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TOPIC HIGHLIGHT

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Pancreatic cancer: Advances in treatment

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Abstract

Pancreatic cancer is a leading cause of cancer mortality and the incidence of this disease is expected to continue increasing. While patients with pancreatic cancer have traditionally faced a dismal prognosis, over the past several years various advances in diagnosis and treatment have begun to positively impact this disease. Identification of effective combinations of existing chemotherapeutic agents, such as the FOLFIRINOX and the gemcitabine + nab-paclitaxel regimen, has improved survival for selected patients although concerns regarding their toxicity profiles remain. A better understanding of pancreatic carcinogenesis has identified several pre-malignant precursor lesions, such as pancreatic intraepithelial neoplasias, intraductal papillary mucinous neoplasms, and cystic neoplasms. Imaging technology has also evolved dramatically so as to allow early detection of these lesions and thereby facilitate earlier management. Surgery remains a cornerstone of treatment for patients with resectable pancreatic tumors, and advances in surgical technique have allowed patients to undergo resection with decreasing perioperative morbidity and mortality. Surgery has also become feasible in selected patients with borderline resectable tumors as a result of neoadjuvant therapy. Furthermore, pancreatectomy involving vascular reconstruction and pancreatectomy with minimally invasive techniques have demonstrated safety without significantly compromising oncologic outcomes. Lastly, a deeper understanding of molecular aberrations contributing to the development of pancreatic cancer shows promise for future development of more targeted and safe therapeutic agents.

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Key words: Pancreatic cancer; Pancreaticoduodenectomy; Treatment advances; Pancreatic oncology; Chemotherapy; FOLFIRINOX; Pancreatic resection

Core tip: Pancreatic cancer is a leading cause of cancer mortality. However, recent advances have improved our ability to treat patients with this highly lethal disease. This review article discusses some of the salient advances in the field, such as improvements in chemotherapeutic regimens, imaging technology, surgical technique, and our understanding of the pathogenesis of pancreatic cancer.

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INTRODUCTION

Pancreatic cancer is the tenth most commonly diagnosed cancer and the fourth leading cause of cancer mortality in the United States; the overall 5-year survival is only 5%[1]. Even patients who undergo complete resection, chemotherapy, and radiation have a 5-year survival of only 20%[2], underscoring the need for novel therapies. In

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the year 2012, 43000 cases of pancreatic cancer were diagnosed and, as the general population continues to age, this incidence is expected to increase[3].

This review article discusses recent advances made in the treatment of pancreatic cancer, such as new chemotherapeutic regimens that have improved survival, the recognition of potentially pre-malignant lesions, the emergence of improved imaging modalities allowing early detection of pancreatic masses, the growing practice of minimally invasive and robotic pancreatic surgery, and an improved understanding of the molecular changes contributing to pancreatic cancer development.

ADVANCES IN CHEMOTHERAPY REGIMENS

Few effective chemotherapeutic options exist for metastatic pancreatic cancer. Since the 1990s, gemcitabine has been considered the standard agent of choice, and, although multiple different agents have been evaluated in combination with gemcitabine or alone, few have demonstrated positive impact on survival in patients with advanced disease[4-9]. More recently, higher response rates have been observed with the FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan, oxaliplatin) regimen and with the gemcitabine + nab-Paclitaxel regimen than with gemcitabine alone. In the Actions Concertées dans les Cancer Colo-Rectaux et Digestifs (ACCORD) 11 trial, 342 patients with metastatic pancreatic cancer were randomly assigned to receive either FOLFIRINOX or single-agent gemcitabine as first-line treatment for pancreatic cancer[10]. Endpoints included overall survival, progression-free survival, tumor response (RECIST criteria), safety, and quality of life. On interim analysis, a significantly improved median overall survival was observed in the FOLFIRINOX arm (11.1 mo *vs* 6.8 mo, HR = 0.57, $P < 0.001$) compared with the gemcitabine arm[10]. However, there were significantly more grade 3-4 toxicities, such as cytopenias, diarrhea, and neutropenic fever, in the treatment group (all $P < 0.01$). Subsequent studies have confirmed the efficacy of the FOLFIRINOX regimen[11,12], but have questioned its applicability to patients of older age, with poor performance status, and with co-morbid conditions[13]. FOLFIRINOX also remains controversial with respect to its tolerability; studies report manageable side effects as well as significant toxicity resulting in treatment discontinuation[11,14]. In small studies, components of the FOLFIRINOX regimen have been dose-attenuated, raising the concern that physician modification of the regimen may affect patient outcomes[15].

