EUROPEAN JOURNAL OF CANCER 45 (2009) 579–587

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Combination of sorafenib and doxorubicin in patients with advanced hepatocellular carcinoma: Results from a phase I extension trial

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ARTICLE INFO

Article history:
Received 18 August 2008
Received in revised form 10 October 2008
Accepted 16 October 2008
Available online 26 December 2008

Keywords:
Doxorubicin
Hepatocellular carcinoma
Safety
Sorafenib
Multikinase inhibitor

ABSTRACT

Sorafenib, an oral multikinase inhibitor, shows efficacy in renal cell and hepatocellular carcinoma (HCC) and is well tolerated whevn combined with doxorubicin in other solid tumours. Eighteen patients with inoperable HCC received doxorubicin 60 mg/m^2 IV for up to six 3-week cycles. Sorafenib 400 mg bid was administered continuously starting day 4. Patients discontinuing doxorubicin were eligible for sorafenib monotherapy. The most frequent grade 3–4 drug-related adverse events were neutropaenia (61%), leukopaenia (45%) and diarrhoea (17%, grade 3). Seven of eight patients who completed six cycles of doxorubicin continued treatment with sorafenib for at least 3 months. Doxorubicin moderately increased AUC (21%) and C_{max} (33%) when administered with sorafenib. The disease control rate for 16 evaluable patients was 69%. Sorafenib plus doxorubicin appears to be well tolerated and more effective in the treatment of HCC than doxorubicin alone. Follow-up with single-agent sorafenib in these patients also appears to be well tolerated.

1. Introduction

Hepatocellular carcinoma (HCC) is the fifth most common solid tumour[1] and the third leading cause of cancer deaths worldwide.[2] Eighty percent of cases occur in Asia and sub-Saharan Africa.[3] Despite a relatively lower incidence in Europe and the United States (US), the rates have roughly doubled from the 1960s and 1970s to the mid 1990s.[4–8]

Current treatment options for HCC are limited. Only 15% of patients qualify for surgical intervention and/or transplantation.[9] Systemic cytotoxic therapies have been largely unsuccessful, yielding marginal anti-tumour activity and exerting no appreciable impact on survival.[10–12] Nonetheless, chemotherapy is used frequently in clinical practice, with doxorubicin as the agent of choice.[10] Outcomes in patients with HCC treated with conventional chemotherapy are generally poor; 5-year survival rates are typically less than 5%.[5] New therapeutic approaches are urgently needed to improve outcomes in this difficult-to-treat patient population.

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2008.10.039

Sorafenib (BAY 43-9006, Nexavar®), an oral multikinase inhibitor with anti-proliferative and anti-angiogenic activities, has been shown to inhibit the activity of the serine/threonine kinases (*c-Raf* and *B-Raf*); vascular endothelial growth factor receptor (VEGFR)-1, -2 and -3 and platelet-derived growth factor receptor (PDGFR)-α and -β as well as *c-Kit*, *Flt-3* and *RET*.[13–15] Preclinical studies have shown that sorafenib suppresses tumour proliferation through inhibition of the *Raf/MEK/ERK* pathway, and tumour angiogenesis through inhibition of VEGF receptors.[15–17]

Sorafenib has demonstrated potent anti-tumour activity in preclinical models of breast cancer, lung cancer, colorectal cancer, renal cell carcinoma (RCC) and HCC, all of which are known to exhibit a dysregulated *Raf* pathway and upregulated angiogenesis.[15,18] Analysis of HCC tumour xenografts has shown that apoptosis, angiogenesis and the *Raf/MEK/ERK* pathway are targeted by sorafenib.[19] Activation of the *Raf* pathway in HCC may result from divergent underlying causes[20]: hepatitis B virus (HBV) transcriptional activation alters the expression of growth-control genes, including *Raf* and *Ras*; hepatitis C virus (HCV) core proteins interact with *Raf* and other members of the MAPK pathway to modulate proliferation; and aflatoxin B_1 is associated with a specific p53 mutation and *Ras* oncogene activation.[21] Sorafenib has been shown to reduce *MEK* and *ERK* phosphorylations, decrease microvessel density and to increase apoptosis in HCC cells *in vivo*.[16]

