

Combination Chemotherapy with Itraconazole for Treating Metastatic Pancreatic Cancer in the Second-line or Additional Setting

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Abstract. *Background:* We evaluated chemotherapy with itraconazole (a common anti-fungal agent that is a potent inhibitor of the Hedgehog pathway, P-glycoprotein, and angiogenesis) for treating progressive pancreatic cancer. *Patients and Methods:* We retrospectively reviewed the medical charts of patients with histologically-diagnosed pancreatic cancer who had received first- or second-line chemotherapy and subsequent chemotherapy with itraconazole. *Results:* A total of 38 patients received docetaxel (35 mg/m²), gemcitabine (1,000 mg/m²), and carboplatin (area under the curve, 4 mg/min/ml) on day 1 and oral itraconazole solution (400 mg) on days -2 to 2, repeated every 2 weeks. One complete response and 13 partial responses were observed, for a response rate of 37%. Eight (21%) patients experienced febrile neutropenia. The median overall survival was 11.4 months (95% confidence interval=8.5-21.2 months). *Conclusion:* Combination chemotherapy with itraconazole is promising for prolonging overall survival, with acceptable toxicities in the second-line setting of pancreatic cancer.

According to the 2012 global cancer statistics, the estimated incidence and mortality of pancreatic cancer (PC) were 338,000 and 330,000 persons per year, respectively (1). Most patients were diagnosed with advanced-stage PC, and the 5-year overall survival (OS) rate in Japan was only 7% (2). For the first-line chemotherapy of locally advanced PC, two randomized phase III trials established the standard regimens of FOLFIRINOX [5-fluorouracil (5-FU), leucovorin,

irinotecan, and oxaliplatin] and gemcitabine plus nab-paclitaxel (3-5); however, no standard-of-care exists for patients whose disease has progressed during or after front-line chemotherapy. Only half of patients receive second-line chemotherapy because of deterioration in their general condition, and the median OS of patients who have received second-line treatment is only 6 months according to a clinical trial (6). Therefore, a new approach to cytotoxic and targeted-therapy is necessary.

Itraconazole, a common anti-fungal agent, is a potent inhibitor of P-glycoprotein (P-gp; ATP-binding cassette sub-family B member 1, multiple drug-resistance 1), which plays a critical role in chemoresistance (7, 8). Itraconazole also inhibits angiogenesis and Hedgehog signals in cancer stem cells (CSCs) (9, 10). Since 2008, we have been treating patients with PC using combination chemotherapy with itraconazole, and we report on our retrospective exploratory study, which aimed to assess the efficacy of itraconazole in the second-line setting of PC.

Patients and Methods

We retrospectively reviewed the medical records of patients with histologically-confirmed PC who had a history of progression during or after prior chemotherapy; subsequently, they received chemotherapy in conjunction with itraconazole at our Hospital. All the patients were referred to our Institution from tertiary Hospitals after PC progressed during or after front-line chemotherapy. Between January 2008 and April 2013, 38 patients with recurrent PC were concurrently treated with chemotherapy and itraconazole. All the patients provided written informed consent, and the treatment protocol was approved by the Institutional Review Board (IRB no.: 2007-0302).

Treatment protocol. A cytotoxic regimen consisting of docetaxel, gemcitabine, and carboplatin (DGC) was administered in combination with itraconazole (11). On day 1, the starting doses of intravenous DGC were 35 mg/m², 1,000 mg/m², and 4 mg/min/ml (area under the curve), respectively. An oral itraconazole solution was administered at

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Table I. Patients' characteristics (N=38).

Age (years)	
Median (range)	57 (34-72)
Sex, n (%)	
Male	36 (68%)
Female	12 (32%)
Location of the primary tumor, n (%)	
Head	19 (50%)
Body	13 (34%)
Tail	6 (16%)
ECOG performance status, n (%)	
0	21 (55%)
1	17 (45%)
CA19-9 level at baseline (IU/ml)	
<100	5 (13%)
Median (range)	1,402 (9.8-37,250)
Site of metastases, n (%)	
Liver	21 (55%)
Lymph nodes	15 (39%)
Lung	12 (32%)
Peritoneum	12 (32%)
No. of metastatic sites, n (%)	
1	13 (34%)
2	14 (37%)
≥3	11 (29%)
No. of prior chemotherapies, n (%)	
1	14 (37%)
≥2	24 (63%)
Agents used in prior chemotherapy, n (%)	
Gemcitabine	33 (87%)
S-1	24 (63%)
Platinum, n (%)	9 (24%)
Oxaliplatin	6 (16%)
Carboplatin	2 (5%)
Cisplatin	1 (3%)
Taxane, n (%)	8 (21%)
Docetaxel	7 (18%)
Paclitaxel	1 (3%)
Irinotecan	6 (16%)
Prior therapy, n (%)	
Surgery	10 (26%)
Radiation	4 (11%)

