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Targeted Drug Therapy in Pancreatic Cancer

Don L. Gibbons, MD, PhD, Robert A. Wolff, MD, and Gauri Varadhachary, MD

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Abstract

Only modest progress has been made in improving the overall survival of pancreatic cancer patients during the past 20 years with standard cytotoxic chemotherapy drugs. More work needs to be done to address the key biologic characteristics of pancreatic cancer that make it so aggressive, metastasizing at an early stage, and more refractory to standard treatments than most other solid tumor types. Here, we discuss the emerging role of targeted therapy in pancreatic cancer and the status of currently available and tested agents. We also point out the potential pitfalls in current trial designs and recommend new methods for testing novel compounds in this heterogeneous and difficult-to-treat group of patients.

Key Words: Targeted therapy, Pancreatic cancer, Chemotherapy, Clinical trials

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1. INTRODUCTION

Pancreatic adenocarcinoma is a challenging disease to treat owing to its late stage of detection, with a disproportionate number of patients presenting with locally advanced or metastatic disease, and its resistance to conventional cytotoxic chemotherapy drugs. As a result, approximately 33,000 of the estimated 37,000 patients diagnosed with pancreatic adenocarcinoma in the United States in 2007 will die of the disease (1). Only 20% of newly diagnosed patients will have early-stage, potentially resectable disease. However, 75% of these will have computed tomography (CT)-occult extrapancreatic disease that eventually leads to recurrence. The 1-year overall survival rate of the remaining 80% of newly diagnosed patients with locally advanced or metastatic pancreatic adenocarcinoma is a dismal 18%.

Historically, chemotherapy for advanced pancreatic adenocarcinoma centered on the use of fluorouracil (5-FU), either alone or in combination with other cytotoxic agents, with significantly variable response rates (2). However, improvements in cross-sectional imaging techniques revealed that in many early studies the benefits of 5-FU treatment were likely overestimated (2,3).

More recent studies have consistently demonstrated that single-agent gemcitabine, a ribonucleotide reductase inhibitor, is modestly effective against pancreatic adenocarcinoma (4). Burris et al. (5) performed the landmark trial comparing gemcitabine and 5-FU that led to gemcitabine’s approval by the U.S. Food and Drug Administration (FDA) and established it as the standard of care for patients with advanced pancreatic cancer. The authors demonstrated both a clinical benefit response (as measured by pain medication need, weight gain, and improvement in performance status) of 23.8% in patients treated with gemcitabine compared to 4.8% for patients treated with 5-FU. The study also revealed a 1-year overall survival rate of 18% with gemcitabine and 2% with 5-FU. Median overall survival durations of 5.6 and 4.4 months were found for patients treated with gemcitabine and 5-FU, respectively ($p = 0.0025$). However, the objective response rates were only 5.4% with gemcitabine and 0% with 5-FU. In other trials, objective response rates of approximately 10% have been found for gemcitabine. Because gemcitabine is associated with relatively mild toxicity, it has become the standard of care for palliative treatment of patients with advanced pancreatic cancer.

Researchers have attempted to optimize the effectiveness of gemcitabine by adjusting the method of delivery to match the mechanism of cellular uptake and activation. On the basis of the results of preclinical and pharmacokinetic studies, an alternative infusion method was devised, termed fixed dose rate (FDR). With FDR infusion, gemcitabine is given at 10 mg/m/hr, rather than the standard 30-minute infusion. The plasma concentration using FDR infusion results in maximal intracellular levels of the active gemcitabine triphosphate moiety. In a multicenter Phase II trial of 92 patients (6), a statistically significant longer median survival duration was found among patients in the FDR arm than in the standard dose schedule arm (5 vs. 8 months). Similarly, the 1- and 2-year overall survival rates in the standard dose versus FDR arms were 9.0% vs. 28.8% and 2.2% vs.18.3%, respectively. Unfortunately, the preliminary results of a recent randomized Phase III trial (ECOG 6201) of 833 patients (7) demonstrated no significant difference in response rate or overall survival between standard-dose gemcitabine, FDR gemcitabine, and standard-dose gemcitabine combined with oxaliplatin.

Recent data from a randomized Phase III trial (8) revealed that gemcitabine combined with oxaliplatin resulted in a higher response rate (26.8% vs. 17.3%), clinical benefit rate (38.2% vs. 26.9%), and progression-free survival (PFS) duration (5.8 vs. 3.7 months).