In a phase II study of 137 patients with advanced HCC who received single-agent sorafenib, the overall best response of stable disease (SD) or better was 41.6%.[22] Recently, the phase III Sorafenib HCC Assessment Randomized Protocol (SHARP) trial demonstrated increased overall survival in patients with advanced HCC who were treated with single-agent sorafenib 400 mg bid, compared with those who received placebo.[23] This was the first trial to show such an increase with a systemic therapy in the HCC patient population. This result led to approvals of sorafenib for the treatment of HCC by the US Food and Drug Administration and by the European Medicines Agency.

The combination of sorafenib and chemotherapeutic agents such as doxorubicin has demonstrated additive antitumour activity *in vitro*.[24] In a phase I dose-escalation study, combining sorafenib and doxorubicin in 34 patients with refractory solid tumours, 15 patients (48%)—four of whom had a diagnosis of HCC—achieved SD for ⩾12 weeks.[25] Sorafenib (400 mg bid) and doxorubicin (60 mg/m^2) were well tolerated, without reaching the toxic dose level.

Long-term safety has not been evaluated in patients receiving the combination of sorafenib plus doxorubicin, for up to the maximum lifetime cumulative dose of doxorubicin, and followed by single-agent sorafenib therapy. To better characterise the long-term safety and efficacy of this drug combination, an extension study of a phase I trial in patients with inoperable HCC was performed. The primary objective of the extension study was to determine the long-term safety of continuously administered sorafenib combined with doxorubicin every 21 days for up to six cycles or up to the maximum lifetime cumulative dose of doxorubicin, and followed by single-agent sorafenib. Secondary objectives included determining the effect of doxorubicin on the pharmacokinetics of sorafenib (and vice versa), as well as tumour response to this combination therapy.

2. Materials and methods

2.1. Patient eligibility

Patients aged ⩾18 years with proven, inoperable HCC who were considered appropriate candidates for systemic therapy were eligible for this study. Inclusion and exclusion criteria have been described previously.[25] All patients provided written informed consent. The study was approved by the institutional review board and conducted in accordance with the Declaration of Helsinki.

2.2. Trial design and treatment

Doxorubicin (60 mg/m^2) was administered as a 30-min intravenous (IV) infusion on day 1 of 3-week cycles. Patients received continuous sorafenib 400 mg bid, beginning on day 4 of cycle 1. The maximum allowable number of doxorubicin cycles was six, to avoid exceeding the safe lifetime cumulative anthracycline dose of 450 mg/m^2. Treatment cycles were further limited in patients who had received prior anthracycline therapy.[25] Patients with partial responses or those showing no signs of progression after six cycles of combined doxorubicin plus sorafenib were permitted to continue single-agent sorafenib therapy.

2.3. Safety and efficacy assessments

Safety measurements included monitoring for adverse events (AEs) using the National Cancer Institute Common Toxicity Criteria, version 2 (NCI CTC v2.0). Left-ventricular ejection fraction (LVEF) was assessed at baseline and after the last doxorubicin infusion using multiple gated acquisition (MUGA) scans.

Tumour response measurements, based on World Health Organization criteria, were performed at baseline and every 8 weeks during the treatment period; responses were confirmed with a second scan 4 weeks later. For patients with SD or an objective response, follow-up assessments for survival were performed every 3 months until progression of disease (PD) and/or death was documented (for a maximum of 2 years).

2.4. Pharmacokinetic assessments

Pharmacokinetic variables were calculated from plasma drug concentration over time using KINCALC (Bayer AG) for non-compartmental evaluations. Analysed variables included C_{max} and area under the curve (AUC) for sorafenib, doxorubicin and doxorubicinol (a doxorubicin metabolite). Plasma concentration of sorafenib was measured on day 21 of cycle 1 (sorafenib alone) and on day 1 of cycle 2 (sorafenib plus doxorubicin). Samples were collected prior to dosing and 0.5, 1, 2, 4, 8, 10 and 12 h afterwards. Pharmacokinetic profiles of doxorubicin and doxorubicinol were determined on days 1–3 of cycle 1 (doxorubicin alone) and on days 1–3 of cycle 2 (doxorubicin plus sorafenib). Plasma samples for pharmaco-

kinetic evaluation of doxorubicin and doxorubicinol were collected prior to dosing and 0.5, 1, 2, 4, 8, 12, 24, 48 and 72 h afterwards. C_{max} and AUC were calculated for sorafenib and doxorubicin (and doxorubicinol) when given alone and in combination.