ECOG, Eastern Cooperative Oncology Group.

a daily dose of 400 mg (days -2 to 2). This regimen was repeated every 2 weeks. A dose modification in the subsequent cycle was considered to maintain the nadir of patients' white blood cell (WBC) and platelet counts within the ranges of 1,000-1,500/mm³ and 30,000-50,000/mm³, respectively. When the WBC count nadir was <1,000/mm³, the docetaxel dose was reduced by 5 mg/m². For a WBC count nadir of ≥1,500/mm³, the docetaxel dose was increased by 5 mg/m². When the platelet count nadir was <50,000/mm³ during a cycle, the carboplatin dose in the next cycle was reduced by 10%. For a platelet count nadir of ≥50,000/mm³, the carboplatin dose was increased by 10%. The doses of gemcitabine and itraconazole (Janssen Pharmaceutical K.K., Tokyo, Japan) were fixed. Granulocyte colony-stimulating factor (G-CSF) was administered according to the manufacturer's recommendations on the drug label until the WBC and absolute neutrophil counts recovered.

Table II. Tumor response to docetaxel, gemcitabine, and carboplatin (DGC) plus itraconazole. The response was recorded during combination chemotherapy (DGC plus itraconazole) which was repeated every 14 days. The median number of cycles was 6 (range=3-11 cycles).

Response	N=38
Complete	1 (3%)
Partial	13 (34%)
Stable disease	16 (42%)
Progressive disease	8 (21%)
Response rate	37% (95% CI=48-78%)

CI, Confidence interval.

The regimen continued until disease progression or until other cytotoxic regimens with itraconazole were used to prevent chemotherapy-induced peripheral neuropathy. The median number of cycles of DGC plus itraconazole was 6 (range=3-11 cycles). All 30 patients who had a complete or partial response, or who achieved stable disease during the administration of DGC plus itraconazole received a subsequent irinotecan-based chemotherapy in combination with itraconazole.

Efficacy was evaluated according to the response evaluation criteria in solid tumors (RECIST), version 1.1. Overall survival (OS) was defined as the time from the first itraconazole administration to death. Adverse events during the DGC plus itraconazole regimen were graded according to the National Cancer Institute common toxicity criteria (NCI-CTC), version 4.0.

Statistical analyses were performed on the observed distributions of OS using the Kaplan-Meier method. All the analyses were performed using XLSTAT 2014 (Addinsoft, Paris, France).

Results

Patients' characteristics. According to RECIST 1.1 criteria, all the patients had distant metastases, and 25 (66%) patients had multiple-organ metastases. Twenty-four (63%) patients had previously undergone more than two regimens of chemotherapy. The patients' and disease's characteristics are summarized in Table I.

Efficacy of combination chemotherapy with itraconazole. During DGC plus itraconazole treatment, one complete and 13 partial responses were observed among the eligible patients (Table II), yielding a chemotherapy response rate of 37% [95% confidence interval (CI)=48-78%]. After discontinuing DGC plus itraconazole, itraconazole was administered in combination with other cytotoxic agents. Three complete and 15 partial responses were observed during the two consecutive regimens of DGC and irinotecan-based chemotherapy in combination with itraconazole. The response rate was 47% (95% CI=31-63%) (Table III). After the induction of combination chemotherapy with itraconazole, four patients underwent primary surgery, one underwent secondary debulking

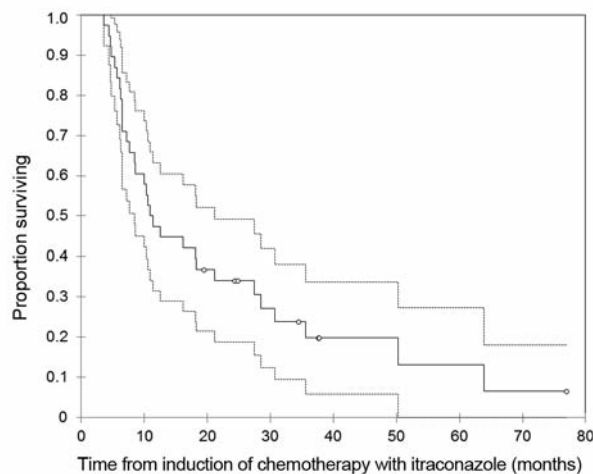


Figure 1. Kaplan-Meier analysis of overall survival after chemotherapy with itraconazole (n=38). The median overall survival is 11.4 months (95% confidence interval=8.5-21.2 months; dotted curves).

surgery, and five underwent radiotherapy. The median OS was 11.4 months (95% CI=8.5-21.2 months) with data on seven patients censored (Figure 1). Among six patients who survived for more than 3 years, five had liver and other metastases. One patient had peritoneal dissemination with massive ascites in addition to ovarian and lymph node metastases. Three patients underwent primary surgery, while the other three underwent radiation therapy after chemotherapy with itraconazole.

