The way forward in treating pancreatic cancer

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The statistics are familiar to us all. In the United States, 42,470 men and women will be diagnosed with, and 35,240 men and women will die of, cancer of the pancreas in 2009 [SEER, 2009]. It is the fourth most common cause of cancer-related death in this country. A combination of lack of effective screening modalities, late diagnosis and ineffective therapy result in survival estimated to be less than 5% at 5 years from the diagnosis.

Recent research has taught us more about the biology of pancreatic cancer. Three precursor lesions have been identified, most commonly PANin (pancreatic intraepithelial neoplasia), but also intraductal papillary mucinous neoplasms and mucinous cystic neoplasms [Maitra *et al.* 2005]. Genetic syndromes, such as hereditary pancreatitis, Peutz–Jeghers, familial atypical multiple mole melanoma, familial pancreatic cancer, and BRCA2 have been recognized, and the responsible mutations PRSS1, STK11/LKB1, p16(MTS-1/CDKN2/INK4a) and BRCA2, respectively, have been identified [Shi *et al.* 2009; Greer *et al.* 2007; Rocco and Sidransky, 2001]. In addition, an elegant study has demonstrated that the dysregulation of multiple genes in a wide variety of pathways may be responsible for most pancreatic cancers [Jones *et al.* 2008]. Some of these genes are relatively well described (KRAS, p53, SMAD4) and others are less well known. Indeed, even the pancreatic cancers' often dense stroma may add to the resistance of this cancer to treatment [Chu *et al.* 2007]. Thus, the complexity of this cancer's biology creates significant barriers to successful treatment of this deadly disease.

For the majority of patients who cannot be cured with local therapy, chemotherapy is utilized

with the current goal being disease control. Gemcitabine (2,2'-difluorodeoxycytidine, dFdC) remains the single most effective drug in our arsenal. Unfortunately, the response rate is a meager 6–11% without chance of cure [Casper *et al.* 1994].

Those patients initially benefit from gemcitabine develop progressive disease 2–3 months later, and the overall survival is only about 6 months.

Clinical research has therefore been focused in three directions: understanding the resistance to gemcitabine and thereby improving its efficacy; adding second agents to gemcitabine; and, finally, searching for unique vulnerabilities in the cancer that could be targeted.

There is potential that the studies of gemcitabine pharmacodynamics will lead researchers to better utilize the drug, creating a platform for 'personalized medicine'. Gemcitabine is extremely hydrophilic and requires specific transport systems to enter the cell such as human equilibrative transporters (hENT) and human concentrative nucleoside transporters [Mackey *et al.* 1998]. Once in the cell, gemcitabine is phosphorylated by deoxycytidine kinase (dCK), the rate-limiting step, to difluorodeoxycytidine. Gemcitabine triphosphate (dFdCTP) is incorporated into DNA, leading to early strand termination. Gemcitabine also inhibits ribonucleotide reductase. The phosphorylated gemcitabine is metabolized by cytidine deaminase. Because pancreatic cancer cells vary in the activity of these different enzymes, different tumors may be more or less sensitive to the drug. For instance, deficient expression of hENT correlates with decreased disease-free and overall survival compared with patients with normally expressed hENT1 [Farrell *et al.*

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2007; Spratlin *et al.* 2004]. Mutation or overexpression of both ribonucleotide reductase subunits M1 and M2 can affect patients' survival, promoting drug resistance [Itoi *et al.* 2007; Davidson *et al.* 2004]. Correlations have been described between certain single nucleotide polymorphisms (SNPs) of CDA and dCK genes and gemcitabine effectiveness and toxicity [Javle *et al.* 2008].

Efforts have been made to circumvent these challenges. An elaidic ester of gemcitabine, CP-4126 (Clavis Pharma), has been developed to enter the cells independently of nucleoside transporters and is currently under investigation, showing promising results in preclinical and early clinical trials [Galmarini *et al.* 2009]. Fixed-dose-rate gemcitabine administration, with infusions of drug at 10 mg/m²/min, was developed and shown to increase the concentration of the dFdCTP [Tempero *et al.* 2003]. However, a recently conducted phase III trial failed to show a clinically significant improvement in survival [Poplin *et al.* 2009]. The combination of gemcitabine and triapine, a ribonucleotide reductase inhibitor, was unsuccessful [Mackenzie *et al.* 2007]. Clearly, our understanding how gemcitabine works *in situ* in pancreatic cancer is still insufficient.

Unlike our track record for the treatment of other cancers, we have not improved the chemotherapy for pancreatic cancer by using it in chemotherapy

combinations, as shown in Table 1. With over 3500 patients in phase III studies comparing gemcitabine with or without a second cytotoxic agent, no statistically significant improvement in survival has been demonstrated in any single study. Studies assessing the benefit of targeted therapies have yielded similarly frustrating results. Only the combination of erlotinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, and gemcitabine showed a statistically significant, if not clinically significant, improvement in survival compared with gemcitabine alone improving overall survival from 5.91 to 6.24 months [Moore *et al.* 2007].

