

Full Length Research Paper

A review of clinical trials of chemotherapy for pancreatic cancer

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Accepted 19 October, 2012

Chemotherapy is playing an important role in treating pancreatic cancer, either when used alone or when combined with surgery and radiotherapy. We summarized 80 eligible clinical trials published from January in 2006 to June in 2011 and discussed the future development of chemotherapy in the treatment of pancreatic cancer. All the clinical trials were divided into 5 groups: single-agent regimen (14 trials), binary combination (27 trials), triple or more combination (13 trials), neoadjuvant/preoperative chemotherapy (4 trials), and targeted therapy (22 trials). Gemcitabine used alone was confirmed effective in 5 trials, while fixed-dose-rate gemcitabine showed apparent toxicities. In 4 trials, oral S-1 seemed feasible and convenient as a second-line agent. Explorations of irinotecan and paclitaxel loaded polymeric micelle as single agents also got positive outcomes. Many trials focused on the gemcitabine-based combinations with drugs like cisplatin, S-1, oxaliplatin, gflufosfamide, etc., and some got positive results. Due to the occurrences of gemcitabine-resistance or even 5-fluorouracil-resistance, second-line combinations have become important and some have shown considerable value. Apart from the binary combination, three or more drugs used together, like FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin) and FOLFIRI (5-fluorouracil, leucovorin, and irinotecan) also exhibited promising activity. A new method called neoadjuvant therapy (treating patients with drugs before surgery) was investigated in 4 trials with encouraging outcomes. In addition, some sites related to tumor cell proliferation and metastasis, such as growth factor receptor, CTLA-4 (CD152), the mammalian target of rapamycin, cyclooxygenase-2, cholecystokinin-2 receptor, leukotriene B4 receptor, peroxisome proliferator-activated receptor gamma and proto-oncogene, have been explored in some clinical trials and are worth further researches.

Key words: Chemotherapy, pancreatic cancer, clinical trials.

INTRODUCTION

Nowadays, pancreatic cancer has become the fourth most common cause of cancer-related death in adults in China and United States (Li et al., 2004). The annual incidence rate of pancreatic cancer is almost identical to the mortality rate (Muhammad, 2008). Although, a lot of efforts have been made, still the current state of pancreatic cancer treatment is unsatisfactory. Merely depending on the improvement of surgery cannot change the dimmed picture. In China, the incidence rate of this malignancy has increased about 6 times since 1970s (Lu

Xing, 1997). About 80% patients have lost chances of operations, because the cancer has become advanced or metastasized when diagnosed (Kelly and Benjamin, 1995). An epidemiological research indicated that the overall resection rate was less than 3% (Bramhall et al., 1995). Even after resections, 5-year survival remains only 7 to 24%, and median survival is only approximately 1 year in most series, implying that surgery alone is inadequate (Nitecki et al., 1995). To argument surgery, chemotherapy plays an important role and has been investigated by many researchers. Gemcitabine, which has been shown to result in improved clinical benefit and slightly longer mean survival time, becomes the first-line chemotherapy for pancreatic cancer (Kulke, 2003). However, published results indicated that prolonged

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exposure to gemcitabine leads to acquired resistance in some pancreatic cancer cells, which is also a major cause of treatment failure (Blaszowsky, 1998). In the past, about 5 years ago, many clinical trials aiming at overcoming the resistance and exploring new approaches to the treatment of pancreatic cancer, have been conducted, using different kinds of chemotherapy drugs.

METHODOLOGY

A PubMed search of clinical trials from January in 2006 to June in 2011 was carried out, using the search terms “pancreatic, cancer, chemotherapy” in the “AND” relationship. All studies related to radiotherapy, getting absolute negative results or phase I trial (focusing on revising dosage) were excluded because of their few connections on the substance. At the end, 80 trials were determined and other relevant studies were included by a further research of some important references. All the 80 investigations were divided into 5 groups: (1) single-agent regimen (114 trials, Table 1); (2) binary combination (27 trials, Table 2); (3) triple or more combination (13 trials, Table 3); (4) neoadjuvant/preoperative chemotherapy (4 trials, Table 4); (5) targeted therapy (22 trials, Table 5).

RESULTS

Single-agent regimen

Gemcitabine

Gemcitabine, as a pyrimidine antimetabolite (Heinemann et al., 1988) has an effective activity in many solid tumors. Identifying its better efficacy than 5-fluorouracil in 1997 (Burris et al., 1997), single-agent gemcitabine has been recommended as the first choice of treating pancreatic cancer (Arshad et al., 2011). A randomized controlled trial (Oettle et al., 2007) supported the use of gemcitabine as adjuvant chemotherapy after curative-intent resection. In the trial, 179 patients received 6 cycles of gemcitabine on day 1, 8, and 15 every 4 weeks and 175 patients received only observation. Median disease-free survival in the gemcitabine group and the observation group was 13.4 months (95% confidence interval, 11.4 to 15.3) and 6.9 months (95% confidence interval, 6.1 to 7.8; $P < 0.001$, log-rank), respectively. Estimated disease-free survival at 3 and 5 years of the gemcitabine group was 23.5 and 16.5%, compared with 7.5 and 5.5% in the observation group. The rate of recurrent disease was lower in the treatment group (74 versus 92%). However, no statistical difference was shown in the overall survival between the two groups.

An analogous trial from Japanese (58 patients in the gemcitabine group and 60 patients in the surgery-only group) was reported by Ueno et al. (2009). Median disease-free survival was longer in the gemcitabine group (11.4 versus 5.0 months; hazard ratio = 0.77, 95% confidence interval: 0.51 to 1.14; $P = 0.19$), while the overall

survival did not show significant differences, which was concurrent with the results of the former trial. Frequent but the most transient hematological toxicities occurred in the gemcitabine group.

To further evaluate the efficacy and safety of gemcitabine, Ishii et al. (2010) reported a study with 50 locally advanced pancreatic cancer patients enrolled from 2006 to 2007 and followed up until 2009. About 62% patients had grade 3 to 4 severe neutropenia, which was transient and without episode of infection. The median overall survival was 15.0 months and 1-year survival rate was 64.0%.

Recently, there are some trials about fixed-dose-rate gemcitabine, which can maintain a critical plasma concentration of gemcitabine, and thus increase tumor cytotoxicity and therapeutic efficacy (Hochster, 2003). Here are two studies introduced, one reported by Poplin et al. (2009) and the other by Mané et al. (2010). The former study enrolled 275 patients in the gemcitabine group, 277 in the fixed-dose-rate gemcitabine group and 272 in the gemcitabine plus oxaliplatin group. The differences of survival efficacy between these groups did not achieve pre-specified criteria significantly. The fixed-dose-rate gemcitabine group had the worst adverse effects of grade 3 to 4 neutropenia and thrombocytopenia. In the latter study, 62 patients with advanced pancreatic or biliary tree adenocarcinoma were registered, among which 59 were assessable for response. The median time to progression and median overall survival were 21 and 37.71 weeks, respectively. Thus, fixed-dose-rate gemcitabine has an effect on pancreatic cancer and can be considered to be combined with other agents.

Gemcitabine sensitivity can be predicted by hENT1 protein which helps in gemcitabine transport into the cells. Farrell et al. (2009) found that hENT1 protein expression was associated with increased overall survival and disease-free survival in pancreatic cancer patients who received gemcitabine.

S-1

In Japan, S-1, an oral fluoropyrimidine, which contains tegafur, 5-chloro-2,4-dihydropyridine, and potassium oxonate at a molar ratio of 1:0.4:1, based on the biochemical modulation of 5-fluorouracil, has been identified to have an effect on gemcitabine-refractory pancreatic cancer, as well as chemotherapy naive pancreatic cancer. In a study of metastatic pancreatic cancer with 40 chemo-naïve patients involved, reported from Japanese national cancer hospital (Okusaka et al., 2008), the overall response rate was 37.5% (1 complete response and 14 partial responses). The median time to progression and median overall survival were 3.7 and 9.2 months, respectively, as well as mostly tolerable and reversible toxicities. Also, from Japanese national cancer hospital, Morizane et al. (2009) reported a study of 40

Table 1. Single-agent regimen.

