The Role of Common Pharmaceuticals in Increasing Survival After Surgical Resection of Pancreatic Cancer

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Introduction

- Despite being only the 12th most common cancer in the UK (approx 8,000 new cases/year), pancreatic cancer is the 5th most common cause of cancer-death, with 1 and 5 year survival rates of 18% and 3.5% respectively [1]
- Tumour "stroma" consists of a variety of cellular and non-cellular components that surround and interact with tumours, resulting in a connective tissue reaction that promotes cancer cell proliferation, invasion and resistance to chemotherapy[2]
- Pancreatic ductal adenocarcinoma (PDAC), which accounts for 95% of pancreatic cancer cases, demonstrates the most significant stromal activity of all solid organ cancers, and therefore represents an ideal therapeutic target to improve survival rates
- Numerous in vitro and in vivo laboratory studies have demonstrated how various existing medications have anti-cancer effects, through both direct disruption of cancer cell activity, and also through inhibition of signalling pathways between cancer cells and stromal cells; these medications include aspirin[3], anti-hypertensives (ACE inhibitors (ACEI)[4], Angiotensin II Receptor blockers (ARB)[5], and Calcium Channel Blockers (CCB)[6]) and statins[7]
- The aim of this study was to investigate whether any of these medications improved survival following surgical resection of pancreatic cancer, and in particular to investigate whether combination therapy may result in a synergistically beneficial effect on survival

Methods

- Retrospective data collection was performed from 164 patients who underwent a "Whipple's" surgical resection of histologically confirmed PDAC. SPSS was used for statistical analysis

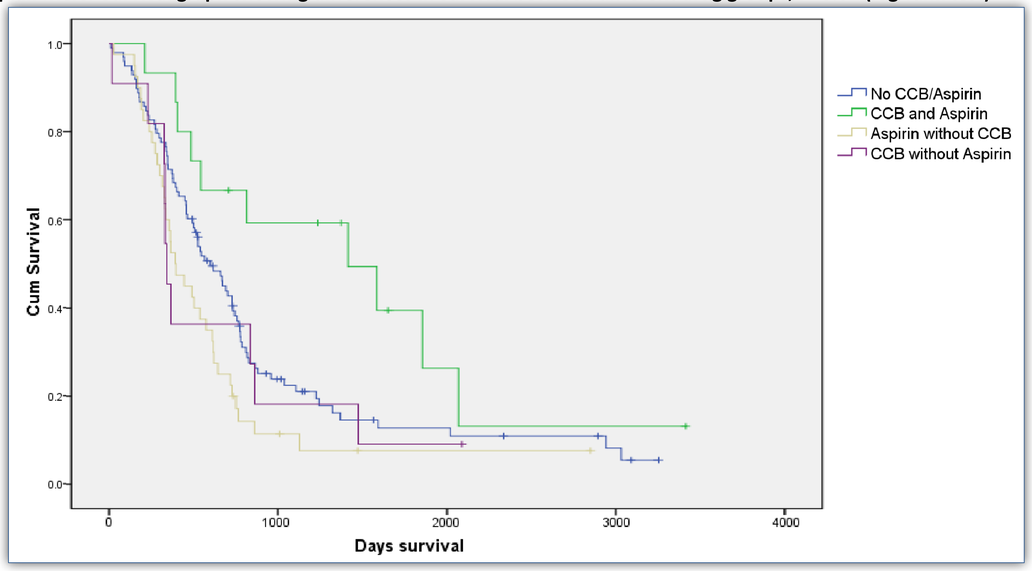
Table demonstrating differences in prognostic indicators between different drug groups. P values calculated using χ^2 tests.

