Pancreatic Disorders & Therapy
ISSN: 2165-7092

Sheng-bin et al., Pancreatic Dis Ther 2013, 3:1
DOI: 10.4172/2165-7092.1000109

Review Article Open Access

Stage II Trial of Capecitabine Joined Together with Thalidomide in Second-Line Medicine of Progressed Pancreatic Growth

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Abstract

Background: To assess the viability and averageness of capecitabine joined together with thalidomide in patients with propelled pancreatic disease (APC) who have beforehand accepted gemcitabine-based treatment. Systems: what added up to 31 patients were enrolled prospectively in Shandong Tumor Hospital from May 2007 to April 2009. Capecitabine was offered to patients twice a day at a dosage of 1,250 mg/m2 for 14-days then emulated by 7-day rest. Thalidomide was controlled 100 mg/day without interference until sickness movement or event of inadmissible poisonous quality.

Results: Two patients put forth fractional reaction (PR), eleven patients indicated stable ailment (SD) and eighteen patients exhibited continuous illness (PD). The average without movement survival (PFS) was 2.7 months (95% expectancy interim (CI), 2.4-3.3) and the average generally speaking survival (OS) was 6.1 months (95% CI, 5.3-6.9). In the subgroup examination, PFS had a huge distinction between the serum CA19-9 level diminishing >25% and diminishing <25%, with 3.0 months (95% CI, 2.5-3.6) and 2.5 months (95% CI, 1.8-3.2), (Log Rank=0.02), separately. Hematological poisonous quality incorporated leukocytopenia, frailty and neutropenia. Non-hematological toxicities incorporated loose bowels, skin rash, nausea/vomiting, hand-foot syndrome, weariness, discombobulation, languor and clogging.

Conclusion: Capecitabine joined together with thalidomide is a generally tolerated second line regimen, in patients with APC obstinate to gemcitabine.

Keywords: Pancreatic cancer; Second line; Capecitabine; Thalidomide

Introduction

Pancreatic malignancy is a regular threatening tumor with downtrodden guess, 5-years survival of 5%, owing to the trouble from distinguishing at an early stage and elevated threatening potential [1]. Just 20% patients who does not have generally propelled or metastatic tumor are resectable [2]. Chemotherapy plays a critical part in the medication of pancreatic malignancy. With the growth of revamped pills, the revamped chemotherapy for pancreatic growth shows up continually. Then again, gemcitabine (GEM) has remained a spine of unique first-line chemotherapy regimen for propelled or metastatic pancreatic disease and regulated illness-identified indications [3]. In first-line medicine, GEM in addition to 5-flurouracil and folinic harsh corrosive (FUFA) fusion had all the earmarks of being generally tolerated and extremely animated in patients. The average without movement survival (PFS) was 9.75 months (95% CI 6.9–12.6) and the average generally speaking survival (OS) was 13.10 months (95% CI 9.6–16.6) [4]. GEM joined together with oxaliplatin was a cut above that of GEM apart from everyone else regarding clinical profit, reaction rate, movement unhindered survival and a helpful slant in survival of generally 2 months in first-line medication [5]. These days, numerous synthesis medicines of GEM in addition to focused on executors for example bevacizumab, cetuximab and erlotinib have been examined in propelled pancreatic tumor (APC). Then again, just erlotinib succeeded right around these mixtures. Subsequently, in 2010, the National Comprehensive Cancer Network (NCCN) prescribed that the medication procedure for patients with propelled or metastatic pancreatic growth is GEM or GEM based regimen [6]. Yet, in first-line medication, the time of alleviation was short. This scenario proposed that the following target is to discover what sort of further medicine after movement will enhance the personal satisfaction and delay the survival time. An expanding number of patients upheld great clinical conditions after streamlined first-line chemotherapy. The proposed patients with a great practical exhibition status ought to be thought about for clinical trial cooperation. Capecitabine (Xeloda) is an orally regulated fluoropyrimidine and usually generally tolerated in treating patients with APC. Medication with capecitabine brought about clinically critical useful impacts on tumor-identified manifestations and yielded goal reaction movement in patients with generally propelled or metastatic pancreatic disease. 10 (24%) of 42 patients encountered a clinical profit reaction (95% CI, 12.1~39.5%) as prove by enhancement in pain relieving devouring, torment power, or Karnofsky exhibition status [7]. In propelled pancreatic ductal adenocarcinoma, capecitabine has been demonstrated single-operator action, with 7% objective reaction rate (ORR), 24% positive clinical profit reaction (CBR) and average survival of pretty nearly 6 months. Capecitabine monotherapy has exhibited clinically critical profit on tumor-identified side effects and actualized incomplete objective reactions in propelled or metastatic pancreatic tumor [8]. Thalidomide is a non-barbiturate soothing and entrancing medication which has against angiogenic and immunomodulatory lands [9] and a novel against-cytokine executor with auxiliary against-angiogenesis movement. It has been substantially used to control development of

