ISSN: 3066-8123
Review Article

Science Set Journal of Cancer Research

Pancreatic Cancer: Review on Advancements, Precision Therapies, and Beyond

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Submitted: 26 December 2023 **Accepted:** 04 January 2024 **Published:** 12 January 2024

https://doi.org/10.63620/MKSSJCR.2024.1007

Citation: *Carlos A Cardenas, Shabnam Abrishami, and Jose Javier Bravo (2024) Pancreatic Cancer: Review on Advancements, Precision Therapies, and Beyond. Sci Set J of Cancer Res, 3(1), 01-06.*

Abstract

This review article provides a comprehensive analysis of the current state of pancreatic cancer research, with a focus on recent advancements in early detection and treatment strategies. Pancreatic cancer presents unique challenges due to late-stage diagnoses and limited treatment options, making it imperative to thoroughly examine the ongoing efforts aimed at improving outcomes for affected individuals. Early Detection of Pancreatic Cancer: Although there are currently no established screening tests for early detection, several research initiatives are actively working towards identifying biomarkers and refining imaging techniques. This section explores the progress made in these studies and discusses their potential impact on diagnosing pancreatic cancer in its early stages. Pancreatic Cancer Treatment: This section addresses the complexities associated with pancreatic cancer treatment, including the challenges of surgical intervention and the conventional use of chemotherapy and radiation. In addition, it provides insights into the latest therapeutic approaches, such as novel drug combinations, neoadjuvant chemotherapy, cancer treatment vaccines, and the role of biomarker testing in treatment recommendations. Testing Treatments for Early-Stage and Advanced Pancreatic Cancer: This section outlines ongoing clinical trials investigating various early-stage and advanced pancreatic cancer therapies. It explores the potential of new adjuvant chemotherapy drug combinations, neoadjuvant chemotherapy, cancer treatment vaccines, immunotherapy, and targeted therapy. In particular, it examines specific drug targets, such as the experimental drug MRTX1133 for KRAS G12D mutations, and the exploration of Ras-directed therapies. Stroma-Modifying Drugs: A dedicated section discusses the significance of stroma-modifying drugs, specifically focusing on the dense stroma commonly found in pancreatic cancers. These drugs aim to break down or remodel the stroma, thereby improving the efficacy of chemotherapy drugs and overcoming resistance in cancer cells.

Clinical Trials and Research Programs: Highlighting the complex nature of pancreatic cancer, this section emphasizes the importance of clinical trials in advancing treatment options. It provides insights into various research programs, including collaborative efforts focused on pancreatic cancer detection, stromal reprogramming, and specialized programs of research excellence. Additionally, it explores initiatives aimed at understanding mutations in RAS genes to develop effective therapies. This review underscores the need for a multifaceted approach to address the challenges posed by pancreatic cancer. Ongoing research, clinical trials, and collaborative efforts hold great promise for significant advancements in understanding, detecting, and treating this complex disease.

Keywords: Pancreatic Cancer, Early Detection, Treatment Strategies, Clinical Trials, Research Programs, Stroma-Modifying Drugs, RAS Mutations

Introduction

Pancreatic cancer poses significant challenges in the field of oncology, characterized by its late-stage diagnosis and limited treatment options. This review aims to explore recent advancements in the understanding and treatment of pancreatic cancer. Given the multifaceted nature of this disease, it is crucial to thoroughly examine efforts focused on early detection and evolving therapeutic strategies. The urgency of early detection is underscored by the absence of established screening tests. Recent research has recognized the link between new-onset diabetes and pancreatic cancer, the incidence of diabetes in individuals diagnosed with pancreatic cancer was 38.1%, with 42.7% devel-

oping new-onset diabetes mellitus (NODM). Among the remaining 57.3%, who had pre-existing diabetes, a significant majority (90%) had uncontrolled diabetes [1].

As a result, efforts are underway to develop a blood test that can identify individuals at risk [2]. Additionally, the development of improved imaging techniques and the exploration of blood tests for early detection in the general population are being pursued [2]. Pancreatic cancer treatment presents several challenges, primarily due to the location of the organ and late-stage diagnoses. Standard treatments, including surgery, chemotherapy, and radiation, form the cornerstone of treatment. However, the complexities associated with surgical intervention necessitate a thorough understanding of the disease. Personalized treatment approaches, such as biomarker testing and genetic analysis, are recommended to enhance treatment efficacy [3].

Significant advancements have been made in testing treatments for both early-stage and advanced pancreatic cancer. Clinical trials investigating new adjuvant chemotherapy drug combinations, neoadjuvant chemotherapy, and cancer treatment vaccines are underway. Notably, immunotherapy and targeted therapy have shown promise as potential avenues for treatment [4]. Specific drugs targeting common mutations, such as KRAS G12D, and immunotherapies like pembrolizumab, are being examined for their potential in advanced pancreatic cancer [5].