2.5. Statistical analyses

The logarithms of C_{max} and AUC were analysed using analysis of variance assuming log-normally distributed data. Based on these analyses, point estimates and exploratory 90% confidence intervals for the ratios (sorafenib ± doxorubicin/sorafenib and sorafenib ± doxorubicin/doxorubicin) were calculated by retransformation of the logarithmic data. The possible association between doxorubicin and doxorubicinol pharmacokinetics (as measured by C_{max} and AUC) with cardiac function (as measured by the difference between baseline LVEF at cycles 1 and 2) was assessed using the Pearson correlation coefficient, *r*. Statistical analyses were performed using SAS software, version 8.2.

3. Results

3.1. Patient characteristics

Eighteen patients with inoperable HCC were enrolled. Patients were predominantly male, stage IV, with SD or PD, and with an Eastern Cooperative Oncology Group (ECOG) performance status of 1 (Table 1). All patients who received prior systemic or surgical anticancer treatment had clinical or radiographic progression within the 2 months preceding study entry. All patients received at least one dose of study medication and were eligible for safety analysis; 16 (89%) were evaluable for efficacy, and 11 (61%) were evaluable for pharmacokinetic analysis. As of August 2006, 1 patient (6%) was still receiving treatment and 17 (94%) were withdrawn from the study—12 (67%) due to PD, 2 (12%) due to non-compliance, 2 (12%) due to AEs and 1 (6%) who was lost to follow-up.

Patients received a median of 94% (753 mg) of the planned sorafenib daily dose and 97% (57.9 mg/m^2) of the planned dose per cycle of doxorubicin (Table 2). Fifteen patients (83%) received at least 70% of the planned dose for sorafenib and doxorubicin. Although a greater proportion of patients required dose reduction or treatment interruption with sorafenib than with doxorubicin (56% versus 28%), 28% of all patients required only one interruption or dose reduction of sorafenib. Treatment duration was similar for both agents, with patients receiving a median of four cycles overall and eight patients (44%) receiving all six planned cycles. Seven of the eight patients who completed six cycles of doxorubicin continued treatment with sorafenib monotherapy and received at least 3 additional months of therapy. Three of these patients received sorafenib treatment for at least 1 year.

3.2. Safety

The most frequent non-haematologic treatment-emergent AEs of any grade were fatigue (89%), diarrhoea (78%), anorexia (56%), vomiting (39%), stomatitis (39%), hand-foot skin reaction (HFSR, 33%), bilirubin abnormality (33%), weight loss (33%), abdominal pain (33%), and dyspnoea (33%). Cardiac-related treatment-emergent AEs were uncommon and generally mild, and included a grade 1 sinus bradycardia, a grade 1 nodal/junctional arrhythmia and a grade 3 sinus tachycardia. The most frequent haematologic abnormalities of any grade were neutropaenia (61%), leukopaenia (50%) and anaemia (33%).

Sixteen patients (89%) had at least one grade 3 or 4 treatment-emergent AE (Table 3). The most frequently observed grade 3 non-haematologic treatment-emergent AEs were fatigue (22% of patients), increased alkaline phosphatase (22%), diarrhoea (17%), dyspnoea (17%) and ascites (17%). Grade 4 non-haematologic treatment-emergent AEs included hepatic and metabolic abnormalities expected with liver dysfunction, including increased serum glutamic oxaloacetic transaminase/aspartate aminotransferase (sGOT/AST) (22%), elevated serum bilirubin (17%), hyponatraemia (11%) and hyperuricaemia (11%). Haematologic grade 3 or 4 treatment-emergent AEs were observed more frequently than non-haematologic events. Grade 3 haematologic AEs included leukopaenia (33%), altered haemoglobin levels (22%), neutropaenia (17%) and lymphopaenia (17%). Forty-four percent of patients had grade 4 neutropaenia; 17% had grade 4 leukopaenia.

