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Efficacy and safety of sorafenib–gemcitabine combination therapy in advanced hepatocellular carcinoma: An open-label Phase II feasibility study

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PURPOSE: Sorafenib is considered a standard of care in advanced hepatocellular carcinoma (HCC). Its combination with gemcitabine, a pyrimidine analogue with limited friendly hepatic profile may prove beneficial in advanced HCC. The primary objective was to evaluate the efficacy and safety of a sorafenib and gemcitabine combination in patients with advanced HCC.

METHODS: This was a non-randomized, open-label, single-arm, multi-centric Phase II study conducted in Pakistan where 30 treatment-naive patients aged between 26 and 73 years with Child–Pugh score A or B were treated with sorafenib (400 mg oral) twice daily for 16 weeks along with gemcitabine (1000 mg/m^2 intravenous) administered on day 1 and day 8 of a four-week cycle for 16 weeks.

RESULTS: Of the 18 patients (60%) who completed all four cycles of treatment, eight patients had stable disease, two had partial response, and eight had progressive disease. There was no complete response. The most common (≥10% patients) treatment-emergent adverse events were gemcitabine-related thrombocytopenia (40%) followed by sorafenib-related hand–foot skin reaction and anorexia (33% each).

CONCLUSION: The efficacy of sorafenib gemcitabine combination therapy is similar to the sorafenib alone treatment. However, frequent dose adjustments due to gemcitabine-related toxicities, delays, and corrective treatments make this combination therapy unsafe in the treatment of advanced HCC.

Hepatocellular carcinoma (HCC) is the fifth leading cause of cancer death worldwide, and the majority of patients are Asians [1,2]. Treatment options for HCC depend on the stage of the disease, co-existing cirrhosis, and the patient's overall condition. While in early stage of cancer, surgical resection or liver transplantation may be curative; however, only about 15% of patients have resectable disease at presentation. The majority of patients present in the advanced disease stage, and hence are considered candidates for non surgical options. Until the late 1990s, there was no worldwide, approved local or systemic therapy for advanced HCC and all available therapies for advanced unresectable and metastatic HCC had limited clinical value, with low response rates, and little impact on the natural history of the disease [3]. It was for the first time that in 2008 a large Phase III trial established the survival benefit of sorafenib in advanced HCC [4]. However, the results remain humble with overall survival benefit of around four months. The need for improvement was therefore well recognized.

HCC is considered to have intrinsic resistance to chemotherapy agents. This is due to increased expression of multidrug resistance transporters and active intracellular metabolism [5]. A large number of controlled and uncontrolled studies performed with different classes of chemotherapeutic agents have yielded low response rates [6–8] After the success of sorafenib, combination regimens with chemotherapeutic agents came under investigation [9].

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Most HCCs develop in cirrhotic livers with impaired liver function and therefore drug hepatic metabolism and its toxicity in this setting is important while considering any therapeutic trial [10]. Gemcitabine, a pyrimidine analogue, is metabolized intracellularly by nucleoside kinases, and excreted mainly in urine. Earlier studies with gemcitabine in patients with liver impairment and elevated aspartate aminotransferase (AST $\geq$2-times the upper limit of normal [ULN]) did not show any increase in toxic effects related to gemcitabine. However, dose reduction was recommended in patients with elevated bilirubin levels (>27 μmol/L) [11] This established a limited hepatic friendly profile of gemcitabine in HCC and the hypothesis was that its combination with sorafenib may be beneficial. Thus, the primary objective of this Phase II study was to evaluate the efficacy and safety of a sorafenib and gemcitabine combination therapy in patients with advanced HCC.

METHODS

Study population
Adult treatment-naïve patients of either sex with advanced HCC were enrolled. Eligible patients were with Child–Pugh score A or B, an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 along with bidimensionally measurable (as per World Health Organization guidelines) and histologically proven unresectable tumors. Child–Pugh B patients were included based on similar pharmacokinetics reported for sorafenib in both A and B stage patients by Abou-Alfa et al. in the Journal of Clinical Oncology in 2005. Additional inclusion criteria included adequate liver function (bilirubin <1.5 $\times$ ULN; alanine aminotransferase and AST <2.5 $\times$ ULN; alkaline phosphatase <4 $\times$ ULN; prothrombin time <1.5 $\times$ ULN), adequate renal function (serum creatinine <1.5 $\times$ ULN), adequate bone marrow (hemoglobin >10 g/dL; absolute neutrophil count >1500/mm^3; platelet count >100 $\times$ 1000 cells/μL), and life expectancy of at least 12 weeks. Patients treated with anticoagulants (coumadin or heparin) earlier were allowed to participate, provided there was no abnormality in these parameters at screening.

