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Multicenter, Open-Label, Phase I/II Study of Tocilizumab, an Anti–Interleukin-6 Receptor Monoclonal Antibody, Combined with Gemcitabine in Patients with Advanced Pancreatic Cancer

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Abstract

Background: To assess the efficacy, safety and pharmacokinetics of tocilizumab + gemcitabine in patients with advanced pancreatic cancer.

Methods: Patients with treatment-naive advanced pancreatic cancer and high inflammatory burden (C-reactive protein ≥ 2 mg/dl) without obvious infections received tocilizumab (8 mg/kg) intravenously every 2 weeks with intravenous gemcitabine (1,000 mg/m^2) on days 1, 8 and 15 of each 4-week cycle until disease progression or study withdrawal. Interleukin-6 signalling inhibition biomarkers were measured. Efficacy analyses included overall survival, progression-free survival, tumour response and clinical symptoms. Adverse events and laboratory parameters were also assessed.

Results: Fifteen patients received tocilizumab+gemcitabine. Tumour response was observed in two patients (13%). Six patients (40%) died within 2 months of treatment start. Median overall survival was 2.5 months (95% confidence interval, 1.4-5.8); median progression-free survival was 1.8 months (95% confidence interval, 0.8-3.6). Overall and progression-free survival tended to be longer in patients with modest than in patients with higher elevations of baseline C-reactive protein. Changes in C-reactive protein and IL-6 occurred. Although tocilizumab +gemcitabine was tolerable, results were inconclusive because of the brevity of the evaluation period resulting from the death or premature withdrawal of patients. Dose interruption attributed to haematologic toxicity was frequently observed.

Conclusions: Tocilizumab+gemcitabine failed to show a clear clinical benefit in patients with advanced pancreatic cancer and high inflammatory burden. To evaluate conclusively the benefit of tocilizumab, future study designs should use a comparator treatment that does not interfere with interleukin-6 signalling and that includes better patient selection criteria.

Keywords: C-reactive protein; Gemcitabine; Interleukin-6 receptor; Pancreatic cancer; Tocilizumab

Introduction

Pancreatic cancer was the fourth leading cause of cancer death in Japan in 2014 [1], and the 5-year survival rate remains <10% [2]. Gemcitabine is the mainstay of treatment for advanced cases; however, its benefit, both alone and combined with other therapies, has been modest [3].Cancer-related inflammation contributes to patient morbidity and mortality [4]. Inflammation is linked to the proliferation and survival of malignant cells, angiogenesis and alteration of immune responses to cancer treatments [4]. Interleukin-6 (IL-6) mediates several biological activities [5] and is a key cytokine of inflammatory response [4]. It is involved in constitutional symptoms such as fever, fatigue and weight loss and in increased production of acute-phase reactants [6,7].

In pancreatic cancer, IL-6 induces cancer cell epithelial-to-mesenchymal transition, migration and invasion [8,9]. Elevated IL-6 levels are associated with more advanced tumour stage 1 and larger tumour burden [10,11]. IL-6 also appears to play a key role in cancer-induced cachexia [12-14], a multifactorial condition characterised by anaemia, progressive muscle wasting, weight loss and poor

performance status (PS) [15,16]. Cachexia is a negative prognostic factor for survival [15]. The IL-6 pathway has thus emerged as an attractive therapeutic target.

Tocilizumab is a humanised anti–human monoclonal antibody that binds specifically to soluble and membrane-bound IL-6 receptors (sIL-6R/mIL-6R), inhibiting IL-6R–mediated signalling. The clinical benefit of IL-6R blockade by tocilizumab in the treatment of various diseases has been demonstrated [17,18].

In this study, we investigated the efficacy, safety and pharmacokinetics of tocilizumab combined with gemcitabine in patients with pancreatic cancer and a high inflammatory burden. Drug–drug interactions and biomarkers were also evaluated.

Patients and Methods

Patients

Major inclusion and exclusion criteria are summarized in Supplemental Table S1. Eligible patients had chemotherapy-naive, unrespectable, locally advanced or metastatic pancreatic cancer and a high inflammatory burden, evidenced by modestly to highly elevated C-reactive protein (CRP ≥ 2 mg/dl) levels, without obvious infections. The study complied with the International Conference on Harmonization guidelines on good clinical practice, the principles of the Declaration of Helsinki and other applicable regulations. Protocols and amendments were approved by the Japanese Ministry of Health, Labour and Welfare and the institutional review board of each centre. All patients provided written informed consent before enrolment.