The most frequent treatment-emergent AEs of any grade assessed by the investigator as related to study treatment were diarrhoea (67%), neutropaenia (61%), leukocytopaenia (44%), HFSR (33%), stomatitis (28%) and alopecia (22%). The only grade 3 drug-related, non-haematologic, treatment-emergent AEs were diarrhoea (17%) and HFSR (11%). No grade 4 drug-related non-haematologic events were reported. Grade 3 or 4 drug-related, haematologic, treatment-emergent AEs included leukopaenia (grade 3, 28%; grade 4, 17%) and neutropaenia (grade 3, 17%; grade 4, 44%).

Six patients (33%) had one or more dose reductions and/or interruptions related to sorafenib administration; these were due to HFSR alone ($n = 2$), HFSR with diarrhoea ($n = 2$) or fatigue ($n = 1$), or diarrhoea alone ($n = 1$). Discontinuation and restart of sorafenib was due to HFSR (any grade) or grade 2 diarrhoea. Reductions in sorafenib dosing were due to grade 1 or 2 HFSR, grade 2 diarrhoea and grade 2 fatigue. No AEs leading to dose reductions and/or interruptions of doxorubicin administration were reported.

Dose-limiting toxicity related to sorafenib was reported in two patients with HFSR that resolved following dose reduction, and in one patient with grade 3 diarrhoea that required hospitalisation and resolved following sorafenib discontinuation, restart and dose reduction.

Serious AEs (leading to hospitalisation or assessed by the investigator as medically important) related to study medication were grade 4 neutropaenia (44%), grade 4 leukopaenia (17%), and HFSR and diarrhoea (grade 3, each 6%) (Table 4). The observed neutropenia and leukopenia were attributed to doxorubicin, with HFSR and diarrhoea attributed to sorafenib.

Two patients withdrew as a result of treatment-emergent AEs: one due to grade 4 renal insufficiency following 77.3 weeks of treatment with study medication, which resolved, and the other due to grade 2 hepatic encephalopathy following 2.3 weeks of treatment, for which there was insufficient follow-up to assess the outcome. One patient treated with

Table 1 – Baseline demographic and disease characteristics of enrolled patients.

Characteristic	Sorafenib + doxorubicin
Number of patients	18
Sex, n (%)	
Male	17 (94)
Female	1 (6)
Race, white, *n* (%)	18 (100)
Age, years	
Median (range)	55.5 (39–78)
Mean ± SD	57.1 ± 12.3
BMI, kg/m^2	
Median (range)	24.8 (20.3–34.0)
Mean ± SD	25.0 ± 3.7
Diagnosis, hepatoma, *n* (%)	18 (100)
Histology, hepatocellular carcinoma, *n* (%)	18 (100)
ECOG status, *n* (%)	
0	4 (22)
1	14 (78)
TNM stage, *n* (%)	
IV-A	4 (22)
IV-B	12 (67)
Not available	2 (11)
Status at entry[a]	
Stable disease	8 (44)
Progressive disease	9 (50)
Not available	1 (6)
Prior treatment, *n* (%)	
Surgery[b]	5 (28)
Systemic chemotherapy[c]	5 (28)
Radiotherapy	1 (6)

Abbreviations: BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; SD, standard deviation; and TNM, tumour, node, metastasis.
a Clinical or radiologic.
b Includes hepatectomy (*n* = 1), lobectomy (*n* = 2) and laparotomy (*n* = 2).
c Prior systemic chemotherapy for these 5 patients was as follows: (1) tamoxifen; (2) doxorubicin and cyclophosphamide; (3) epirubicin; (4) 5-fluorouracil, cisplatin, doxorubicin, interferon alfa-2b, tamoxifen, and gemcitabine; and (5) gemcitabine and 5-fluorouracil/leucovorin.

