

ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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Current Controversies in the Management of Pancreatic Cancer

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H&O Could you describe the issues regarding the role of radiation in the treatment of pancreatic cancer?

RW The role of radiation, particularly as postoperative therapy, is one of the controversial areas in the management of this disease. Data from studies conducted in Europe suggest that radiation does not provide any significant benefit when given postoperatively after surgical resection and may in fact have a deleterious effect.¹ In the United States, radiation has been a standard component of adjuvant therapy for pancreatic cancer but no studies here have compared chemoradiation with chemotherapy alone. Typically, all patients in the United States are enrolled in clinical trials in which radiation is part of postoperative therapy.

Unfortunately, since 1985 no further improvements in survival have been observed using either postoperative chemotherapy or postoperative radiation therapy; median survival has remained at approximately 20 months. Sadly, a large Radiation Therapy Oncology Group study, reported at the 2006 Annual Meeting of the American Society of Clinical Oncology, continued to show a median survival of 20.6 months in the best arm of the study.²

H&O What possible new approaches are being considered?

RW At the University of Texas M. D. Anderson Cancer Center and other institutions, investigators are exploring preoperative therapy for the treatment of pancreatic

cancer. Whether this therapy is to involve chemotherapy alone or chemoradiation is not a major issue, as so little progress has been made in the postoperative setting over the past two decades.

Promising findings were reported at the 2006 American Society of Clinical Oncology meeting by Viret and colleagues,³ who studied preoperative radiotherapy plus docetaxel in patients with resectable pancreatic adenocarcinoma. Studies presented by Varadhachary et al⁴ and by Nakamori et al⁵ point to the potential efficacy of preoperative therapy as well as the need for further studies to identify the optimal approach.

H&O Must a choice be made between preoperative and postoperative therapy?

RW Typically yes, but it may depend on the exact therapeutic approach. As a general rule, radiation is administered only once to any given patient. There is more flexibility with chemotherapy. It may be possible for a patient to receive preoperative chemotherapy, followed by surgery, followed by additional chemotherapy. One study found that this approach improved survival in patients with resectable gastric cancer, and this model has been explored in a variety of disease settings.³ In some settings, patients who received chemotherapy perioperatively experienced an improvement in survival. Radiation is typically given either before or after surgery.

H&O How are changes in the way patients are categorized impacting the treatment of pancreatic cancer?

RW Pancreatic cancer patients are grouped into three categories: resectable disease, localized but inoperable disease (locally advanced unresectable), and metastatic disease (clear evidence of cancer spread). With advances in imaging, a fourth category is emerging: borderline resect-

able. These patients have tumors touching some arterial structures, such as the superior mesenteric artery or the vessels of the celiac axis, such as the hepatic or splenic artery, but the tumors are not completely wrapped around these structures. These patients seem to be in a grey zone, neither unresectable nor resectable. Several such patients have been treated with chemoradiation or chemotherapy with the result being that enough of the tumor has been destroyed at the periphery, making surgery to remove the tumor completely possible.⁷

One of the barriers to improving surgery has been that 20–30% of patients are left with a positive surgical margin. However, recent evidence indicates that in both resectable and borderline patients, the likelihood of obtaining a larger negative resection is increased by the tumor destruction resulting from preoperative chemoradiation.

H&O Does preoperative therapy shrink the tumor?

RW In pancreatic cancer, tumor destruction is not the same as tumor shrinkage. Often, a fair amount of tumor cell death will occur within a mass as a result of therapy, but the mass itself does not necessarily decrease in size. When the mass is removed, it may be that only 30% is composed of viable cancer cells, with the remainder being dead tissue. Prior to surgery, decreased levels of the tumor marker CA19-9, a crude surrogate for tumor activity, may indicate tumor destruction. After receiving chemotherapy or chemoradiation, patients with operable or borderline resectable cancers will often show a decrease in the previously elevated level of CA19-9.

H&O Is it possible to completely destroy a tumor with preoperative therapy?

