Impact of Combination Chemotherapy with Itraconazole on Survival for Patients with Recurrent or Persistent Ovarian Clear Cell Carcinoma

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Abstract. *Background: Recurrent ovarian clear cell carcinoma (CCC) rarely responds to cytotoxic agents. Itraconazole is a potent inhibitor of the P-glycoprotein efflux pump, angiogenesis, and the Hedgehog pathway. We evaluated the efficacy of chemotherapy with itraconazole for CCC. Patients and Methods: Medical charts of patients with CCC who had received chemotherapy with itraconazole were retrospectively reviewed. Results: Among nine patients with CCC, five had a history of progression with paclitaxel and carboplatin, and none had received prior treatment with bevacizumab or other targeted therapy. Eight patients received docetaxel (35 mg/m^2, day 1) and carboplatin-based (area under the curve, 4 mg·min^{-1}·mL^{-1}; day 1) chemotherapy with an oral itraconazole solution (400 mg, days -2 to 2), repeated every two weeks. The response rate, median progression-free survival and overall survival were 44% (95% confidence interval [(CI)=12-77%], 544 days (95% CI=82-544 days) and 1,047 days (95% CI=462-1332 days), respectively. Conclusion: Chemotherapy with itraconazole is promising for patients with CCC.*

According to the 2008 global cancer statistics, 230,000 women were estimated to have had a diagnosis of epithelial ovarian carcinoma (EOC), with 140,000 of them dying due to their disease (1). Clear cell carcinoma (CCC) of the ovary is a histological subtype of EOC that accounts for 5% of all EOCs diagnosed in Western countries and 20% of those diagnosed in Japan; this subtype is resistant to treatment with conventional cytotoxic anticancer agents (2-7). The median overall survival (OS) for individuals with recurrent or persistent disease is 7-10 months (8, 9).

None of the currently available anti-neoplastic agents has been definitively shown to be active and effective for the treatment of ovarian CCC, nor has the mechanism underlying resistance to chemotherapy been clearly delineated. The morphological features of ovarian CCC are similar to those of renal CCC, with both responding poorly to conventional chemotherapy and both expressing transporter efflux pumps, namely ATP-binding cassette sub-family B member 1 (ABCB1) commonly called P-glycoprotein (P-gp) and ABCC1 (also known as MRP) (10-12). Both the P-gp and MRP are membrane polypeptides that function as ATP-dependent pumps. Thus, resistance to paclitaxel and platinum has been associated with the *ABCB1* and *ABCC1* genes, respectively (13).

Itraconazole (ITCZ), a common anti-fungal agent, has been shown *in vitro* to reverse P-gp-mediated resistance associated with docetaxel, paclitaxel, vinblastine, daunorubicin, and doxorubicin in a concentration-dependent manner (14-16). Its potential for inhibiting angiogenesis and the Hedgehog pathway, resulting in decreased *in vitro* and *in vivo* tumor growth, has also been reported (17-18). A randomized study of treatment with or without ITCZ in patients with leukemia has shown a higher disease-free survival rate among patients treated with ITCZ (19). Recently, a randomized phase II trial of non-small cell lung cancer (NSCLC) showed prolonged OS in patients receiving a drug combination that included ITCZ (p=0.012) (20).

At the Kohnan Hospital, Kobe, Japan, patients with recurrent or persistent solid tumors are referred from surrounding tertiary care hospitals. With the approval of the Institutional Review Board and written informed consent from the patients, cytotoxic chemotherapy with ITCZ has been administered since 2008. This ovarian carcinoma regimen was administered to patients with non-ovarian epithelial carcinoma

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and demonstrated favorable survival outcomes. In the present study, we present the outcomes of chemotherapy with ITCZ for patients with recurrent or refractory CCC.

Patients and Methods

The medical charts of Kohnan Hospital patients with histologically diagnosed CCC who received chemotherapy in conjunction with ITCZ treatment between 2008 and 2013 were reviewed.

Adverse events during the first regimen of concurrent administration of ITCZ with chemotherapy were graded according to the National Cancer Institute Common Toxicity Criteria, version 4.0. Efficacy was evaluated according to the Response Evaluation Criteria In Solid Tumors (RECIST), ver. 1.1, for patients with initial measurable disease and according to serum cancer antigen 125 (CA-125) concentrations for patients without measurable disease [criteria of the Gynecologic Cancer InterGroup (GCIG)] (21, 22).

