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What's new in pancreatic cancer treatment pipeline?

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There is still a substantial need for the development of new treatments for patients with pancreatic cancer. In this chapter, we will document that there is quite a bit of an increase in research activity with development in two major areas including (1) agents in the pipeline which already have hints of antitumor activity in patients with pancreatic cancer (therapeutic monoclonal antibodies and vaccines as well as more conventional cytotoxics), and; (2) agents in the pipeline which have just started (or will soon start) in clinical trial. These agents range from a gene-therapy approach to radiation enhancement to inhibitors of protein with increased expression in the very hypoxic pancreatic cancer tissue, to new monoclonal antibodies. With the level of investigational activity in pancreatic cancer it is very likely that several new therapeutic approaches to the disease will be forthcoming.

Key words: vascular endothelial growth factor (VEGF); epidermal growth factor receptor (EGFR); gastrin; hypoxia inducible factor alpha (HIF-1α); vaccine; thioredoxin reductase; polo-like kinase; thioredoxin; gemcitabine; bevacizumab; cetuximab; TNFerade; sorafenib; prostate specific cancer antigen (PSCA).

As is well outlined in this volume, pancreatic cancer is a terrible malignancy with the vast majority of patients succumbing to the disease.[1] In fact there has been 'defeatism and nihilism' in clinicians seeing and caring for patients with pancreatic cancer leading to journal articles entitled 'Should future studies of chemotherapy be carried out in pancreatic cancer?'.[2] Perhaps it was a self-fulfilling prophecy that because it was felt unlikely there was a chance for progress against the disease (at least with a chemotherapeutic approach) that there was no reason to try and advances against the disease were not forthcoming.

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However, in 1995–1996 things began to change ever so slightly with first the early reports of patients with advanced pancreatic cancer benefiting from receiving the new agent gemcitabine.[3,4] In 1997, there was the final report that in a randomized controlled trial of weekly gemcitabine versus weekly 5-fluorouracil (5FU) that gemcitabine provided not only a significant clinical benefit (e.g. less need for pain medication, less of a deterioration in performance status) of 23.8 versus 4.8% but also an improvement in median survival of 5.65 versus 4.41 months ($p = 0.0025$) and in 1-year survival from 2% for 5FU to 18% for gemcitabine.[5] Obviously this was only a very modest improvement in survival. However, it did clearly indicate that chemotherapy could have an impact on survival for patients with advanced pancreatic cancer.

As is well covered in this volume, there has been a tremendous amount of work trying to improve on the activity of gemcitabine with the development of various combinations of other established and new agents as well as other modalities with gemcitabine. Some of these regimens such as gemcitabine plus erlotinib or gemcitabine plus capecitabine have just recently been shown to moderately improve survival over the use of gemcitabine alone.[6,7] However, of even greater interest is the use of gemcitabine in patients felt to have resectable pancreatic cancer. In beautiful work by Neuhaus and colleagues, patients with resectable disease had their surgery and within 6 weeks after operation were randomized to receive gemcitabine versus observation (after stratification for positive or negative resection margins, nodal tumor involvement, and tumor stage).[8] A total of 179 patients were randomized to gemcitabine and 177 to observation. The primary endpoint for the study was disease free survival which was 14.2 months for patients receiving adjuvant gemcitabine versus 7.5 months for patients just being observed ($p < 0.05$). Of interest is that the disease-free survival was better for patients receiving adjuvant gemcitabine versus placebo both in patients with or without positive margins and in both patients with or without positive lymph nodes (caution in this interpretation because this was a subset analysis). The secondary endpoint for the study, overall survival, has not yet been reached.[8]

The reason we have covered the above work by Neuhaus and colleagues is to emphasize that perhaps when a drug such as gemcitabine, which has quite (in fact very) modest activity in patients with advanced metastatic pancreatic cancer is used in an adjuvant situation, the impact has the potential to be quite dramatic. This certainly has also been the case in patients with breast cancer for the agent trastuzumab (Herceptin) were the drug has very modest activity in patients with advanced disease but rather incredible activity in combination with chemotherapy for patients with breast cancer treated in an adjuvant situation.[9] What this means to investigators in the area of therapeutics for patients with pancreatic cancer is that even modest advances applied early in the disease might also have quite a substantial impact on the disease. In fact it teaches us a lesson that in the future, some of the new therapeutic agents discussed below should be moved into an adjuvant situation as soon as possible (even though currently the majority of patients with pancreatic cancer do not present with resectable disease).

The other point that we want to emphasize in this introduction is that the findings of a new agent such as gemcitabine which has very modest activity in patients with advanced pancreatic cancer can really stir interest in investigators propelling them to try new agents and new approaches for patients. As is noted in Figure 1, for the years before approval of gemcitabine for patients with advanced pancreatic cancer (see arrow in Figure 1) there were a total of 20–80 abstracts per year in the two major cancer meetings American Association for Cancer Research (AACR) and American Society for Clinical Oncology (ASCO). However, after the introduction of gemcitabine showing