Study design, assessments and outcomes

This was a multicentre, open-label, phase I/II study. Trial registry number is JapicCTI-090889 (JAPIC clinical trials information). In step 1, the initial tolerability of tocilizumab and gemcitabine combination therapy (tocilizumab+gemcitabine) was to be determined in six patients according to dose-limiting toxicities (DLTs) reported during cycle 1.

If patients were withdrawn because of reasons other than DLTs, additional patients were to be enrolled up to an accrual of six evaluable patients. If no more than two-sixths of patients experienced DLTs, another 24 patients were to be enrolled in step 2. The independent data review committee (IDRC) periodically reviewed the study data and made recommendations as appropriate regarding the conduct of the study.

Patients received tocilizumab (8 mg/kg) intravenously every 2 weeks with intravenous gemcitabine (1,000 mg/m^2) on days 1, 8 and 15 of each 4-week treatment cycle (in step 1 cycle 1: tocilizumab on days 2 and 16; gemcitabine on days 1, 9 and 16). Dose reduction was permitted only for gemcitabine.

Criteria for tocilizumab withdrawal and definitions of DLTs and end points are presented in Supplemental Table S2. End points included overall survival (OS), progression-free survival (PFS), tumour response, safety, clinical symptoms and pharmacokinetic/pharmacodynamic and biomarker assessments. Supplemental Table S3 contains a schedule of study assessments.

Statistical analysis

This study was exploratory and had low statistical power. Statistical methods for analysis of efficacy and safety data are summarised in Supplemental Table S4.

Results

Study conduct

This study was performed at eight sites in Japan from September 2009 to November 2010. Of nine patients treated with tocilizumab +gemcitabine in step 1, three did not complete cycle 1 (progressive disease, n=2; consent withdrawal, n=1). Because no DLTs were observed during cycle 1 in six evaluable patients, after endorsement by the IDRC, the study proceeded to step 2, in which enrolment of 24 additional patients commenced. Enrolment was suspended when six of 15 patients enrolled in step 1 (n=9) or 2 (n=6) died within 2 months of treatment start. The study was terminated prematurely because of the shortened evaluation period, which made assessing the safety and efficacy of the tocilizumab+gemcitabine combination difficult.

Patients

Patient disposition is presented in Figure 1, and patient demographics are shown in Table 1. All patients had measurable adenocarcinoma-type disease with a high inflammatory burden (evidenced by a median baseline CRP value of 10.6 mg/dl [range, 1.3-26.4 mg/dl]). No patients had previously undergone surgery with postoperative adjuvant chemotherapy.

Median (range) numbers of tocilizumab and gemcitabine infusions were 3 (1-9) and 4 (1-12), respectively. Median gemcitabine dose intensity per week over a 4-week treatment cycle was 502 mg/m^2 (range, 249-751 mg/m^2).

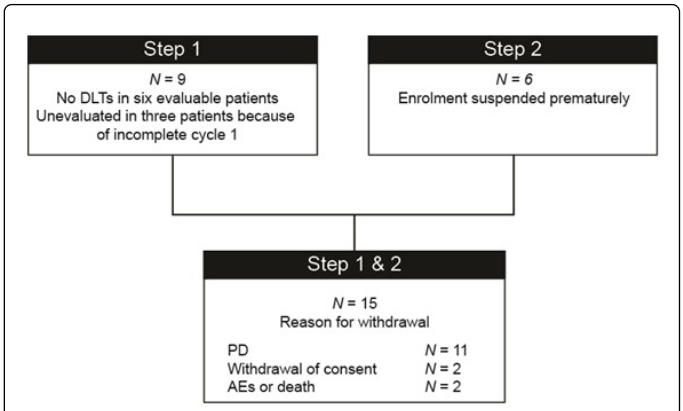

Figure 1: Patient disposition. AE: Adverse Event; DLT: Dose-limiting Toxicity; PD: Progressive Disease.

Safety

All 15 patients treated with tocilizumab+gemcitabine experienced adverse events (AEs), and 13 (87%) had grade ≥ 3 AEs. Commonly reported grade ≥ 3 AEs were thrombocytopenia (40%), leucopenia (40%), neutropenia (33%), lymphocytopenia (13%) and hyperglycemia

(13%) (Table 2). Grade 1 infections, including oral candidiasis and nasopharyngitis, occurred in three patients (20%).