Patients were excluded if they had uncontrolled hypertension, clinically active serious infection (>Grade 2 as per National Cancer Institute-Common Terminology Criteria v3.0), extra-hepatic metastasis, or history of bleeding diathesis. Pregnant or breastfeeding females, patients with seizure disorder requiring medication (such as steroids or anti-epileptics), patients undergoing renal dialysis, and patients requiring trans-arterial catheter embolization were excluded from the study.

The Independent Ethics Committee or Institutional Review Board at each study site approved the protocol and the study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and in accordance with ICH Good Clinical Practice guidelines, applicable regulatory requirements, and in compliance with the respective protocol. All patients provided written informed consent.

Study design
This was a 16-week, non-randomized, open-label, single arm, multi-centric, Phase II study conducted in Pakistan from 1st September 2008 to 30th December 2009.

Safety and toxicity evaluations were completed at baseline and on days 1 and 8 of each cycle before the administration of gemcitabine or at the time of early withdrawal. Interim analysis for efficacy was performed at 8 weeks (after two cycles) and on completion of the 4th cycle.

Study medication
Patients were treated with sorafenib 400 mg oral twice daily for 16 weeks along with gemcitabine 1000 mg/m^2, intravenous, administered on days 1 and 8 of a four-week cycle for 16 weeks. At 16 weeks an evaluation was required and patents having stable disease, complete or partial remission were continued on treatment combination until any reason for study withdrawal. Gemcitabine dose reduction of 20% was allowed in patients with underlying cirrhosis liver having increased bilirubin, but not exceeding 27 μmol/L. As the potential dose limiting toxicity for gemcitabine is myelosuppression, its dose reduction by 20% was further allowed in case of clinically significant toxicities (National Cancer Institute-Common Terminology Criteria v3.0) and in case of dose delays due to toxicities for more than seven days.

Study withdrawal
All patients were required to complete four cycles unless there was disease progression, consent withdrawal, or clinically significant toxicities for more than seven days despite corrective measures. Neutrophil growth factors for primary prophylaxis were not allowed except in secondary settings when there were delays due to persisting Grade 2 neutropenia or more, for more than seven days, and on occurrence of a

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single febrile neutropenic episode. Re-escalation of the study drug was permitted with appropriate prophylaxis in patients who had completely resolved adverse event. Dose modification for sorafenib was not allowed in the absence of any known sorafenib-related toxicities with the exception of thrombocytopenia for which the gemcitabine dose would be modified first. The treatment was discontinued in case of sorafenib-related Grade 3 or 4 toxicities.

Efficacy assessment

The primary efficacy assessment was tumor response which was done in accordance with the Response Evaluation Criteria for Solid Tumors (RECIST 1.0). The investigator performed the tumor measurements at baseline and at 8 weeks or two cycles (interim analysis). For a patient to be regarded as achieving stable disease, a ≥16-week of documented non-progression was required.

Safety assessment

All drug-related adverse events were analyzed according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 3.0, and all serious adverse events regardless of causal relationship to study drugs were recorded.

Statistical analysis

The data was analyzed using Statistical Package for the Social Sciences (SPSS) computer program. Chi-square test was applied to examine any significant association between tumor response and other categorical variables (Child class, ECOG status, Alpha fetoprotein levels, uni/multicentricity). A p value of < 0.05 was considered significant.

RESULTS

Demographics

The study enrolled 30 Asian patients aged between 26 and 73 years (both ages inclusive) (median age: 55.3 years); the majority were men (77%). Baseline demographics and disease characteristics are shown in Table 1. Overall, 18 (60%) patients completed all four cycles of treatment; four patients expired, two of whom had gastrointestinal hemorrhage from esophageal varices, and the other two had disease-related decline in liver function and hepatic failure. Of the eight patients who were withdrawn from the study, two had progressive disease at interim evaluation on eight-week treatment, and six (33%) had persisting gemcitabine-related Grade 3/4 thrombocytopenia despite corrective measures (including

Table 1. Demographics and baseline characteristics of intent- to-treat population.

