EUROPEAN JOURNAL OF CANCER 48 (2012) 196–201

Available at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.ejconline.com

A phase II study of sunitinib as a second-line treatment in advanced biliary tract carcinoma: A multicentre, multinational study

Jun Ho Yi [a,d], *Sumitra Thongprasert* [b], *Jeeyun Lee* [a], *D.C. Doval* [c], *Se Hoon Park* [a], *Joon Oh Park* [a], *Young Suk Park* [a], *Won Ki Kang* [a], *Ho Yeong Lim* [a,*]

[a] *Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul 135-710, South Korea*

[b] *Department of Medicine, Faculty of Medicine, ChiangMai University, ChiangMai, Thailand*

[c] *Department of Medical Oncology, Rajiv Gandhi Cancer Institute & Research Centre, New Delhi, India*

[d] *Division of Medical Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea*

ARTICLE INFO

Article history:
Available online 14 December 2011

Keywords:
Biliary tract cancer
Second-line chemotherapy
Sunitinib

ABSTRACT

Background: Biliary tract carcinoma (BTC) is rare in the West, but not uncommon in Asia and is a highly fatal malignancy. VEGF expression is related with poor outcome in patients with BTC. Therefore, we conducted a phase II study to evaluate the efficacy and safety of sunitinib as second-line treatment.

Methods: This was a prospective, single-arm, multicentre, multinational study. Patients with unresectable, metastatic BTC who progressed after first-line chemotherapy were eligible. Sunitinib was administered at 37.5mg once daily continuously with 4-week cycle. The primary end point was the time to progression (TTP).

Results: Between May 2009 and October 2010, a total of 56 patients were enrolled from three countries. The median age was 55 years (range 38–75) and male to female ratio was 37:19. Median TTP was 1.7 months (95% confidence interval (CI) 1.0–2.4). The objective response rate was 8.9% (5 partial response) and disease control rate was 50.0%. (23 stable disease) Grade 3–4 toxicities were observed in 46.4% of the patients with neutropenia and thrombocytopenia being the most frequent (21.4%).

Conclusions: This phase II study suggests that sunitinib monotherapy demonstrated marginal efficacy in metastatic BTC patients although toxicity should be concerned in Asian population.

1. Introduction

Biliary tract cancers (BTCs) encompass adenocarcinomas arising in the intra or extrahepatic biliary tree and in the gall bladder. BTC is a relatively uncommon malignancy in Western countries,[1] but has a high incidence in Asia and Latin America.[2,3] Surgery is the only curative treatment option for BTCs; however, only 25% of the cases are resectable at presentation and the relapse rate is high after surgery.[4] Palliative chemotherapy is usually considered for patients with unresectable or advanced BTCs. While a combination of gemcitabine and platinum agents seems to be a reasonable treatment

* *Corresponding author:* Address: Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50 Irwon-dong, Gangnam-gu, Seoul 135-710, South Korea. Tel.: +82 2 3410 3459; fax: +82 2 3410 1754.
E-mail address: hoylim@skku.edu (H.Y. Lim).

0959-8049/$ - see front matter
doi:10.1016/j.ejca.2011.11.017

option as first-line treatment,[5–8] no standard therapy has yet been established following occurrence of gemcitabine refractoriness.[9]

Several studies have reported that vascular endothelial growth factor (VEGF) is overexpressed in BTCs and that the VEGF expression is associated with more advanced stage and worse prognosis.[10–12] This suggests the possibility that VEGF may represent a potential therapeutic target. Indeed, Zhu et al. have demonstrated that anti-VEGF treatment with bevacizumab, combined with gemcitabine plus cisplatin, showed antitumour activity and resulted in median overall survival (OS) of 12.7 months and progression free survival (PFS) of 7.0 months in patients with advanced BTCs.[13] In a study by Lubner et al., anti-VEGF treatment with bevacizumab, along with erlotinib, resulted in meaningful clinical outcomes, with over 50% of patients with advanced BTCs showing documented stable disease.[14]