Study	Publishing time	Phase	No. of patients	Treatment	Median PFS/TTP [§] (months)	Median OS (months)	Survival rate (%)			Comment
							1 year	3 years	5 years	
Oettle H	January 2007	-	179	G	13.4	22.1	72.5	34	22.5	RCT
			175	Surgery-only	6.9	20.2	72.5	20.5	11.5	
Ueno H	September 2009	III	58	G	11.4	22.3	78	48	24	Randomized
			60	Surgery-only	5.0	18.4	75	40	11	
Ishii H	January 2010	II	50	G	-	15.0	64	-	-	-
Poplin E	August 2009	III	275	G	2.6	4.9	16	-	-	Randomized
			277	GEM FDR	3.5	6.2	21	-	-	
			272	GEMOX	2.7	5.7	21	-	-	
Mane JM	May to June 2010	-	59	GEM FDR	4.9 [§]	8.8	-	-	-	Including biliary tree cancer
Okusaka T	April 2008	II	40	S-1	3.7 [§]	9.2	32.5	-	-	-
Morizane C	January 2009	II	40	S-1	2.0	4.5	14.1	-	-	-
Nakai Y	August 2010	-	29	S-1	2.5	7.7	-	-	-	-
Sudo K	February 2011	II	21	S-1	4.1	6.3	-	-	-	-
Ueno H	March 2007	II	40	I	-	7.3	29.5	-	-	-
Yi SY	May 2009	II	33	I	2.0	6.6	-	-	-	-
Ciulean TE	June 2009	III	148	Glu+BSC	-	3.5	-	-	-	Randomized
			155	BSC	-	2.8	-	-	-	
Chabot JA	April 2010	-	23	Gem-based therapy	-	14	56	-	-	-
		-	32	Proteolytic enzyme	-	4.3	16	-	-	
Saif MW	February 2010	II	56	GPM	2.8, 3.2 [§]	6.5	-	-	-	-

-: Not sure if phase II or III; G: gemcitabine; GEM FDR: fixed-dose-rate gemcitabine (10 mg/m²/min); GEMOX: gemcitabine and oxaliplatin; I: irinotecan; Len: lentinan; GPM: paclitaxel micelle; Glu: glufosfamide; BSC: best supportive care. PFS: progression-free survival; TTP (§): time to progression. OS: overall survival; RCT: randomized controlled trial.

of 40 patients with gemcitabine-refractory metastatic pancreatic cancer. Fatigue and anorexia were common, but mostly tolerable and reversible. Partial response rate was 15.95% without complete response. The median progression-free

survival, median overall survival and 1-year survival rate were 2.0 months, 4.5 months and 14.1%, respectively.

Another 2 trials of S-1 in patients with gemcitabine-resistant metastatic pancreatic cancer

were published recently by Nakai et al. (2010) and Sudo et al. (2011), respectively. The first study had 108 patients enrolled, among which 29 patients used S-1. The objective response rate, progression-free survival and overall survival for

Table 2. Combination regimens of two agents.

Study	Publishing time	Phase	No. of patients	Treatment	Median PFS/TTP [§] (months)	Median OS (months)	Survival rate (%)		Comment
							1 year	5 years	
Clayton AJ	January 2006	II	36	G+Cis	5.75 [§]	9.5	41.7	-	-
Heinemann V	August 2006	III	95	G+Cis	5.3	7.5	25.3	-	Randomized
			95	G	3.1	6.0	24.7	-	
Colucci G	August 2010	III	199	G	3.9	8.3	34	-	Randomized
			201	G+Cis	3.8	7.2	30.7	-	
Min Kyoung Kim	January 2009	-	22	G+S-1	4.6 [§]	8.5	27.3	-	Outpatient-based regimen
Gyeong-Won Lee	September 2009	II	32	G+S-1	4.92 [§]	7.89	-	-	-
Oh DY	February 2010	II	38	G+S-1	5.4 [§]	8.4	34	-	-
Lee KH	July 2009	II	48	G+OX	5.6 [§]	9.4	-	-	-
Fortune BE	2009	-	17	GEM FDR+OX	2.6	6.4	29.4	-	Following GSDR failure
Chiorean TE	2010	II	29	G+Glu	3.7	6	32	-	-
Neri B	2009	-	33	G+I	9.2 [§]	11.8	-	-	-
Stathopoulos GP	September 2006	III	71	G+I	2.8 [§]	6.4	24.3	-	-
			74	G	2.9 [§]	6.5	21.8	-	-
Cunningham D	November 2009	III	266	G	3.8	6.2	22	-	Randomized
			267	G+Cap	5.3	7.1	24.3	-	
Roehrig S	May 2010	-	60	G+5-FU	4 [§]	7.3	-	-	-
Nakamori S	March 2011	II	36	G+UFT	-	7	-	-	-
Melnik MK	August 2010	II	40	G+Eto	3.1 [§]	7.2	11.4	-	-
Ridwelski K	April 2006	II	43	G+Doc	-	9.0	13.9	-	-
Katopodis O	February 2011	II	31	Cap+Doc	2.4	6.3	14.7	-	-
Kim YJ	February 2009	II	28	5-FU+Pac	2.5 [§]	7.6	-	-	-
Oh SY	June 2010	-	14	IROX	1.4 [§]	4.1	-	-	Pilot study
Kosuge T	2006	-	41	5-FU+Cis	-	12.5	-	26.4	RCT
			43	Nothing	-	15.8	-	14.9	
Mitry E	2006	II	18	OXFU	0.9	1.3	-	-	-
Neoptolemos JP	2010	-	551	5-FU+LV	23.0	14.1	-	-	-
			537	G	23.6	14.3	-	-	-
Epelbaum R	2010	-	17	G+Cur	2.5 [§]	5	-	-	-

-: Not sure if phase II or III; G: gemcitabine; Cis: cisplatin; OX: oxaliplatin; GEM FDR: fixed-dose-rate gemcitabine; I: irinotecan; Cap: capecitabine; 5-FU: 5-fluorouracil; UFT: uracil/tegafur; Eto: etoposide; Doc: docetaxel; Pac: paclitaxel; IROX: irinotecan and oxaliplatin; Glu: glufosfamide; OXFU: oxaliplatin and 5-FU; Cur: curcumin. PFS: progression-free survival; TTP(§): time to progression; OS: overall survival; RCT: randomized controlled trial; GSDR: standard-dose-rate (30 min) gemcitabine.

Table 3. Combination regimens of three or more agents.

Study	Publishing time	Phase	No. of patients	Treatment	Median PFS/TTP [§] (months)	Median OS (months)	1-year survival rate (%)	Comment	
Ghosn M	February 2007	-	30	FOLFOX-6	4 [§]	7.5	18.5	-	-
Novarino A	February 2009	II	23	FOLFOX	2.7 [§]	4	-	-	-
Pelzer U	March 2009	II	37	FOLFOX	2.8 [§]	5.13	-	-	-
Taieb J	March 2007	II	40	FOLFIRI.3	5.6	12.1	51	-	-
Gebbia V	October 2010	-	40	FOLFIRI	3.7 [§]	6	-	-	-
Conroy T	May 2011	-	171	FOLFIRIOX	6.4	11.1	-	-	Randomized
			171	G	3.3	6.8	-	-	
Chang HJ	September 2009	II	45	GOFL	5.1 [§]	8.7	-	-	-
				GEMOXEL	4.3	7.8	-	-	-
Hess V	December 2010	I/II	45	-	-	-	-	-	-
Pericay Pijaume C	January 2011	-	40	GEMTG	3.87 [§]	6.3	-	-	-
Lee S	2009	II	31	FAM	2.3 [§]	6.7	-	-	Incl. other cancers
Kruth J	December 2010	-	28	DocMitoCape	4.5	6.8	-	-	Incl. other cancers

-: Not sure if phase II or III; FOLFOX: 5-FU+leucovorin(LV) +OX; FOLFIRI: 5-FU+ LV +Iri; FOLFIRIOX: FOLFIRI+OX; GOFL: G+OX+5-FU/LV; GEMOXEL: G+OX +Cap; GEMTG: G+ tegafur+ LV; FAM: 5-FU+doxorubicin+mitomycin-C; DocMitoCape: Cap+doxorubicin+mitomycin-C. PFS: Progression-free survival; TTP (§): time to progression. OS: overall survival.

Table 4. Neoadjuvant/preoperative chemotherapy.

Study	Publishing time	Phase	No. of patients	Treatment	1-year survival rate (%)	Resection rate (%)	Median OS (months)	Surgical radicality (%)		Comments
								R0	N0	
Palmer DH	July 2007	II	24	G	42	38	9.9	75	25	Randomized
			26	G+Cis	62	70	15.6	75	44	
Heinrich S	May 2008	II	28	G+Cis	-	93	26.5	80	-	-
Sahora K	March 2011	II	33	G+OX	-	39	22 ₍₁₎ , 12 ₍₂₎	69	-	-

-: Not sure if phase II or III; G: gemcitabine; Cis: cisplatin; OX: oxaliplatin; Median OS (months): (1): undergoing tumor resection; (2): without resection; R0: Reported proportion of study patients with negative resection margins; N0: negative lymph nodes.

