

Current and Future Strategies for Treating Metastatic Pancreatic Cancer

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What is the current standard of care for treating metastatic pancreatic cancer?

The standard of care in this country is chemotherapy with gemcitabine (Gemzar, Lilly). Up until the 1990s, the best agent available for treating this disease was 5-fluorouracil (5-FU). In the mid-1990s, a randomized, phase III trial evaluating gemcitabine versus 5-FU found that patients receiving gemcitabine experienced an improved 1-year survival, a slight improvement in median survival, and an improved clinical benefit response, a parameter measuring some specific symptoms of the disease. These findings, published by Burris et al in the *Journal of Clinical Oncology* in 1997, led to gemcitabine becoming the standard of care for this disease.

What have subsequent studies with chemotherapy combinations found?

Subsequent to the study that established gemcitabine as the standard of care, multiple drugs have been tested either against gemcitabine alone or in combination with gemcitabine versus gemcitabine alone. Some of these studies have shown a trend toward improvement, but none have shown definite benefit. For example, a study of 5-FU plus gemcitabine had a trend toward improved survival and improved progression-free survival. However, this trial did not demonstrate that adding 5-FU resulted in clinical benefit. The combination did not improve symptoms more than gemcitabine alone, nor did it significantly improve the 1-year survival.

Cisplatin (Platinol, Bristol-Myers Squibb) showed a similar effect when added to gemcitabine. There may have been a trend toward improvement in survival, but this improvement was not statistically significant. In addition, this combination added toxicity. One of the advantages of gemcitabine is that it is very well tolerated by most patients. Obviously, the addition of an agent that is associated with toxicity without adding significant benefit would not be desirable.

Why haven't any combination chemotherapy regimens improved outcomes?

Some of these agents may have improved outcomes, but not to a degree that was clinically significant. Some drugs do not combine well with others, which may be part of the problem. However, gemcitabine combines well with platinum agents in other disease settings. Pancreatic tumors are highly resistant, and it is likely this characteristic that makes patients less responsive to this combination.

Which chemotherapy combination has shown the most promising results so far?

A study conducted by Louvet et al evaluated the combination of oxaliplatin (Eloxatin, Sanofi-Synthelabo) and gemcitabine. The survival time was very long for patients receiving this combination, although it was not statistically significantly longer than the gemcitabine-alone arm. However, the data from this trial were intriguing in that patients receiving gemcitabine alone had a very long survival time. The benefit from the combination may have been diminished in the analysis of the data because the standard arm did better than any other standard arm in other studies.

Why might patients receiving gemcitabine alone in this study have had such a long survival time?

This result may have been due to patient selection. One issue present in many pancreatic cancer trials is that the patient population includes both locally advanced disease and metastatic disease. Patients with locally advanced disease have a better prognosis, so it is likely that the more patients with locally advanced disease enrolled in a trial, the better the median survival will be. Also, in the trial by Louvet et al, patients with locally advanced disease received chemotherapy plus radiation after receiving a few cycles of chemotherapy alone. This additional treatment may or may not have affected the results. These factors could have played a role in extending the median survival in both treatment arms, but at the same time made it difficult to determine whether there was a statistically significant difference between the 2 regimens.

Another feature of this study is that when oxaliplatin is added to gemcitabine, the way in which gemcitabine is given is changed: the infusion rate was slowed down in order to increase the effectiveness of the drug. In a small trial conducted by Drs. Abbruzzese and Tempero and the University of Texas M. D. Anderson Cancer Center, slowing the infusion rate of gemcitabine, known as fixed-dose rate (FDR), resulted in an improvement in the benefit from the drug, although this trial was too small to be conclusive.

Is the combination of oxaliplatin and gemcitabine continuing to be studied?

Yes. In the Eastern Cooperative Oncology Group trial 6201, patients are being randomized to receive standard gemcitabine, FDR gemcitabine, or FDR gemcitabine plus oxaliplatin. Hopefully, this trial will clarify the issues raised by the study by Louvet et al.

What agents should not be studied further in combination with gemcitabine?

According to several studies, irinotecan (Camptosar, Pfizer) and exatecan (Daichi) do not work in combination with gemcitabine. These agents have not shown any benefit in any parameter other than response, which is not necessarily clinically meaningful. It may be that these agents would be more effective in combinations that do not include gemcitabine.

Could you discuss the incorporation of targeted agents into studies of metastatic pancreatic cancer therapy?

Over 90% of patients with pancreatic cancer may overexpress the epidermal growth factor receptor (EGFR). This protein can drive the growth of cancer cells, and therefore blocking the receptor may block the growth of cancer. In a phase II study by Abbruzzese et al, patients with previously untreated pancreatic cancer received gemcitabine plus cetuximab (Erbix, ImClone/Bristol-Myers Squibb), an EGFR inhibitor. The median survival time was just over 6 months, which is not very different from that seen with patients who received gemcitabine alone, however, the 1-year survival rate was very promising, suggesting that this combination might extend life for a group of patients. There is an ongoing Southwest Oncology Group randomized study of cetuximab plus gemcitabine versus gemcitabine alone that should clarify the efficacy of this combination.

One of the benefits of cetuximab is that this agent is well tolerated, with very few patients stopping therapy due to toxicity. Many patients experience a rash that, although problematic, is treatable.