Sunitinib is an orally administered inhibitor of multiple receptor tyrosine kinases that are involved in tumour proliferation and angiogenesis; specifically, platelet-derived growth factor receptor (PDGFR), VEGF receptor, stem cell factor receptor (KIT), Fms-like tyrosine kinase (Flt-3) and rearranged during transfection (RET). This agent has shown efficacy against many solid cancers, including metastatic clear cell renal cell carcinoma,[15] imatinib-refractory gastrointestinal stromal tumour[16] and pancreatic neuroendocrine tumour.[17] In addition, an objective response has been observed in phase 2 trials in patients with breast cancer,[18] non-small cell lung cancer,[19] colorectal cancer[20] and prostate cancer.[21] In the present study, we conducted a phase II, multinational, multicentre trial to analyse the efficacy and toxicity of sunitinib in patients with advanced biliary tract cancer following failure of first-line treatment. This study has been registered at www.clinicaltrials.gov as # NCT01082809.

2. Materials and methods

2.1. Study design

This was an open label, phase II, single arm, multicentre, multinational study conducted at Samsung Medical Center, Seoul; Korea, Rajiv Gandhi Cancer Institute & Research Centre, New Delhi, India and ChiangMai University, ChiangMai, Thailand. The protocol was approved by the institutional review board of each institute and the trial was conducted in accordance with the Declaration of Helsinki. All patients were required to give written informed consent before enrolment. Pfizer provided sunitinib gratis, but the company was not involved in the accrual or analysis of the data or in the preparation of the manuscript.

2.2. Patients

Patients aged $\geqslant$18 years, with unresectable or metastatic adenocarcinoma of biliary tract that was confirmed histologically or cytologically, were enrolled in the study. Other inclusion criteria are as follows: Eastern Cooperative Oncology Group (ECOG) performance status 0–2; measurable or evaluable lesion per Response Evaluation Criteria in Solid Tumours (RECIST) criteria 1.1; one prior treatment of cytotoxic chemotherapy including adjuvant treatment within 12 months; adequate haematological (neutrophils $\geqslant$1500/μL, platelets $\geqslant$75,000/μL, haemoglobin $\geqslant$9.0 g/dL), hepatic (serum aspartate aminotransferase (AST) and serum alanine aminotransferase (ALT) $\leqslant 5 \times$ upper limit of normal (ULN); total bilirubin $\leqslant$ 3.0 mg/dL) and renal function (serum creatinine $\leqslant 1.5 \times$ ULN). Patients with severe co-morbid illness and/or active infections, pregnant or lactating women, or active central nervous system metastases not controllable with radiotherapy or corticosteroids were excluded from the study.

2.3. Treatment and statistics

Sunitinib was administered orally at the starting dose of 37.5 mg daily, continuously, comprising a 4-week cycle. An abdominopelvic CT scan was taken every cycle. Individual response was evaluated according to RECIST 1.1 criteria and sunitinib was administered until progression, unacceptable toxicity, or withdrawal of consent. If a patient experienced dose-limiting toxicity attributed to sunitinib, administration delay and/or dose reduction was carried out as planned. For grade 3 toxicity, sunitinib was withheld until the toxicity was grade 1 or less (2 or less in case of haematologic toxicity), then treatment was resumed at the same dose. If the toxicity recurred with grade 3 severity, sunitinib dose was reduced by 12.5 mg each time. When grade 4 toxicity occurred, sunitinib was withheld until the toxicity became grade 1 or less (2 or less in case of haematologic toxicity), then treatment was resumed with a dose reduced by one level (i.e. −12.5 mg/day). Patients who developed grade 3 or 4 lymphopenia continued sunitinib treatment without interruption.