The dense stroma in pancreatic cancers poses a significant barrier to treatment efficacy. To address this challenge, researchers are exploring the use of stroma-modifying drugs [6]. These agents aim to remodel the stroma and enhance drug penetration, offering potential solutions to improve treatment outcomes [6]. Clinical trials play a critical role in advancing pancreatic cancer treatment. Collaborative efforts, such as the Pancreatic Cancer Cohort Consortium, Pancreatic Cancer Detection Consortium, Pancreatic Ductal Adenocarcinoma Stromal Reprogramming Consortium, and Pancreatic SPOREs, are supported by various research programs [7-10].

These initiatives emphasize the importance of ongoing research, clinical trials, and collaboration in driving significant advancements in understanding, detecting, and treating pancreatic cancer. In the face of the complexities posed by pancreatic cancer, a holistic approach that embraces ongoing research, clinical trials, and collaborative initiatives is advocated as the key to significant advancements in understanding, detecting, and treating this challenging disease. By leveraging the latest advancements and collaborative efforts, we can strive towards improved outcomes for patients with pancreatic cancer.

Epidemiology and Risk Factors

Pancreatic cancer, characterized by its high mortality rate, demands a nuanced understanding of its epidemiology and the diverse array of risk factors influencing its incidence. Pancreatic Cancer Awareness Month in November underscores the critical importance of awareness, early detection, and proactive management of the disease [11].

Family History and Genetic Predisposition

• Genetic Predisposition and Family History [12]

- Building on the impact of family history, stress the role of genetic testing for first-degree relatives diagnosed with pancreatic cancer.
- Introduce key inherited genetic mutations and syndromes associated with a higher risk, underlining the importance of genetic counseling.

Association with Diabetes

• Diabetes Connection [13]

- Illuminate the intricate relationship between diabetes and pancreatic cancer, both as a risk factor and a potential symptom.
- Highlight ongoing research, such as PanCAN's Early Detection Initiative, focusing on the early detection of pancreatic cancer in individuals with new-onset diabetes [2].

Smoking and Ethnic Disparities

• Modifiable Risk Factors [14]

- Elaborate on smoking as a significant modifiable risk factor, contributing to a substantial percentage of exocrine pancreatic cancer cases.
- Discuss racial and ethnic disparities, with Black Americans and Ashkenazi Jews facing elevated incidences, possibly linked to specific genetic mutations.

Obesity and Pancreatitis [15]

• Correlation with Obesity

- Delve into the correlation between obesity and an increased risk of pancreatic cancer, emphasizing the role of excessive abdominal fat.
- Highlight the heightened risk associated with chronic and hereditary pancreatitis, providing insights into the conditions leading to pancreatic inflammation.

Age, Diet, and Alcohol Consumption

• Age-Related Increase and Dietary Impact [16]

- Stress the age-related increase in pancreatic cancer risk, with the majority of diagnoses occurring in individuals over the age of 60.
- Explore the impact of diet, with red and processed meats potentially elevating risk, while diets rich in fruits and vegetables may offer protective effects.
- Touch upon the potential link between heavy alcohol use and pancreatic cancer, with increased risk observed in those exceeding three alcoholic drinks daily.

Chemical Exposure and Gum Disease [17]

• Environmental Factors

- Discuss emerging research indicating a potential association between certain environmental chemicals, heavy metals, and an elevated risk of pancreatic cancer.
- Highlight the connection between periodontal (gum) disease, tooth loss, and pancreatic cancer, emphasizing the need for holistic health considerations.

Advocacy, Communication, and Prevention [18]

• Empowering Individuals:

- Empower individuals with pancreatic cancer or concerning symptoms to advocate for their health, emphasizing open communication with healthcare providers.
- Stress the importance of regular visits to primary care providers for preventive care, wellness maintenance, and personalized risk assessment.

Epidemiology Overview

Pancreatic cancer exhibits intricate epidemiology characterized by elevated male predominance, global prevalence, and its substantial contribution to cancer mortality. Recognizing its multifaceted etiology, continuous investigation assumes paramount significance in deciphering the complexities underlying pancreatic cancer and formulating efficacious interventions for prevention and management [19].

Global Incidence and Mortality Statistics [20]

- Pancreatic cancer is more common in men than in women.
- Globally, the incidence of pancreatic cancer is 5.5 per 100,000 for men and 4.0 per 100,000 for women.
- Pancreatic cancer has an exceptionally high mortality rate, making it one of the four or five most common causes of cancer-related deaths.
- The average lifetime risk of pancreatic cancer is about 1 in 64.
- Incidence rates for pancreatic cancer are highest in Northern America and Western Europe.