Characteristics	No CCB/Aspirin, n (%) n=98	CCB and Aspirin, n (%) n=15	Aspirin without CCB, n (%) n=40	CCB without Aspirin, n (%) n=11	P value
Sex					
Male	56 (57.1)	5 (33.3)	25 (62.5)	8 (72.7)	0.169
Age					
<60	39 (39.8)	5 (33.3)	8 (20.0)	3 (27.3)	0.157
≥60	59 (60.2)	10 (66.7)	32 (80.0)	8 (72.7)	
BP status					
Hypertensive	27 (27.6)	13 (86.7)	22 (55.0)	11 (100.0)	0.000
Non-hypertensive	71 (72.4)	2 (13.3)	18 (45.0)	0 (0.0)	
BMI					
<18.5	2 (2.0)	0 (0)	1 (2.5)	0 (0.0)	0.307
18.5-25	52 (53.1)	5 (33.3)	24 (60.0)	3 (27.3)	
>25	41 (41.8)	9 (60.0)	14 (35.0)	8 (72.7)	
Adjuvant Chemotherapy					
Received post-op	69 (70.4)	9 (60.0)	23 (57.5)	9 (81.8)	0.333
not received	24 (24.5)	5 (33.3)	13 (32.5)	1 (9.1)	
CA19-9					
<47	27 (27.6)	3 (20.0)	9 (22.5)	1 (9.1)	0.437
47-1000	51 (52.0)	7 (46.7)	20 (50.0)	7 (63.6)	
>1000	8 (8.2)	3 (20.0)	6 (15.0)	3 (27.3)	
ASA grade					
1-2	81 (82.7)	12 (80.0)	22 (55.0)	8 (72.7)	0.008
3-4	17 (17.3)	3 (20.0)	18 (45.0)	3 (27.3)	
Resection Value					
R0	14 (14.3)	6 (40.0)	9 (22.5)	5 (45.5)	0.020
R1	83 (84.7)	9 (60.0)	31 (77.5)	6 (54.5)	
T status					
T1-2	3 (3.1)	2 (13.3)	1 (2.5)	0 (0.0)	0.199
T3-4	95 (96.9)	13 (86.7)	39 (97.5)	11 (100.0)	
N status					
N0	7 (7.1)	3 (20.0)	5 (12.5)	0 (0.0)	0.242
N1	90 (91.8)	12 (80)	35 (87.5)	11 (100.0)	

Results

- No significant survival benefit was observed with respect to ACEI/ARB (n=41) or statins (n=39), including in combination with aspirin or CCB
- Median survival was significantly higher in the CCB+Aspirin group (n=15) compared with the group taking neither drug (n=98); 1414 vs 601 days (P=0.029, log-rank test)
- Univariate cox regression revealed those receiving CCB and Aspirin had a 51.5% lower risk of death as compared to those taking neither drug; HR 0.485 (CI=0.250-0.942, P=0.033)
- No significant survival benefit was observed in the CCB alone group (n=11); HR 1.215 (CI=0.627-2.353, P=0.564), whilst the Aspirin alone group (n=40) showed worsening survival on univariate analysis; HR 1.540 (CI=1.035-2.293, P=0.033)
- Multivariate cox regression analysis revealed neither Aspirin nor CCB had a statistically significant impact on survival when given alone, however in combination the survival benefit was significant; HR 0.332 (CI=0.126-0.870, P=0.025)

Kaplan Meier Survival graph showing differences in survival between different drug groups, P=0.01 (log-rank test)



Conclusions

- This study has demonstrated a greater than twofold increase in median survival time in those taking a combination of CCB+Aspirin post surgical resection of PDAC. This effect appears to be synergistic, as taking either in isolation yielded no significant survival benefit
- In vitro studies of stroma-cancer interactions would be of interest to investigate the underlying mechanisms underpinning combination therapy, including in conjunction with chemotherapy agents
- A randomised controlled trial, including palliative patients, would be a safe and effective modality to determine the true prognostic benefit of polypharmacy, as this study is limited by the retrospective nature and low patient numbers in certain drug groups
- Combining multiple medications into one tablet has proven to be a viable option in improving prognosis for cancer patients. This is a result of their ability can catalyse the inhibition of some of the multiple biochemical pathways which play a role in cancer development[8]. This could offer a significant survival benefit, especially in diseases such as pancreatic cancer, for which conventional chemotherapy remains ineffective

References: **1.** CRUK statistics - http://www.cancerresearchuk.org/cancer-info/cancerstats/types/pancreas **2.** Maitra A et al, Pancreatic cancer. Annu Rev Pathol. 2008;3:157–188. 3. Plassmeier, L., et al., *Aspirin prolongs survival and reduces the number of Foxp3+ regulatory T cells in a genetically engineered mouse model of pancreatic cancer*. Langenbecks Archives of Surgery, 2013. 398(7): p. 989-96 **4.** Arafat, H.A., et al., *Antihypertensives as novel antineoplastics: angiotensin-I-converting enzyme inhibitors and angiotensin II type 1 receptor blockers in pancreatic ductal adenocarcinoma*. Journal of the American College of Surgeons. 204(5): p. 996-1005; discussion 1005-6 **5.** Masamune, A., et al., *The angiotensin II type I receptor blocker olmesartan inhibits the growth of pancreatic cancer by targeting stellate cell activities in mice*. Scand J Gastroenterol, 2013. 48(5): p. 602-9. **6.** Sato K et al, Inhibitory effect of calcium channel blockers on growth of pancreatic cancer cells. Pancreas. 1994 Mar;9(2):193-202. 7. Ishikawa, S., et al., *The role of oxysterol binding protein-related protein 5 in pancreatic cancer*. Cancer Sci, 2010. 101(4): p. 898-905.8. Alexis F. Nano-polypharmacy to treat tumors: coencapsulation of drug combinations using nanoparticle technology. Mol Ther. 2014 Jul;22(7):1239-40.

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