The primary endpoint of this study was time to progression (TTP), which was calculated from the date of starting sunitinib treatment to the date of objective tumour progression, unacceptable toxicity, or consent withdrawal. The secondary endpoints were toxicity profiles established by the National Cancer Institute Common Toxicity Criteria for Adverse Events (CT-CAE) 3.0, response rate, duration of response and overall survival duration (OS; which was calculated from the date of starting sunitinib treatment to the date of death or the last visit). TTP and OS analyses were calculated by the Kaplan–Meier product–limit method. Expecting 12 months of accrual period and 6 months of follow-up period, this phase II study was designed with two sided, $\alpha = 0.05$, and 90% power to detect a median TTP of 4.0 months in the treated arm, as compared with a null median TTP of 2.0 months ($N = 54$).

3. Results

3.1. Patient characteristics

Between May 2009 and October 2010, a total of 56 patients were enrolled in this study, consisting of 37 patients from South Korea, 17 patients from Thailand and two patients from India. The median age was 55 years (range 38–75) and male to female ratio was 37:19 (66.1%:33.9%). In total, 35 patients (62.5%) had intrahepatic duct cancer, 6 (10.7%) had extrahepatic duct cancer and 15 (26.8%) had gall bladder cancer. Histological examination revealed that, the cohort had 53 (94.6%) cases of adenocarcinoma, 2 (3.6%) cases of adenosquamous

Table 1 – Baseline characteristics of patients (*n* = 56 patients).

	N (%)
Age, median (range)	55 (38–75)
Sex	
Male (%)	37 (66.1)
Female (%)	19 (33.9)
ECOG[a] performance status score	
0	13 (23.2)
1	39 (69.6)
2	4 (7.2)
Primary tumour site	
Intrahepatic duct	35 (62.5)
Extrahepatic duct	6 (10.7)
Gall bladder	15 (26.8)
Histology of tumour	
Adenocarcinoma	53 (94.6)
Adenosquamous cell carcinoma	2 (3.6)
Papillary adenocarcinoma	1 (1.8)
Prior surgery	
No	39 (69.6)
Curative surgery	10 (17.9)
Palliative surgery	7 (12.5)
First-line palliative chemotherapy	
Gemcitabine	1 (1.8)
Gemcitabine + Cisplatin	12 (21.4)
Gemcitabine + Oxaliplatin	20 (35.7)
Gemcitabine + Carboplatin	6 (10.7)
5-FU + Cisplatin	15 (26.8)
5-FU + Carboplatin	2 (3.6)
Site of metastasis	
Liver	45 (80.4)
Bone	3 (5.4)
Distant lymph node(s)	33 (58.9)
Brain	1 (1.8)
Lung	13 (23.2)
Peritoneum	13 (23.2)
Pleura	7 (12.5)
Abdominal wall	1 (1.8)

[a] ECOG, Eastern Cooperative Oncology Group.

cell carcinoma and 1 case (1.8%) of papillary adenocarcinoma. A total of 10 patients (17.9%) had undergone curative resection, 7 (12.5%) had undergone palliative resection, and the other 39 (69.6%) had unresectable disease at the time of initial diagnosis. First-line palliative chemotherapy consisted of gemcitabine-based chemotherapy (alone or plus platinum agents) for 39 patients (70%) and 5-FU-based chemotherapy (alone or plus platinum agents) for 17 (30%). Details are shown in Table 1.

3.2. *Survival and response*

With a median follow-up duration of 16.7 months (range 3.4–23.0), median TTP was 1.7 months (95% confidence interval (CI), 1.0–2.4) (Fig. 1). Only one patient was no longer in progression-free status at the time of analysis and 10 patients stopped the treatment due to unacceptable toxicity. The objective response rate was 8.9% (95% CI 3.0–19.6) and the disease control rate was 50.0% (95% CI 36.3–63.7) with five patients achieving a partial response (PR), 23 patients showing stable disease (SD) and 28 patients showing progressive disease (PD) by RECIST 1.1 (Table 2). The median duration of disease control status (PR + SD) was 2.4 months. (95% CI 2.0–2.8) The median OS was 4.8 months (95% CI 3.8–4.8) (Fig. 2), with 44 deaths recorded at the time of analysis. When calculated from the date of diagnosis as an advanced disease, the median OS was 12.9 months (95% CI, 11.3–14.5 months).