Despite the ubiquity of Ras mutation in pancreatic cancers, Ras-directed therapy using farnesyl transferase inhibitors has been unsuccessful. Anti-angiogenesis approaches, with bevacizumab and axitinib, were surprisingly unsuccessful [Kindler, 2007; Philip *et al.* 2007]. Matrix metalloproteinase inhibitors, marimastat and BAY 12-9566, were tested against gemcitabine alone and were found to be inferior [Richards, 2005; Moore *et al.* 2003]. Peptide vaccines, allogene modified tumor cell vaccines and vector-based vaccines remain largely experimental with few exceptions. A phase III study looking at sequential combination of gemcitabine plus GV1001, a telomerase peptide vaccine, compared with single-agent gemcitabine had to be closed prematurely when interim analysis showed no survival benefit [Buanes *et al.* 2009].

Table 1. Median overall survival in phase III trials of patients with advanced pancreatic cancer treated with gemcitabine combinations.

	Number of patients	Gemcitabine	Gemcitabine + study drug	p-value
Oxaliplatin	832	4.9	5.7	NS
Oxaliplatin	326	7.1	9.0	NS
Capecitabine	319	7.2	8.4	NS
Exatecan	349	6.2	6.7	NS
Cisplatin	195	6.0	7.5	NS
Cisplatin	107	4.6	6.9	NS
Irinotecan	145	6.5	6.4	NS
Irinotecan	360	6.6	6.3	NS
Pemetrexed	565	6.3	6.2	NS
5-FU (bolus)	322	5.4	6.7	NS
Marimastat	239	5.4	5.4	NS
Cetuximab	735	6.0	6.5	NS
Bevacizumab	602	5.8	5.2	NS
Bevacizumab*	607	6.0*	7.1	NS
Erlotinib	569	5.9	6.2	0.038
Tipifarnib	688	6.0	6.3	NS

*Combination of gemcitabine and erlotinib; 5-FU, 5-fluorouracil; NS, not significant.

There is a plentiful supply of new drugs currently being studied. CP-4126 may prove to be a better gemcitabine. Nab-paclitaxel, an albumin-bound nanoparticle form of paclitaxel, appears to provide some clinical benefit when combined with gemcitabine [Von Hoff *et al.* 2009]. This formulation increases tumor concentration of paclitaxel by binding of albumin to SPARC (secreted protein acid rich in cysteine), a protein involved in cell stroma interactions, cell migration and wound repair. Therefore, it appears to target not only cancer cells but also cancer stroma. EndoTAG-1, a cationic liposomal formulation of paclitaxel, targets negatively charged endothelial cells of tumor blood vessels. AMG655 is a monoclonal antibody agonist of TRAIL receptor 2/Death Receptor 5 (TR-2/DR5) which ultimately leads to apoptosis of sensitive cells, apparently exhibiting some synergism with gemcitabine as shown in recently reported phase I study [Kindler *et al.* 2009]. Masitinib is a tyrosine kinase inhibitor which targets c-KIT, platelet-derived growth factor receptor and fibroblast growth factor receptor 3. Preclinical data showed masitinib-enhanced antitumor toxicity of gemcitabine, and this combination is currently undergoing clinical trials. Other targeted therapies include, among others, Hedgehog inhibitors, insulin growth factor antagonists and a transforming growth factor-beta antagonist.

So, as we can see, there is no deficit of new targets and therapeutic agents in pancreatic cancer. However, unfortunately, there have been a multitude of encouraging phase II studies that could not be confirmed in large and expensive (in patient resources and money) phase III studies. Clearly, our threshold for considering a combination or new drug as 'promising' is either too low or just wrong. Development of better statistical tools to screen among positive phase II studies for truly promising leads need to be developed. Further, we are trying a 'one size fits all' approach to a disease with a multitude of genetic alterations and phenotypic variations that may vary from cancer to cancer. Instead, if we use a new chemotherapeutic agent with known mechanism of action, we should verify that this particular tumor has the susceptible phenotype, that the drug gets to the cancer and has the expected activity. If we use a 'targeted' drug, we should check that the tumor has the target and that the target can be engaged by our new drug. We need to develop methods to solve these problems as we develop new agents. To do so will require the

development of biomarkers to assess susceptibility, and the utilization of tumor biopsies to assay for the presence of markers, as is routinely done for breast cancer and more recently for colon cancer [Lievre *et al.* 2008; Harris *et al.* 2007]. In addition, we can consider developing techniques for early signals of activity, perhaps utilizing *in vivo* techniques, such as magnetic resonance spectroscopy (MRS) or 6-[18F]fluoro-1-dopa positron emission tomography (FD-PET) to enhance our understanding of drug activity. A multipronged approach to pancreatic cancer, with improved understanding of the complexity of the challenge and the variability between different patients and their tumors, should be our goal.

Conflict of interest statement

Dr. Sedov declares no conflict of interest in preparing this editorial. Dr. Poplin is currently consultant for Clovis Oncology.

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