Through the implementation of these targeted

therapies, medical professionals have managed to revolutionize cancer treatment, granting individuals optimal care that greatly improves their prognosis and overall quality of life [10].

CLINICAL APPLICATIONS OF PRECISION ONCOLOGY

Precision oncology has made a significant impact on the cancer treatment landscape over the past two decades. Earlier, clinicians had limited options for cancer care, usually relying on general approaches like chemotherapy or radiation for all patients across indications. With advancements in precision medicine, tumor molecular profiling has enabled the selection of targeted therapies, offering newer approaches and improved clinical outcomes. Combining these targeted agents with either older approaches or newer drugs surpassing the early therapeutic window has emerged as a research field with powerful molecular agents, holding immense promise. Machine learning and artificial intelligence are promising tools that can provide patient-specific "omic" input data to address nuances of tumors and patients [11]. In recent years, immune checkpoint inhibitors targeting the PD-1:PD-L1 axis revealed a new immune evasion mechanism used by tumors. Tumors exploit immunosuppressive mechanisms seen in chronic inflammation, injury, or infection to escape immune detection. Monoclonal antibodies were developed to block these molecules, leading to a breakthrough in cancer treatment. These antibodies were approved by the FDA as monotherapy and were also combined with other treatments. The identification of HLA-restricted tumor-specific neopeptides, resulting from tumor genome mutation and transcriptomic processing, is an exciting development. Chemo- or radiation-induced damage increased the presence of immunogenic/HLA-epitopes, promoting the infiltration of antitumor cytotoxic T-cells. Precision oncology has reached a steady state, allowing for future developments in target discovery, input data, and algorithms. Precision oncology can be expanded to various fields with actionable alterations in tumors. Key issues and challenges, such as cancer-proofing genomes, preventing drug resistance, heterogenic models, and big data, are also addressed [12-16].

CASE STUDIES

As cancer genomics continues to make significant strides in scientific research, the University of Utah's esteemed cancer center is dedicated to expanding and amplifying its already robust capabilities in the field of melanoma research. Recognizing the critical importance of this work, they remain steadfast in their commitment to investing in necessary infrastructure enhancements, utilizing cutting-edge gene selection techniques, and fostering collaboration with key stakeholders from diverse backgrounds and expertise. By pursuing these strategic avenues, the University of Utah's cancer center is actively propelling advancements in precision oncology, which in turn brings us one step closer to the ultimate triumph over the challenging adversary that is melanoma [13].

CHALLENGES AND FUTURE DIRECTIONS

Precision oncology has made significant advances over the past decade, resulting in the approval of numerous targeted agents and their integration into standard oncology practice. However, challenges remain in the implementation of precision oncology, patient access, and drug development pace, and the potential risks of overpromising and underdelivering are significant. Furthermore, issues of access and equity cannot be solved by scientific efforts alone; greater involvement from civic and governmental leaders is essential. Ongoing efforts to identify and implement the best knowledge translation models to support equitable patient access should be continued and ramped up globally. Medical science is undergoing an unprecedented transformation, and the long excitement of the dawn of precision medicine must now be tempered with pragmatism [14]. Big data and biomedical knowledge are disrupting and advancing various fields, including biomedicine. They have revolutionized our understanding of disease at the molecular level, drug discovery, and human physiology. Next-generation sequencing technology is generating vast genomic data that can be used to create individual tumor portraits. These portraits help categorize patients into treatment groups for investigational drugs. Precision medicine in cancer has had success with targeted therapies, but there are challenges in implementing computational and data-driven approaches. Success stories have come from discovering "simple targets" that can counteract single gene aberrations, finding secondary therapies to combat drug resistance, and obtaining regulatory approvals for therapeutic agents [15-18].

CONCLUSION

Precision oncology is revolutionizing cancer treatment by focusing on personalized approaches based on the molecular characteristics of each patient's tumor. Targeted therapies, such as small molecules and monoclonal antibodies, have shown promise in controlling cancer growth more effectively and with fewer side effects than traditional treatments. Despite the success, challenges such as drug resistance, equitable access, and integration of big data remain critical hurdles. Moving forward, further advancements in genomic technologies, artificial intelligence, and immunotherapy will be essential to enhance treatment

outcomes and ensure broader access to precision medicine, particularly in underrepresented patient populations.

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