3.3. *Toxicity profile*

During a total of 125 cycles of chemotherapy (median 1.0 cycle per patient, range 1–17), 26 (46.4%) patients experienced grade 3 or 4 adverse events (AEs). The most common grade 3 or 4 AEs were neutropenia and thrombocytopenia, with 12 patients (21.4%) experiencing each of these AEs (Table 3). Due to these AEs, 24 (44.4%) and 9 (16.7%) patients experienced at least one cycle of treatment delay and dose reduction, respectively. Reasons for delaying treatment were as follows: non-drug related adverse event, 3 cases; sunitinib-related haematology toxicity, 13 cases and sunitinib-related non-haematology toxicity, 8 cases. Dose reduction was initiated in 3 cases due to sunitinib-related haematological toxicity, in 4 cases due to sunitinib-related non-haematological toxicity and in 2 cases due to both toxicities.

4. Discussion

Our study showed the following: (1) Second-line sunitinib demonstrated a median TTP of 1.7 months (95% CI 1.0–2.4), objective response rate of 8.9% (95% CI 3.0–19.6) and a disease control rate of 50.0% (95% CI 36.3–63.7) in 54 Asian patients with advanced BTCs who had shown progressive disease after first-line cytotoxic chemotherapy; (2) 46.4% of patients had experienced grade 3 or 4 adverse events, which resulted in frequent dose reductions and treatment delays.

Owing to the rarity of BTCs and the heterogeneous patient population, conducting a well-designed clinical trial in BTC patients is difficult, especially with respect to second-line treatment. A recently published randomised phase III trial carried out on 410 patients with advanced BTCs, using a combination of gemcitabine and cisplatin, showed improved overall survival and progression-free survival by 30% over gemcitabine alone.[5] Based on this result, the National Comprehensive Cancer Network (NCCN) guidelines[22] now recommend a combination of gemcitabine and cisplatin as category 1 treatment. However, no firm recommendation other than clinical trials is given as the second-line option.

Only a few studies have covered this subject. In their phase II study conducted on 32 patients who showed 5-FU refractoriness,[23] Oh et al. reported that second-line gemcitabine treatment resulted in a response rate of 6.9% and a median TTP of 1.6 months. Grade 3 or 4 neutropenia and thrombocytopenia were observed in 14.1% and 12.8% of patients, respectively. Sasaki et al. evaluated the feasibility of a combination of gemcitabine and cisplatin in 20 BTC patients who were refractory to gemcitabine and TS-1.[24] Although this combination failed to show any response, a moderate prolongation of TTP

