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SYSTEMIC THERAPY IN PANCREATIC CANCER: FROM CYTOTOXIC REGIMENS TO MOLECULARLY TARGETED TREATMENT

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Background: Most patients with pancreatic cancer present with locally advanced or metastatic disease, making systemic therapy the cornerstone of treatment. Despite incremental progress, durable responses remain uncommon, and the tumor's dense stroma and immunosuppressive microenvironment contribute to treatment resistance.

Objective: This review outlines the evolution of systemic therapy for pancreatic cancer and highlights strategies under active investigation.

Main findings: Combination chemotherapy regimens, including FOLFIRINOX, gemcitabine plus nab-paclitaxel, and more recently NALIRIFOX, have improved survival over gemcitabine alone in fit patients with metastatic disease, and multi-agent chemotherapy is now standard in the adjuvant setting following resection. Neoadjuvant therapy is increasingly used for borderline resectable and locally advanced disease to improve margin-negative resection rates. Molecular profiling has identified actionable subgroups: patients with germline BRCA mutations may benefit from platinum-based therapy and PARP inhibitor maintenance, while rare tumors with mismatch repair deficiency, NTRK fusions, or KRAS wild-type alterations may respond to targeted agents or immunotherapy. Because KRAS mutations occur in more than 90% of PDAC, direct KRAS inhibitors, including pan-RAS and mutation-specific agents, represent a major area of clinical development. Immune checkpoint inhibitors have shown minimal activity in unselected patients, prompting research into combinations that modify the tumor microenvironment.

Conclusion: Treatment of pancreatic cancer is gradually moving from uniform cytotoxic therapy toward biomarker-guided approaches. Routine germline and somatic testing should be offered to all patients, and enrollment in clinical trials remains essential given the limited efficacy of current options.

Keywords: pancreatic cancer, chemotherapy, FOLFIRINOX, KRAS, PARP inhibitors, precision oncology

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