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Received January 21, 2013; **Accepted** March 19, 2013; **Published** March 21, 2013

Citation: Sheng-bin S, Meng W, Zuo-xing N, Xiao-yong T, Yun-Liu Q (2013) Stage II Trial of Capecitabine Joined Together with Thalidomide in Second-Line Medicine of Progressed Pancreatic Growth. Pancreatic Dis Ther 3: 109. doi:10.4172/2165-7092.1000109

propelled robust tumor in mixture help and ended up being successful at constricting weight misfortune in APC patients with cachexia [10]. It confined tumor hyperplasia by way of the epoxy iodide chemical 2 pathway as opposed to repressing angiogenesis and decreasing vessels thickness [11]. Thalidomide has distinctive components of movement and action in diverse threatening tumors [12]. It has been assessed and has demonstrated action opposite strong tumors and has an antiangiogenic and immunomodulatory impacts, incorporating the restraint of vascular endothelial development element, essential fibroblast development element and tumor putrefaction component alpha [13]. This stage II trial was outlined to assess the viability and wellbeing of capecitabine joined together with thalidomide in GEM pretreated patients with by regional standards progressed or metastatic pancreatic malignancy.

Patients and Methods

What added up to 31 patients were enrolled prospectively in Shandong Tumor Hospital from May 2007 to April 2009. Patients with mainly progressed or metastatic pancreatic disease affirmed by histology and cytology, appropriated capecitabine joined together with thalidomide as second-line medicine. The patient's determination criteria were 20-74 years old, the Eastern Cooperative Oncology Group (ECOG) exhibition status (PS) ≤ 2, adequate hematological (white platelet number ≥ 4.0×10 9/l, neutrophil number ≥ 1.5×10 9/l, platelet check ≥ 100×10 9/l and hemoglobin ≥ 10 g/dl), hepatic (AST/ALT ≤ 2.5×upper cutoff points of typical; bilirubin ≤ 1.5 mg/dl) and renal (creatinine leeway ≥ 60 ml/min or creatinine ≤ upper breaking points of typical) methods, future of 12 weeks and with 1 measurable injury in any event consistent with the changed reaction assessment criteria in unyielding tumors (RECIST). All patients received clinical examination in this trial. Stomach registered tomography (CT), midsection X-beam and plasma CA 19.9 estimation were performed before using capecitabine in addition to thalidomide. Patients who had not gained GEM as a major aspect of their past regimen, or with enormous pleural emission or ascites, animated attending danger, mind metastasis, former systemic medicine with 5-FU (gemcitabine in addition to capecitabine; Oxaliplatin/fluorouracil/LV; gemcitabine in addition to S-1; S-1), earlier radiotherapy, pregnant or lactating ladies were prohibited from this trial. All patients were illuminated and assented to this medication and the trial was sanctioned by the morals trustees of Shandong area tumor doctor's facility.

Medicine

Medicine comprised of thalidomide with 100 mg/day was offered to patients without planned intrusions when beginning on the 1st day of chemotherapy, joining with capecitabine 1,250 mg/m^2 b.i.d managed with nourishment for 14 back to back days then accompanied by a rest time of 7 days for each 3-weeks cycle. Unfriendly occasions were reviewed as per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCICTCAE, adaptation 3.0). The starting dosages were resolved with hinging on the figure surface region (BSA). This medicine course was rehashed until the presence of sickness movement or unsuitable poisonous quality or the patient no longer wished to proceed the medication.

Assessment and Statistical Investigation

Consistent with RECIST, tumor reaction was surveyed by CT check after the second chemotherapy cycle. In view of the RECIST guideline, complete reaction (CR), halfway reaction (PR), stable sickness (SD) and ongoing infection (PD) were resolved. Level of tumor marker carbohydrate antigen (CA19-9) was measured each month until medication washout. PFS was numberd from the date of medicine start to documentation of malady movement or expiration. OS was measured from the medicine of capecitabine joined with thalidomide until expiration or the final catch-up. The Kaplan–Meier system was used to build the PFS and OS bends.

