New frontiers in the therapeutic landscape for metastatic pancreatic cancer

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The treatment of adenocarcinoma of the pancreas remains a formidable therapeutic challenge. Compared to other malignancies, this disease is frequently diagnosed late in its course and has an unusual predisposition for early invasion and metastasis.

Pancreatic carcinoma has been considered to be relatively resistant to conventional cancer therapies. In addition, the desmoplastic response associated with pancreatic cancer makes traditional ' response' assessment difficult. A better marker may be serial measurements of CA 19-9, a sialyated Lewis a antigen. Declining levels of CA 19-9 correlate well with improved survival and ultimately, this simple test may replace expensive radiographic studies. Recently, the nucleoside analogue gemcitabine has been shown to have modest effectiveness in controlling symptoms and improving survival. Through a better understanding of the pharmacokinetics of gemcitabine, it has been possible to improve the activation of this prodrug resulting in better therapeutic efficacy. We have shown that administration of gemcitabine using a fixed dose rate (10 mg/m^2/min) results not only in an improved concentration of the intracellular phosphorylated gemcitabine, but also in improved survival. Of the new gemcitabine drug combinations, gemcitabine combined with cisplatin or oxaliplatin seem to provide the most benefit. Trials with gemcitabine and moderate dose cisplatin or with fixed dose rate gemcitabine and oxaliplatin have shown improvements in time to progression, as well as a trend toward improved survival. To a lesser extent, a recent randomised trial of gemcitabine combined with capecitabine also delayed progression but not overall survival. A failure to show an overall survival benefit in these recent studies has most likely been due to a crossover effect of increasingly effective second time therapies for patients who begin treatment with standard infusion gemcitabine.

Based on the known genotypic and phenotypic alterations in pancreatic adenocarcinoma, further advances in therapy are anticipated by the application of a rational approach to drug discovery. Although the potential menu of targets is still unfolding, some attractive new agents are well on their way towards Food and Drug Administration, USA approval for use in pancreatic adenocarcinoma and others are in the pipeline of application in this disease. The EGFR pathway has been a popular target and a recent randomised trial of gemcitabine plus erlotinib (a tyrosine kinase inhibitor of VEGRr) has shown a small but significant improvement for medium survival compared to gemcitabine alone. Cetuximab, an antibody targeting EGFR, has shown promising results in a Phase II trial and is under investigation in a large randomised trial. In addition, pancreatic adenocarcinoma displays a number of host-tumour interactions suggesting that this malignancy can co-opt its environment to enhance progression, invasion, and metastasis. The VEGF pathway may be very important in this regard. Bevacizumab, an antibody neutralising VEGF, has shown encouraging activity in combination with gemcitabine in the Phase II setting. This agent also is under evaluation in a large randomised Phase III trial. Other molecules targeting the VEGR receptor are in the pipeline and many are already in Phase II testing for first or second line therapy. Finally, vaccine strategies using GM-CSF transected allogeneic tumour cells or using selected appropriate antigens such CEA or MUC1 combined with an array of growth co-stimulatory molecules are undergoing clinical evaluation in the setting of both metastatic disease as well in adjuvant therapy.

In the future, targeted agents will likely be used in combination and conventional chemotherapy drugs. Future treatment strategies will rely on predictive molecular diagnostics or novel imaging approaches for appropriate patient selections paving the way for tailored therapy. Selecting therapy based on ' likelihood of benefit' will be more efficient and more effective.