Favorable outcomes are also beginning to be observed with the use of this regimen in the neoadjuvant setting for patients with borderline resectable or locally unresectable disease. In a recent study of 21 patients with either unresectable or borderline resectable pancreatic cancer who received neoadjuvant FOLFIRINOX, a 33% R0 resection rate was achieved (55% borderline resectable, 10% locally unresectable) and 24% of patients demonstrated a significant pathologic response[16]. Despite concerns of toxicity and tolerability, in the carefully selected patient with good performance status and early or advanced disease, FOLFIRINOX demonstrates potential for improved oncologic outcomes.

Nab-paclitaxel (trade name, Abraxane) is a nanoparticle albumin-bound (nab) paclitaxel that was initially developed to avoid hypersensitivity reactions resulting from solvents used to dissolve the agent[17]. It was approved by the FDA in 2004 for use in metastatic breast cancer and metastatic non-small cell lung cancer[18,19]. In the phase Ⅲ Metastatic Pancreatic Adenocarcinoma Clinical Trial (MPACT), the addition of nab-paclitaxel to gemcitabine demonstrated improved median overall survival (8.5 mo *vs* 6.7 mo, HR = 0.72, $P < 0.001$), improved 1-year survival (35% *vs* 22%), improved 2-year survival (9% *vs* 4%), and improved objective response rate (23% *vs* 7%) when compared with gemcitabine alone[20]. Although this response is not as dramatic as those observed with FOLFIRINOX, this regimen was well-tolerated and demonstrated a safer toxicity profile. It has emerged as an option for patients who cannot tolerate FOLFIRNOX because of poor performance status.

The role of nab-paclitaxel was investigated in pancreatic cancer after molecular profiling done on pancreatic tumors demonstrated high levels of the albumin-binding protein SPARC (secreted protein acidic and rich in cysteine)[21]. Nab-paclitaxel has demonstrated anti-tumor activity in cancers of the breast and lung, particularly in tissues that express high levels of SPARC[22]. It is believed that among patients with pancreatic cancer, tumors with high SPARC expression serve as albumin-binding sites that sequester nab-paclitaxel and concentrate drug levels intratumorally[23]. Another mechanism proposed involves an albumin receptor (gp60) on endothelial cells that transports paclitaxel into the tumoral interstitial space[24].

Gemcitabine plus erlotinib is another multi-drug regimen that has shown improved progression-free survival and overall survival[25,26]. However, due to their greater potential for improved outcomes, FOLFIRINOX and gemcitabine + nab-paclitaxel are the preferred treatment options for patients with acceptable performance status.

EARLY IDENTIFICATION AND TREATMENT OF PREMALIGNANT LESIONS

Early detection and management of adenomatous polyps, in situ lesions, and other premalignant or potentially malignant entities of the colon and breast have resulted in less mortality due to these cancers. It is now believed that pancreatic ductal adenocarcinoma also arises from a series of similar progressive genetic mutations and specific precursor lesions, such as pancreatic intraepithelial neoplasia (PanIN), intraductal papillary mucinous neoplasms (IPMN), and mucinous cystic neoplasms.

PanINs are by far the most common of these precur-

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sor lesions[27]. Autopsy studies have shown that panINs increase with age, are more common in the head of the pancreas, and are seen at much higher rates in pancreata with tumors than those with pancreatitis[28-30]. They involve the same molecular events seen in the development of adenocarcinoma of other organs, such as activation of K-ras mutants, overexpression of p53, and loss of p16 and SMAD4[31]. Although no specific sequence has been elucidated, certain mutations (K-ras, p16) occur before others (TP53, SMAD4), and higher grades of panIN indicate higher levels of mutations[32].