Table 5. Targeted therapy.

Study	Publishing time	Phase	No. of patients	Treatment	Median PFS/TTP [§] (months)	Median OS (months)	Survival rate (%)			Comments
							1 year	2 years	3 years	
Feliu J	January 2011	II	42	GEM FDR+Erl	5 [§]	8	35	-	-	-
Okusaka T	February 2011	II	107	G+Erl	3.48	9.23	33	-	-	-
Raymond E	February 2011	III	86	Sun	11.4	-	-	-	-	RCT
			85	PI	5.5	-	-	-		
Fountzilias G	November 2008	II	53	Gef	4.1	7.3	27	-	-	-
Mitry E	July 2010	II	22	Mas	6.4 [§]	7.1	-	-	-	-
Strumberg D	December 2010	II	56	Nim	1.56	4.2	-	-	-	-
Kullmann F	April 2009	II	64	Cet+G+OX	3.9 [§]	7.1	-	-	-	-
Philip PA	August 2010	III	357	G	3	5.9	-	-	-	-
			362	Cet+G	3.4	6.4	-	-	-	-
Kindler HL	August 2010	III	302	G+Bev	3.8	5.8	-	-	-	RCT
			300	G+PI	2.9	5.9	-	-	-	
Javle M	June 2009	II	50	G+Cap+Bev	5.8	9.8	35.5	-	-	-
Van Cutsem E	May 2009	III	301	G+Erl+PI	3.6	6.0	-	-	-	Randomized
			306	G+Erl+Bev	4.6	7.1	-	-	-	
Ko AH	November 2010	II	36	Erl+Bev	1.3 [§]	3.4	-	-	-	-
Yao JC	February 2011	-	207	Eve	11.0	-	-	-	-	Randomized
			203	PI	4.8	-	-	-	-	
Lipton A	April 2010	II	21	G+Erl+Cel	-	18	80	20	-	-
Saif MW	January- August 2009	II	68	LY+G	3.7	7.1	-	-	-	Randomized, double-blind
			67	PI+G	3.4	8.3	-	-	-	
Shimizu K	January- February 2009	-	29	Len	-	12.1	-	-	20	-
Yanagimoto H	September 2010	II	21	PPV	-	9	38	-	-	-
Ramanathan RK	March 2011	II	16	PX-12	0.9	3.2	-	-	-	-

-: Not sure if phase II or III; G: gemcitabine; OX: oxaliplatin; GEM FDR: fixed-dose-rate gemcitabine; Erl: erlotinib; Sun: sunitinib; Gef: gefitinib; Mas: masitinib; Nim: nimotuzumab; Cet: cetuximab; Bev: bevacizumab; PI: placebo; Cap: capecitabine; Eve: everolimus; Cel: celecoxib; Len: lentinan; PPV: personalized peptide vaccination; LY: LY293111. PFS: progression-free survival; TTP(§): time to progression; OS: overall survival; RCT: randomized control trial.

second-line chemotherapy with S-1 were 17.2%, 2.5 and 7.7 months, respectively. The second study, with 21 patients enrolled, showed a marked drop of CA19-9 in 28% of the 18 evaluable patients. The median progression-free survival was 4.1 months and the median overall survival was 6.3 months.

Irinotecan

Irinotecan, acting by inhibiting DNA topoisomerase, thereby interfering with DNA replication and cell division (Creemers et al., 1994), is active in the treatment of pancreatic cancer. In the National Cancer Center Hospital of Japan (Ueno et al., 2007), 40 patients with metastatic pancreatic cancer were chosen to accept irinotecan and 10 patients obtained responses (overall response rate: 27.0%, partial response rate: 2.7%) in 37 assessable patients. The median overall survival was 7.3 months with 29.5% 1-year survival. Adverse effects were tolerated except that one patient died of disseminated intravascular coagulation syndrome induced by neutropenia with watery diarrhea. In 2009, the Samsung Medical Center of Sungkyunkwan University reported a study of irinotecan as second-line regimen for advanced pancreatic cancer (Yi et al., 2009). Patients (33) pretreated with gemcitabine were included with median age of 59 years. The trial resulted in 2.0 months of median progression-free survival and 6.6 months of median overall survival, as well as mainly gastrointestinal toxic effects, which were predictable and manageable.

Other drugs

Recently, researchers have explored some other drugs as monotherapy. Most failed to be identified effective, like glufosfamide (Ciuleanu et al., 2009) and pancreatic proteolytic enzyme (Chabot et al., 2010), probably because of the knowledge limitation. Paclitaxel, a compound abstracted from taxus, can stagnate cell mitosis by promoting the formation of microtubules. Saif et al. (2010) conducted a clinical trial of paclitaxel loaded polymeric micelle (a new formulation of paclitaxel, which has less side effects compared with the traditional one Taxol), which enrolled 56 patients suffering from advanced pancreatic cancer with 3 patients showing response effects (1 complete response, 2 partial responses). The median time to progression was 3.2 months (95% confidence interval, 2.6 to 4.2), median progression-free survival was 2.8 months (95% confidence interval, 1.4 to 4.0) and median overall survival was 6.5 months (95% confidence interval, 5.1 to 7.9). Disease control rate (complete response + partial response + stable disease) was 60.0%. The study group drew the conclusion that "paclitaxel loaded polymeric micelle monotherapy resulted in overall survival and other efficacy parameters preferable to that seen historically with gemcitabine."

Binary combination

Gemcitabine and cisplatin

According to the preclinical evidence that gemcitabine can increase cisplatin-induced DNA cross links and inhibit their repair, and cisplatin can enhance the incorporation of gemcitabine triphosphate into DNA (Peters et al., 1995), the combined use of gemcitabine and cisplatin is reasonable.

Clayton et al. (2006) reported a phase II study to access the combination of gemcitabine and cisplatin in patients with advanced pancreatic cancer. Of the 35 evaluable patients, hematological toxicity was significant, but mostly asymptomatic, with 3 episodes of neutropenic sepsis and 2 severe episodes of bleeding. The median time to progression was 5.75 months, median survival was 9.5 months, 6-month survival was 72.2%, and 1-year survival was 41.7%. All of these data were considered effective.

Also in 2006, a randomized phase III trial was reported by Heinemann et al. (2006). 190 patients with advanced pancreatic cancer were randomly assigned to receive gemcitabine and cisplatin or only gemcitabine. The combination treatment group had prolonged median progression-free survival (5.3 vs. 3.1 months) and median overall survival (7.5 vs. 6.0 months), which did not achieve statistical differences and higher rate of stable disease (60.2 vs. 40.2%; $P < 0.001$).

The latest study from Italy (Colluci et al., 2010) randomly assigned 400 patients to receive gemcitabine alone ($n = 199$) or gemcitabine and cisplatin ($n = 201$). The median overall survival was 8.3 months, median progression-free survival was 3.9 months, objective response rate was 10.1%, and clinical benefit rate was 23.0% in the gemcitabine group versus 7.2 months, 3.8 months, 12.9% and 15.1% in the gemcitabine and cisplatin group. All of these parameters failed to reach statistical significance. Combination therapy was associated with more hematologic toxicities, but without relevant difference in non-hematologic toxicity. Apart from the former two studies, this trial came into a negative result without any improvement compared with gemcitabine alone.

Gemcitabine and S-1

Three clinical trials from Korea were found in PubMed studying the combination of gemcitabine and S-1, all gaining positive findings, thus indicating the utility of the coadunation. The first one, reported by Min Kyoung et al. (2009), who enrolled 22 patients with advanced or metastatic pancreatic cancer, among which 19 patients had metastases, including 11 multiple liver metastases. After 25.4 months of follow-up, the median time to progression and median overall survival were 4.6 (95% confidence interval, 2 to 7.2 months) and 8.5 months (95% confidence

interval, 6.8 to 10.1 months), respectively, and 1-year survival rate was 27.3%, no intolerable adverse effect occurred. 20 patients (91%) received chemotherapy on an outpatient basis. It seems that gemcitabine plus S-1 are useful and tolerable.

In the same year from Gyeongsang National University (Gyeong-Won et al., 2009), 32 chemo-naïve patients, receiving gemcitabine and S-1, showed 44% partial response, 25% stable disease and 25% progression disease. The median time to progression was 4.92 months (95% confidence interval: 4.16 to 5.67 months), and the median overall survival was 7.89 months (95% confidence interval: 5.96 to 9.82 months). Longer survival time was associated with better performance status.