Characteristics	Tocilizumab+Gemcitabine
	n=15
Sex, n (%)	
Female	3 (20)
Male	12 (80)
Age, years	
Median	69
Range	44–75
ECOG PS, n (%)	
0	8 (53)
1	7 (47)
Stage, n (%)	
IV	15 (100)
Tumor location, n (%)	
Head	3 (20)
Body	2 (13)
Body/tail	3 (20)
Tail	7 (47)
Metastasis, n (%)	
Any	15 (100)
Liver	14 (93)
Lung	2 (13)
Lymph node	12 (80)
Other	8 (53)
Baseline CRP,† mg/dl	
Median	10.6
Range	1.3–26.4
Baseline IL-6, pg/ml	
Median	20.3
Range	5.6–138

Table 1: Patient demographics and characteristics. †Measured before dose on day 1. All patients had CRP ≥2 mg/dL at the screening visit. CRP, C-reactive protein; EGOG PS, Eastern Cooperative Oncology Group performance status; IL-6, interleukin-6.

Seven patients (47%) reported 12 serious AEs: four (27%) experienced drug-related AEs including fatigue, neutropenia, disseminated intravascular coagulation (DIC) and haemorrhagic shock (one patient), gastrointestinal perforation and peritonitis (one patient), anorexia (one patient) and death (one patient). One patient developed bile duct stricture, which was caused by the underlying disease but resolved within 24 days; the patient continued study treatment.

Six patients died within 2 months after treatment start: four died of progressive disease (PD), one died suddenly, and one died of multiorgan failure (MOF). The MOF occurred after withdrawal and was due to PD and post-study chemotherapy with tegafur/gimeracil/oteracil.

	n (%)	
	(n=15)	
	All grades	Grade ≥ 3
Patients with ≥ 1 AE	15 (100)	13 (87)
Hematotoxicity		
Thrombocytopenia	11 (73)	6 (40)
Leukopenia	7 (47)	6 (40)
Neutropenia	5 (33)	5 (33)
Lymphocytopenia	3 (20)	2 (13)
Non-hematotoxicity		
Nausea	11 (73)	-
ALT increased	7 (47)	1 (7)
Anorexia	7 (47)	1 (7)
Pleural effusion	4 (27)	1 (7)
AST increased	7 (47)	-
Weight decreased	4 (27)	-
Diarrhea	4 (27)	-
Vomiting	4 (27)	-
Rush	4 (27)	-
Malaise	4 (27)	-
Hyperglycemia	3 (20)	2 (13)
Fatigue	3 (20)	1 (7)
Constipation	3 (20)	-
Proctalgia	3 (20)	-

Table 2: Most common adverse events. AEs: Adverse Events; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase.

Five patients died within 28 days after the last dose of study drug; three of these patients were among the four who died of PD within 2 months after treatment start. Of the remaining two patients, one belonged to the group of six patients who died within 2 months after treatment start. He died suddenly on day 11 despite resuscitation efforts after receiving 1 dose of tocilizumab and 2 doses of gemcitabine. The cause of death was considered most likely myocardial or pulmonary infarction. The other patient developed DIC on day 64. His treatment had been discontinued on day 59 because of PD, and he

died of haemorrhagic shock caused by DIC (likely a result of PD) on day 69.

One of 15 patients withdrew because of AEs (gastrointestinal perforation and peritonitis developed on day 27). These events were considered most likely to have been caused by PD and were resolved after 16 days by surgical intervention.

In 11 patients (73%), treatment was interrupted because of AEs; the most common were haematologic complications, including thrombocytopenia (53%), neutropenia (27%) and leucopenia (27%). None of these patients experienced bleeding or serious infection temporally associated with these events. Anti–tocilizumab antibodies were detected in two patients. No infusion-related reactions were reported.

Efficacy

Median (95% confidence interval [CI]) OS and PFS were 2.5 (1.4-5.8) months and 1.8 (0.8-3.6) months, respectively. Two patients achieved partial response (PR), and two had stable disease (SD). The best overall response rate was 13% (95% CI, 2%-40%), and the disease control rate was 27% (95% CI, 8%-55%). There was no clear trend in clinical symptoms as evaluated by the Brief Fatigue Inventory–Japanese version or the MD Anderson Symptom Inventory–Japanese version. Improvement in Eastern Cooperative Oncology Group PS occurred in two of seven patients who had a baseline PS of 1.

Biomarker Analyses

Initially, CRP decreased to below baseline levels after tocilizumab administration in all patients, irrespective of their eventual OS, PFS and overall tumour response. These reductions were generally sustained in two patients who achieved PR and two patients who had SD. The survival duration for these patients was 8.9, 8.0, 6.7 and 4.1 months, respectively. CRP levels gradually returned to baseline in some patients with PD and/or upon tocilizumab withdrawal (Figure 2A).