Toxicities. During the administration of a total of 233 cycles of the DGC-plus-itraconazole regimen, all 38 patients received G-CSF. Twenty-three (61%) patients had grade 4 neutropenia, and seven (18%) had grade 4 thrombocytopenia. Eight (21%) patients experienced febrile neutropenia, and their absolute neutrophil counts recovered after 7 days. Twenty-three (61%) patients required packed red blood cell transfusion when their hemoglobin levels decreased to <8.0 g/dl. No patient required platelet transfusion.

Elevated alanine aminotransferase levels (grade 3 or more) were observed in three patients (8%). Increased blood bilirubin levels before the first administration of itraconazole were observed in six patients (16%), in which the levels of ≥ 2.0 to <3.0 and 3.0 or more times the upper normal limit were observed in three (8%) and three (8%) patients, respectively. However, increased blood bilirubin levels were not observed in any of the 38 enrolled patients during the administration of the DGC-plus-itraconazole regimen. Increased serum creatinine (grade 2 or more) was not observed. In addition, there were no treatment-related deaths during the DGC-plus-itraconazole regimen or the subsequent irinotecan-based regimens with itraconazole.

Table III. Tumor response to docetaxel, gemcitabine, and carboplatin (DGC) plus itraconazole followed by other regimens with itraconazole. Thirty-five patients received irinotecan-based chemotherapy in combination with itraconazole following DGC plus itraconazole.

Response	N=35
Irinotecan-based chemotherapy plus itraconazole	
Complete response	3 (8%)
Partial response	15 (39%)
Stable disease	12 (32%)
Progressive disease	5 (13%)
Response rate	47% (95% CI=31-63%)
Other regimens with itraconazole	
	3 (8%)

CI: Confidence interval.

Discussion

Herein, we demonstrated that the administration of combination chemotherapy with itraconazole was safe and efficacious for treating patients with refractory metastatic PC. During the two consecutive itraconazole-containing regimens, 47% patients showed a response. The median overall survival was 11.4 months (95% CI=8.5-21.2 months), which was favorable compared to that of a historical control (12).

The concept of adding itraconazole to cytotoxic chemotherapy was primarily based on previous reports which indicated that itraconazole enhanced the effect of taxanes by inhibiting P-gp (7, 8). In 2007, the potential of itraconazole for inhibiting angiogenesis was reported by a group at John Hopkins Medical School (9). They identified itraconazole as a potential anticancer drug among >3,000 United States Food and Drug Administration-approved drugs that were tested. In 2010, Kim *et al.* reported that itraconazole inhibited the Hedgehog signaling pathway in CSCs and in cancer growth (10). Since 2013, several studies have reported on the clinical benefits of itraconazole (11, 13-15). Improved OS by adding itraconazole to cytotoxic agents was reported in a prospective randomized phase II study on the second-line treatment of non-small cell lung cancer and in a retrospective multivariate analysis of refractory ovarian cancer; the respective hazard ratios were 0.19 ($p=0.012$) and 0.27 ($p=0.006$), respectively (16, 17).

After exposure to cytotoxic agents, residual tumors are characterized by features of CSCs (18). Gemcitabine-resistant pancreatic cells express elevated levels of pancreatic CSC markers, and CSC-rich residual tumors pre-treated with gemcitabine significantly express P-gp compared to other ATP-binding cassette transporters (19, 20). Itraconazole has the highest affinity among anti-fungal agents which serve as substrates for P-gp (21). Docetaxel as a single-agent has

modest antitumor activity in PC (22). The resistance of pre-treated cancer cells or CSCs to docetaxel can be reversed with itraconazole treatment (7, 23). Gemcitabine and platinum have a synergic effect with docetaxel, and have been administered in several clinical studies (24, 25).