Progression-free survival (PFS) was defined as the time from the date of the first ITCZ administration to the date of objectively determined disease progression, increased CA-125 level, or health status deterioration, including increased cancer pain or the onset of new cancer pain. OS was defined as the time from the date of the first ITCZ administration to death.

Statistical analyses were performed on the observed distributions of PFS and OS using the Kaplan–Meier method. Statistical analyses were conducted using XLSTAT 2012 (Addinsoft, Paris, France).

Results

Patients' characteristics. Between 2008 and 2012, 41 patients with recurrent or persistent EOC were concurrently treated with chemotherapy and ITCZ. Nine patients were histologically-diagnosed with CCC, including a mixed type in one patient referred from a tertiary hospital. The diagnosis was reviewed from the pathological reports of the tertiary hospitals. One patient was initially diagnosed with International Federation of Gynecology and Obstetrics stage IIIC ovarian cancer by cytology and radiology at the tertiary hospital, and was referred to our hospital after progression during the initial paclitaxel and carboplatin (TC) regimen. The diagnosis of pure CCC was made by analysis of the primary surgical specimen after neoadjuvant chemotherapy with ITCZ. The Eastern Cooperative Oncology Group (ECOG) performance status (PS) was 0 in seven patients, 2 in one patient, and 3 in one patient (this patient had malignant ascites requiring paracentesis). Five patients had a history of progression during treatment with a TC regimen. None of the patients received bevacizumab or other targeted therapies as these therapies were not approved for use in patients with EOC in Japan. One patient, without measurable disease, had ascites and peritoneal thickening detected by computed tomography. The overall patients' characteristics are summarized in Table I.

Regimens with ITCZ. The most common regimen, administered to five patients, was combined chemotherapy with docetaxel, carboplatin, gemcitabine, and ITCZ. The starting doses of intravenous docetaxel, carboplatin and

Table I. *Patients' characteristics (n=9)*.

Variable	
Age (years)	
median	53
Range	49-64
FIGO stage	
IA	2
IC	4
IIIC	2
IV	1
Histology	
Pure CCC	8
Mixed (CCC and endometrioid)	1
Primary surgery	
TAH/BSO/OMT/LND	7
TAH/BSO/OMT	1
paracentesis*	1
History of secondary surgery	2
Lung resection	1
Abdominal cytoreduction	1
History of radiation	1
History of prior chemotherapy	
Number of previous regimens	
1	4
2	3
≥ 3	2
TC regimen	9
Progression on TC regimen	5
PFI before chemotherapy with ITCZ (months)	
≤1	1
1<PFI≤3	5
3≤PFI<6	2
7	1
Recurrence sites	
Peritoneum only	4
LN only	2
Lung, peritoneum, LN	1
Lung, LN	1
Lung, liver	1
Patients	
With measurable disease	8
Without measurable disease	1
ECOG PS	
0	7
2	1
3	1
Serum albumin (g/dl)	
Median	4.2
Range	3.3-4.7
Regimens of chemotherapy with ITCZ	
TXT/Carbo/Gem	5
TXT/Carbo/DXR	3
CPT/Gem/DXR	1

*Histologically-diagnosed at surgery after chemotherapy with ITCZ. FIGO, International Federation of Gynecology and Obstetrics; CCC, clear cell carcinoma; TAH, total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy; OMT, omentectomy; LND, pelvic and paraaortic lymphadenectomy; TC, paclitaxel and carboplatin; PFI, platinum-free interval, interval following the most recent platinum-based chemotherapy; ITCZ, itraconazole; LN, lymph nodes; ECOG, Eastern Cooperative Oncology Group; PS, performance status; TXT, docetaxel; Carbo, carboplatin; Gem, gemcitabine; DXR, doxorubicin; CPT, irinotecan.

Table II. *Response rate following chemotherapy with itraconazole.*

Response		
RECIST 1.1 (measurable disease)	8	
Complete response	1	
Partial response	2	
Stable disease	4	
Progressive disease	1	
Response rate	38%	(95% CI=4-71%)
GCIG criteria (RECIST 1.1 and CA-125)	9	
Complete response	1	
Partial response	3	
Stable disease	4	
Progressive disease	1	
Response rate	44%	(95% CI=12-77%)

RECIST, Response Evaluation Criteria in Solid Tumors, ver. 1.0; GCIG, Gynecologic Cancer InterGroup.