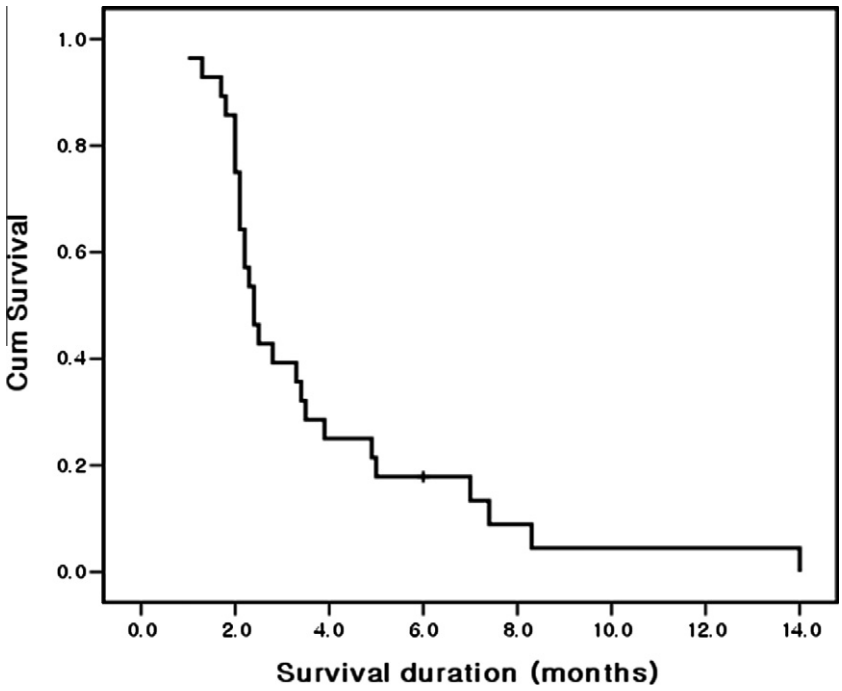

Fig. 1 – Progression free survival curve of patients.

Table 2 – Tumour response (*n* = 56 patients).

	N (%)	
Complete response	0	(0)
Partial response	5	(8.9)
Stable disease	23	(41.1)
Progressive disease	28	(50)
Response rate	8.9%	
Disease control rate	50%	

(3.6 months) and OS (5.9 months) was observed. Again, in the same study, haematological toxicities were the most bothersome events, with grade 3 or 4 neutropenia, anaemia or thrombocytopenia being frequent (15–35%). When TS-1, an oral fluoropyrimidine agent, was evaluated in two Japanese studies,[25,26] moderate efficacy was found, with a TTP of over 5.0 months and a response rate of about 20%.

Several molecular targeted agents had been tried as treatments for BTCs. Erlotinib, an epidermal growth factor recep-

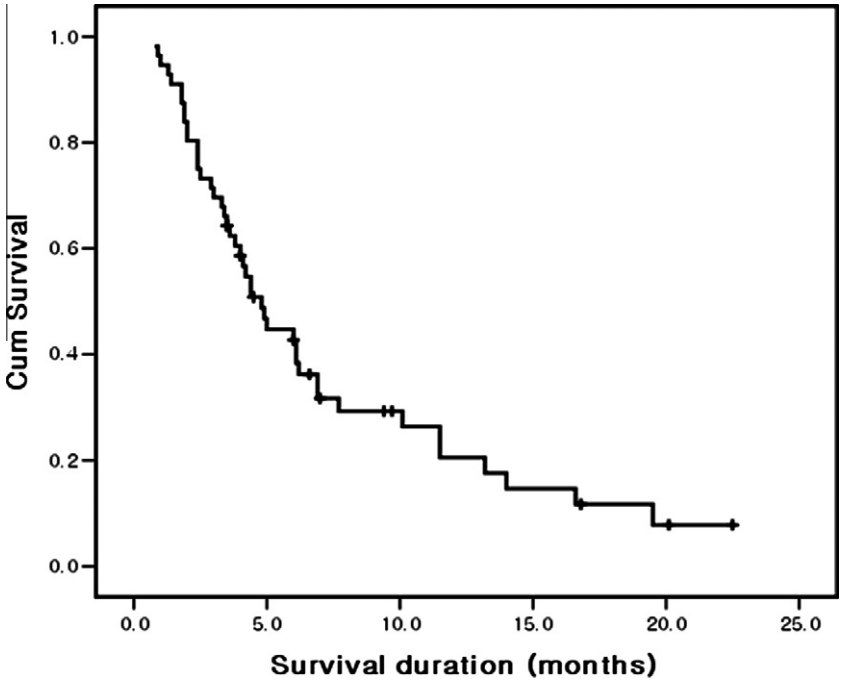

Fig. 2 – Overall survival curve of patients.

Table 3 – Adverse events (*n* = 56 patients).