Table 2 – Administration of sorafenib and doxorubicin to all patients.

Parameter	Sorafenib + doxorubicin (*n* = 18)	
	Sorafenib	Doxorubicin
Planned dose	800 mg daily	60 mg/m^2 per cycle
Actual dose[a]		
Median (range)	753 (369–800)	57.9 (28.0–62.6)
Mean ± SD	685 ± 135	53.8 ± 10.6
Percent planned dose received, *n* (%)		
30% to <50%	1 (6)	1 (6)
50% to <70%	2 (11)	2 (11)
70% to <90%	6 (33)	1 (6)
⩾90%	9 (50)	14 (78)
Treatment, weeks		
Median (range)	15.0 (1.9–156.1)	14.1 (3.0–21.1)
Mean ± SD	29.3 ± 39.4	12.2 ± 7.4
Patients with dose reduction/interruption, *n* (%)	10 (56)	5 (28)

Abbreviation: SD, standard deviation.
a Sorafenib: daily dosing in mg and doxorubicin: mg/m^2 per cycle.

study medication for 16.9 weeks died from a pulmonary embolism due to liver transplantation 3.9 weeks after the last treatment.

Haematologic parameter changes ⩾2 toxicity grades from baseline frequently observed among patients included leukopaenia (78%), neutropaenia (72%), lymphopaenia (44%) and

Table 3 – Grade ⩾ 3 adverse events[a].

Grade 3 or 4 adverse event	Sorafenib + doxorubicin (*n* = 18)	
	Grade 3 *n* (%)	Grade 4 *n* (%)
Leukocyte	6 (33)	3 (17)
Haemoglobin	4 (22)	0
Fatigue	4 (22)	0
Alkaline phosphatase abnormality	4 (22)	0
Neutrophil	3 (17)	8 (44)
Bilirubin abnormality	3 (17)	3 (17)
GGT	3 (17)	1 (6)
Diarrhoea	3 (17)	0
Dyspnoea	3 (17)	0
Ascites (non-malignant)	3 (17)	0
Lymphopaenia	3 (17)	0
PTT	3 (17)	0
Hypokalaemia	2 (11)	0
HFSR	2 (11)	na
Platelet	2 (11)	0
sGPT (ALT) abnormality	2 (11)	1 (6)
Anorexia	1 (6)	0
sGOT (AST) abnormality	1 (6)	4 (22)
Hyponatraemia	1 (6)	2 (11)
Hyperuricaemia	1 (6)	2 (11)
Fever (non-neutropaenia)	1 (6)	0
Febrile neutropaenia	1 (6)	0
Thrombosis/embolism	1 (6)	0
Anorexia	1 (6)	0
Chest pain	1 (6)	0
Creatinine abnormality	1 (6)	0
Hypocalcaemia	1 (6)	0
Depressed level of consciousness	1 (6)	0
Sinus tachycardia	1 (6)	0
Haemorrhage/bleeding[b]	1 (6)	0
Hypoalbuminaemia	1 (6)	0
Amylase abnormality	1 (6)	0
Lipase abnormality	1 (6)	0
Hyperglycaemia	1 (6)	0
Hyperkalaemia	1 (6)	0
Hypernatraemia	1 (6)	0
Hypocalcaemia	1 (6)	0
Renal failure	0	2 (11)

Abbreviations: GGT, gamma-glutamyl transpeptidase; PPT, partial thromboplastin time; HFSR, hand-foot skin reaction; na, not applicable; sGPT/ALT, serum glutamic pyruvic transaminase/alanine aminotransferase; and sGOT/AST, serum glutamic oxaloacetic transaminase/aspartate aminotransferase.

a One patient (6%) died from pulmonary embolism due to liver transplantation (grade 5 adverse event).

b Associated with surgery.