Table III. *Hematological toxicity (≥grade 3) and non-hematological toxicity (≥grade 1) during the cycles of chemotherapy with itraconazole.*

	No. of patients (%)		
Adverse events	Grade 3	Grade 4	≥Grade 3
Anemia	9	0*	9 (100)
Leukopenia	6	3	9 (100)
Neutropenia	1	8	9 (100)
Thromobocytopenia	3	6	9 (100)
Febrile neutropenia			0
Transfusion			
Platelets			0
Packed red blood cells *			9 (100)

	No. of patients		
Adverse events	Grade 1	Grade 2	≥Grade 3
AST increased	4	0	0
ALT increased	4	0	0
Anorexia	0	4	0
Allergic reaction	0	1	0

*Packed red blood cells were transfused when hemoglobin levels fell below 8.0 g/dl. AST, aspartate aminotransferase; ALT, alanine aminotransferase.

gemcitabine were 35 mg/m^2 (day 1), area under the curve (AUC) of 4 mg min/ml (day 1), and 1,000 mg/m^2 (day 1), respectively. An oral ITCZ solution was administered at a daily dose of 400 mg (days −2 to day 2). The regimen was repeated every two weeks. Dose modification of carboplatin and docetaxel in the next cycle was aimed at maintaining white blood cell (WBC) and platelet counts within 1,000-1,500/mm^3 and 30,000-50,000/mm^3, respectively. Briefly, when the WBC count nadir was <1,000/mm^3, the docetaxel dose was reduced by 5 mg/m^2; for a WBC count nadir of ≥1,500/mm^3, it was increased by 5 mg/m^2. When the platelet count nadir was <50,000/mm^3 during a cycle, the carboplatin dose in the next cycle was reduced by 10%; for a platelet count nadir of ≥50,000/mm^3, it was increased by 10%. Gemcitabine and ITCZ doses were fixed. Granulocyte colony-stimulating factor (G-CSF) was administered according to the manufacturer's recommendations on the drug label until the WBC count and absolute neutrophil count (ANC) recovered.

Efficacy. The response rates for patients receiving chemotherapy in conjunction with ITCZ were 38% [95% confidence interval (CI)=4-71%] according to the RECIST 1.1 criteria and 44% (95% CI=12-77%) according to the GCIG criteria (Table II). The median PFS after induction of chemotherapy with ITCZ was 544 days (95% CI=82-544 days), with data on four patients censored (Figure 2). One patient had a grade 2 allergic reaction to carboplatin during the fourth cycle, and the cytotoxic agents were modified. One patient underwent intra-hepatic arterial chemoembolization 82 days after induction of chemotherapy with ITCZ because liver metastases showed stable disease whereas lung metastases decreased. One patient with primary lung metastases underwent abdominal cytoreductive surgery after 203 days when a radiological response was confirmed. Another patient was still alive at the time of reporting; this patient has shown response for 544 days. The median OS after induction of chemotherapy with ITCZ was 1,047 days (95% CI=462-1332 days), with data on three patients censored (Figure 2). Among the seven patients who experienced progression during chemotherapy with ITCZ, five received different regimens including ITCZ.

Toxicities. During combination chemotherapy with the initial regimens and ITCZ, all patients received G-CSF, and the WBC count and ANC recovered within four days. None of the patients experienced febrile neutropenia or required platelet transfusion. All patients required packed red blood cell transfusions when their hemoglobin levels fell below 8.0 g/dl (Table III).

Discussion

The OS of patients with recurrent or persistent ovarian CCC in this study was higher than that reported for other published studies. The survival curves for the 113 patients with recurrent CCC reported by Kajiyama *et al.* (9), the 20 patients reported by Yoshino *et al.* (8), the 51 recurrent patients with a treatment-free interval of less than six months