Changes in IL-6 levels were negligible in patients who achieved disease control with tocilizumab+gemcitabine. In patients who experienced PD, IL-6 levels tended to increase with treatment (Figure 2B). sIL-6R levels increased in all patients regardless of eventual response (Figure 2C).

The median hemoglobin level was 11.5 g/dl at baseline and gradually decreased after treatment initiation (11.4 g/dl at 2 weeks, 10.5 g/dl at 4 weeks and 10.3 g/dl at 6 weeks). Changes in hemoglobin level were disassociated from improvements in treatment outcome. Changes in hepcidin 20, 22 and 25 levels are presented in Supplemental Figure S1.

In exploratory subgroup analyses (Table 3), patients with highly elevated baseline CRP levels (≥ 10.6 mg/dl) tended to achieve poorer median OS with tocilizumab+gemcitabine therapy than patients with modest CRP elevation (1.6 months vs 5.8 months; P=0.0937). Patients with elevated baseline IL-6 levels and those with lower baseline platelet counts showed a trend towards shorter OS (data not shown).

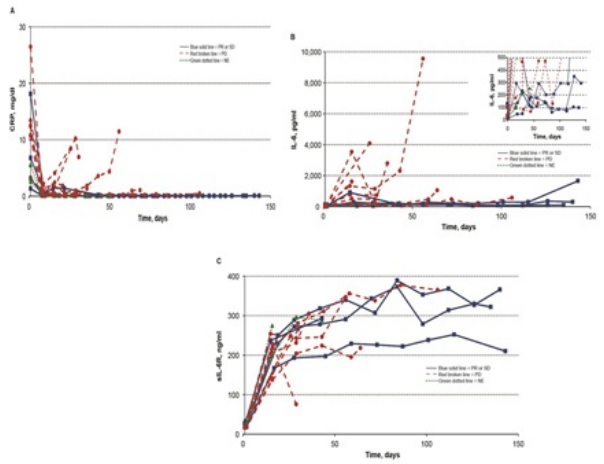

Figure 2: Serum biomarker levels by study day for each enrolled patient. (A) CRP. (B) IL-6. (C) sIL-6R. CRP, C-reactive Protein; IL-6, Interleukin 6; NE, Not Evaluable; PD: Progressive Disease; PR: partial response; SD, stable disease; sIL-6R: Soluble Interleukin-6 Receptor. "Blue solid line = PR, SD", "Red broken line = PD" and "Green dotted line = NE".

Subpopulation	n	OS, months	PFS, months	DCR
		Median (95% CI)	Median (95% CI)	% (95% CI)
Sex				
Female	3	4.1 (1.4-8.9)	4.4 (1.0-4.4)	67 (9-99)
Male	12	2.3 (1.0-5.8)	1.0 (0.5-1.9)	17 (2-48)
Age				
<65 years	5	3.6 (1.0-6.7)	3.6 (0.5-3.6)	40 (5-85)
≥ 65 years	10	2.3 (0.9-8.1)	1.0 (0.5-4.4)	20 (3-56)
Baseline ECOG PS				
0	8	2.7 (0.9-5.8)	0.8 (0.5-4.6)	25 (3-65)
1	7	2.5 (1.4-6.7)	1.9 (1.0-3.6)	29 (4-71)
Baseline CRP				
<10.6 mg/dl†	7	5.8 (3.6-6.7)‡	3.6 (1.0-4.4)	43 (10-82)
≥ 10.6 mg/dl†	8	1.6 (0.9-2.5)‡	0.9 (0.5-1.9)	13 (0-53)
Baseline IL-6				
<20.3 pg/ml†	7	4.1 (1.4-6.7)	3.6 (1.0-4.4)	43 (10-82)
≥ 20.3 pg/ml†	8	1.8 (0.9-2.5)	1.3 (0.5-1.9)	13 (0-53)

Table 3: Summary of exploratory subgroup analyses for OS, PFS, and DCR. †Median at baseline. ‡P=0.0937 for <10.6 mg/dl *vs* ≥ 10.6 mg/dl. CI, confidence interval; CRP, C-reactive protein; DCR: Disease Control Rate; EGOG PS: Eastern Cooperative Oncology Group performance Status; IL-6: Interleukin-6; OS: Overall Survival; PFS: Progression-free Survival.

The median gemcitabine dose intensity per week over a 4-week treatment cycle was similar irrespective of baseline CRP level but was lower in patients with decreased (<190×10^9/L) baseline platelet counts (250 mg/m^2 *vs* 541 mg/m^2).