	Grade 1–2 (%)	Grade 3–4 (%)
General weakness	22 (39.3)	2 (3.6)
Neuropathy	11 (19.6)	0 (0.0)
Mucosal inflammation		
Stomatitis	28 (50.0)	1 (1.8)
Diarrhoea	9 (16.1)	2 (3.6)
Hand-foot syndrome	20 (35.7)	6 (10.7)
Haematologic toxicity		
Neutropenia	10 (17.9)	12 (21.4)
Anaemia	9 (16.1)	3 (5.4)
Thrombocytopenia	24 (42.9)	12 (21.4)

tor (EGFR) tyrosine kinase inhibitor (TKI), was evaluated as single agent.[27] Among 42 patients, 24 (57%) had received prior chemotherapy. At the primary endpoint of the study, the 24-week progression-free rate was 17% (7 patients). Sorafenib is an oral multikinase inhibitor that targets similar kinases to sunitinib. It has been evaluated in one published phase II study. Bengala et al. reported that, when used as a single agent, the response rate and progression-free survival were 2% and 2.3 months (range 0–12), respectively[28] in 46 patients with advance BTCs. The common toxicities were skin rash (35%) and fatigue (33%); 22% of patients required a dose reduction.

The major limitation of the current study is that the frequency of intolerable toxicity forced modification of the treatment schedule or dosage and resulted in limited exposure of the treatment. Twenty-six (46.4%) had experienced grade 3 or 4 AEs and owing to these AEs, 24 (44.4%) and 9 (16.7%) experienced at least one cycle of treatment delay and dose reduction, respectively. This observed high incidence of sunitinib-induced toxicity in Asians is consistent with previous studies[29,30] and the limited exposure to treatment could have impacted clinical outcomes.

In conclusion, this study suggests that a daily dose of 37.5 mg of sunitinib shows acceptable anti-tumour effect and considerable but manageable toxicity in metastatic BTC patients who have failed to previous chemotherapy. Further study is needed to develop more promising salvage regimen to improve the clinical outcomes in this population.

Conflict of interest statement

None declared.