Results

Understanding aspects

Between May 2007 and April 2009, what added up to 31 patients were selected in this trial. 14 (45.2%) patients were female and 17 (54.8%) were male, with an average time period characterized by 59.5 (range: 34-75 years). ECOG PS scores were 0, 1, 2 (15, 14 and 2 patients), separately. One patient had by regional standards propelled malady and 30 patients had metastatic malady. Each of the 31 patients had beforehand advanced or accompanied GEM-based help (GEM apart from everyone else: 17 patients, GEM in addition to Oxaliplatin: 14patients). All patients accepted two cycles medication at least (2-5 cycles, Median 3). The trademark of patients was displayed in table 1.

Reaction

What added up to 31 patients were evaluable for reaction. 2 patients (6.5%) demonstrated PR, 11 patients (35.5%) had SD and 18 patients (58.1%) had PD. There was no complete reaction in this trial. The reaction rate was 6.5% and infection control rate (PR in addition to SD) was 41.9%. 14 patients had the serum CA19-9 level diminishing >25% from benchmark after two cycles (Table 2). The PFS was 2.7 months (95% CI, 2.4–3.3) (Figure 1) and the average OS was 6.1 months (95% CI, 5.3–6.9) (Figure 2). In the subgroup examination, consistent with the serum CA19-9 level, PFS had a huge distinction right around the serum CA19-9 level diminishing >25% and diminishing <25%. PFS were 3.0 months (95% CI, 2.5–3.6) and 2.5 months (95% CI, 1.8–3.2) (Log Rank=0.02, Figure 3), individually.

Factor		Patients (%)
Median age (range)		59.5 (34–75)
Gender	Male	17 (55.0%)
	Female	14 (45.0%)
Performance status	0	15 (48.0%)
	1	14 (45.0%)
	2	2 (6.0%)
Primary tumor site	Head	20 (65.0%)
	Body and tail	11 (35.0%)
Prior chemotherapy	GEM alone	17 (55.0%)
	GEM plus other drugs	14 (45.0%)
Stage of disease	Locally advanced	1 (3.0%)
	Metastatic	30 (97.0%)

Table 1: Characteristics of patients (n=31).

Response	No. of patients (%)
Partial response (PR)	2 (6.45%)
Stable disease (SD)	11 (35.48%)
Progressive disease (PD)	18 (58.65%)
Median overall survival (OS), (95% CI)	6.1 (5.3–6.9) months
Median progression-free survival(PFS):	2.7 (2.4–3.3) months
CA19-9 level decreasing >25%	14 (45.16%)
Median progression-free survival(PFS): CA19-9 level decreasing <25%	3.0 (2.5–3.6) months
Median progression-free survival(PFS):	2.5 (1.8–3.2) months

Table 2: Response.

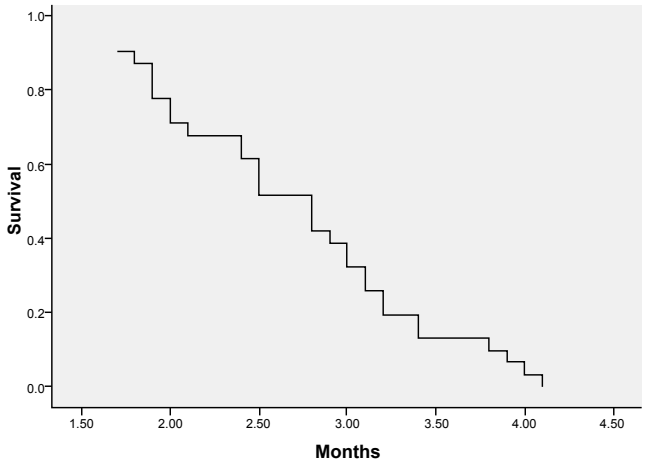

Figure 1: Progression-free survival (PFS) in population.

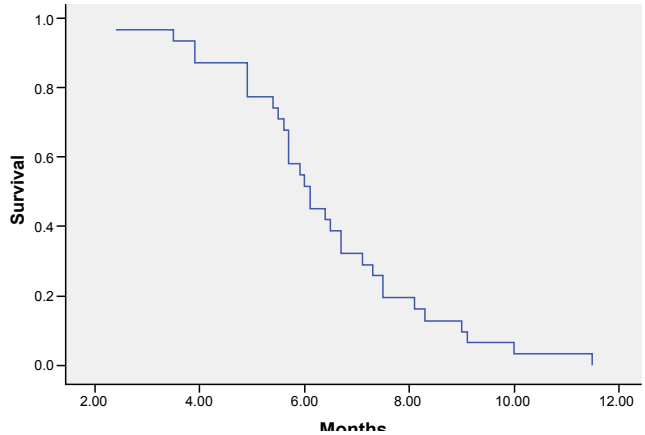

Figure 2: Overall survival (OS) calculated from the date of treatment with capecitabine plus thalidomide.

