Current approaches to novel therapeutics in pancreatic cancer

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Summary

Pancreatic cancer is one of the most refractory neoplasms to medical treatment. Until now there has been only modest improvement in the treatment of this disease. Standards of care for combined-modality treatment of resectable as well as locally advanced, unresectable disease have not been uniformly accepted to date because of an equivocal or conflicting data. The inception of gemcitabine introduced the new era in the management of metastatic pancreatic cancer, however, new therapeutic approaches still need to be defined. The article discusses the current knowledge of the biology of this lethal disease, its impact on treatment options, and explores novel therapeutic modalities that are likely to improve outcomes and survival for patients in the future.

Introduction

Pancreatic cancer remains a significant public health concern. Current data indicate that 5% of all cancer-related deaths are due to pancreatic cancer, which places it as the fourth leading cause of cancer-related death for both men and women [1]. Unfortunately, more than 80% of patients with carcinoma of the exocrine pancreas are resectable/metastatic at diagnosis. Furthermore, pancreatic cancer is relatively resistant to both chemotherapy and radiotherapy and these options are used primarily for palliation [2]. The incidence of pancreatic cancer significantly increased from 1940 to 1970 with a plateau at approximately 28,000 new cases annually since 1970s [1]. This trend could be explained by the steady decline in the incidence of pancreatic cancer in White men, which peaked between 1970 and 1974. However, rates for White women and African Americans may have increased slightly. Overall incidence of pancreatic cancer is approximately 30–40% higher in US Black population than it is in Caucasians [3,4]. Male to female ratio is approximately 1.3 to 1. Incidence in the United States is approximately 10.1/100,000 person-year among males and 7.5/100,000 among females, age-adjusted [5]. Adenocarcinomas account for 95% of all exocrine pancreatic neoplasms. They are most often multicentric and 75% are located in the head of the pancreas. Because of difficulties in diagnosis, the aggressiveness of this malignancy and lack of effective therapy, the overall 5-year survival is 3% and after a successful pancreaticoduodenectomy, it approaches 20% [6]. The environmental carcinogen most strongly linked to pancreatic cancer is cigarette smoke. There is a dose-response relationship to the duration and number of cigarettes consumed [7]. The data of the recent large prospective epidemiologic studies have largely excluded caffeine and alcohol as risk factors for pancreatic cancer [8]. Diabetes mellitus has been implicated as both an early manifestation and a predisposing factor, but the mechanism has not been clearly established. It appears that there is an association between chronic pancreatitis and pancreatic cancer. The identification of mutations in the k-ras oncogene in regions of mucosal cell hyperplasia in patients with chronic pancreatitis offers molecular evidence of the link between chronic inflammation and pancreatic cancer [9,10]. Genetic factors beyond k-ras mutations are covered in a subsequent section of the manuscript. Five to eight percent of pancreatic cancer cases are associated with a familial predisposition. Patients with MEN type I
[11,12], hereditary pancreatitis [13,14], hereditary nonpolyposis colon cancer/Lynch syndrome II [15], Von Hippel–Lindau syndrome [16], ataxia-teleangiectasia [17], and the familial atypical multiple mole melanoma syndrome [18,19] are at risk of developing both endocrine and exocrine pancreatic tumors. Progress has been made in understanding molecular genetic abnormalities leading to familial pancreatic cancer. However, pancreatic cancer remains a highly lethal disease due to its aggressiveness, difficulties in early diagnosis, and lack of effective systemic therapy. Therefore, it is of paramount importance that new therapeutic modalities are explored. In this review, we will address the current knowledge of the biology of pancreatic cancer and its impact on treatment options. In addition, we will explore novel therapeutic approaches.

Current standards of chemotherapy and radiotherapy for patients with pancreatic cancer

Adjuvant treatment

Although the only curative therapy of pancreatic cancer to date is surgical resection, most studies document high rates of both local recurrence and distant metastases [20]. External beam radiation therapy (EBRT) and concomitant fluorouracil (5-FU) chemotherapy were demonstrated to prolong survival in patients with locally advanced adenocarcinoma of the pancreas [21]. The most representative studies done in the adjuvant setting are the Gastrointestinal Tumor Study Group (GITSG) and the European Organization for Research and Treatment of Cancer (EORTC).

The GITSG trial was a prospective, randomized, controlled study enrolling 43 patients. Twenty-two patients were randomized to no adjuvant treatment after pancreaticoduodenectomy and 21 patients were randomized to combined chemoradiation (500 mg/m²/day of 5-FU for 6 days and 40 Gy of radiation) followed by bolus 5-FU weekly for 2 years. Neither life-threatening toxicity nor death was encountered. The study was terminated prematurely because of an unacceptably low rate of accrual combined with the observation of increasingly large survival differences between the study arms. The study demonstrated a significant survival advantage for patients who received combined chemoradiation following curative resection. Median survival in the observation group was 10.9 months compared to 21.0 months for those randomized to treatment [22,23]. The major criticism of the trial was that due to a prolonged recovery, 5 (24%) of the 21 patients in the adjuvant chemoradiation arm could not begin treatment until more than 10 weeks after pancreaticoduodenectomy. Therefore, a selection bias was introduced into the trial because only patients who recovered rapidly from surgery and had a good performance status were considered for the trial. Moreover, the recruitment into this trial has been restricted to patients with negative microscopic margins, a group with favorable prognosis.

In the EORTC trial, 218 patients were randomized between 1987 and 1995 to receive either chemoradiation (40 Gy radiation in a split course and 5-FU given as a continuous infusion at a dose of 25 mg/kg/day during EBRT) or no further treatment after pancreaticoduodenectomy for adenocarcinoma of the pancreas or periampullary region, distal common bile duct and duodenum. Analysis was performed on 207 patients, 114 (55%) of whom had pancreatic cancer. Eleven patients were deemed ineligible because of incomplete resection. The median survival was 24.5 months for the chemoradiation group versus 19 months for the observation group (p = 0.2); for patients with pancreatic cancer, the median survival was 17.1 months for those who received chemoradiation and 12.6 months for those who received surgery alone (p = 0.099) [24,25]. Therefore, the authors recommended that postoperative chemoradiation should not be considered standard therapy. The major concerns raised regarding the EORTC trial were due to the following: (1) there was no precise anatomic and pathologic distinction between pancreatic and periampullary adenocarcinoma, (2) unexplained high proportion of periampullary carcinoma, (3) selection bias as patients were considered for enrollment in this trial after recovery from pancreaticoduodenectomy, (4) 21 (20%) of 104 assessable patients randomized to receive chemoradiation did not actually get the treatment due to patient refusal, medical comorbidities or rapid progression of the tumor, (5) there was no assessment of the completeness of surgical resection, (6) no defined method of follow-up and the possibility that the recurrent disease was underestimated [20].

The role of postoperative adjuvant therapy was also addressed by European Study Group of Pancreatic Cancer (ESPAC-1) which suggested that chemotherapy, rather than chemoradiation, is the essential component of adjuvant therapy. This trial