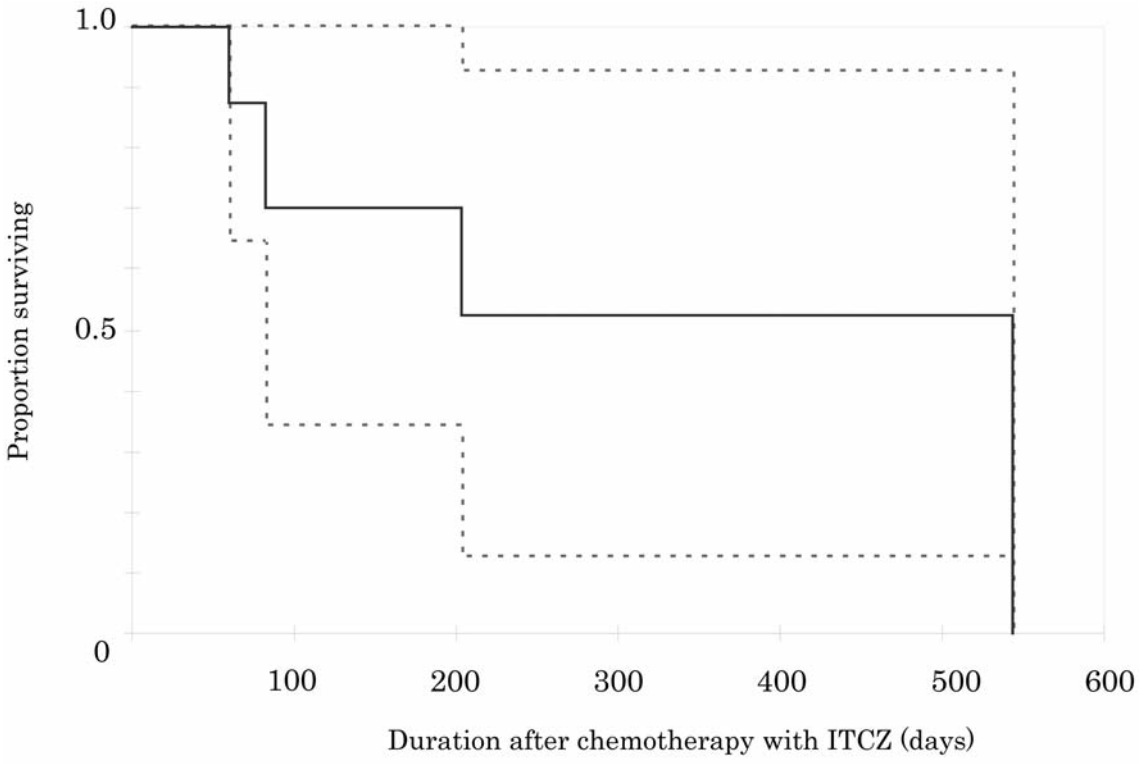

Figure 1. *Kaplan–Meier analysis of progression-free survival (PFS) after chemotherapy and itraconazole (n=9). The median PFS was 524 days (95% confidence interval >67 days).*

reported by Takano *et al*. (23), and the five patients with platinum-resistant disease treated without ITCZ at our hospital matched the lower limit of the 95% CI calculated in this study. The OS of the nine patients treated in the present study was significantly higher than that of the five patients previously treated without ITCZ at our hospital (p=0.006).

In a previous randomized phase II trial of NSCLC, concomitant ITCZ therapy did not show improved PFS compared to therapy without ITCZ in 23 enrolled patients (20). However, the OS was significantly longer among patients receiving ITCZ. On the basis of their findings in a non-clinical study, Chong *et al*. and Kim *et al*. suggested that the reason for the success of the first clinical trial involving ITCZ was the anti-angiogenesis effects of ITCZ (17, 18).

Bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor, has been the most extensively studied agent for EOC-targeted therapy. Two randomized trials, GOG 218 and ICON 7, demonstrated prolonged PFS when bevacizumab was administered as first-line induction and maintenance chemotherapy but an OS benefit was not observed (24, 25). The GOG 218 study demonstrated a 3.8-month improvement in PFS with an additional 51 weeks' treatment, 10% of risk for grade 3 to 4 hypertension, and 2.3% risk for grade 3 or worse gastrointestinal perforation, hemorrhage, or fistula formation (26). Cohn *et al*. reported that the addition of bevacizumab was not cost-effective (27). Furthermore, in the OCEANS randomized trial for recurrent EOC, bevacizumab did not prolong OS (28). For NSCLC, the ECOG 4599 trial demonstrated a statistically significant (2-month) improvement in OS with more severe toxicities–the incidence of treatment-related deaths was 3.5% when bevacizumab was administered (29). However, a confirmatory trial (AVAiL) did not demonstrate an OS benefit (30). Considering the results of clinical trials involving patients with EOC and NSCLC, the survival advantage of ITCZ-treated patients in our study and in Kim *et al*.'s trial is extraordinary and cannot be fully-explained by the anti-angiogenesis effects of ITCZ in combination with chemotherapy.