The last study, enrolling 38 patients with unresectable pancreatic cancer, was reported by Oh et al. (2010). Of 34 assessable patients, 11 achieved partial responses (no complete response). The median time to progression and median overall survival were 5.4 and 8.4 months, respectively, without severe toxicity.

Gemcitabine and oxaliplatin

It has been indicated in one particular study that the combination of oxaliplatin and gemcitabine in pancreatic tumor-bearing mice has a synergistic antitumor effect (Moschidis et al., 2007). Lee et al. (2009) reported results for a group of 48 patients with advanced pancreatic cancer, who received oxaliplatin and gemcitabine infusion. Of the 44 evaluable patients, the response rate, median overall survival, and median time to progression were 18.2%, 9.4 and 5.6 months, respectively. 16 patients obtained clinical benefits, and the global quality of life scores improved by 11.71.

Fortune et al. (2009) from the Ohio State University Medical Center reported a study, which focused on the fixed-dose-rate gemcitabine combined with oxaliplatin in 17 patients with metastatic pancreatic cancer refractory to standard-dose-rate gemcitabine. Of all patients, 24% had partial responses, 29% had stable disease and 47% had progressive disease. The median progression-free survival was 2.6 months and the median overall survival was 6.4 months. There was no unexpected toxicity. Interesting activity was shown in this trial, supporting this kind of combination.

Gemcitabine and glufosfamide

A phase III trial administered gemcitabine and glufosfamide (a cytotoxic alkylating agent prodrug) to patients with metastatic pancreatic cancer previously treated with gemcitabine, showing a slightly increased overall survival compared with best supportive care, but not reaching statistically significance (median survival: 3.4 versus 2.8 months; $P = 0.19$) (Ciuleanu et al., 2009). Another phase II trial was carried out by Chiorean et al.

(2010) and it showed a promising activity of this combination (confirmed partial response rate: 18%; stable disease: 39%; progression-free survival: 3.7 months; overall survival: 6 months), but with pronounced hematologic and renal toxicities, needing further researches in the dosage of glufosfamide.

Gemcitabine and fluorouracil/prodrug of fluorouracil

As an oral and tumor-selective fluoropyrimidine, capecitabine can provide prolonged fluorouracil exposure at lower peak concentrations (Ishikawa et al., 1998). Gemcitabine and capecitabine are both nucleoside analogs by inhibiting different targets and have shown synergistic antitumor activity in an intergroup multicenter phase II study (Stathopoulos et al., 2010). A study (Cunningham et al., 2009) also supported this kind of combination. A total of 533 patients with advanced pancreatic cancer were randomly assigned to gemcitabine ($n = 266$) and gemcitabine plus capecitabine ($n = 267$) arms, resulting in apparent improved objective response rate (19.1% vs. 12.4%; $P = 0.034$), progression-free survival (hazard ratio, 0.78; 95% confidence interval, 0.66 to 0.93; $P = 0.004$) and overall survival (hazard ratio, 0.86; 95% confidence interval, 0.72 to 1.02; $P = 0.08$) in the combination group. However, an earlier study from a Swiss group (Bernhard et al., 2008) showed no difference between gemcitabine plus capecitabine ($n = 160$) and gemcitabine ($n = 159$) arms when comparing clinical benefit response (19 versus 20%).

Roehrig et al. (2010) reported a study applying palliative first-line treatment of weekly high-dose 5-fluorouracil as 24 h-infusion and gemcitabine to 60 patients with metastatic pancreatic cancer. 7% patients achieved responses and 59% achieved tumor control (complete response + partial response + stable disease). Median time to progression and overall survival were 4 months and 7.3 months, respectively. This study also identified the normal range of performance status and tumor markers (CEA and CA19-9) were related with good benefit from the combination therapy.

In a latest trial conducted by Nakamori et al. (2011), pre-administered uracil/tegafur (prodrug of 5-fluorouracil) plus gemcitabine were used in 36 patients with unresectable/recurrent pancreatic cancer, getting the results of 25% partial response, 56% stable disease, 19% progression and 7 months of median overall survival.

Gemcitabine/fluorouracil and alkaloids

Gemcitabine and irinotecan: Due to the efficacy of gemcitabine or irinotecan as monotherapy, it appears that combining these two agents have encouraging effects. Before 2006, some trials had explored the combination and several achieved positive results. Similar results were reported by Neri et al. (2009) with 33 patients enrolled. Of

32 evaluable patients, 10 responded to treatment (2 complete responses and 8 partial responses) and 11 got stable diseases. The median time to progression and median survival were 9.2 (95% confidence interval: 6.0 to 12.4) and 11.8 (95% confidence interval: 7.7 to 15.9) months, respectively, with 22% 2-year survival.

However, a study of gemcitabine and irinotecan did not achieve statistical increase when compared with gemcitabine monotherapy as first-line treatment in 145 patients (71 in the combination group, 74 in the gemcitabine group) with locally advanced or metastatic pancreatic cancer (Stathopoulos et al., 2006). The overall response rate was: 15% in the combination group (95% confidence interval 5.96 to 24.0) and 10% in the gemcitabine group (95% confidence interval 2.97 to 17.03). The median time to progression was 2.8 and 2.9 months, median survival time was 6.4 and 6.5 months, and 1-year survival was 24.3 and 21.8% for the 2 groups, respectively.

Gemcitabine and etoposide: Activated RAS mutations, which can increase the sensitivity of tumor cell for gemcitabine and etoposide, are present in over 90% of pancreatic cancer (Barbacid, 1990). According to this theory, a trial to evaluate gemcitabine and etoposide, which comprised of 40 chemo-naïve patients with locally advanced or metastatic pancreatic cancer, was conducted by Melnik et al. (2010). Of 35 evaluable patients, 10 exhibited partial responses, 12 had stable disease and 20 showed a more than 20% decrease in CA 19-9 biomarker levels. Median overall survival was 7.2 months, median time to progression was 3.1 months and 1-year survival rate was 11.4%. 12 patients showed improved quality of life and 3 patients showed stable situation. The primary dose-limiting toxicities were hematologic toxicity and fatigue.

Gemcitabine and docetaxel: Patients (n = 68) with advanced/unresectable/metastasized pancreatic cancer were enrolled in a multicenter phase I (n = 25) and phase II study (n = 43) and received gemcitabine and docetaxel (Ridwelski et al., 2006). After determining the tolerability maximum of the combined agents in phase I, a total of 139 chemotherapy cycles were conducted in phase II, coming into the results of 18.6% overall response, 41.9% stable disease, 9 months of median overall survival and 13.9% 1-year survival rate. In addition, quality of life was acceptable and side effects were moderate. Due to the promising outcomes, further evaluation in a prospective phase III study setting was wanted by the author group.

Capecitabine and docetaxel: A report from Hellenic Oncology Research Group (Katopodis et al., 2011) drew the conclusion that the combination of docetaxel and capecitabine as second-line chemotherapy may confer

good disease control associated with improvement of quality of life, due to the results of a trial in 31 patients with metastatic pancreatic cancer. Partial responses were observed in 3 patients, stable disease in 7 and disease progression in 21. The median progression-free survival was 2.4 months and median overall survival was 6.3 months, with the estimated 1-year survival rate of 14.7%.

5-Fluorouracil and paclitaxel: Another argument to support the combination of fluorouracil and alkaloids as second-line chemotherapy for gemcitabine-refractory pancreatic cancer was offered by Kim et al. (2009). In this trial, of 20 evaluable patients (total 28, receiving paclitaxel and 5-fluorouracil), 10% got partial responses and 20% showed stable disease, with 2.5 and 7.6 months of median time to progression and overall survival, respectively. Besides the earlier combinations, gemcitabine and exatecan were explored by Abou-Alfa et al. (2006), but showed no superior to gemcitabine alone with respect to overall survival.

Fluorouracil and cisplatin/oxaliplatin/leucovorin

A randomized controlled trial evaluating the effect of 5-fluorouracil and cisplatin after curative resection of pancreatic cancer was reported by Kosuge et al. (2006). Patients (89) after surgery were randomized to receive chemotherapy (45 patients, arm A) or nothing (44 patients, arm B) with 4 ineligible patients (3 in arm A and 1 in arm B). Toxicity was minor and acceptable among the eligible patients in arm A. The estimated 5-year survival rate was 26.4% in arm A and 14.9% in arm B. The median duration of survival was 12.5 and 15.8 months, and the recurrence rate at 5 years was 73.6 and 80.8% in arm A and arm B, respectively. The regimen was still safe and tolerable even without statistically significant difference between the results.