anaemia (39%), which are common side-effects of treatment with doxorubicin. The high incidence of hepatic toxicity changes ⩾2 grades from baseline—most of which involved bilirubin (62%), albumin (24%) and alkaline phosphatase (17%)—is expected in a patient population with HCC. In our extension study, changes in metabolic parameters ⩾2 grades from baseline occurred less frequently than haematologic parameters and included hyponatraemia (38%), hypokalaemia (28%) and hypoglycaemia (28%). In addition, 24% of patients had elevations in lipase levels, and 18% had elevations in amylase levels. Such findings have previously been reported in association with sorafenib.[26,27]

Seven of eight patients who completed six cycles of doxorubicin continued treatment with single-agent sorafenib for at least 3 additional months. Two of these patients required sorafenib dose reduction after the last doxorubicin infusion because of diarrhoea (*n* = 1) or of hand-foot skin reaction combined with fatigue (*n* = 1).

LVEF multigated (radionuclide) angiogram assessments at screening and after the last doxorubicin infusion of the study were available for eight patients, including six who completed six cycles of doxorubicin and for whom assessments at baseline and following doxorubicin treatment were available. Five patients had no change or a decrease ⩽10% in LVEF. Three patients experienced a ⩾10% LVEF decrease: one patient, after six cycles of doxorubicin, had a drop in LVEF from 68% at baseline to 51% at 6 weeks after the last doxorubicin infusion; another patient, after five cycles of

Table 4 – Grade ⩾ 3 serious adverse events.

Serious adverse event	Sorafenib + doxorubicin (n = 18)	
	Grade 3 n (%)	Grade 4 n (%)
Ascites (non-malignant)	3 (17)	0
Diarrhoea	1 (6)	0
Thrombosis/embolism	1 (6)	0
Fatigue	1 (6)	0
Creatinine abnormality	1 (6)	0
Haemorrhage/bleeding[a]	1 (6)	0
Depressed level of consciousness	1 (6)	0
Dyspnoea	1 (6)	0
HFSR	1 (6)	0
Neutropaenia	0	8 (44)
sGOT (AST)	0	4 (22)
Leukocytopaenia	0	3 (17)
Bilirubin	0	3 (17)
Renal failure	0	2 (11)
Hyperuricaemia	0	2 (11)
Hyponatraemia	0	2 (11)
sGPT (ALT)	0	1 (6)
GGT	0	1 (6)
Pulmonary embolism	0	1 (6)[b]
Dysphagia or aphasia	0	0

Abbreviations: HFSR, hand–foot skin reaction; sGOT/AST, serum glutamic oxaloacetic transaminase/aspartate aminotransferase; sGPT/ALT, serum glutamic pyruvic transaminase/alanine aminotransferase; and GGT, gamma-glutamyl transpeptidase.

a Associated with surgery.

b One patient (6%) died (grade 5 adverse event) from pulmonary embolism due to liver transplantation.

doxorubicin, had a drop in LVEF from 55% at baseline to 49% after the fifth doxorubicin infusion, which subsequently increased to 51% at 3 weeks after the last doxorubicin infusion and the third patient, after six cycles of doxorubicin, had a drop in LVEF from 64% at baseline to 57% at 1 week after the last doxorubicin infusion.

Data to assess the possible association of doxorubicin or doxorubicinol pharmacokinetics with cardiac function were available for five patients in cycles 1 and 2. No significant correlation was observed between doxorubicin or doxorubicinol AUC and the difference in LVEF in cycle 1 ($P = 0.52$ and $P = 0.80$, respectively) and cycle 2 ($P = 0.91$ and $P = 0.99$, respectively). Similarly, no significant correlation was observed for doxorubicin or doxorubicinol C_{max} in cycle 1 ($P = 0.77$ and $P = 0.30$, respectively) and cycle 2 ($P = 0.20$ and $P = 0.97$, respectively).

3.3. *Pharmacokinetics*

The plasma concentration–time profiles of sorafenib (400 mg bid PO) with and without concomitant doxorubicin administration (60 mg/m^2 IV) among 11 evaluable patients are shown in Fig. 1. No relevant changes were observed in C_{max} or in AUC_{0-8} of sorafenib at steady state when doxorubicin was administered (Table 5). Simultaneous administration of sorafenib and doxorubicin increased the doxorubicin C_{max} and AUC means by 33% and 21%, respectively, while the effect of sorafenib on doxorubicinol pharmacokinetics was less pronounced, with mean increases in C_{max} and AUC_{0-24} by 16% and 5%, respectively (Table 6).