Early Detection and Screening Initiatives for Pancreatic Cancer

Detecting pancreatic cancer in its early stages is a significant challenge due to the lack of established screening tests. However, ongoing research initiatives are dedicated to developing effective tools for early detection [21].

New-Onset Diabetes as a Risk Factor

New-onset diabetes has been identified as a notable risk factor for pancreatic cancer. Studies have shown a correlation between the development of pancreatic cancer and the onset of diabetes. To further investigate this link, the National Cancer Institute (NCI) has provided funding for the New Onset Diabetes (NOD) Study. This study aims to enroll 10,000 individuals with new-onset diabetes or hyperglycemia and develop a blood test that can be used for additional pancreatic cancer screening [22].

Research Projects and Imaging Techniques

The Pancreatic Cancer Detection Consortium (PCDC), supported by the NCI, plays a pivotal role in advancing early detection methods for pancreatic cancer. Through various research projects, the PCDC focuses on developing blood tests that can identify pancreatic cancer at an early stage [23].

In addition, efforts are being made to enhance pancreatic imaging techniques. The objective is to improve the sensitivity of these imaging methods to detect even the smallest tumor deposits in the pancreas [23].

Detection of pancreatic cancer remains a challenge, but ongoing research initiatives are dedicated to finding effective screening tools. The relationship between new-onset diabetes and pancreatic cancer is being explored through the NOD Study, while the PCDC's research projects aim to develop blood tests for early detection. Furthermore, advancements in imaging techniques are being pursued to improve the ability to detect tiny tumor deposits in the pancreas [2].

Treatment

Pancreatic cancer poses unique challenges when it comes to selecting appropriate treatment options due to its aggressive nature and complex anatomical location. Surgical interventions are often limited due to the advanced stages of the disease at the time of diagnosis. However, there are various standard treatment approaches available, including surgery, chemotherapy, radiation, or a combination of these modalities, depending on the stage of the cancer [24-25].

Standard Treatment Approaches

The primary treatment modalities for pancreatic cancer involve a comprehensive approach that encompasses surgical intervention, chemotherapy, and radiation therapy. However, surgical options may be constrained due to the tumor's anatomical location and the advanced stage of the disease at the time of diagnosis [25].

Personalized Treatment Recommendations

To optimize treatment outcomes, personalized treatment recommendations play a crucial role. This is achieved through the utilization of biomarker testing and genetic profiling [26]. These diagnostic tests enable healthcare professionals to customize treatment plans based on the patient's specific genetic makeup and tumor characteristics. By tailoring the treatment approach, the effectiveness of the treatment can be maximized.

Clinical Trials and Innovative Therapies

Active participation in clinical trials is of utmost importance in the dynamic landscape of pancreatic cancer treatment. Ongoing research focuses on exploring innovative therapies and improving treatment outcomes. Clinical trials are currently investigating novel adjuvant chemotherapy drug combinations and neoadjuvant chemotherapy for early-stage pancreatic cancer. These trials offer hope for enhanced survival rates and improved disease control. Precision therapies targeting the prevalent KRAS G12D mutations in pancreatic cancer have demonstrated promising results in tumor size reduction, notably exemplified by the experimental drug MRTX1133 [27]. These advancements, coupled with the development of drugs for G12C and G12D mutations, signify significant strides in precision therapeutics. Noteworthy emerging developments in the field encompass combination therapies, immunotherapies, gene editing technologies, liquid biopsies, and strategies targeting the tumor microenvironment. While further research is warranted, these innovative approaches instill hope for more efficacious and tailored treatments for pancreatic cancer [27].

Immunotherapy and Targeted Therapy

Immunotherapy and targeted therapy are emerging treatment modalities that hold considerable promise for patients with metastatic pancreatic cancer. Immunotherapy utilizes the body's immune system to selectively target and eliminate cancer cells, while targeted therapy focuses on specific molecular targets that drive tumor growth [4].

Promising drug targets encompass Ras-directed therapies, olaparib, and pembrolizumab. Ras-directed therapies aim to inhibit the activity of mutated Ras proteins, which play a significant role in pancreatic tumor growth. Olaparib, a poly (ADP-ribose) polymerase (PARP) inhibitor, exhibits potential in treating patients with BRCA mutations [28]. Pembrolizumab, a programmed death receptor-1 (PD-1) inhibitor, has shown encouraging results in patients with high microsatellite instability or mismatch repair deficiency [29].

Monitoring and Long-Term Care following Pancreatic Cancer Treatment

Once pancreatic cancer treatment concludes, individuals embark on a critical phase of post-treatment monitoring and survivorship. This pivotal period necessitates regular medical check-ups, ongoing support, and adjustments to one's lifestyle to optimize outcomes [30].