In the same year, Mitry et al. (2006) reported the valuable use of oxaliplatin combined with 5-fluorouracil as second-line treatment of advanced pancreatic cancer which was offered after failure of oxaliplatin alone or infusional 5-fluorouracil alone. 18 out of 32 patients treated in the single-agent arms received oxaliplatin and 5-fluorouracil after progression, showing no objective response and 17% disease stabilization. Median time to progression from the start of second-line treatment was 0.9 months. Median overall survival was 4.9 months from the start of front-line therapy and 1.3 months from the start of second-line therapy.

Later in 2010, fluorouracil plus leucovorin were identified having identical efficacy with gemcitabine (Median survival: 23.0 vs. 23.6 months; median progression-free survival: 14.1 vs. 14.3 months), but more adverse events in 1088 patients (551 receiving fluorouracil plus leucovorin, 537 receiving gemcitabine) with completely resected pancreatic cancer in a randomized controlled

trial reported by Neoptolemos et al. (2010).

Irinotecan and oxaliplatin

For patients with gemcitabine- and 5-fluorouracil-refractory pancreatic cancer, few drugs have been used with relatively good results. In 2010, a pilot study from Korea using irinotecan and oxaliplatin got a partial response rate of 21.4%, a stable disease rate of 28.6%, time to tumor progression of 1.4 months and overall survival of 4.1 months in 14 patients, supporting the regimen as a feasible and tolerable salvage therapy (Oh et al., 2010).

Gemcitabine and curcumin

Epelbaum et al. (2010) from Rambam Health Care Campus in Israel recruited 17 patients with advanced pancreatic cancer and treated them with curcumin plus gemcitabine. At the beginning of the trial, curcumin was given by mouth and then intolerable side events occurred, causing low compliance and having to reduce the dose. One of the 11 evaluable patients (9%) had partial responses, 4 (36%) had stable disease, and 6 (55%) had tumor progression. Time to progression was 1 to 12 months (median 2.5), and overall survival was 1 to 24 months (median 5). The prevention of high oral dose may limit systemic effect of curcumin, which needs to be modified in future study.

Triple or more combination

FOLFOX

FOLFOX is short for the combination of 5-fluorouracil, leucovorin and oxaliplatin, having achieved positive evaluations either as second-line or first-line therapy in recent several studies. For example, in 2007, Hotel-Dieu de France University Hospital reported that an interesting response rate and a tolerable level of toxicity were obtained when using FOLFOX-6 as the first-line treatment for locally advanced or metastatic pancreatic cancer (Ghosn et al., 2007)

Two years later, Novarino et al. (2009) analyzing the median time to progression (11.6 weeks) and overall survival (17.1 weeks) of 17 assessable patients (total 23) receiving FOLFOX after been pre-treated with gemcitabine-containing schedule, drew the conclusion that the regimen had some activities and needed further investigations. A similar trial (Pelzer et al., 2009) of 37 gemcitabine-refractory patients was also treated with FOLFOX, but at a different dosage and dosing interval, drew the same conclusion based on the results: 12 weeks of median time to progression, 22 weeks of median overall survival and 49% overall disease control (complete remission = 3%; partial remission = 3%; stable

disease > 12 weeks = 43%).

FOLFIRI

FOLFIRI (5-fluorouracil, leucovorin and irinotecan) was recently identified useful as second-line treatment after failure of gemcitabine-based therapy for advanced pancreatic cancer. Taieb et al. (2007) explored this new combination in 40 patients and identified its activity with a manageable toxicity profile, 37.5% response rate, 27.5% stable disease, 5.6 months median progression-free survival and 12.1 months overall survival.

A multicenter experience of the Gruppo Oncologico Italia Meridionale (Gebbia et al., 2010) also studied the regimen and summarized that it was able to induce an objective response in a relatively small fraction of the gemcitabine-refractory pancreatic adenocarcinoma patients.

In a latest study reported by Conroy et al. (2011), the trial of FOLFIRINOX (FOLFIRI plus oxaliplatin) as first-line therapy displayed a survival advantage, but an increased toxicity was discovered when compared with gemcitabine. 342 patients with metastatic pancreatic cancer were randomly assigned to receive FOLFIRINOX or gemcitabine. In the comparison of the overall survival median (11.1 versus 6.8 months), median progression-free survival (6.4 vs. 3.3 months) and objective response rate (31.6 versus 9.4%), superiority of FOLFIRINOX was obvious ($P < 0.001$). After 6 months of follow-up, 31% patients in the FOLFIRINOX group had a definitive drop of the quality of life versus 66% in the gemcitabine group (hazard ratio, 0.47; 95% confidence interval, 0.30 to 0.70; $P < 0.001$).

Gemcitabine related combination

In a study from Taiwan (Ch'ang et al., 2009), using biweekly gemcitabine followed by oxaliplatin and simplified 48-h infusion of 5-fluorouracil/leucovorin (GOFL) in 45 patients with advanced pancreatic cancer, exhibited promising activity on the basis of some datum like overall response rate (33.3%), disease-control rate (68.9%), clinical benefit response rate (46.2%), median time to progression (5.1 months) and overall survival (8.7 months).

In 2010, the combination of gemcitabine, oxaliplatin and capecitabine (GEMOXEL) was administered to 45 advanced pancreatic cancer patients, finally manifesting its feasibility (Hess et al., 2010). After a median follow-up of 27.2 months, the median progression-free survival was 4.3 months. Patients lived for a median time of 7.8 months.

In 2011, gemcitabine, oral tegafur and leucovorin (GEMTG) gained promising efficacy and security in a trial (Pericay Pijaume et al., 2011) which recruited 40 advanced pancreatic cancer patients. Overall response rate was 22.5%, median time to progression was 3.87 months,

median time to treatment failure was 2.97 months and median overall survival was 6.3 months.

Doxorubicin, mitomycin and 5-fluorouracil/capecitabine

In a study published in 2009, a modified FAM regimen (5-fluorouracil, doxorubicin, and mitomycin-C) was used as salvage chemotherapy for pancreatic and biliary tract cancer and was acknowledged as an effective chemotherapy regimen with tolerable toxicity (Lee et al., 2009). Of the 31 patients progressive after gemcitabine-based treatment (15 had pancreatic cancer), 4 patients showed partial responses and 8 had stable disease. The median time to progression and overall survival time were 2.3 and 6.7 months.

Treatment that consisted of capecitabine, doxorubicin, and mitomycin-C was applied to 28 pretreated patients suffering from pancreatic, gallbladder and bile duct cancer in a trial conducted by Kruth et al. (2010) and resulted in a high tumor control rate (6 patients achieving partial remissions, 7 achieving minor remissions, 6 having stable disease), 4.5 months median progression-free survival, 6.8 months median overall survival and a safety profile.

Apart from the aforementioned classifications, combination of 5-fluorouracil, folinic acid plus cisplatin followed by gemcitabine or the reverse sequence and therapy of gemcitabine administered at a fixed dose rate or in combination with cisplatin, docetaxel, or irinotecan in metastatic pancreatic cancer were explored in a randomized phase III trial (Dahan et al., 2010) and a randomized phase II study (Kulke et al., 2009) respectively, but did not get significant difference between these groups.

Neoadjuvant/preoperative chemotherapy

Gemcitabine and cisplatin

Palmer et al. (2007) from University of Birmingham reported the results for a group of 50 patients, among which 24 received gemcitabine and 26 received gemcitabine and cisplatin before pancreatic resection. At the end, 27 patients underwent pancreatic resection, 9 in the gemcitabine arm and 18 in the combination arm, without increase in surgical complications. 1-year survival rate was 62% in the combination group versus 42% in the gemcitabine group. The advantages of high resection rate and encouraging survival rate were observed in the combination therapy with gemcitabine and cisplatin.

In a study from Swiss Hepato-Pancreato-Biliary Center, the same combination therapy was administered to 28 patients with resectable adenocarcinoma of the pancreatic head (Heinrich et al., 2008). Patients (26) had resectable cancer on restaging examinations and the R0 resection rate was 80%. Median disease-free survival

and overall survival were 9.2 and 26.5 months, with improved quality of life.

A prospective phase II trial also from Heinrich (2008) found that pancreaticoduodenectomy after neoadjuvant chemotherapy was safe and associated with low morbidity and mortality rates. In addition, given histologic response and cytopathic effects, the combination of gemcitabine and cisplatin as neoadjuvant chemotherapy was an effective treatment.