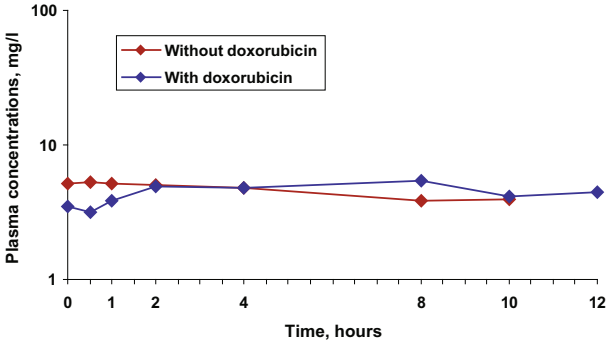

Fig. 1 – Plasma concentration–time course of sorafenib after oral administration of sorafenib (400 mg bid), with and without concomitant doxorubicin (60 mg/m^2), in patients with hepatocellular carcinoma (HCC).

3.4. *Anti-tumour activity*

Among 16 evaluable patients, there were no complete responses (CRs), one partial response (PR) (6%) of 122.7 weeks, 10 patients with SD (63%; median duration, 17.2 weeks [range, 5.8–75.0]) and five with PD (31%). Overall, the disease control rate (CR + PR + SD) was 69%, with a median duration of 17.4 weeks.

4. Discussion

The results of this phase I extension trial support findings reported in an earlier phase I dose-escalation study of combina-

Table 5 – PK parameters of sorafenib 400 mg po bid with and without concomitant administration of doxorubicin 60 mg/m² IV (geometric means [geometric CV]).

Parameter	Sorafenib + doxorubicin ($n = 11$[a])	
	C_{max} (mg/l)	AUC_{0-8} (mg h/l)
Sorafenib alone	7.0 (54)	34.8 (60)
Sorafenib + doxorubicin	6.0 (56)	37.1 (49)
Ratio sorafenib + doxorubicin to sorafenib alone	0.86	1.07

Abbreviations: PK, pharmacokinetic; IV, intravenous; CV, coefficient of variation; C_{max}, maximum concentration of drug; and AUC, area under the curve.

a Reflects pharmacokinetic data available from 10 patients with hepatocellular carcinoma and 1 patient with cholangiocarcinoma.

Table 6 – PK parameters of doxorubicin and doxorubicinol after administration of 60 mg/m² IV doxorubicin, with and without sorafenib 400 mg bid (geometric means [geometric CV]).

Parameter	C_{max} (μg/l) ($n = 11$[a])	AUC (μg h/l) ($n = 11$[a])
Doxorubicin		
Doxorubicin alone	2500 (62)	2159 (38)
Doxorubicin + sorafenib	3330 (34)	2603 (27)
Ratio doxorubicin + sorafenib versus doxorubicin alone	1.33	1.21
Doxorubicinol		
Doxorubicin alone	12.9 (18)	220 (27)[b]
Doxorubicin + sorafenib	15.0 (23)	232 (21)[b]
Ratio doxorubicin + sorafenib versus doxorubicin alone	1.16	1.05

Abbreviations: PK, pharmacokinetics; IV, intravenous; CV, coefficient of variation; C_{max}, maximum concentration of drug; and AUC, area under the curve.

a Reflects PK data available from 10 patients with hepatocellular carcinoma and 1 patient with cholangiocarcinoma.

b AUC_{0-24}.

tion therapy with sorafenib plus doxorubicin in patients with refractory solid tumours.[25] In this study, combination therapy with sorafenib plus doxorubicin was generally well tolerated. Whereas 83% of the patients reported AEs related to either drug, most of which were mild to moderate in intensity, 33% experienced sorafenib-related AEs, most commonly HFSR that resulted in dose reduction or treatment interruption.