IPMN belong to a heterogenous group of cystic lesions and are also considered precursor lesions for the development of invasive carcinoma. Main-duct IPMNs connect to the main duct of Wirsung while side-branch IPMNs originate from smaller branches off the main duct. Main duct and branch duct IPMNs were associated with malignancy in 70% and 25% of cases, respectively. Other groups have produced similar findings[33]. There is a strong consensus for resection of main-duct IPMNs due to their higher risk for associated malignancy.

Mucinous cystic neoplasms comprise around 25% of all resected cystic neoplasms[34]. They are characterized by dense stroma surrounding a tumor with mucin-producing epithelial cells, which are susceptible to various degrees of atypia. In a study of mucinous cystic neoplasms by the Massachusetts General Hospital, the risk of malignancy among 163 cases was 17.5%, and all malignant tumors had either nodules or were greater than 4 cm in size[35]. Patients are typically managed by surgical resection. If non-operative management is pursued, lifelong surveillance is essential.

With the widespread use of radiographic imaging and improvement in its resolution, there has been an increase in the incidence of cystic lesions, which are now found in approximately 1% of all abdominal computed tomographic scans obtained[36]. Given the variable potential for malignancy, groups have developed criteria to characterize these lesions and risk-stratify patients. The diagnostic algorithm often includes endoscopic ultrasound (EUS) with fine needle aspiration of cyst fluid to assess cytology, the presence of mucin, tumor markers carcinoembryonic antigen, and DNA for loss of heterozygosity and K-ras mutations.

High resolution endoscopic ultrasound (EUS) is an imaging modality that is able to detect focal lesions as small as 2-3 mm in size[37]. Studies have shown that EUS is superior or at least equal to computed tomography (CT) or magnetic resonance imaging in its sensitivity for detecting lesions, determining tumor size and extent, and assessing lymph node involvement and vascular invasion[38,39]. Conventional CT scans also provide detailed high-resolution views of pancreatic tumors in relation to the superior mesenteric artery, celiac axis, superior mesenteric vein, and portal vein, and this imaging modality remains the preferred choice for initial evaluation of most patients suspected to have pancreatic cancer.

Early detection of pre-malignant and potentially malignant lesions represents a significant advance in the treatment of pancreatic cancer. Since invasive pancreatic cancer is rarely cured, resection of these premalignant lesions is believed to be warranted. However, further refinements in our understanding of premalignant lesions and more accurate risk-stratification of patients is necessary so that patients with a low risk of malignancy can avoid an operation.

ADVANCES IN SURGICAL PRACTICE

Surgery plays a critical role in the management of pancreatic cancer, and many advances in surgical practice patterns as well as surgical technique have resulted in reduced perioperative morbidity and mortality. Centralization of pancreaticoduodenectomy, for example, to higher-volume centers with higher-volume surgeons, has contributed to a reduction in postoperative mortality, such that the risk of mortality at high volume centers is currently as low as 3%[40].

Historically, pancreatic tumors were considered either resectable or unresectable. In 2003, the National Comprehensive Cancer Network introduced the "borderline resectable" classification for pancreatic cancer, which refers to tumors that are involved with nearby structures so as to be neither clearly resectable nor clearly unresectable[41]. Aggressive management of this group of patients with neoadjuvant chemotherapy has made surgery feasible and may have improved survival in selected patients. The safety of vascular reconstruction in conjunction with pancreaticoduodenectomy has also been demonstrated in a systematic review of the literature[42].

Aside from more complex open surgeries, pancreatic cancer is also being increasingly approached laparoscopically. Early studies show that minimally invasive approaches can be performed safely and facilitate shorter hospital stay, earlier return to preoperative activity level, and reduced postoperative recuperation allowing for less delay in time to adjuvant chemotherapy or radiation[43-45]. With evolving technology and experience, laparoscopic distal pancreatectomy has become a standard approach for benign and malignant lesions of the pancreatic body and tail. In a multicenter study comparing open and laparoscopic distal pancreatectomy for patients with pancreatic ductal adenocarcinoma, Kooby *et al*[46] showed that there were no significant differences in positive margin rates, number of nodes examined, number of patients with at least one positive node, or overall survival, and that there was shorter hospital stay (7.4 d *vs* 9.4 d, $P = 0.06$) in the laparoscopic distal pancreatectomy group.