Gemcitabine and oxaliplatin

Sahora et al. (2011) reported a trial of gemcitabine and oxaliplatin as neoadjuvant treatment for locally advanced, non-metastasized pancreatic cancer and got positive results. Of the 33 patients, 39% had a curative resection with 69% R0 resection. Median overall survival of patients who underwent tumor resection was 22 months when compared with 12 months for those without resection. The median recurrence-free survival rate after resection was 10 months.

Targeted therapy

Inhibitor of tyrosine kinase

Erlotinib: In many tumors, epidermal growth factor receptor (EGFR) is overexpressed, often related to poor prognosis (Ueda et al., 2004). Erlotinib, an EGFR tyrosine-kinase inhibitor, has been demonstrated having antitumor activity in pancreatic cell lines (Durkin et al., 2003). The use of erlotinib in combination with gemcitabine for chemotherapy-naïve patients with locally advanced, unresectable or metastatic pancreatic carcinoma had been approved effective in many studies before 2006. Recently, positive results of 2 phase II trials about erlotinib and gemcitabine have been published. One was from Spain (Feliu et al., 2011), using fixed-dose-rate gemcitabine in combination with erlotinib. Of the 42 advanced pancreatic cancer patients, 1 achieved complete response, 11 achieved partial responses, 11 showed stable disease and 19 showed progression disease. Median time to progression was 5 months, median overall survival was 8 months and 1 year survival rate was 35%. The other is from Japan (Okusaka et al., 2011), exhibiting similar toxicity and efficacy in Japanese patients with unresectable pancreatic cancer when compared with Western patients.

Gefitinib: Early in 2008, a trial of another EGFR inhibitor, gefitinib, administered with gemcitabine to 53 patients who suffered from inoperable or metastatic pancreatic cancer, showed promising results (Fountzilias et al., 2008). Responses were seen in 6 patients, as well as stable disease in 12 patients. 92% had main toxicity of

myelotoxicity. Median progression-free survival was 4.1 months and median survival was 7.3 months with 1 year survival rate of 27%.

Sunitinib: A multinational, randomized, double-blind, placebo-controlled phase III trial of sunitinib, a tyrosine kinase inhibitor of platelet-derived growth factor receptor (PDGFR) and vascular endothelial growth factor receptor (VEGFR) for the treatment of pancreatic neuroendocrine tumors was carried out by Raymond et al. (2011) based on the active results in preclinical models and phase I and II trials. 171 patients were randomly assigned in a 1:1 ratio to receive either sunitinib or placebo with best supportive care. The study had to be halted early because of more serious adverse events and deaths in the placebo group and a difference in progression-free survival favoring sunitinib, even though advantages can still be seen in the sunitinib group. Compared with 5.5 months in the placebo group, median progression-free survival of the sunitinib group was 11.4 months (hazard ratio for progression or death, 0.42; 95% confidence interval, 0.26 to 0.66; $P < 0.001$). In addition, the objective response rate was apparently higher in the sunitinib group (9.3 versus 0%). At the end of observation, 9 deaths were reported in the sunitinib group (10%) versus 21 deaths in the placebo group (25%) (hazard ratio for death, 0.41; 95% confidence interval, 0.19 to 0.89; $P = 0.02$).

Masitinib: Masitinib is a selective kinase inhibitor that blocks c-kit, PDGFR, Lyn, focal adhesion kinase phosphorylation activity and to a lesser extent the fibroblast growth factor receptor 3 tyrosine kinase activities, all of these playing important roles in pancreatic cancer progression. A report about the safety and activity of masitinib combined with gemcitabine in 22 patients was published Mitry et al. (2010). The median time to progression was 6.4 months and median overall survival was 7.1 months, both longer in patients with locally advanced pancreatic cancer and Karnofsky score (80 to 100) than those with metastatic pancreatic cancer or Karnofsky score (70). All these encouraging datum supported the initiation of a phase III trial.

Monoclonal antibodies

Nimotuzumab/cetuximab: Nimotuzumab, a humanized monoclonal anti-EGFR antibody, was confirmed safe and well tolerated, and showed higher progression-free survival in stable disease patients (complete response: 0; partial response: 0; stable disease: 6 patients; median progression-free survival: 19.2 weeks for patients with stable disease, 6.7 for all; median overall survival: 18.1 weeks) in a phase II trial by Strumberg et al. (2010) who

signified that a randomized controlled trial combined with gemcitabine had been initiated to improve efficacy.

Cetuximab is a another monoclonal antibody against the EGFR, but no improved outcome was observed neither in a multicenter phase II study by Kullmann et al. (2009) or in a phase III study by Philip et al. (2010).

Bevacizumab: Bevacizumab is a recombinant humanized monoclonal antibody against vascular endothelial growth factor A (VEGF-A) (Ferrara et al., 2004). Kindler et al. (2005) reported promising results of a phase II trial exploring gemcitabine and bevacizumab in metastatic pancreatic cancer patients. Thus, the Cancer and Leukemia Group B evaluated this regimen in a randomized phase III trial (Kindler et al., 2010), getting 13% response, 5.8 months median overall survival and 3.8 months median progression-free survival in the gemcitabine/bevacizumab group versus 10%, 5.9 and 2.9 months in the gemcitabine/placebo. These data failed to show improved survival.

Javle et al. (2009) explored the combination of gemcitabine, capecitabine and bevacizumab and got active results (complete response rate: 22%; progression-free survival: 5.8 months; overall survival: 9.8 months). In the same year, Van Cutsem et al. (2009) attempted the addition of bevacizumab to gemcitabine plus erlotinib, but did not observe apparent increase in overall survival (7.1 versus 6.0 months; hazard ratio, 0.89; 95% confidence interval, 0.74 to 1.07; $P = 0.2087$) even with a much longer progression-free survival (4.6 versus 3.6 months; hazard ratio, 0.73; 95% confidence interval, 0.61 to 0.86; $P = 0.0002$) compared with placebo. In the next year, the therapy of bevacizumab and erlotinib for gemcitabine-refractory metastatic pancreatic cancer was identified safe but relatively ineffective by a phase II trial (Ko et al., 2010).

Ipilimumab: Ipilimumab, able to block the interaction of B7-1/B7-2 and CTLA-4 (CD152) and thus reducing the apoptosis of activated lymphocytes, was used as single agent for locally advanced or metastatic pancreatic adenocarcinoma in a phase II trial reported by Royal et al., (2010) with one subject experiencing a delayed response which implied further study.

Inhibitor of the mammalian target of rapamycin

Although, the precise mechanism is unclear, the mammalian target of rapamycin, a protein kinase as the principal mediator of signals in the PI3K/Akt pathway, played an important role in mitogen stimulation (Rowinsky, 2004). Thus, inhibition of mammalian target of rapamycin may be an efficient anticancer strategy for pancreatic cancer.

Everolimus, an oral inhibitor of mammalian target of

rapamycin was used in 207 patients and showed significantly prolonged progression-free survival (11.0 versus 4.6 months; hazard ratio, 0.35; 95% confidence interval, 0.27 to 0.45; $P < 0.001$) and low rate of severe adverse events when compared with placebo ($n = 203$) for advanced pancreatic neuroendocrine tumors in a report from University of Texas M.D. Anderson Cancer Center (Yao et al., 2011).

Javle et al. (2010) investigated mammalian target of rapamycin inhibitor (temsirolimus) and combined mammalian target of rapamycin and EGFR inhibitors (everolimus plus erlotinib) in two prospective clinical trials (Trial A and Trial B). Only 5 patients were enrolled in trial A (2 died within a month, 1 developed dehydration and another developed asthenia). Of the 16 patients in trial B, 15 showed progressive disease as well as 1 non-evaluable. Pretreatment biopsies revealed a higher pAkt/Akt ratio in tumor specimens than that in non-malignant pancreatic tissue. The author group considered that "Future strategies should aim for a broader targeting of the PI3K pathway in pancreatic cancer".

Inhibitor of cyclooxygenase-2

Cyclooxygenase-2, over-expressed in 45 to 75% of pancreatic cancer is identified as being associated with pancreatic carcinogenesis, chemoresistance, increased invasion and promotion of angiogenesis (Merati et al., 2001). In 2010, Lipton et al. (2010) combined celecoxib (a selective oral cyclooxygenase-2 inhibitor) with gemcitabine and irinotecan to treat 21 patients with advanced pancreatic cancer and got partial response rate of 20% and stable response of 80%, median overall survival of 18 months, 80% 1 year survival and 20% 2 year survival. Moreover, CA19-9 showed a marked reduction in all evaluable patients, pain was relieved and quality of life got improvement in many patients with tolerable toxicity.