Takano *et al*. reported the case of a patient with ovarian CCC treated with temsirolimus who showed response for 14 months (31). This patient received a combination of trabectedin, oxaliplatin, and bevacizumab and showed response for 12 months (32). The patient had been initially treated with bevacizumab and was re-treated with bevacizumab in combination with cytotoxic agents. To date, this patient has demonstrated the longest PFS and OS among cases of recurrent or refractory ovarian CCC precisely

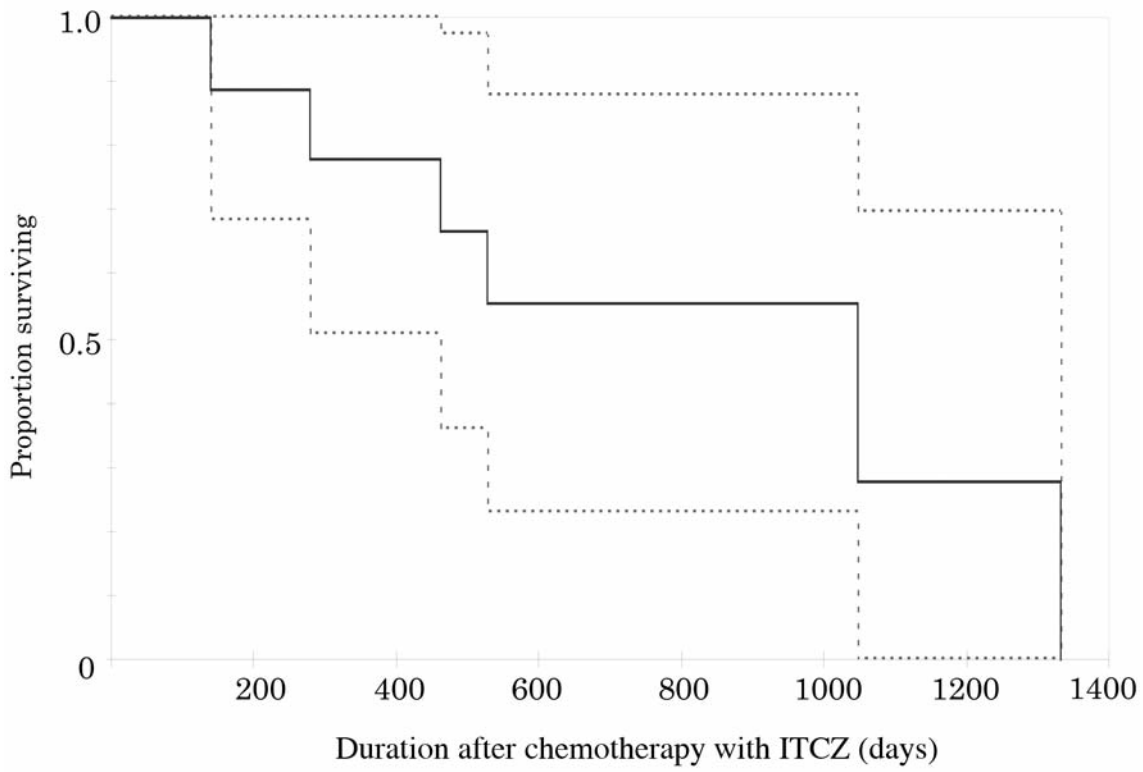

Figure 2. *Kaplan–Meier analysis of overall survival (OS) after chemotherapy with itraconazole (n=9) The median OS was 1047 days (95% confidence interval=462-1332 days).*

described in the literature. In colorectal cancer, the continuous use of bevacizumab, beyond disease progression, prolongs OS (33, 34). In ovarian cancer, a retrospective study showed that re-treatment with bevacizumab prolongs PFS but not OS (35). The favorable OS in the current study might be associated with the continuous use of ITCZ, which produced fewer toxicities and was associated with a reduced cost compared to bevacizumab.

Recent trends in the development of anticancer agents have focused on cancer stem cells (CSCs) to prolong patient OS or even be curative. CSCs are drug-resistant (36), with one of the mechanisms of chemoresistance being the efflux of cytotoxic agents by P-gp (37). Interestingly, ITCZ has the highest affinity among anti-fungal agents that serve as P-gp substrates (38). The resistance of cancer cells to docetaxel and paclitaxel was reversed by treatment with ITCZ (14-16).