REFERENCES

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J Clin* 2010;**60**:277–300.
2. Shin HR, Oh JK, Masuyer E, et al. Epidemiology of cholangiocarcinoma: an update focusing on risk factors. *Cancer Sci* 2010;**101**:579–85.
3. Eslick GD. Epidemiology of gallbladder cancer. *Gastroenterol Clin North Am* 2010;**39**:307–30. ix.
4. de Groen PC, Gores GJ, LaRusso NF, Gunderson LL, Nagorney DM. Biliary tract cancers. *N Engl J Med* 1999;**341**:1368–78.
5. Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med* 2010;**362**:1273–81.
6. OT FuruseJ, Miyazaki MA, et al. A randomized study of gemcitabine/cisplatin versus single-agent gemcitabine in patients with biliary cancer. *J Clin Oncol* 2009;**27**. Abstr. 4579.
7. Sharma A, Dwary AD, Mohanti BK, et al. Best supportive care compared with chemotherapy for unresectable gall bladder cancer: a randomized controlled study. *J Clin Oncol* 2010;**28**:4581–6.
8. Lee J, Kim TY, Lee MA, et al. Phase II trial of gemcitabine combined with cisplatin in patients with inoperable biliary tract carcinomas. *Cancer Chemother Pharmacol* 2008;**61**:47–52.
9. Valle JW. Advances in the treatment of metastatic or unresectable biliary tract cancer. *Ann Oncol* 2010;**21**(Suppl.):vii345–vii348.
10. Hida Y, Morita T, Fujita M, et al. Vascular endothelial growth factor expression is an independent negative predictor in extrahepatic biliary tract carcinomas. *Anticancer Res* 1999;**19**:2257–60.
11. Nakashima T, Kondoh S, Kitoh H, et al. Vascular endothelial growth factor-C expression in human gallbladder cancer and its relationship to lymph node metastasis. *Int J Mol Med* 2003;**11**:33–9.
12. Mobius C, Demuth C, Aigner T, et al. Evaluation of VEGF A expression and microvascular density as prognostic factors in extrahepatic cholangiocarcinoma. *Eur J Surg Oncol* 2007;**33**:1025–9.
13. Zhu AX, Meyerhardt JA, Blaszkowsky LS, et al. Efficacy and safety of gemcitabine, oxaliplatin, and bevacizumab in advanced biliary-tract cancers and correlation of changes in 18-fluorodeoxyglucose PET with clinical outcome: a phase 2 study. *Lancet Oncol* 2010;**11**:48–54.
14. Lubner SJ, Mahoney MR, Kolesar JL, et al. Report of a multicenter phase II trial testing a combination of biweekly bevacizumab and daily erlotinib in patients with unresectable biliary cancer: a phase II Consortium study. *J Clin Oncol* 2010;**28**:3491–7.
15. Motzer RJ, Hutson TE, Tomczak P, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2009;**27**:3584–90.
16. Demetri GD, van Oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. *Lancet* 2006;**368**:1329–38.
17. Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med* 2011;**364**:501–13.
18. Burstein HJ, Elias AD, Rugo HS, et al. Phase II study of sunitinib malate, an oral multitargeted tyrosine kinase inhibitor, in patients with metastatic breast cancer previously treated with an anthracycline and a taxane. *J Clin Oncol* 2008;**26**:1810–6.
19. Socinski MA, Novello S, Brahmer JR, et al. Multicenter, phase II trial of sunitinib in previously treated, advanced non-small-cell lung cancer. *J Clin Oncol* 2008;**26**:650–6.
20. Saltz LB, Rosen LS, Marshall JL, et al. Phase II trial of sunitinib in patients with metastatic colorectal cancer after failure of standard therapy. *J Clin Oncol* 2007;**25**:4793–9.
21. Dror Michaelson M, Regan MM, Oh WK, et al. Phase II study of sunitinib in men with advanced prostate cancer. *Ann Oncol* 2009;**20**:913–20.
22. *NCCN Clinical Practice Guidelines in Oncology*: NCCN.org; 2011 Contract No.: Document Number.
23. Oh SY, Jeong CY, Hong SC, et al. Phase II study of second line gemcitabine single chemotherapy for biliary tract cancer

patients with 5-fluorouracil refractoriness. *Invest New Drugs* 2011;**29**:1066–72.
24. Sasaki T, Isayama H, Nakai Y, et al. Feasibility study of gemcitabine, cisplatin combination chemotherapy for patients with refractory biliary tract cancer. *Invest New Drugs* 2010.
25. Sasaki T, Isayama H, Yashima Y, et al. S-1 monotherapy in patients with advanced biliary tract cancer. *Oncology* 2009;**77**:71–4.
26. Sasaki T, Isayama H, Nakai Y, et al. Multicenter phase II study of S-1 monotherapy as second-line chemotherapy for advanced biliary tract cancer refractory to gemcitabine. *Invest New Drugs* 2010.
27. Philip PA, Mahoney MR, Allmer C, et al. Phase II study of erlotinib in patients with advanced biliary cancer. *J Clin Oncol* 2006;**24**:3069–74.
28. Bengala C, Bertolini F, Malavasi N, et al. Sorafenib in patients with advanced biliary tract carcinoma: a phase II trial. *Br J Cancer* 2010;**102**:68–72.
29. Uemura H, Shinohara N, Yuasa T, et al. A phase II study of sunitinib in Japanese patients with metastatic renal cell carcinoma: insights into the treatment, efficacy and safety. *Jpn J Clin Oncol* 2010;**40**:194–202.
30. Yoo C, Kim JE, Lee JL, et al. The efficacy and safety of sunitinib in korean patients with advanced renal cell carcinoma: high incidence of toxicity leads to frequent dose reduction. *Jpn J Clin Oncol* 2010;**40**:980–5.