Chemotherapy for Resectable and Advanced Pancreatic Cancer

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This article will review the pertinent data on the use of chemotherapy for all stages of pancreatic cancer. For patients with metastatic disease, fluorouracil (5-FU) was the standard of care for several decades until a single

Although a relatively uncommon disease, pancreatic adenocarcinoma has had a major impact on public health (much greater than incidence rates would suggest) because of associated high morbidity and mortality rates.[1] Drs. Berlin and Rothenberg have written a comprehensive synopsis of the state of conventional cytotoxic chemotherapy and radiation therapy for surgically resected and advanced pancreatic cancer. They provide the historical precedents for the treatment algorithms that have traditionally governed clinical management of the disease. We will highlight several points from their article, including (1) combination chemotherapy in advanced disease, (2) treatment controversies surrounding locally advanced disease, and (3) limitations of available data with regard to adjuvant therapy.

The Hope of Future Strategies

Berlin and Rothenberg discuss emerging strategies such as the use of gemcitabine (Gemzar)-based combinations and protracted-dose infusion gemcitabine. The latter is an example of a rationally designed tactic aimed at increasing the therapeutic index of gemcitabine by promoting higher levels of intracellular triphosphate, the active metabolite of gemcitabine. It remains to be seen whether this approach will prove to be superior to single-agent gemcitabine and whether metered-dose infusion gemcitabine can be combined with other active agents, the limiting factor being hematologic toxicity.

The gemcitabine-based combinations of perhaps most interest include those with irinotecan (CPT-11, Camptosar),[2] docetaxel (Taxotere),[3] cisplatin (Platinol), and fluorouracil (5-FU).[4,5] Although, to date, multiple phase II trials have demonstrated improved response rates and median survivals compared to historical controls, no combination has proven to be superior to single-agent gemcitabine in a randomized comparison. Several ongoing trials in North America and Europe have been designed to help clarify the relative efficacy of these combinations. It is possible that among selected patient groups (including those with good performance status), combination therapy will prove to be superior to single-agent gemcitabine. In addition, as pointed out by the authors, the ultimate goal of improved therapies for metastatic disease is to move them forward into the adjuvant setting, where modest responses may lead to meaningful gains in survival.

With regard to locally advanced, unresectable, nonmetastatic disease, the authors discuss the issue of how best to treat this patient population. In short, we currently do not know what the optimal strategy should be. Clinical trials in inoperable pancreatic cancer have increasingly incorporated both locally advanced patients and patients with overt metastatic disease in the same study, while stratifying for disease stage. The omission of irradiation in locally advanced patients is controversial, but the true effect of radiation therapy, in the absence of a significant pain syndrome, is currently unknown.

For patients with borderline resectable/unresectable disease, the combination of chemotherapy and radiation remains experimental, ie, an effort to facilitate surgical resection. The number of patients whose disease is truly unresectable but becomes resectable by virtue of chemoradiation is considered to be anecdotal, the interpretation depending on how resectability is defined.

A Potent Radiosensitizer

The role of gemcitabine as a radiosensitizer is reviewed, including strategies for altering the schedule and frequency of gemcitabine as well as altering the total radiation dose, volume, and fractionation. Gemcitabine is appreciated as an extremely potent radiosensitizer, which therefore may also engender significant toxicity. The optimal way to administer gemcitabine with radiation has not been defined, and as the authors appropriately point out, gemcitabine-based chemoradiation remains an experimental consideration.
The Cancer and Leukemia Group B (CALGB) recently completed a phase II trial of gemcitabine administered twice weekly to locally advanced patient populations. Blackstock et al have reported the preliminary results of this experience.[6] Randomized trials will be required to determine whether gemcitabine-based chemoradiation is indeed superior to traditional 5-FU-based radiation.

Assessing the Role of Adjuvant Therapy

A significant portion of the article by Berlin and Rothenberg is devoted to the controversies of adjuvant therapy. To date, only one randomized trial of adjuvant therapy in pancreatic cancer, conducted by the Gastrointestinal Tumor Study Group, has been completed in the United States.[7,8] The ongoing Radiation Therapy Oncology Group (RTOG) study has the distinction of being the second. Other trials such as the European Organization for Research and Treatment of Cancer (EORTC) study and the European Study Group of Pancreatic Cancer (ESPAC-1) trial—which were designed to definitively answer the question of the true merits of adjuvant chemoradiotherapy—have major methodologic limitations including a flawed statistical design (ESPAC-1 study) and being significantly underpowered (EORTC study). Therefore, no adequately designed, powered, and contemporarily conducted studies are available for clinical guidance.

Rightly or wrongly, adjuvant 5-FU-based chemoradiation has been adopted as a standard of care. In our opinion, adjuvant chemoradiation probably provides a modest survival benefit, with small, well-differentiated node- and margin-negative tumors being the subgroups most likely to benefit. The RTOG is to be congratulated on efforts to move the field forward with an adequately designed and powered and appropriately stratified clinical trial, which will complete accrual later this year. One major criticism of the RTOG study, however, is the lack of a surgery-alone arm, which was omitted because it was felt that accrual would suffer appreciably. Thus, this study will not address the role of adjuvant therapy per se. It will answer the question of whether gemcitabine administered before and after 5-FU-based chemoradiation improves survival compared to 5-FU alone and 5-FU-based chemoradiation.

Berlin and Rothenberg rightly conclude that the future of therapy for pancreatic cancer will be based largely on a better understanding of the biology of the disease, the use of novel and rationally designed therapies, and the combination of conventional cytotoxic therapy and radiation with these approaches. Currently available agents offer only modest hope for improvement.

References:


