Available online at www.sciencerepository.org

Science Repository

Research Article

Are we used the appropriate therapy regimens on advanced pancreatic cancer?

Yuxi DUAN[1#], Liqiong YANG[1#], Fangfang LIU[2], Shu YANG[3] and Fan XU[3*]

[1]*School of Pharmacy, Chengdu Medical College, Sichuan, China, 610500*
[2]*Art College, Southwest Minzu University, Chengdu, Sichuan, China, 610041*
[3]*Department of Public Health, Chengdu Medical College, Sichuan, China, 610500*
[#]*These authors contributed equally*

ARTICLEINFO

Article history:
Received: 17 May, 2019
Accepted: 13 June, 2019
Published: 23 July, 2019

Keywords:
Advanced Pancreatic Cancer
chemotherapy regimens
treatment-related toxicity

ABSTRACT

Even through numerous combinations of chemotherapy regimens are used to treat on the advanced pancreatic cancer, APC; however, the survival rate (overall survival and progress free survival) and treatment-related toxicity remain challenge. Here we provided neutral and failed outcomes that treat the APC in clinical trials, this need us to think twice whether we were used the appropriate therapy regimens, to enlarge the survival rate and to reduce the treatment-related toxicity. Evidences of treatment on APC are need indeed to assistant our physician decision making correctly.

Background of advanced pancreatic cancer

Advanced Pancreatic Cancer (APC) is characteristic with high mortality, increasing incidence, relative survival rate presents 20% in one-year and 8% in five-year during all APC stages [1-3]. APC may occur when the pancreas cells grow exponentially and uncontrollably, they will be dividing and spreading rapidly, forming malignant tumors. The treatment timing window of APC depends on the stage or extent of the cancer, the treatment options include surgery, ablative treatments to destroy the tumor, radiation, and chemotherapy [4]. In the advanced stage of pancreatic cancer, oral or injectable drugs usually kill cancer cells, but in fact only control the growth of cancer cells. The drugs used mainly include gemcitabine with nab-paclitaxel and FOLFIRINOX (a cocktail of oxaliplatin, irinotecan, 5FU, and leucovorin), which can increase the overall survival by several months [5].

Our previous meta-analysis study [6] disclosed that there are not less than 20 therapy regimens. Even through many combinations of drugs birthed, combined with frontline drug gemcitabine, such as "gemcitabine+X". Unfortunately, the overall survival and progress free survival of APC patients were not improved significantly. There is big question worth us thinking twice, there are too much choices for frontline in clinic, however the evidence-based medicine of them remains challenge. Are we used the appropriate therapy regimens on APC? Namely, are there any drug abuses during the treatment on APC?

In order to clarify this question, we have collected the clinical trial data from http://Clinicaltrail.gov, searching with the key words "advanced pancreatic cancer", and then selected filter with "has results" and "has publication". We selected the results that authors stated failed or neutral in the publications. There are 14 articles reported failed in the clinical trials and 3 publications stated neutral result. Generally, we kept the first author, published year, sample size, drugs, overall survival (OS), progress free survival (PFS) and drug against biomarker. Details please see (Table 1 and 2).

OS and PFS comparison in failed and neutral results on APC

Generally, there ware 14 studies ranged from 2011 to 2018, recruited 2448 APC patients (1385 male and 1063 female) to conduct the clinical trials, details please see (table 1). Averagely the OS was 8.25 months and PFS was 4.39 months in failed studies. It is noteworthy that Faivre in 2017 tested sunitinib malate to treat APC and achieved 38.6 months of OS and 12.6 months of PFS. However, Wolpin reported that hydroxychloroquine to cure APC, unfortunately, there were 1.8 months both in OS and PFS. Even through many combination tests, however, the benefit for APC patients are still remains low extremely.

[*]*Correspondence to: Prof Fan XU, Department of Public Health, Chengdu Medical College, Sichuan,China, 610500; E-mail: xufan@cmc.edu.cn*

http://dx.doi.org/10.31487/j.DDA.2019.01.01

Table 1: Clinical trial failed outcome on pancreatic cancer

Year	Author	N	M	F	Drug	OS	PFS	Biomarkers
2011	Kindler HL[7]	314	191	123	Gemcitabine; AG-013736	8.5	4.4	vascular endothelial growth factor (VEGF)
		316	188	128	Gemcitabine; Placebo	8.3	4.4	
2012	Ko AH[8]	29	18	11	Cetuximab; Bevacizumab; Gemcitabine	5.41	4.17	epidermal growth factor receptor (EGFR); vascular endothelial growth factor (VEGF)
		29	14	15	Cetuximab; Bevacizumab	3.55	1.91	
2013	Rougier P[9]	275	157	118	Placebo; Gemcitabine	7.8	3.7	Vascular endothelial growth factor (VEGF)
		271	160	111	Aflibercept; Gemcitabine	6.5	3.7	
2013	Wu C[10]	30	16	14	Etanercept; Gemcitabine	5.43	0.3	tumor necrosis factor α (TNF-α)
		8	3	5	Gemcitabine	8.1	1.8	
2014	Propper D [11]	104	59	45	Erlotinib	4.0	1.5	epidermal growth factor receptor (EGFR)
		103	59	44	Placebo	3.1	1.5	
2014	Infante JR[12]	80	39	41	Gemcitabine; GSK1120212	8.4	16.1	circulating free DNA (cfDNA)
		80	46	34	Placebo; Gemcitabine	6.7	15.1	
2014	Wolpin BM [13]	10	5	5	Hydroxychloroquine 400mg	1.8	1.8	LC3-II
		10	6	4	Hydroxychloroquine 600mg	3.0	1.6	
2015	Catenacci DV[14]	53	27	26	Gemcitabine hydrochloride; hydrocortisone/placebo	6.1	2.5	hedgehog (Hh) pathway; Sonic hedgehog (SHH)
		53	31	22	Gemcitabine hydrochloride; Vismodegib	6.9	4.0	
2016	Noonan AM[15]	36	22	14	Wild-type reovirus; Carboplatin; paclitaxel	7.31	4.94	vascular endothelial growth factor (VEGF); normal T cell expressed and secreted (RANTES); IL-6, IL-8
		37	19	18	Carboplatin; Paclitaxel	8.77	5.2	
2017	Chung V[16]	62	22	40	Fluorouracil; Oxaliplatin	6.7	2.0	KRAS protein
		58	35	23	MK2206; Selumetinib	3.9	1.9	
2017	Faivre S[17]	86	42	44	Sunitinib malate	38.6	12.6	vascular endothelial growth factor receptors (VEGFRs); platelet-derived growth factor receptors (PDGFRs)
		85	40	45	Placebo	29.1	5.8	
2017	Ko AH[18]	66	38	28	OGX-427	6.9	3.8	heat shock protein 27 (Hsp27)
		66	37	29	Placebo	5.3	2.7	
2017	Laquente B[19]	65	42	23	LY2603618; Gemcitabine	7.8	3.5	Checkpoint kinase 1 (CHK1)
		34	20	14	Gemcitabine	8.3	5.6	
2018	Van Cutsem E[20]	44	22	22	Gemcitabine; Placebo	7.6	2.8	MEK1/2-dependent effector proteins (ERK 1/2)
		44	27	17	Gemcitabine; Pimasertib	7.3	3.7	

Note：OS, overall survival; PFS, progress free survival; M: male; F: female.

Table 2: Clinical trail neutral outcome on pancreatic cancer

Year	Author	N	M	F	Drug	OS	PFS	Biomarkers
2008	Spano JP[21]	69	35	34	Gemcitabine	5.6	3.7	Vascular endothelial growth factor (VEGF)
		34	16	18	Gemcitabine; AG-013736	6.9	4.2	
2015	Hobday TJ[22]	58	29	29	Bevacizumab; Temsirolimus	34	13.2	vascular endothelial growth factor (VEGF)
2016	Stein SM[23]	37	21	16	MPC modified FOLFIRINOX	10.2	6.1	
		31	20	11	LAPC modified FOLFIRINOX	26.6	17.8	

Note：OS, overall survival; PFS, progress free survival; M: male; F: female.

Furthermore, there were 3 studies clarified neutral results in OS and PFS result, ranged from 2008 to 2016, totally recruited 229 APC patients (121 male and 108 female), details please see (Table 2). Averagely the OS was 16.6 months and PFS was 9 months in neutral studies. For example, Spano in 2008 reported gemcitabine plus AG-013736 achieved better OS and PFS (6.9 and 4.2) than gemcitabine single used.

Perspective

Currently, we have many choices when facing different and strange realistic situation of APC patients. However, it is hard to make decision to select the most appropriate and fitful regimens for patients due to unsoiled systemic evidences. According to our previous meta-analysis study disclosed that there are 14 categories of treatment-related toxicity

in any combination of chemotherapy regimens [6]. Consequently, the adverse events could not be avoided.

With respecting the drug abuse in cure on APC, this is an open question. The current evidence uncovered that APC patients benefit less on OS or PFS. Unfortunately, the treatment-related toxicities accompany with therapy, patients did not only endure the pain from the cancer, but also need to be tolerant of the side reactions. Evidence medicine on APC treatment are need to be strength to balance the benefit and lost in vast degree from patients' perspective.

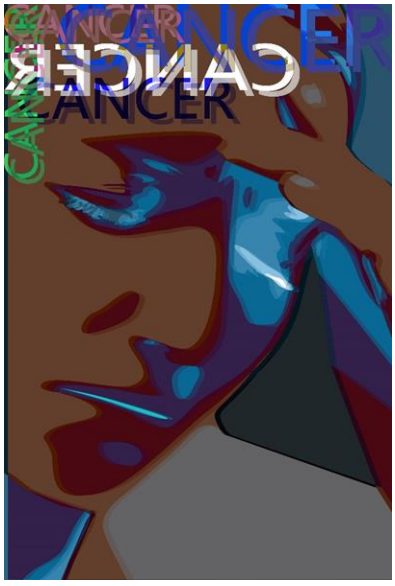

Figure 1: Difficult to make the decision

Funding

This work was supported by Chengdu Medical College nature science foundation (CYZ18-08, CYZ18-20, CYZ18-33)

Authors' contribution

XF summarized the general idea and draft the manuscript, DYX and YLQ performed the data collection and table construction, YS conducted the quality control, LFF drafted the concept photograph.

