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Perspective

Integrating Targeted Therapies into Pancreatic Cancer Care

Natasha Reid*

Department of Pancreatic Surgery, University of Cape Town, Cape Town, South Africa

DESCRIPTION

Pancreatic Cancer (PC), particularly Pancreatic Ductal Adenocarcinoma (PDAC), remains one of the deadliest malignancies worldwide, with a five-year survival rate of less than 12%. Despite advances in surgery, chemotherapy, and radiotherapy, outcomes remain dismal due to late diagnosis, aggressive tumor biology, and high resistance to conventional treatments. Over the past decade, the emergence of targeted therapies has offered new avenues for treatment by focusing on specific molecular alterations and signaling pathways driving tumor growth. While progress has been made, the journey of targeted therapies in PC has been fraught with challenges, yet also presents promising opportunities for the future.

Targeted therapy is designed to block specific molecules or pathways essential for cancer cell proliferation, survival, and metastasis. In PC, several genetic mutations and dysregulated signaling pathways have been identified as potential therapeutic targets. The most common mutation is in the *KRAS* oncogene, present in over 90% of PDAC cases. *KRAS* mutations drive uncontrolled cell growth through downstream pathways such as RAF-MEK-ERK and PI3K-AKT. Other frequent alterations include inactivation of tumor suppressor genes like *TP53*, *CDKN2A*, and *SMAD4*. These insights have laid the groundwork for the development of therapies aimed at disrupting the molecular underpinnings of PC.

One of the most significant breakthroughs has been the development of KRAS G12C inhibitors, which directly target the mutant KRAS protein. Although KRAS mutations in PC are often non-G12C subtypes, early clinical studies with KRAS inhibitors have shown activity in select patients, raising hope for a broader class of KRAS-directed drugs. Beyond KRAS, therapies targeting DNA Damage Repair (DDR) pathways have gained traction. Patients with germline BRCA1 or BRCA2 mutations, which impair homologous recombination repair, benefit from Poly ADP-Ribose Polymerase (PARP) inhibitors such as olaparib. This marks a milestone in precision oncology, as it represents one of the few approved targeted therapies in PC.

The Tumor Microenvironment (TME) in PC is another critical focus for targeted therapy. PDAC is characterized by a dense desmoplastic stroma composed of fibroblasts, extracellular matrix, and immune cells. This unique TME acts as both a physical barrier to drug delivery and a contributor to immune evasion. Efforts to target stromal components, such as Hedgehog signaling inhibitors, initially showed promise but later failed in clinical trials due to unexpected tumor-promoting effects. More recently, strategies have shifted toward modulating the TME to enhance drug penetration and immune response, such as targeting Fibroblast Activation Protein (FAP) or reprogramming tumor-associated macrophages (TAMs).

Angiogenesis inhibitors, which target the vascular endothelial growth factor (VEGF) pathway, have demonstrated success in other cancers but limited efficacy in PC, possibly due to the hypovascular nature of PDAC tumors. Similarly, Epidermal Growth Factor Receptor (EGFR) inhibitors, such as erlotinib, showed only modest survival benefits when combined with chemotherapy. These mixed outcomes highlight the complexity of translating targeted therapies into meaningful clinical benefit for PC patients.

The integration of targeted therapies with other modalities presents a major opportunity. Combining targeted drugs with chemotherapy, immunotherapy, or radiotherapy may overcome resistance and improve efficacy. For instance, PARP inhibitors are being evaluated in combination with immune checkpoint inhibitors to exploit the immunogenicity of DDR-deficient tumors. Similarly, *KRAS* inhibitors are being combined with MEK or SHP2 inhibitors to block compensatory signaling pathways. These combination strategies reflect a growing recognition that multi-targeted approaches may be necessary to address the heterogeneity of PC.

Another promising direction lies in biomarker-driven treatment. Advances in genomic sequencing and liquid biopsy technologies enable the identification of actionable mutations and real-time monitoring of tumor evolution. This paves the way for personalized therapy, ensuring that patients receive treatments tailored to their unique molecular profile. Clinical trials such as the Know Your Tumor (KYT) initiative have demonstrated that matching patients with biomarker-directed therapies significantly improves outcomes compared to standard approaches.

Correspondence to: Natasha Reid, Department of Pancreatic Surgery, University of Cape Town, Cape Town, South Africa, E-mail: nreid@uct.ac.za

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Despite these advances, challenges remain formidable. Intratumoral heterogeneity, rapid development of drug resistance, and the immunosuppressive microenvironment continue to limit the durability of targeted therapies. Moreover, the relatively low prevalence of actionable mutations in PC means that only a subset of patients currently benefits from these strategies. Access to advanced diagnostics, high treatment costs, and regulatory hurdles further complicate widespread implementation.

CONCLUSION

Targeted therapies have opened a new chapter in the management of pancreatic cancer, offering a glimpse of progress against a historically intractable disease. While current successes are modest, they underscore the importance of molecularly guided therapy and provide a foundation for future innovation. Continued research into novel druggable targets, rational combination therapies, and biomarker-driven patient selection is essential to unlock the full potential of targeted therapies. With ongoing advances in precision medicine, the hope remains that pancreatic cancer will one day shift from a lethal diagnosis to a manageable disease.