The Hedgehog signaling pathway plays a key role in embryogenesis, and it is re-activated in various cancer types (26). Patched and Smoothened proteins, members of the Hedgehog signaling pathway, were detected in approximately 70% of human PC specimens (27). Pancreatic CSCs exhibit up-regulation of the sonic Hedgehog pathway (28). Inhibition of Hedgehog signaling by cyclopamine reduces the self-renewal of pancreatic CSCs, and reverses chemoresistance (29). Combined treatment with cyclopamine and gemcitabine had a synergistic effect on tumor growth in a xenograft model (30, 31). The microenvironment of PC has abundant stroma, and the Hedgehog pathway is highly active in a paracrine manner. The Hedgehog signal inhibitor, AZD8542, inhibited tumor growth and metastasis by affecting the surrounding microenvironment in a mouse model (32).

Vismodegib is the first and only oral inhibitor of the Hedgehog signaling pathway; it is approved by the United States Food and Drug Administration for the treatment of basal cell carcinoma. A phase II randomized trial on patients with untreated PC demonstrated that a combination of vismodegib and gemcitabine yielded a response rate of 8%, with a median progression-free survival and OS of 4.0 months and 6.9 months, respectively. The clinical benefit of the addition of vismodegib was not shown, although a crossover of 42% of patients in the gemcitabine-plus-placebo arm was observed (33). A recent interim analysis of a single-arm phase II study on patients with untreated PC demonstrated that vismodegib in combination with gemcitabine plus nab-paclitaxel led to a response rate of 43% with a median progression-free survival and OS of 5.5 months and 10 months, respectively. Adverse events included 37.5% with grade 3 or worse neutropenia and 7% with febrile neutropenia (34). When comparing the efficacy with that of gemcitabine plus nab-paclitaxel in a randomized phase III trial (5), the addition of vismodegib to gemcitabine plus nab-paclitaxel may be effective. In a clinical trial for the treatment of basal cell carcinoma, Kim *et al.* reported that itraconazole-alone inhibited cell proliferation, the expression of the Hedgehog pathway activity, and tumor size. However, in patients with a history of vismodegib treatment there were no significant changes in proliferation or tumor size (14), even though itraconazole inhibits the Hedgehog signaling pathway by a mechanism distinct from that of vismodegib (35).

An increased expression of vascular endothelial growth factor and its receptors were demonstrated in PC (36); however, its antibody bevacizumab, alone or in combination with gemcitabine or erlotinib, was ineffective in clinical studies (37, 38). Therefore, the potential inhibition of angiogenesis may

have less of an impact on the present findings than blockage of P-gp and Hedgehog signaling by itraconazole.

In the second-line setting for patients pre-treated with gemcitabine, phase II studies showed the promise of regimens of FOLFOX-4 (5-FU, leucovorin, and oxaliplatin) and single-agent nab-paclitaxel. The reported median OS were 7.8 months and 7.3 months, respectively (12, 39). The current study demonstrated a median OS of 11.4 months and a 95% CI of 8.5-21.2 months. Thirty-five (92%) patients received DGC plus itraconazole followed by an irinotecan-based regimen with itraconazole. Itraconazole is likely to have improved efficacy for cytotoxic chemotherapy.

Patients enrolled in this study were all referred after undergoing first- or second-line chemotherapy at prior tertiary Hospitals. A question was raised about whether the biological behavior of tumor of the enrolled patients was different from those of historical studies and if the tumors had an indolent nature. The pre-treatment interval (PTI) was calculated from the first date of initial treatment to the first date of DGC plus itraconazole. We assessed the correlation between PTI and the efficacy of DGC plus itraconazole. Neither the response rate nor the OS after DGC plus itraconazole were associated with the PTI (data not shown).

Our present study has some limitations because of the sample size and its observational nature. In addition, data were pooled retrospectively. The dose modification was complicated and demanded for close monitoring. All the patients received G-CSF, and 23 (61%) patients underwent packed red blood cell transfusion; however, no patient underwent platelet transfusion. The high response observed in this study may have resulted from the use of triple cytotoxic agents. Cytotoxic regimens in combination with itraconazole should be further investigated with regard to their efficacy, toxicities, and compliance for daily practice. Based on the promising results of DGC plus itraconazole for patients with refractory breast or ovarian cancer (11, 15, 17), we launched a phase II study of a regimen consisting of docetaxel, gemcitabine, and itraconazole, with simple dose modification and continuation until disease progression for gynecological malignancy (UMIN000013951). For the treatment of PC, docetaxel can be replaced with nab-paclitaxel (40). This study's findings are encouraging for patients with advanced or refractory PC because they can take advantage of the efficacy and limited toxicity of itraconazole. Furthermore, itraconazole is not an expensive drug; therefore, it would be affordable to patients in less developed countries, and it may also reduce the medical costs in developed countries.

Conflicts of Interest

The Authors declare no financial conflicts of interest with regard to this study.

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