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Pancreatic cancer: current standards, working towards a new therapeutic approach

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Abstract

Pancreatic cancer is the fourth leading cause of cancer deaths with a 5-year survival of 4–6%. Clinical challenges remain to be addressed, since few promising approaches to treat pancreatic cancer have been reported. Here we discuss the potential of a new biotherapeutic agent composed of a lysosomal protein (Saposin C, SapC) and an acidic phospholipid (dioleoylphosphatidylserine, DOPS) which can be assembled into stable nanovesicles (SapC-DOPS) for tackling pancreatic cancer. Phosphatidylserine (PS) is a lipid biomarker on membrane surface of pancreatic cancer cells and can be effectively targeted by SapC-DOPS nanovesicles for cancer-selective therapy. SapC-DOPS nanovesicles have shown excellent pre-clinical therapeutic and safety profiles. Safety profiles which suggests that this new approach is potentially a viable option for pancreatic cancer therapy that is worthy of further clinical development.

Keywords

chemotherapy; combination treatment; metastases; monotherapy; new approach; pancreatic cancer therapy; resistance; SapC-DOPS nanovesicles; toxicity

Pancreatic cancer remains the fourth most common cause of cancer-related death in men and women in the USA. In 2013, an estimated 45,220 people will be diagnosed with pancreatic cancer and 38,460 people will die of it [1]. The 5-year survival is 6%, and the majority of patients are diagnosed with metastatic disease. Median survival is 9 to 10 months for

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patients with locally advanced unresectable disease and about 4.5 months for those who present with metastases [2]. The incidence and mortality rates in pancreatic cancer are nearly identical, reflecting the inadequacy of current therapies. In order to look forward to new therapeutic approaches, it is important to understand the current acceptable standards of care based on landmark clinical trials in pancreatic cancer. Multiple potential therapeutic strategies exist, but this paper will focus on the current evidence-based category 1 National Comprehensive Cancer Network guidelines in metastatic disease as well as discuss saposin C-dioleoylphosphatidylserine (SapC-DOPS) nanovesicles as a potential new approach in the treatment of pancreatic cancer.

No chemotherapy agent with single-agent activity has been consistently associated with objective response rates above 10%, or median survival longer than 5–7 months. Gemcitabine is a National Comprehensive Cancer Network category 1 recommendation for patients with pancreatic cancer, particularly those with metastatic pancreatic cancer who do not wish to be treated with a very intensive chemotherapy regimen or those with an Eastern Cooperative Oncology Group performance status of two or greater who are not considered candidates for a more intensive first-line chemotherapy regimen. In a pivotal Phase II study of gemcitabine in patient with 5 fluorouracil (5-FU) – refractory pancreatic cancer, ‘clinical benefit’ was defined as an improvement in pain, performance status or weight without deterioration in any other factor [3], the objective response rate for patients with measurable disease was 11% with a clinical benefit in 27%. A subsequent trial was conducted that included 126 previously untreated patients with stage IV or locally advanced pancreatic cancer who were randomly assigned to 5-FU or gemcitabine [4]; gemcitabine was associated with significantly better clinical response (24 vs 5%), median overall survival (5.6 vs 4.4 months) and 1-year survival (18 vs 2%) compared to 5-FU. This led to the US FDA approval of gemcitabine for this disease in 1996.

Following gemcitabine approval, multiple Phase III clinical trials comparing gemcitabine to various chemotherapy doublets incorporating gemcitabine plus a study drug were embarked upon with no significant benefit observed until 2013. Since pancreatic cancers often express receptors for EGF [5], studies incorporating small-molecule tyrosine kinase inhibitors of the EGF receptor such as erlotinib, as well as monoclonal antibodies directed against this molecule, were conducted. A Phase III trial from the National Cancer Institute of Canada that directly compared gemcitabine with and without erlotinib in patients with metastatic or locally advanced pancreatic cancer demonstrated a statistically significant improvement in overall survival (6.2 vs 5.9 months) [6]. Following the results of this trial, the FDA approved erlotinib hydrochloride in combination with gemcitabine for the treatment of patients with locally advanced, unresectable or metastatic pancreatic carcinoma in 2005.

FOLFIRINOX, consisting of 5-FU, leucovorin, oxaliplatin and irinotecan, demonstrated superiority over gemcitabine in a randomized Phase II study. The study was expanded to a Phase III trial of 342 patients which showed a statistically significant improvement in overall survival (11.1 vs 6.8 months). Treatment-related toxicity was significantly worse with FOLFIRINOX and included grade 3 or 4 neutropenia (46 vs 21%), vomiting (15 vs 8%), diarrhea (13 vs 2%), thrombocytopenia (9.1 vs 3.6%), sensory neuropathy (9 vs 0%) and febrile neutropenia (5.4 vs 1.2%) [7]. Despite greater toxicity, FOLFIRINOX

significantly improved global health status as compared to gemcitabine. Based on these results, FOLFIRINOX is now considered a category 1 recommendation for advanced pancreatic cancer.