Self-renewal and multi-lineage differentiation and the development of metastatic disease associated with CSCs are associated with the Hedgehog signaling pathway (39). CSCs and the Hedgehog signaling pathways have been reported to play important roles in the development and progression of EOC (40-42). As a result, Hedgehog inhibitors have been investigated in clinical trials. A phase II randomized trial of saridegib (IPI-926), a synthetic derivative of cyclopamine (11-deoxyjervine), for the treatment of metastatic pancreatic cancer was terminated after an interim analysis demonstrated a more favorable OS rate in the placebo-plus-gemcitabine arm (43). A phase II randomized trial of vismodegib, approved for advanced basal cell carcinoma by the United States Food and Drug Administration in 2012, demonstrated that the addition of vismodegib to gemcitabine did not improve response, PFS, or OS in patients with metastatic pancreatic cancer (44). Kim *et al*. reported that ITCZ inhibited the Hedgehog signaling pathway by a mechanism distinct from that of saridegib or vismodegib (18).

The current study protocol was first designed in 1999 to examine concurrent chemotherapy with cyclosporine A, a potent P-gp inhibitor, as part of the therapeutic concept, and demonstrated favorable outcomes in recurrent cancers (45, 46). In 2008, the protocol was modified to replace cyclosporine A with ITCZ, with the approval of the Institutional Review Board. The triplet regimen of chemotherapy with ITCZ showed a favorable survival outcome in cases of solid tumors, including pancreatic cancer, chorangiocarcinoma, NSCLC, and breast cancer. Therefore, the chemotherapy regimens for recurrent ovarian

cancer were modified from those for non-ovarian epithelial carcinoma, according to the individual's prior chemotherapy history. The triplet of cytotoxic agents administered with ITCZ in the present study was extraordinary in recurrent EOC, and the dose modification was complicated for the treating gynecologists. Gemcitabine was effective in combination with cisplatin or docetaxel in patients with EOC with a platinum-free interval of less than six months (47, 48) and might be a candidate among cytotoxic agents for recurrent or persistent CCC (8, 49). The GINECO retrospective study showed that patients who experienced relapse within six months of prior therapy and then received platinum-based combination chemotherapy showed a higher response rate and longer PFS and OS than those who received non-platinum therapy (50). Several trials of carboplatin-based chemotherapy also showed favorable outcomes (51, 52). However, the standard regimen for recurrent EOC patients with a platinum-free interval of less than six months is a single non-platinum agent, and increased toxicity without a survival advantage has been reported for non-platinum combination chemotherapies (53, 54). Moreover, a combination of three cytotoxic agents for EOC would not be supported by gynecologists because of the failure of a large clinical trial (GOG 182-ICON 5) to demonstrate an advantage of adding additional agents to the standard TC regimen (55). In the current study, the adequacy of the initial doses of chemotherapeutic agents and dose modifications is presently unclear. The hematological toxicities observed in the patients were severe when compared with those encountered in historical studies. The non-hematological toxicities might have been underestimated given the retrospective nature of this study. Nevertheless, adverse events during chemotherapy with ITCZ were manageable and febrile neutropenia or platelet transfusion was not noted.

ITCZ is not an expensive drug, and its use may be affordable for patients in developing countries and might reduce treatment costs in developed countries. For patients with leukemia, ITCZ has been used prophylactically to prevent fungal infections (56, 57). In addition, the first clinical trial of ITCZ with pemetrexed for patients with lung cancer did not increase the occurrence of adverse events. In our hospital, over 300 patients with recurrent or persistent cancer have been treated with chemotherapy in combination with ITCZ, and ITCZ-related deaths have not been reported. Therefore, chemotherapy with ITCZ seems to be feasible for use in conjunction with adequate cytotoxic agents. However, ITCZ does interfere with CYP3A and the blood-brain barrier (58). A fatal case involving a possible interaction between ITCZ and vinorelbine has been reported (59). Therefore, a feasibility study of single or double cytotoxic agents in conjunction with ITCZ, preferably through monitoring of serum drug concentrations, is warranted.

Conflicts of Interest

The Authors have no financial conflicts of interest to disclose.

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