Gastrin antagonist

Gastrin and cholecystokinin, two kinds of gastrointestinal peptides and having similar affinities for the cholecystokinin2 receptor, can stimulate the growth of several human pancreatic cancer cell lines in culture and pancreatic xenograft rodent models (Clerc et al., 2002). Thus, the cholecystokinin2 receptor has become target for the treatment of pancreatic cancer in some trials, of which the latest one was reported by Meyer et al. (2010) using the oral cholecystokinin2 receptor antagonist Z-360 in combination with gemcitabine in patients with advanced pancreatic cancer. 33 patients were randomly allocated to Z-360 120 mg ($n = 9$), 240 mg ($n = 12$) or placebo ($n = 12$), and they showed a stable disease of 62.5, 25 and 60%, respectively. More patients showed improvement in pain in Z-360 group. An encouraging trend

trend towards reduced pain and improved survival was observed for those receiving 120 mg Z-360.

Another cholecystokinin2/gastrin receptor antagonist, gastrazole, showing efficacy but poor oral bioavailability and needing continuous venous infusion was reported initially for 10 patients (Black, 2009).

Other targeted drugs

LY293111: LY293111 is a novel oral anticancer agent with leukotriene B4 receptor antagonist and peroxisome proliferator-activated receptor gamma agonist properties. The rationale of a randomized double-blind phase II trial comparing gemcitabine plus LY293111 versus gemcitabine plus placebo in advanced adenocarcinoma of the pancreas (Saif et al., 2009) was derived from promising results used alone or in combination with gemcitabine in pancreatic cancer xenograft models (Meyer et al., 2010). However, the results did not demonstrate any benefit of adding LY293111 to gemcitabine.

Lentinan: Lentinan, a kind of glucan in mushroom, can stimulate immunological function mainly by enhancing the functions of T-Lymphocytes and macrophages (Wasser, 2002). A study of orally administered superfine dispersed lentinan for advanced pancreatic cancer from Tokyo Women's Medical University (Shimizu et al., 2009) showed that the median survival time was 12.1 months and 20% were alive for 3 years in 25 eligible patients, which could be considered effective.

Personalized peptide vaccination: A phase II study (Yanagimoto et al., 2010) of personalized peptide vaccination, combined with gemcitabine for 21 non-resectable pancreatic cancer patients, found boosted cellular and humoral responses in the post-vaccination peripheral blood mononuclear cells and plasma from 14 of 18 and 13 of 18 patients tested, respectively, and showed correlation between immune boosting and overall survival (9.0 months) with a hazard ratio of 0.2 (95% confidence interval, 0.06 to 0.73; log-rank $P = 0.0239$).

PX-12: PX-12 is a small molecular irreversible inhibitor of thioredoxin-1, a proto-oncogene that stimulates tumor growth and inhibits apoptosis (Kirkpatrick et al., 1998). Following progression after gemcitabine-based therapy, PX-12 was tried to be administered to 16 patients with advanced pancreatic cancer and identified well tolerated with uncommon grade ≥ 3 adverse events (Ramanathan et al., 2011). Two patients had stable disease, which was the best response. There was no consistent decrease in thioredoxin-1 or CA 19-9 levels in the duration of the therapy. As none of the initially treated 16 patients had a

progression-free survival > 4 months (median progression-free survival: 0.9 months; median survival: 3.2 months), the investigators terminated the study early.

Tipifarnib: K-ras mutations are responsible for permanent activation of the K-ras oncoprotein and are found in 70 to 90% of pancreatic cancers. Tipifarnib, a farnesyltransferase inhibitor, finally inhibiting K-ras gene function, seems a rational target in pancreatic cancer research. In a trial (688 patients) (Van Cutsem et al., 2004), no statistically significant differences in survival parameters were observed. The median overall survival for the gemcitabine + tipifarnib arm was 193 versus 182 days for the gemcitabine + placebo arm ($P = 0.75$); 6-month and 1-year survival rates were 53 and 27 versus 49 and 24% for the control arm, respectively; median progression-free survival was 112 versus 109 days for the control arm.

DISCUSSION

In the part of single-agent regimen, traditional agents like gemcitabine are the main subjects of researches. For resected pancreatic cancer, significantly longer median disease-free survival after curative resection was observed in the gemcitabine group (about twice than that of the surgery-only group), but without statistically different overall survival in a randomized controlled trial and a randomized phase III trial (Oettle et al., 2007; Ueno et al., 2009). For locally advanced pancreatic carcinoma, gemcitabine monotherapy still demonstrated far better survival than historical data for 5-fluorouracil-based chemotherapy (Ishii et al., 2010). Thus, it is full of enough reasons to recommend gemcitabine as standard treatment for either resected or locally advanced pancreatic cancer. Fixed-dose-rate gemcitabine, a new schedule of administration of gemcitabine, based on the theory that a critical plasma concentration of gemcitabine can increase its tumor cytotoxicity and therapeutic efficacy was considered having relevant antitumor activity in a trial conducted by Mane et al. (2010) and exhibited longer median disease-free survival and overall survival than standard gemcitabine in a phase III, randomized study (Poplin et al., 2009). Apparent toxicity occurred in both trials, which will limit the use of fixed-dose-rate gemcitabine.

In four studies using S-1 as second-line agent to treat gemcitabine-resistant advanced pancreatic cancer (mainly metastatic pancreatic cancer) (Okusaka et al., 2008; Morizane et al., 2009; Nakai et al., 2010; Sudo et al., 2011), median time to progression was more than 2 months (2 to 4.1), median overall survival was more than 4.5 months (4.5 to 9.2) and well tolerated toxicity was observed in all trials, implying its antitumor activity and safety. Compared with other second-line drugs, S-1 is

more feasible and convenient because it can be given orally. Single-agent irinotecan was explored as first-line therapy for patients with metastatic pancreatic cancer in a trial conducted by national cancer center hospital of Japan (Ueno et al., 2007) and showed noticeable efficacy. Single-agent irinotecan was also explored as second-line treatment in advanced pancreatic cancer (Yi et al., 2009) and obtained positive outcomes, especially in patients with good performance status. However, these two trials are just phase II studies without matched control groups so that it is hard to conclude that irinotecan can be a good option as first-line or second-line agent for advanced pancreatic cancer. Several trials tried to study new drugs, but few achieved satisfactory data except paclitaxel loaded polymeric micelle. In a trial by Saif et al. (2010), paclitaxel loaded polymeric micelle seemed well tolerated and had comparable efficacy parameters to that seen historically in gemcitabine ± erlotinib. Currently, preclinical studies of the combination of paclitaxel loaded polymeric micelle with gemcitabine are under performance by the same author group.

Gemcitabine-based combination is the main stream of studies, some getting improved prognosis at some extent. A phase II study (Clayton et al., 2006) supported the efficacy of gemcitabine and cisplatin, but with significant hematological toxicity. A randomized phase III trial (Heinemann et al., 2006) applied modified schedule of the combination and achieved effective and safe results. However, the sample size of the two trials was considered too small to demonstrate the potentially relevant differences in survival. The latest randomized study from Italy (Colucci et al., 2010) consisting of 400 patients, did not show improvement, but decrease even though not reaching statistical significance in the addition of weekly cisplatin to gemcitabine when compared with gemcitabine alone. The use of gemcitabine and cisplatin did not show significant improvement in overall survival (hazard ratio, 0.91; 95% confidence interval, 0.82 to 1.01) in the newest meta-analyses updated in this study. There are three clinical trials (Min Kyoung et al., 2009; Gyeong-Won et al., 2009; Oh et al., 2010) all concluding that gemcitabine and S-1 combination was effective and tolerable with about 8 months median overall survival for locally advanced or metastatic pancreatic cancer in the palliative setting. Randomized controlled trial is needed to demonstrate if it is more efficient than gemcitabine single therapy. Nowadays, the usage of gemcitabine and S-1 in a postoperative adjuvant setting is under investigation.

The authors of a multicenter phase II study (Lee et al., 2009) supported gemcitabine plus oxaliplatin as a reasonable first-line option for advanced pancreatic cancer patients. A small trial (Fortune et al., 2009) explored fixed-dose-rate gemcitabine combined with oxaliplatin and also got encouraging results. In a phase II trial (Chiorean et al., 2010), glufosfamide and gemcitabine exhibited higher response rate (18% confirmed) and 1-year survival (32%) than single agent gemcitabine, but

with more myelosuppressive and nephrotoxic toxicity than that in the glufosfamide alone study (Ciuleanu et al., 2009). The gemcitabine and capecitabine regimen significantly improved response rate and progression-free survival in a phase III randomized trial (Cunningham et al., 2009), but showed no indication of difference in clinical benefit response or quality of life in another phase III randomized trial (Bernhard et al., 2008) when compared with gemcitabine alone. Gemcitabine and 5-fluorouracil as a 24 h-infusion were implied as feasible and capable of tumor control with tolerable toxicity in a palliative first-line treatment of metastatic pancreatic cancer (Roehrig et al., 2010). In addition, the oral pro-drugs of 5-fluorouracil and uracil/tegafur, also have activity when added to gemcitabine in a multicenter phase II study (Nakamori et al., 2011) having potential value in the outpatient setting.