Following encouraging results of a Phase I/II study of nanoparticle albumin-bound (nab)-paclitaxel in combination with gemcitabine in patients with previously untreated metastatic pancreatic cancer [8], a Phase III study was initiated. There was a statistically significant median overall survival benefit of 8.5 versus 6.7 months in the nab-paclitaxel–gemcitabine group compared to the gemcitabine arm. The most common adverse events of grade 3 or higher were neutropenia (38% in the nabpaclitaxel– gemcitabine group versus 27% in the gemcitabine group), fatigue (17 vs 7%), neuropathy (17 vs 1%) and febrile neutropenia (3 vs 1%) [9]. Following the results of this trial, the FDA approved nab-paclitaxel in combination with gemcitabine for the first-line treatment of patients with metastatic adenocarcinoma of the pancreas in 2013.

Therapeutic strategies targeting angiogenesis were evaluated in a Phase III study but were unsuccessful [10], and strategies for molecular targeting of *RAS* mutations are currently under study [11] as well as multiple vaccine trials. Although obvious progress has been made in chemotherapy for pancreatic cancer over recent years, significant challenges persist, including chemotherapy toxicities, resistance to chemotherapy, genetic and epigenetic complexity and heterogeneity and redundancies or multiple ‘cross-talks’ in molecular signaling pathways. Below, we present a novel approach using protein-lipid (SapC-DOPS) nanovesicles that have shown robust preclinical therapeutic potential for pancreatic cancer by selectively targeting surface acidic phospholipids of cancer cells [12].

Saposin C (SapC) is a stable 80-amino acid protein that distributes in lysosomes of all cell types. SapC, a membraneassociated molecule, induces fusion of acidic phospholipid-rich membranes in acidic pH environments, as are often found around tumor cells [13–16]. PS is an abundant acidic phospholipid that naturally occurs in biologic membranes. A unique lyophilized formulation of SapC and an acidic phospholipid DOPS can be used to obtain stable nanovesicles with an average diameter of approximately 200 nm using a co-solvent water system [12,17–19]. Administration of SapC-DOPS nanovesicles has been shown to have potent cancer-selective targeting and anti-tumor efficacy in xenografted preclinical pancreatic cancer models [12].

Increased surface PS exposure has been identified on human pancreatic cancer cells [12]. Surface PS level of pancreatic cancer cells appear to be higher compared to other tumor types. Fusiogenicity of SapC leads to the selective targeting function of SapC-DOPS nanovesicles to pancreatic cancer cells through surface-exposed PS. This targeting effect can be effectively blocked by specific PS-binding proteins in cancer cells, such as lactadherin or β2-glycoprotein [12,19]. Clearly, tumor cell-death induction activity by SapC-DOPS correlates with surface PS levels on human pancreatic cancer cells. SapC-DOPS anti-pancreatic cancer efficacy is independent of genetic alterations of single or multiple genes/proteins. There is no significant correlation between genetic profile and PS exposure in tested human pancreatic cancer cells.

In fact, SapC-DOPS has shown strong inhibitory impact on pancreatic cancer cells regardless of their genetic modifications. In untransformed cells, asymmetric membrane acidic phospholipid distribution leads to a low PS exposure on the outer membrane surface. Therefore, SapC-DOPS shows weak binding to these cells and has a strong safety profile. No gross toxicities were observed in a preclinical safety investigation [18]. Interestingly, combination treatment of gemcitabine with SapC-DOPS shows synergic efficacy that is likely due to PS exposure enhancement by gemcitabine [Qi et al., Unpublished Data]. Such a combination approach can be adopted with other agents or therapeutics that can increase surface PS on pancreatic cancer cells.

A mechanism of action study demonstrated that SapC-DOPS nanovesicles induce apoptotic cell death of human pancreatic cancer cells in part via a ceramide- and caspase-mediated signaling pathway [12,18]. SapC enhances the biological activity of lysosomal acid sphingomyelinase (ASMase). In cancer cells, ASMase leaks out from lysosomes and moves to plasma membranes. SapC can stimulate the activity of ASMase when SapC-DOPS nanovesicles fuse with surface PS of cancer cell membranes. This activation elevates the levels of ceramide, a secondary messenger, followed by activation of caspases that induce apoptotic cell death [12,18].

In addition to its therapeutic application, SapC-DOPS nanovesicles can also incorporate hydrophobic or hydrophilic probes and agents for pancreatic cancer imaging and detection. It has been demonstrated that fluorescently labeled SapC-DOPS nanovesicles allow selective visualization of primary and metastatic pancreatic tumors *in vivo* [12,20]. The nanovesicles can also carry contrast agents (iron or gadolinium) for MRI of cancer [21]. Preclinical studies of SapC-DOPS as a novel anticancer agent demonstrate a toxicology and pharmacology profile that favors advancement to early-phase clinical trials. We propose testing this in pancreatic cancer and considering this in other tumors with high surface PS expression.