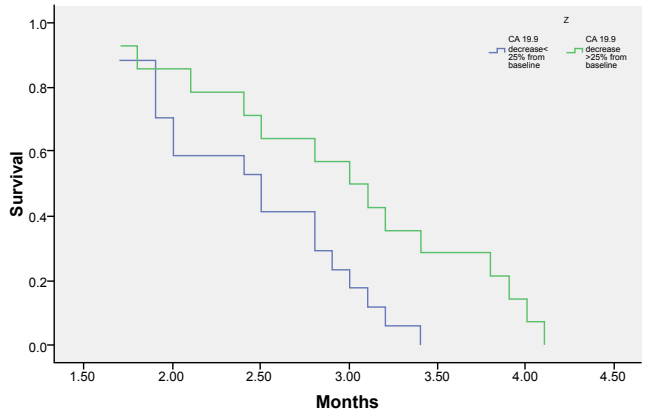

Figure 3: Progression-free survival (PFS) of CA19-9 level decreasing >25% and <25% (p=0.02).

Poisonous quality

What added up to 129 cycles were regulated in this trial, with an average of 3 cycles for every patient (reach, 2-5 cycles). During that timeframe of last examination, all patients had suspended medication. The most regular purposes behind end were infection movement (28 patients, 90.0%), grade 3 loose bowels (2 patients, 0.6%, the third cycle happened), and persistent refusal (1 patient, 0.3%, the fourth cycle cannot). Hematological harmfulness was mellow, incorporating leukocytopenia, neutropenia and pallor. Non-hematological toxicities held loose bowels, skin rash, nausea/vomiting, hand-foot syndrome, weariness, tipsiness, sluggishness and clogging. In this study no evaluation 4 lethality and no medication-identified passing were watched (Table 3).

Discussion

Pancreatic malignancy is a harmful ailment with unfortunate guess. At present, there is no standard medicine for second-line treatment of patients with APC who advance after GEM-based help. The average survival with best supportive consideration in patients who have foundered GEM help is give or take 2 months, and about a large part of patients with GEM-pretreated malady may be petitioners for further medicine [14]. In second-line medicine, few randomized information existed for patients with APC. Capecitabine in fusion with docetaxel is animated and decently-tolerated regimen in the medicine of patients with pancreatic tumor beforehand treated with gemcitabine based-therapy [15]. 24 patients are evaluable for poisonous quality and reaction. 3 patients accomplished a PR. SD for 2 or more cycles was watched in 70.8% of patients (n=17). 45 % (n=11) of patients had a 50% or more decline in CA19–9 levels. Grade III and IV toxicities closed weariness in 4 pts (17%), hand-foot syndrome in 4 patients (17%), loose bowels, pallor and mucositis in 2 patients (9%) and fringe neuropathy in one patient. Oxaliplatin/fluorouracil/LV was fundamentally connected with upgraded PFS and OS, contrasting and fluorouracil/LV alone [16]. What sorts of second-line plan might be utilized as the standard medication? The National Comprehensive Cancer Network guidelines right now suggested fluorinated pyrimidine-based help as second-line chemotherapy after GEM flop in the chose patients (Table 4) [17]. In second line medicine, fluorouracil joined together with LV was used as metabolic feature, where PFS or OS has accomplished certain healing adequacy. In this trial, 2 patients indicated PR and 11 patients with SD, 18 patients with PD. The reaction rate was 6.5% and the ailment control rate was 41.9%. In the CONKO-003 trial, second-line medication with oxaliplatin in addition to FUFA fundamentally enhanced average survival in patients with APC, contrasting and best supportive consideration, actualizing an average survival of fair 9 weeks [18].

Capecitabine monotherapy in GEM-pretreated patients with APC demonstrated that 27 patients were evaluable for reaction: no CR or

Toxicity	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Leukocytopenia	6 (19.35)	3 (9.68)	0	0
Neutropenia	4 (12.90)	1 (3.23)	0	0
Thrombocytopenia	2 (6.45)	0	0	0
Anemia	7 (22.58)	2 (6.45)	0	0
Diarrhea	6 (19.35)	2 (6.45)	3 (9.67)	0
Nausea/vomiting	11 (35.48)	3 (9.68)	0	0
Skin rash	5 (16.13)	3 (9.68)	0	0
Hand-foot syndrome	5 (16.13)	2 (6.45)	0	0
Fatigue	14 (45.16)	4 (12.90)	0	0
Dizziness	8 (25.80)	1 (3.23)	0	0
Drowsiness	7 (22.58)	7 (22.58)	0	0
Constipation	9 (29.03)	1 (3.23)	0	0

Table 3: Toxicity.