Myelotoxicity and cardiotoxicity are significant concerns with the use of single-agent doxorubicin.[28] The incidence of grade 3 or 4 myelotoxicity has been shown to be as high as 60% among patients given single-agent doxorubicin 60 mg/m² every 3 weeks.[29] The probability of developing impaired myocardial function is estimated to be 5–8% with doxorubicin 450 mg/m² (the maximal accumulated dose).[28] Despite the association of doxorubicin with toxicity, only one treatment-emergent cardiotoxicity event (sinus tachycardia) that was not considered related to either study medications was observed in our study. High risk of doxorubicin-associated cardiotoxicity is defined as a decrease from baseline LVEF of >10%, to a final LVEF of ⩽50%,[30] thereby enabling detection of cardiotoxicity in patients receiving doxorubicin-based therapy.[31,32] In our study, among eight evaluable patients, seven (88%) had no sign of cardiotoxicity. Only one patient experienced marginal changes in LVEF (10.9% reduction of LVEF in cycle 5, compared with baseline). In addition, LVEF was not associated with alterations in doxorubicin or doxorubicinol pharmacokinetic parameters. The combination of sorafenib and doxorubicin yielded no additional toxicities other than those related to the individual drugs. Collectively, these findings show no indication of increased cardiotoxicity due to doxorubicin when administered in combination with sorafenib 400 mg bid PO. However, the observation period in this study may not have been long enough to accurately assess a potential long-term cardiotoxicity of doxorubicin.

Sorafenib has been associated with dermatologic toxicity in previous studies in patients with RCC[33] and HCC.[22] In the present study, 11% of patients reported grade 3 HFSR. Gastrointestinal and constitutional events, also reported for sorafenib in previous studies, were grade ⩽ 3. The prevalence of hepatic AEs is likely attributable to the underlying liver dysfunction in patients with HCC.

Pharmacokinetic analysis showed that concomitant administration of doxorubicin with sorafenib had minimal effects on the pharmacokinetic parameters of sorafenib. However, concomitant administration of sorafenib with doxorubicin moderately increased C_{max} and AUC of doxorubicin and, to a lesser extent, the C_{max} and AUC_{0-24} of doxorubicinol. AEs observed in this extension study are similar to those observed in the earlier phase I dose-escalation trial,[25] although seven patients continued to receive extended single-agent therapy.

In this study, the combination of sorafenib and doxorubicin resulted in a disease control rate of 69%, including two patients who maintained SD for >70 weeks, compared with historical reports of 10–40% for doxorubicin alone.[34–36] The combination of sorafenib with doxorubicin, which has been shown to be synergistic *in vitro*,[24] may potentially minimise

the development of resistance by phenotypically and genotypically heterogeneous hepatic cancers[37] by targeting multiple mechanisms of tumour growth (e.g. cell proliferation and angiogenesis). Increased activity of *Raf-1*, which is inhibited by sorafenib, has been associated with resistance to doxorubicin in preclinical studies.[38,39]

The present study demonstrates that combination therapy with oral sorafenib (400 mg bid) and IV doxorubicin (60 mg/m^2 once every 3 weeks) is well tolerated by patients with advanced HCC. Although pharmacokinetic analyses showed moderate drug interaction between the two agents, this interaction did not appear to negatively affect the toxicity profile. Combination therapy with sorafenib and doxorubicin showed promising activity in patients with HCC. This novel combination of cytotoxic and targeted therapy is being investigated in a phase II double-blind randomised study of 96 patients with advanced HCC treated with the combination of sorafenib plus either doxorubicin or placebo.[40]

Conflict of interest statement

M. Ludwig and E. Brendel are employees of Bayer Schering Pharma, Elberfeld, Germany. O. Christensen is an employee of Bayer HealthCare Pharmaceuticals, Montville, NJ, USA.

Acknowledgements

This study was sponsored by Bayer Schering Pharma, Elberfeld, Germany. The study sponsor contributed to the design of the study; analysis and interpretation of data; writing of the manuscript and the decision to submit the manuscript for publication. The authors wish to acknowledge Nelson Erlick, DPM, MS and John D. Zoidis, MD, for their editorial assistance in the preparation of this manuscript.

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