Pharmacokinetic/Pharmacodynamic Results

Mean serum tocilizumab concentrations over cycle 1 in step 1 are presented in Supplemental Figure S2. After the first tocilizumab infusion, the maximum serum tocilizumab concentration (CMax) and half-life were 122 ± 17 μg/ml and 7 ± 2 days, respectively. The mean drug concentration at the expected time of minimum concentration (Ctrough) increased to approximately 60 μg/ml after the second tocilizumab administration. Tocilizumab did not appear to alter gemcitabine pharmacokinetics (Supplemental Table S5).

Discussion

Our study was prematurely terminated because of the deaths of one-third of the patients within 2 months of treatment initiation and the early withdrawal of patients who experienced PD or AEs. This is to be expected in a population of patients with advanced disease associated with a very poor prognosis.

Moderate to high CRP levels at baseline normalised rapidly after the start of tocilizumab treatment; these reductions were generally sustained in patients who derived clinical benefits. Survival times in these patients ranged from 4.1 to 8.9 months. Based on our historical experience, this does not necessarily reflect negative results. In previous data from our institution, patients with CRP levels ≥ 2 mg/dl showed a median survival duration of 3.4 months, whereas those with CRP levels<0.5 mg/dl and ≥ 0.5-<2 mg/dl achieved a median survival of 7.9 and 5.9 months, respectively (Mitsunaga et al.)

In this study, serum IL-6 levels increased noticeably along with tocilizumab administration only in patients with PD. Elevated serum IL-6 and IL-1β levels are associated with elevated CRP levels in patients with advanced pancreatic cancer, and patients with higher levels of both IL-6 and IL-1β achieve poorer outcomes with gemcitabine monotherapy [19-21]. Our observed OS and PFS durations with tocilizumab+gemcitabine were consistent with those reported for gemcitabine monotherapy, although patients in our study appeared biased towards poorer prognoses, as evidenced by their much higher baseline CRP and IL-6 values.

Consistent with the gemcitabine monotherapy study, our exploratory subpopulation analysis indicated that patients with modestly elevated baseline CRP achieved better OS and PFS outcomes with tocilizumab+gemcitabine than did those with higher CRP levels. Based on this finding and the sustained lower CRP levels observed during tocilizumab treatment regardless of baseline CRP, we expect that increases in tocilizumab dose will not improve outcomes in patients with markedly elevated baseline CRP levels. Therefore, exclusion of patients with high CRP levels should be considered when designing future studies of IL-6 inhibitors in advanced pancreatic cancer.

Because most patients experienced early PD or died, treatment effects on cachectic symptoms, including anaemia, could not be clearly determined. However, a randomised, placebo-controlled, phase II study of the anti–IL-6 monoclonal antibody ALD518 in patients with non–small cell lung cancer proved that anaemia/cachexia can be improved by IL-6 signalling blockade [22]. The lack of clear improvement in cachectic symptoms in our study may be attributable to differences in the cancer type or the target population. Furthermore, the apparent absence of improvements in cachexia/anaemia in our study may be explained partially by the impact of concurrent gemcitabine treatment because some cachectic symptoms can be exacerbated by chemotherapy itself [23].

Hepcidin plays a key role in the regulation of iron metabolism [24,25] and constitutes a biomarker for anaemia. We demonstrated marked, sustained decreases in levels of all three evaluated hepcidin isoforms in all patients and gradual decreases in hemoglobin levels, both of which appeared to correspond to CRP normalization. This suggests that IL-6 blockade with tocilizumab may improve iron metabolism when CRP is normalised. Tocilizumab may be a clinical option to help improve quality of life in patients with manifestations of cancer cachexia (e.g. anaemia).

Nonhaematologic AEs in this study were generally consistent with those expected from clinical trials of gemcitabine/gemcitabine-based regimens in patients with advanced pancreatic cancer; however, grade ≥ 3 thrombocytopenia leading to interruption of gemcitabine was frequent. Transient decreases in platelets have been observed with tocilizumab in other indications [26], suggesting haematologic toxicities associated with gemcitabine might be exacerbated when given in combination with tocilizumab.

In conclusion, we did not detect any clear signal of clinical benefit from tocilizumab+gemcitabine treatment in patients with advanced pancreatic cancer. Further studies comparing the efficacy of tocilizumab and agents that do not inhibit IL-6 signalling in selected patient populations are needed to elucidate whether inhibition of IL-6 signalling can benefit patients with advanced pancreatic cancer.

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