Regimen	Evaluable patients	Response rate	Disease control rate
Irinotecan	33	9.0%	48.0%
Paclitaxel	30	10.0%	46.7%
Capecitabine	27	0	39.0%
Capecitabine plus celecoxib	35	9.0%	37.1%
S-1	47	4.0%	36.0%
Oxaliplatin plus capecitabine	39	2.6%	28.2%
Oxaliplatin plus 5-fluorouracil	17	0	23.5%
Pemetrexed	52	3.8%	23.1%
Selumetinib	21	0	16.0%
Capecitabine plus thalidomide	31	6.5%	42.0%

Table 4: The efficacy of second-line chemotherapy.

PR was watched, yet 15 patients (39%) encountered SD. The average PFS was 2.3 months and average OS with 7.6 months, separately [8]. Oxaliplatin in addition to capecitabine were used as second-line help to treat 39 evaluable patients, 1 single demonstrated PR and 10 people encountered SD. The average OS was 23 weeks (95% CI, 17.0-31.0) and average PFS was 9.9 weeks (95% CI, 9.6-14.5) [19]. In a trial of selumetinib versus capecitabine, the average OS was 5.4 months and 5.0 months, individually. Malady movement occasions were encountered from 32 (84%) and 28 (88%) patients. The average PFS was 2.1 months and 2.2 months, separately [20]. Capecitabine in addition to celecoxib as second-line medication of progressed pancreatic and biliary tract tumors is a sheltered treatment alternative after washout of past GEM-holding regimen with an OS rate of 9% and average survival term of 1 week [21]. In the investigation of capecitabine in addition to celecoxib, 3 patients affirmed PR (95% CI: 0–18%) and 10 patients with SD in (29%).

Thalidomide is a pill with a powerful hostile to-angiogenic impact and might standardize tumor vasculature. In this way, it is used in the medicine of tumor about as bevacizumab. Epidermal development variable receptor (EGFR) transformations were extraordinary in pancreatic tumors, not connected with clinical guess and medication reaction [22]. In a case report demonstrating efficaous come about by mixture of thalidomide, irinotecan and cerecoxib, they acknowledged the system of activity as accompanies. Thalidomide diminished the security of TNF-mRNA and COX-2 mRNA. On the other hand, it doesn't totally hinder COX-2 statement. In a trial, the blend of thalidomide, celecoxib and irinotecan in flat-measurements been used and this blend stood for a practical medication for patients of pancreatic disease with repeat or metastases [12]. Kimberly directed a trial of thalidomide in patients with metastatic carcinoid and islet unit tumors that 18 patients with metastatic carcinoid neuroendocrine carcinomas were enlisted. No patients accomplished CR or PR. The best reaction was SD in 11 of 16 reaction-evaluable patients (69%) [23].

In perspective of poisonous quality, 2 patients encountered evaluation 3 looseness of the bowels and no patients happened evaluation 3\4 hematological poisonous quality. The harmfulness incorporated leukocytopenia, sickliness and neutropenia. Non-hematological toxicities held looseness of the bowels, skin rash, nausea/vomiting, hand-foot syndrome, weariness, tipsiness, laziness and stoppage. A stage II trial of thalidomide in patients with metastatic carcinoid and islet cell tumors demonstrated that Grade 3 toxicities incorporated tipsiness with orthostatic hypotension, tactile neuropathy, exhaustion, hemorrhagic cystitis and profound venous thrombosis. Grade 1–2 toxicities were exhaustion, stoppage, dry mouth, sluggishness and dizziness/syncope [22]. A stage I trial was composed to figure out the most extreme tolerance dosage and measurement-restraining harmfulness of gemcitabine/oxaliplatin/5-FU/thalidomide (GOFT) in patients with APC. The danger incorporated evaluation 3 leukopenia and stomatitis, grade 1/2 paleness, grade 1/2 sickness, grade 1 loose bowels, grade 1 alopecia, grade 1 skin and grade 1 hypersensitivity [24].

In finish, capecitabine in addition to thalidomide was generally tolerated in a second-line medication for GEM-hard-headed pancreatic growth patients. Capecitabine joined with thalidomide has justified to further examination dependent upon the support of its wellbeing profile and clinical movement. Constraint of this trial untruths in modest example measure and more proof-based solution is demanded to be further enhanced.

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