The Eastern Cooperative Oncology Group is conducting a trial of cetuximab in combination with irinotecan plus docetaxel (Taxotere, Aventis). In the early stage of this trial, reported by Dr. Burtness of Yale University, a promising 9-month median survival time was observed (ASCO 2004). This study has proceeded to a randomized, phase II trial of the same combination with or without cetuximab. This study is not taking into account whether or not patients

have tumors overexpressing EGFR, although tissue will be analyzed retrospectively. The main purpose of this study is to determine whether either regimen is promising enough to proceed to a phase III study.

Is it known whether EGFR expression definitely correlates with cancer growth in pancreatic cancer?

It is not possible to evaluate this question in pancreatic cancer because almost all patients overexpress EGFR. However, in every disease thus far in which this has been assessed, staining for EGFR was not predictive of anything. It is true that overexpression does not necessarily mean that the tumor is dependent on the protein. If the tumor is not dependent on EGFR, then blocking this protein will have no effect because other factors are causing tumor growth. Also, even if a stain for a tumor does not reveal overexpression, there may still be some level of expression. Several thousand copies of a protein are necessary in order to be seen on a stained cell. Patients who stain negative may be positive for expression, but not overexpression. Tumors may be just as dependent on the protein for growth in these individuals as they are in individuals who stain positive for EGFR. The current trial evaluating cetuximab in pancreatic cancer does not focus on EGFR positivity. Although the question of whether tumor growth is related to EGFR can be studied retrospectively, it needs to be approached prospectively in other diseases, such as colon cancer, in which the expression of EGFR is more variable.

Could you discuss the use of rubitecan in metastatic pancreatic cancer treatment?

At the 2004 annual meeting of the American Society of Clinical Oncology (ASCO), a study was presented in which patients refractory to gemcitabine were randomized to receive rubitecan (Orathecin, SuperGen) or the physician's choice of therapy. There was not a statistically significant difference in survival between the 2 arms. Progression-free survival was 10 days longer for patients receiving rubitecan, a finding that was statistically significant but not necessarily clinically meaningful.

Patients who progressed on the physician's-choice arm were able to receive rubitecan upon progression, and these patients experienced a longer survival time than patients who did not cross over. However, it is important to note that this group of patients was healthy enough to receive additional therapy, implying selection of a group that was already doing better. There were hints of activity in patients receiving rubitecan, but more proof of its benefit in terms of either quality or quantity of life is needed. There are 2 completed trials of this agent that will hopefully clarify the efficacy of this agent in the treatment of metastatic pancreatic cancer. The data has been pending for a long time now, but hopefully will be available soon.

Is bevacizumab being studied in pancreatic cancer?

Yes, bevacizumab (Avastin, Genentech) has been studied in pancreatic cancer, with promising results. In combination

with gemcitabine for locally advanced and metastatic pancreatic cancer, the median survival time was 8.7 months, as reported at this year's ASCO meeting (Kindler, ASCO 2004). The median survival time had originally been reported as 12 months, but as more patient data became available, the time decreased. However, 8.7 months is still very good, considering that gemcitabine alone has consistently shown an approximately 6-month median survival, with the exception of the study by Louvet et al. A randomized trial is now being conducted by the Cancer and Leukemia Group B evaluating bevacizumab plus gemcitabine versus gemcitabine alone.

All 3 cooperative group trials discussed here are extremely worthwhile and should answer some major questions about the treatment of metastatic pancreatic cancer. These are multicenter trials, and most patients should be within reasonable distance of a center where this study is being conducted.

Have any anti-EGFR tyrosine kinase inhibitors been studied for the treatment of pancreatic cancer?

There was a trial conducted by the National Cancer Institute of Canada studying the combination of erlotinib (Tarceva, OSI) plus gemcitabine versus gemcitabine alone. This trial is completed but results are not available yet. Positive findings would raise interest in studying gefitinib (Iressa, AstraZeneca) in this disease setting.

Considering the relatively short survival time of patients with metastatic pancreatic cancer and the many combinations that need to be evaluated, is there some other approach to designing phase III studies that might enable more rapid evaluation?

There are 2 issues to consider here. First, the regulatory environment would favor a study evaluating gemcitabine versus another agent or gemcitabine plus another agent versus gemcitabine alone. This approach is the only way to have a new drug approved for this indication. However, it is possible to conduct a randomized, phase II study and, if the primary endpoint is met, then the study can continue

as a randomized, phase III study. This design can shorten the length of some phase III studies and has the advantage of not treating as many patients with what turns out to be an ineffective approach.

Right now, we need to start thinking more broadly about combining agents together. There are drugs that have shown some signs of activity. We need to consider how they can be best utilized in combination, rather than how they can be combined with gemcitabine. Gemcitabine is an excellent drug and should be tested in combination with other agents. However, there may be some agents that are more synergistic in combinations that do not include gemcitabine, or with which the toxicity profile matches better.

Another issue is that patients with locally advanced disease should not be included in the same trials as patients with metastatic disease, both in phase II and phase III. Including both stages in the patient population makes the results more difficult to interpret, and may be misleading, particularly in phase II studies.

Suggested Reading

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