Post-Treatment Follow-Up: Underscore the significance of consistent follow-up appointments with healthcare professionals subsequent to treatment completion.

Delve into the frequency of check-ups and the essentiality of imaging tests to diligently monitor for any potential signs of cancer recurrence [30].

Biomarker and Genetic Testing: Highlight the pivotal role played by biomarker and genetic testing in the post-treatment monitoring process.

Elucidate how these tests aid in the detection of any lingering cancer cells or potential genetic factors that may influence ongoing care decisions [23].

Management of Treatment Side Effects: Recognize the possible long-term side effects stemming from pancreatic cancer treatment.

Offer valuable insights on effective strategies to manage and cope with these side effects, ultimately enhancing the overall quality of life [31].

Survivorship and Rehabilitation: Survivorship encompasses various aspects that go beyond the completion of treatment. It involves addressing physical, emotional, and practical elements to ensure a fulfilling life after overcoming cancer.

Physical Rehabilitation: Explore rehabilitation programs designed to restore physical health and functionality.

Emphasize the significance of physical therapy, exercise routines, and dietary adjustments in promoting overall well-being.

Mental and Emotional Support: Acknowledge the emotional challenges, that may persist even after treatment [32].

Encourage individuals to seek guidance from counseling services, support groups, or mental health professionals to navigate the emotional aspects of survivors [33].

Lifestyle Adjustments and Well-Being Following Pancreatic Cancer Treatment

After completing treatment for pancreatic cancer, individuals often need to make certain lifestyle adjustments to enhance their overall well-being and reduce the risk of recurrence. These adjustments are essential for promoting a healthier future and improving the quality of life for cancer survivors.

Smoking Cessation and Healthy Habits: One crucial lifestyle change post-pancreatic cancer is quitting smoking. Emphasizing the importance of smoking cessation is vital to reduce the risk of cancer recurrence. By quitting smoking, individuals can significantly improve their chances of long-term survival and reduce the harmful effects of tobacco on their health [34].

In addition to quitting smoking, adopting a healthy lifestyle is vital for pancreatic cancer survivors. Encouraging the adoption of healthy habits, such as regular exercise, a balanced diet, and adequate sleep, can have a positive impact on overall well-being. Regular physical activity helps maintain physical fitness, reduces stress, and boosts mental well-being. A balanced diet, rich in fruits, vegetables, whole grains, and lean proteins, provides essential nutrients to support optimal health [35]. Adequate sleep allows the body to restore and rejuvenate, enhancing its ability to cope with the challenges of recovery.

Regular Screening and Preventive Measures

Regular screenings and preventive measures are also crucial for individuals who have undergone pancreatic cancer treatment. Discussing the significance of ongoing cancer screenings and the importance of preventive measures is essential. By staying vigilant about their health, reporting any unusual symptoms promptly, and participating in recommended screenings, individuals can detect any potential signs of recurrence at an early stage. Early detection plays a vital role in successful treatment and long-term survival [36].

Following pancreatic cancer treatment, individuals often need to make lifestyle adjustments to improve their well-being and reduce the risk of recurrence. By emphasizing smoking cessation, promoting a healthy lifestyle, and encouraging regular screenings and preventive measures, individuals can take proactive steps toward a healthier future [36].

Conclusion

In this discourse on pancreatic oncology, a confluence of precision therapeutics, early detection imperatives, genetic insights, and global epidemiological perspectives delineates the current landscape and future trajectories. The elucidation navigates intricate terrains, shedding light on the multifaceted dimensions of pancreatic cancer.

Precision therapeutics, exemplified by targeted modalities, signifies a paradigm shift in therapeutic avenues for RET-altered thyroid and lung cancers. Simultaneously, initiatives like the NCI-funded New Onset Diabetes (NOD) Study and the Pancreatic Cancer Detection Consortium (PCDC) underscore the imperative of early detection in advancing diagnostic acumen.

Genetic revelations redefine risk stratification, extending beyond familial antecedents. Genetic counselors play a pivotal role in

informed decision-making, while germline testing, irrespective of familial history, introduces a personalized preventive paradigm.

Post-treatment survivorship discourse emphasizes a holistic ethos, integrating physical, emotional, and lifestyle dimensions into a patient-centric continuum of care.

Epidemiological insights offer a comprehensive understanding of pancreatic cancer's prevalence and mortality globally, equipping stakeholders with insights for interventions attuned to diverse populations.

As this synthesis concludes, the collective mandate is clear, a commitment to sustained inquiry, interdisciplinary collaboration, and transformative progress. In this denouement, the narrative of pancreatic cancer transforms from cryptic to conquerable, where scientific rigor converges with compassionate care. This elucidation serves not just as a conclusion but a prologue, a herald of a future where pancreatic cancer yields to the relentless tenacity of collective human endeavor.

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