Management of Metastatic Pancreatic Adenocarcinoma

Ahmad R. Cheema, MD[a,b], Eileen M. O'Reilly, MD[c,d,*]

KEYWORDS

• Pancreatic cancer • Metastatic disease • Gemcitabine • Nab-paclitaxel
• FOLFIRINOX • Targeted agents • Immune therapy

KEY POINTS

- Progress in the treatment of pancreatic ductal adenocarcinoma (PDAC) has been incremental, mainly ensuing from cytotoxic systemic therapy, which continues to be a standard of care for metastatic disease.
- Folinic acid, 5-fluorouracil (5-FU), irinotecan, and oxaliplatin (FOLFIRINOX) and gemcitabine plus nab-paclitaxel have emerged as new standard therapies, improving survival in patients with good performance status.
- Novel therapeutics targeting the peritumoral stroma and tumor-driven immune suppression are currently a major focus of research in metastatic disease.
- Identification of reliable and validated predictive biomarkers to optimize therapeutics continues to be a challenge.
- Continued efforts toward better understanding of tumor biology and developing new drugs are warranted because a majority of patients succumb within a year of diagnosis, despite an increasing number of therapeutic options available today.

INTRODUCTION

In the year 2016, there will be approximately 53,000 estimated new individuals diagnosed with PDAC in the United States, representing approximately 3% of all cancer

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[a] Department of Medicine, Icahn School of Medicine at Mount Sinai, 1 Gustave Levy Pl, New York, NY 10029, USA; [b] Department of Medicine, Mount Sinai St. Luke's-West Hospital Center, 1111 Amsterdam Avenue, New York, NY 10025, USA; [c] Rubenstein Center for Pancreatic Cancer Research, Memorial Sloan Kettering Cancer Center, 300 East 66th Street, Office 1021, New York, NY 10065, USA; [d] Weill Cornell Medical College, 1300 York Avenue, New York, NY 10065, USA
* Corresponding author. Rubenstein Center for Pancreatic Cancer Research, Memorial Sloan Kettering Cancer Center, 300 East 66th Street, Office 1021, New York, NY 10065.
E-mail address: oreillye@mskcc.org

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cases.[1] Despite the low incidence, pancreatic cancer is the fourth leading cause of cancer-related death among both men and women in the United States, with a high mortality-to-incidence ratio, and is expected to become the second leading cause of cancer-related mortality by 2030.[2,3] PDAC is the most common histologic subtype, found in more than 85% of cases. Surgical resection is curative in a minority of patients; however, 70% to 80% of patients have unresectable disease, with more than 50% having distant metastases at the time of initial diagnosis, where the treatment goals are to control disease, palliate symptoms, and prolong survival.[2] For PDAC, the expected 5-year survival for all patients is approximately 6% to 7% and less for patients who are diagnosed with metastatic disease de novo.[2,4] Putative explanations for poor outcomes are generally attributed to the asymptomatic early stages of the disease, lack of effective screening tools, early metastatic dissemination, relative resistance of the tumor to cytotoxic and targeted therapies, dense stroma, hypoxic microenvironment, and immune suppression.

Over the past several years, tangible improvements in outcomes have been observed in patients with metastatic PDAC with the increasing use of new chemotherapeutic regimens. Gemcitabine plus albumin-bound paclitaxel and FOLFIRINOX have generated median overall survivals (OSs) ranging from 8.5 to 11.1 months for patients with good performance status.[5,6] For patients with poor performance status, however, median OS is typically in the 3-month to 6-month range.

Through extensive research over the past decade, remarkable advances have been made in understanding the molecular pathogenesis and underpinnings of PDAC. Major advances include elucidation of genetic alterations present in PDAC as well as defining the role of signaling pathways, peritumoral stroma, and immune system in tumor initiation, spread, and resistance to systemic therapies. Therefore, various targeted and immune therapies have been designed and are currently being investigated. Despite encouraging results in phase I/II studies, substantial impact in outcomes has not yet been observed. Therefore, PDAC remains a serious challenge for patients, families, and the scientific community.

This review discusses the current management options for patients with metastatic PDAC, with particular emphasis on the current state of the art along with current clinical trials and a focus on novel agents and immune therapeutics.

FIRST-LINE SYSTEMIC THERAPY

Systemic therapy is the mainstay of treatment of patients with metastatic PDAC, with proved efficacy in terms of prolonging survival. Historically, 5-FU as a single agent or 5-FU–based regimens were the standard treatments for patients with advanced disease, until the advent of gemcitabine.[7,8]

Single-agent Gemcitabine

Gemcitabine is an S-phase–specific pyrimidine antimetabolite that is converted by cellular kinases into difluorodeoxycytidine triphosphate. This active metabolite then competes with deoxycytidine to inhibit DNA synthesis.[9] In 1997, gemcitabine was approved by the US Food and Drug Administration (FDA) as monotherapy for metastatic PDAC after Burris and colleagues[10] demonstrated that gemcitabine was superior to 5-FU in patients with baseline Karnofsky performance scale score (KPS) greater than or equal to 50%; 126 patients with advanced PDAC were randomized to receive either gemcitabine (1000 mg/m^2 over 30 minutes weekly for 7 weeks, followed by a week of rest, and then weekly for 3 of 4 weeks) or weekly bolus of 5-FU (600 mg/m^2). Clinical benefit response, the principal endpoint of this trial, defined by