RW On rare occasions, a complete pathologic response has been observed, meaning that when the mass is removed, no viable tumor cells are present. This outcome occurs in approximately 20–25% of rectal cancer patients and in 30–35% of esophageal cancer patients. In pancreatic cancer, there are anecdotal reports of patients whose tumors were completely destroyed prior to surgery. However, these anecdotal reports lend further support to the potential efficacy of preoperative therapy.

H&O Has there been resistance to administering preoperative therapy?

RW Yes. There was similar resistance in the settings of esophageal and rectal cancers, but over time the surgical community changed its view of preoperative therapy for these diseases. With pancreatic cancer, it has taken quite

some time for preoperative therapy to be considered even for evaluation in a clinical trial; this resistance has been somewhat puzzling considering the lack of progress over the years using an upfront surgical approach followed by postoperative therapy.

H&O What is the role of radiation in patients with inoperable disease?

RW The role of radiation in patients with inoperable disease is another area of controversy. Traditionally, patients in the United States are treated with chemotherapy and radiation. In a recent European study of inoperable pancreatic cancer, patients were randomized to receive systemic chemotherapy alone or chemoradiation followed by further chemotherapy.⁸ According to the study findings, patients who received chemotherapy alone had a longer survival time than those receiving chemoradiation. Further study is needed before such findings could be incorporated into treatment approaches. However, the data have caused clinicians to scrutinize more carefully the role of radiation, even in locally advanced inoperable disease.

H&O What are the current issues regarding patients with metastatic disease?

RW Currently, the standard therapy for metastatic disease remains controversial, with no broad consensus on the best approach. Since its regulatory approval in 1997, gemcitabine (Gemzar, Eli Lilly) has been used for the treatment of metastatic pancreatic cancer. In an effort to augment the benefit of this agent, investigators have combined it with cytotoxic chemotherapy agents including 5-fluorouracil, irinotecan, cisplatin, oxaliplatin, and capecitabine. Gemcitabine has also been combined with molecular agents to include marimastat, a matrix metalloproteinase inhibitor, the epidermal growth factor receptor (EGFR) inhibitor erlotinib (Tarceva, OSI/Genentech), bevacizumab (Avastin, Genentech), an antibody to vascular endothelial growth factor, and the EGFR inhibitor cetuximab (Erbix, Bristol-Myers Squibb/ImClone). Thus far, no regimen combining gemcitabine with a cytotoxic agent has shown a statistically significant benefit compared with gemcitabine alone. However, gemcitabine plus erlotinib provides a 2-week survival advantage compared with gemcitabine alone, with a 1-year survival rate of 24% versus 17%, respectively. Although the data are statistically significant, many physicians consider these differences to be clinically insignificant.

There is much interest in being able to determine which patients are likely to benefit from the addition of erlotinib to gemcitabine, so that patients could be better selected for this regimen.

Studies investigating the potential role of platinum analogs in combination with gemcitabine have found that the combination does appear to increase the response rate, and there may indeed be a small advantage to adding a platinum analog to gemcitabine therapy. The benefit may be modest, extending survival by several weeks to a couple of months. A similar modest survival benefit has been observed with gemcitabine plus capecitabine versus gemcitabine alone.

Clinical trials now underway include one conducted by the Cancer and Leukemia Group B comparing gemcitabine plus bevacizumab with gemcitabine alone. Another study, conducted by the Southwest Oncology Group, is evaluating gemcitabine with or without cetuximab.

For all of these various approaches, a benefit is more likely to be seen in patients who are healthy overall, with a good performance status, compared with patients who are debilitated or who have a significant tumor burden. Investigators have begun to consider how clinical trials might be better designed in order to identify the subset of patients likely to benefit from a particular therapeutic approach.

H&O What would be the possible selection criteria?

RW Patients may be selected according to characteristics such as health, the level of tumor burden, or, eventually, molecular characteristics. There may be one molecular signature that would favor one combination over another.

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