Conflict of Interest

The authors declare that they have no competing interests

REFERENCES

1. Siegel RL, Miller KD, Jemal A (2018) Cancer statistics, 2018. *CA Cancer J Clin* 68: 7-30. [Crossref]
2. Srivastava S, Koay EJ, Borowsky AD, De Marzo Am, Ghosh S et al. (2019) Cancer overdiagnosis: a biological challenge and clinical dilemma. *Nat Rev Cancer* 19: 349-358. [Crossref]
3. Kamisawa T, Wood LD, Itoi T, Takaori K (2016) Pancreatic cancer. *Lancet* 388: 73-85. [Crossref]
4. Mahmood J, Shukla HD, Soman S, Samanta S, Singh P et al. (2018) Immunotherapy, Radiotherapy, and Hyperthermia: A Combined Therapeutic Approach in Pancreatic Cancer Treatment. *Cancers (Basel)* 10. [Crossref]
5. Soefje SA (2019) Managing the economic impact of advanced pancreatic cancer. *Am J Manag Care* 25: S11-S16. [Crossref]
6. Chen J, Chen L, Yu J, Xu Y, Wang X et al. (2019) Meta-analysis of current chemotherapy regimens in advanced pancreatic cancer to prolong survival and reduce treatment-associated toxicities. *Mol Med Rep* 19: 477-489. [Crossref]
7. Kindler HL, Ioka T, Richel DJ, Bennouna J, Letourneau R et al. (2011) Axitinib plus gemcitabine versus placebo plus gemcitabine in patients with advanced pancreatic adenocarcinoma: a double-blind randomised phase 3 study. *Lancet Oncol* 12: 256-262. [Crossref]
8. Ko AH, Youssoufian H, Gurtler J, Dicke K, Kayaleh O et al. (2012) A phase II randomized study of cetuximab and bevacizumab alone or in combination with gemcitabine as first-line therapy for metastatic pancreatic adenocarcinoma. *Invest New Drugs* 30: 1597-1606. [Crossref]
9. Rougier P, Riess H, Manges R, Karasek P, Humblet Y et al. (2013) Randomised, placebo-controlled, double-blind, parallel-group phase III study evaluating aflibercept in patients receiving first-line treatment with gemcitabine for metastatic pancreatic cancer. *Eur J Cancer* 49: 2633-2642. [Crossref]
10. Wu C, Fernandez SA, Criswell T, Chidiac TA, Guttridge D et al. (2013) Disrupting cytokine signaling in pancreatic cancer: a phase I/II study of etanercept in combination with gemcitabine in patients with advanced disease. *Pancreas* 42: 813-818. [Crossref]
11. Propper D, Davidenko I, Bridgewater J, Kupcinskas L, Fittipaldo A et al. (2014) Phase II, randomized, biomarker identification trial (MARK) for erlotinib in patients with advanced pancreatic carcinoma. *Ann Oncol* 25: 1384-1390. [Crossref]
12. Infante JR, Somer BG, Park JO, Li CP, Scheulen ME et al. (2014) A randomised, double-blind, placebo-controlled trial of trametinib, an oral MEK inhibitor, in combination with gemcitabine for patients with untreated metastatic adenocarcinoma of the pancreas. *Eur J Cancer* 50: 2072-2081. [Crossref]
13. Wolpin BM, Rubinson DA, Wang X, Chan JA, Cleary JM et al. (2014) Phase II and pharmacodynamic study of autophagy inhibition using hydroxychloroquine in patients with metastatic pancreatic adenocarcinoma. *Oncologist* 19: 637-638. [Crossref]
14. Catenacci DV, Junttila MR, Karrison T, Bahary N, Horiba MN et al. (2015) Randomized Phase Ib/II Study of Gemcitabine Plus Placebo or Vismodegib, a Hedgehog Pathway Inhibitor, in Patients With Metastatic Pancreatic Cancer. *J Clin Oncol* 33: 4284-4292. [Crossref]
15. Noonan AM, Farren MR, Geyer SM, Huang Y, Tahiri S et al. (2016) Randomized Phase 2 Trial of the Oncolytic Virus Pelareorep (Reolysin) in Upfront Treatment of Metastatic Pancreatic Adenocarcinoma. *Mol Ther* 24: 1150-1158. [Crossref]
16. Chung V, McDonough S, Philip PA, Cardin D, Wang-Gillam A et al. (2017) Effect of Selumetinib and MK-2206 vs Oxaliplatin and Fluorouracil in Patients With Metastatic Pancreatic Cancer After Prior Therapy: SWOG S1115 Study Randomized Clinical Trial. *JAMA Oncol* 3: 516-522. [Crossref]
17. Faivre S, Niccoli P, Castellano D, Valle JW, Hammel P et al. (2017) Sunitinib in pancreatic neuroendocrine tumors: updated progression-

free survival and final overall survival from a phase III randomized study. *Ann Oncol* 28: 339-343. [Crossref]

18. Ko AH, Murphy PB, Peyton JD, Shipley DL, Al-Hazzouri A et al. (2017) A Randomized, Double-Blinded, Phase II Trial of Gemcitabine and Nab-Paclitaxel Plus Apatorsen or Placebo in Patients with Metastatic Pancreatic Cancer: The RAINIER Trial. *Oncologist* 22: 1427-1129. [Crossref]
19. Laquente B, Lopez-Martin J, Richards D, Chang DZ, Kim G et al. (2017) A phase II study to evaluate LY2603618 in combination with gemcitabine in pancreatic cancer patients. *BMC Cancer* 17: 137. [Crossref]
20. Van Cutsem E, Hidalgo M, Canon JL, Macarulla T, Bazin l et al. (2018) Phase I/II trial of pimasertib plus gemcitabine in patients with metastatic pancreatic cancer. *Int J Cancer* 143: 2053-2064. [Crossref]
21. Spano JP, Chodkiewicz C, Maurel J, Wong R, Wasan H et al. (2008) Efficacy of gemcitabine plus axitinib compared with gemcitabine alone in patients with advanced pancreatic cancer: an open-label randomised phase II study. *Lancet* 371: 2101-2108. [Crossref]
22. Hobday TJ, Qin R, Reidy-Lagunes D, Moore MJ, Strosberg J et al. (2015) Multicenter Phase II Trial of Temsirolimus and Bevacizumab in Pancreatic Neuroendocrine Tumors. *J Clin Oncol* 33: 1551-1556. [Crossref]
23. Stein SM, James ES, Deng Y, Cong X, Kortmansky JS et al. (2016) Final analysis of a phase II study of modified FOLFIRINOX in locally advanced and metastatic pancreatic cancer. *Br J Cancer* 114: 737-743. [Crossref]