In a small trial reported by Neri et al. (2009), long median time to progression (9.2 months) and overall survival (11.8 months) were observed in the combination of gemcitabine and irinotecan. However, a multicenter phase III trial (Stathopoulos et al., 2006), which seemed more convincing due to the large sample size and the establishment of control group, did not gain meaningful difference between this combination and gemcitabine alone groups. In a clinical trial (Melnik et al., 2010), the combination of gemcitabine and etoposide was generally well-tolerated and exhibited a response rate (28%) similar to other published studies (4.1 to 33%). Interestingly, 4 patients showed remarkable overall survival, among which 2 living more than 2 years. The authors offered a hypothesis that specific molecular subsets particularly sensitive to this regimen might exist, needing follow-up researches. In a phase I/II study (Ridwelski et al., 2006), weekly administration of docetaxel at a lower dosage plus gemcitabine showed a higher overall response rate than single infusion of a high dosage of docetaxel protocol used before, implying the importance of dosage and administration intervals. The addition of curcumin to gemcitabine was newly explored just in a small trial (only 17 patients) (Epelbaum et al., 2010) and the formulations of curcumin was not optimal, which needs further studies of large size sample.

Recently, due to the frequency of gemcitabine-refractory, second-line combination has become more important. Combination chemotherapy associated with fluorouracil or its pro-drugs is a nice trend of research. For example, in a study from Hellenic Oncology Research Group (Katopodis et al., 2011), a degree of activity and good tolerance of the combination of docetaxel and capecitabine were indicated in patients with advanced pancreatic adenocarcinoma in a palliative setting. In a study for patients with gemcitabine-resistant pancreatic cancer but good performance status (Kim et al., 2008), 5-fluorouracil and paclitaxel were deemed as a good therapeutic choice. Another study (Mitry et al., 2006) brought arguments, although quite modest to

support the value of second-line chemotherapy of 5-fluorouracil plus oxaliplatin. Compared with gemcitabine, the combination of fluorouracil and leucovorin was identified having equal efficacy in a randomized controlled trial (Neoptolemos et al., 2010), while in another randomized controlled trial (Kosuge et al., 2006), 5-fluorouracil and cisplatin failed to show any significant benefit.

What can we do if failing after gemcitabine-based and 5-fluorouracil-based treatment? Few studies have focused on this issue. In 2010, a pilot study from Korea (Oh et al., 2010) demonstrated that the irinotecan and oxaliplatin regimen constituted a feasible and tolerable salvage therapy in patients with gemcitabine-refractory and 5-fluorouracil-refractory advanced pancreatic cancer. More exploratory studies like this are wanted.

Different regimens consisting of more than 2 agents have been involved in many trials but mostly without comparison groups so that definitive conclusions are difficult to make. Even though, inspirations still can be seen from these trials. For example, FOLFOX with various schedules of administration was deemed as a safe and active regimen either as first-line treatment (Neoptolemos et al., 2010) or as second-line treatment (Novarino et al., 2009; Pelzer et al., 2009). FOLFIRI, administered in different methods, also showed promising activity in the fighting with pancreatic cancer (Taïeb et al., 2007; Gebbia et al., 2010). Especially in a randomized trial (Conroy et al., 2011), FOLFIRI added with oxaliplatin had a convincing advantage of median progression-free survival and overall survival. Otherwise, a randomized phase II trial comparing FOLFIRI.3 with FOLFOX identified modest activities of the 2 regimens in pre-treated patients, no superior nor inferior to each other (Yoo et al., 2009). Gemcitabine related combinations, like GOFL, GEMOXEL or GEMTG, exhibited similar median overall survival with a range of 6.3 to 8.7 and merited further investigations. Doxorubicin, mitomycin and 5-fluorouracil/capecitabine were used together as salvage therapy for bilio-pancreatic cancer in two trials (Lee et al., 2009; Kruth et al., 2010) and got an average median overall survival of 6.75 months, not bad results in terms of second-line therapy.

Due to the potential benefits like increasing the rate of adjuvant therapy, early treatment of micrometastases, conversion of non-resectable to resectable disease, etc., neoadjuvant therapy has been researched in many trials, among which most are related with chemoradiotherapy. Here, only preoperative chemotherapy is within the range of discussion and merely 4 relative trials (3 about gemcitabine and cisplatin (Palmer et al., 2007; Heinrich et al., 2008), 1 about gemcitabine and oxaliplatin (Sahora et al., 2011) were found. Through these trials, the trend of down-staging locally advanced pancreatic cancer from a non-resectable to resectable stage and the safety of the following surgery were observed. However, information bias should be considered because the subjective definition of resectability always varies on the basis of

different institutions' level.

The development of targeted therapy is flourishing nowadays and breakthrough may be made in this reign in the future. Various growth factor receptors such as epidermal growth factor receptor (EGFR), Vascular endothelial growth factor receptor (VEGFR), Platelet-derived growth factor receptors (PDGFR), etc., have become the most common targeted sites, most of which are tyrosine kinase inhibitors, including erlotinib, gefitinib, sunitinib and masitinib. Consistent with results before, erlotinib, an inhibitor of EGFR, was characterized as safe and effective when combined with gemcitabine in two recent trials (Feliu et al., 2010; Okusaka et al., 2011). So, erlotinib plus gemcitabine is a good option with little risk. Another tyrosine kinase inhibitor of EGFR, gefitinib, has been demonstrated to be having promising activity combined with gemcitabine in a phase II study (Fountzilias et al., 2008) and needs further investigations. The data from a randomized controlled trial (Raymond et al., 2011) showed that using sunitinib rationally to inhibit VEGFR and PDGFR resulted in meaningful improvements in progression-free survival, objective response rate, and overall survival among patients with pancreatic neuroendocrine tumors. Moreover, based on a phase II studies, Mitry (2010) deemed that masitinib, mainly blocking c-kit, PDGFR and focal adhesion kinase, was encouraging in the treatment of advanced pancreatic cancer and deserved a phase III trial.

Nimotuzumab and cetuximab, as monoclonal antibodies against EGFR, show flat activity for treating pancreatic cancer. For example, in a multicenter phase II study (Kullmann et al., 2009), the addition of cetuximab to the combination of gemcitabine and oxaliplatin did not result in a prolonged survival in comparison with earlier studies evaluating gemcitabine plus oxaliplatin only. According to the newest research (Garrido et al., 2009), nimotuzumab binds bivalently to the overexpressed EGFR in tumor cells, and transiently binds monovalently to the receptor in normal cells, while cetuximab binds tightly in neither tumor nor normal cells. Thus, less toxicity will be caused by nimotuzumab.

Since 2006, a total of 4 trials tried bevacizumab (against VEGF-A) in combination with different agents (including 1 randomized controlled trial) for treating various stages of pancreatic cancer and drew different conclusions. It is hard to feature bevacizumab as effective or not because of too many varieties. In a randomized controlled trial (Kindler et al., 2010), no survival benefit was gotten from bevacizumab even when combined with gemcitabine.

Many new sites, including CTLA-4, mammalian target of rapamycin, cyclooxygenase-2, cholecystokinin2 receptor, leukotriene B4 receptor, peroxisome proliferator-activated receptor gamma and proto-oncogene, have become targets in many trials. Besides, some specific immunopotentiators, like lentinan and personalized peptide vaccination, have been explored in some trials (Wasser et al., 2002; Shimizu et al., 2009).

No matter the results obtained in these trials, whether good or bad, lots of implications can be made, which may become rationales of further explorations.

Conclusion

Gemcitabine-based chemotherapy is still under investigations and can be considered the first choice for treating pancreatic cancer so far. More prospective randomized trials using a controlled arm without treatment are needed to definitely demonstrate and validate the role of second-line treatment in gemcitabine-refractory pancreatic cancer. Targeting the specific biologic mechanisms involved in pancreatic cancer cell proliferation and metastasis, has been deemed as a new therapeutic approach with nice prospect.

ACKNOWLEDGEMENTS

This work was supported in part by grants from the National Natural Science Foundation of China (No. 30972910) and China Postdoctoral Science Foundation (No. 20060390294).

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