Laparoscopy has been extended to pancreaticoduodenectomy as well, and several case series have demonstrated feasibility, safety, and efficacy of this approach as compared to open surgery[47]. The robotic platform is also being increasingly adopted in pancreatic surgery. This approach overcomes limitations of laparoscopy, such as two-dimensional visualization, lack of dexterity, and poor ergonomics. In a series of 30 patients undergoing robot-

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assisted major pancreatectomy and reconstruction, Zureikat *et al*[48] reported an overall pancreatic fistula rate of 27% and a 90-d Clavien grade Ⅲ-Ⅳ complication rate of 23%. They concluded that robot-assisted surgery can be performed safely with postoperative complication rates comparable to those of open pancreatectomy[48]. Further experience and larger, controlled studies are needed to clearly define potential benefits and elucidate long-term oncologic outcomes of minimally invasive pancreaticoduodenectomy.

ADVANCED UNDERSTANDING OF GENETIC AND MOLECULAR FACTORS

Many genetic alterations, including germ line and somatic mutations, contribute to the development of pancreatic cancer. Recent studies indicate that pancreatic cancer cells carry an average of 63 genetic mutations per cancer, and these mutations can be grouped into twelve core signaling pathways[49]. Over 90% of pancreatic cancers possess mutations in the k-ras oncogene, which is mutated in 20%-30% of all human malignancies[50]. Mutations within this oncogene are most often located on exon 1 of codon 12 and sometimes on codons 61 and 13[50,51]. Mutated k-ras upregulates several pathways, such as the PI3K-AKT pathway, which is involved in a series of important cellular functions, including survival and proliferation[52]. Other oncogenes involved in pancreatic carcinogenesis include those involved with the Notch signaling pathway[53] and the sonic hedgehog pathway[54].

The most widely recognized tumor suppressor gene (TSG) implicated in pancreatic cancer development is p53, which is found to be mutated in over 75% of specimens[55]. Other TSGs of importance include DPC4 (Deleted in Pancreatic Cancer, locus 4), LKB1 (liver kinase B1), p16, MAPK (mitogen activated protein kinase), and BRCA 2. These various discoveries contribute to the development of more targeted therapies and may also provide prognostic information. Over 50% of pancreatic adenocarcinomas have been demonstrated to have an inactivating mutation in SMAD4[56]. Tascilar *et al*[56] measured SMAD4 protein expression in 249 pancreatic adenocarcinomas and found that patients with this mutation had significantly longer survival than those without it (19.2 mo *vs* 14.7 mo), even after adjusting for other factors such as tumor size, margins, lymph node status, pathological stage, blood loss, and use of adjuvant chemoradiotherapy.

Whole exome sequencing and copy number analysis of a prospective cohort of 142 patients with pancreatic cancer recently defined 16 significantly mutated genes, ranging from those which were previously known to contribute to pancreatic cancer pathogenesis (KRAS, TP53, CDKN2A, SMAD4, MLL3, TGFBR2, ARID1A, SF3B1) to newly discovered genes involved in chromatin modification (EPC1, ARID2), DNA damage repair (ATM), and other mechanisms (ZIM2, MAP2K4, NALCN, SLC16A4, MAGEA6)[57]. Larger studies are needed to determine whether these mutations are more prevalent among specific demographic groups or whether they affect oncologic outcomes.

CONCLUSION

Pancreatic cancer remains a highly lethal disease. By the time patients are diagnosed, the disease may often be advanced, precluding patients from surgery. Recent advances in chemotherapeutic regimens have not only improved our ability to treat patients with metastatic disease, but have also shown favorable outcomes in the neoadjuvant setting. Advances in imaging technology and a better understanding of the pathogenesis of pancreatic cancer are allowing earlier diagnosis and early aggressive management of potentially pre-malignant entities. Emergence of high volume centers, the incorporation of imaging technology, and the availability of specialty services, such as interventional radiology, have reduced perioperative morbidity and mortality associated with pancreaticoduodenectomy. Furthermore, advances in surgical technology are allowing these procedures to be performed in less invasive fashion and are demonstrating safety and feasibility. Despite these advances, there remains room for improvement. Today's pancreatic oncologists must focus on further understanding the genetic and molecular factors contributing to oncogenesis and on the development of more targeted and less toxic systemic therapies.

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