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Biographies

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References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin. 2013; 63(1):11–30. [PubMed: 23335087]
2. Bilimoria KY, Bentrem DJ, Ko CY, et al. Multimodality therapy for pancreatic cancer in the U.S.: utilization, outcomes, and the effect of hospital volume. Cancer. 2007; 110(6):1227–1234. [PubMed: 17654662]
3. Rothenberg ML, Moore MJ, Cripps MC, et al. A phase II trial of gemcitabine in patients with 5-FU-refractory pancreas cancer. Ann Oncol. 1996; 7:347–353. [PubMed: 8805925]
4. Burris HA 3rd, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol. 1997; 15(6):2403–2413. [PubMed: 9196156]
5. Bruns CJ, Solorzano CC, Harbison MT, et al. Blockade of the epidermal growth factor receptor signaling by a novel tyrosine kinase inhibitor leads to apoptosis of endothelial cells and therapy of human pancreatic carcinoma. Cancer Res. 2000; 60(11):2926–2935. [PubMed: 10850439]
6. Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol. 2007; 25(15):1960–1966. [PubMed: 17452677]
7. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011; 364(19):1817–1825. [PubMed: 21561347]
8. Von Hoff DD, Ramanathan RK, Borad MJ, et al. Gemcitabine plus nab-paclitaxel is an active regimen in patients with advanced pancreatic cancer: a phase I/II trial. J Clin Oncol. 2011; 29(34): 4548–4554. [PubMed: 21969517]
9. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013; 369(18):1691–1703. [PubMed: 24131140]
10. Kindler HL, Niedzwiecki D, Hollis D, et al. Gemcitabine plus bevacizumab compared with gemcitabine plus placebo in patients with advanced pancreatic cancer: phase III trial of the Cancer and Leukemia Group B (CALGB 80303). J Clin Oncol. 2010; 28(22):3617–3622. [PubMed: 20606091]
11. Alberts SR, Schroeder M, Erlichman C, et al. Gemcitabine and ISIS-2503 for patients with locally advanced or metastatic pancreatic adenocarcinoma: a North Central Cancer Treatment Group phase II trial. J Clin Oncol. 2004; 22(24):4944–4950. [PubMed: 15611509]
12. Chu Z, Abu-Baker S, Palascak MB, et al. Targeting and cytotoxicity of SapC-DOPS nanovesicles in pancreatic cancer. PLoS One. 2013; 8:e75507. [PubMed: 24124494]
13. Qi X, Chu Z. Fusogenic domain and lysines in saposin C. Arch Biochem Biophys. 2004; 424(2): 210–218. [PubMed: 15047193]
14. Qi X, Leonova T, Grabowski GA. Functional human saposins expressed in Escherichia coli. Evidence for binding and activation properties of saposins C with acid beta-glucosidase. J Biol Chem. 1994; 269(24):16746–16753. [PubMed: 8206997]
15. Qi X, Qin W, Sun Y, et al. Functional organization of saposin C. Definition of the neurotrophic and acid beta-glucosidase activation regions. J Biol Chem. 1996; 271(12):6874–6880. [PubMed: 8636113]
16. Wang Y, Grabowski GA, Qi X. Phospholipid vesicle fusion induced by saposin C. Arch Biochem Biophys. 2003; 415(1):43–53. [PubMed: 12801511]

17. Abu-Baker S, Chu Z, Stevens A, et al. Cytotoxicity and selectivity in skin cancer by SapC-DOPS nanovesicles. J Cancer Ther. 2013; 3:321–326.

18. Qi X, Chu Z, Mahller YY, et al. Cancer-selective targeting and cytotoxicity by liposomal-coupled lysosomal saposin C protein. Clin Cancer Res. 2009; 15(18):5840–5851. [PubMed: 19737950]

19. Wojton J, Chu Z, Mathsyaraja H, et al. Systemic delivery of SapC-DOPS has antiangiogenic and antitumor effects against glioblastoma. Mol Ther. 2013; 21(8):1517–1525. [PubMed: 23732993]

20. Unruh D, Turner K, Srinivasan R, et al. Alternatively spliced tissue factor contributes to tumor spread and activation of coagulation in pancreatic ductal adenocarcinoma. Int J Cancer. 2014; 134(1):9–20. [PubMed: 23754313]

21. Kaimal V, Chu Z, Mahller YY, et al. Saposin C coupled lipid nanovesicles enable cancer-selective optical and magnetic resonance imaging. Mol Imaging Biol. 2011; 13(5):886–897. [PubMed: 20838909]