Parameter	Values
Age (years), mean (SD)	55.3 ± 10.02
Range (years)	26–73
Sex, n (%)	
Males	23
Females	7
Child–Pugh stage[a], n (%)	
A	24 (80%)
B	6 (20%)
ECOG performance status[b], n (%)	
0	15 (50%)
1	15 (50%)
Alpha fetoprotein levels, n (%)	
Normal/insignificant (≤500 IU)	8 (27%)
High (>500 IU)	22 (73%)
Character, n (%)	
Unifocal	11 (37%)
Multifocal	19 (63%)
Hepatitis C, n (%)	
Positive	20 (67%)
Hepatitis B, n (%)	
Positive	4 (13%)
No viral evidence	6 (20%)
Cirrhotic liver	30 (100%)
BCLC[c] stage C	30 (100%)

BCLC, barcelona clinic liver cancer classification; ECOG, eastern cooperative oncology group; SD, standard deviation.
[a]The Child–Pugh system evaluates the severity of liver disease, with patients divided into classes from A to C, with class C representing the worst prognosis.[b]The ECOG performance status assesses the daily living abilities of the patient, on a scale ranging from 0 (fully active) to 5 (dead).
[c]The BCLC system ranks hepatocellular carcinoma in five stages, ranging from 0 (very early stage) to D (terminal stage).

dose adjustments and dose delay for more than 1 week).

Primary efficacy

Among 18 patients, eight (44%) patients achieved stable disease while two (11%) patients showed partial response. No complete response was observed (Table 2).

There was no significant association found between tumor response and any of the variables: Child–Pugh score ($p = 0.260$), ECOG performance ($p = 0.264$), AFP levels ($p = 0.64$) and uni/multicentricity ($p = 0.712$).

Safety

The most common ($\geq 10\%$ patients) treatment-emergent adverse events (TEAEs) were hematological events; gemcitabine-related thrombocytopenia was most common (40%) TEAE and required frequent dose modifications and delays. Six patients were withdrawn from the study due to persisting thrombocytopenia of $\geq$Grade 2 despite corrective treatment and dose delay for more than seven days. Dose modifications (reduction by 20% of calculated gemcitabine dose) due to thrombocytopenia alone were common: two on the average in all patients who completed all eight doses (four cycles). All patients experienced delay in dose at least once up to seven days due to persisting thrombocytopenia. Blood transfusion was required as corrective measure for anemia in two patients, and platelet transfusion was required in four patients for persisting Grade 3–4 thrombocytopenia. Hand-foot skin reaction (33%) and anorexia (33%) were the most common adverse events due to sorafenib (Table 3).

DISCUSSION

In the present study, of the 60% patients who completed all four cycles of treatment, 11% had partial response while 44% had stable disease, and the remaining 44% had progressive disease. In contrast, the SHARP trial conducted earlier with sorafe-

Table 2. Summary of efficacy measures.

	Sorafenib + Gemcitabine treatment
Total assessed, n (%)	18 (60)
Level of response, n (%)	
Complete response	0 (0)
Partial response	2 (11)
Stable disease	8 (44)
Progressive disease	8 (44)

Note: The level of response was measured according to RECIST (Response Evaluation Criteria in Solid Tumors) by independent radiologic review.

Table 3. Incidence of drug-related adverse events (safety population, $n = 30$).

Adverse event	Grade ½ n (%)	Grade ¾ n (%)	Total n (%)
Neutropenia	4 (13)	0 (0)	4 (13)
Anemia	6 (20)	2 (7)	8 (27)
Thrombocytopenia	4 (13)	6 (20)	10 (33)
Deteriorating liver function	4 (13)	2 (7)	6 (20)
Diarrhea	2 (7)	4 (13)	6 (20)
Hand–foot skin reaction	10 (33)	0	10 (33)
Anorexia	10 (33)	0	10 (33)
Fatigue	4 (13)	0	4 (13)
Vomiting	3 (10)	0	3 (10)
Epistaxis	2 (7)	0	2 (7)
Alopecia	3 (10)	0	3 (10)
Hypertension	2 (7)	0	2 (7)

Listed are adverse events, as defined by the National Cancer Institute Common Terminology Criteria (version 3.0).

nib alone showed 71% of patients with stable disease at the end of the treatment period [4] This may be because of the difference in the baseline characteristics between the two populations. The Asian population enrolled in the present study was much younger (mean age: 55 years) compared with the population in the SHARP study (mean age: 64 years) [12] The population in our study was similar to the Asia–Pacific population studied by Cheng et al. (mean age: 51 years). The tumor load, ECOG status, and Child–Pugh status in our study population were also similar to the study by Cheng et al. [13]. compared with the baseline population characteristics of the SHARP trial [12] The study by Cheng et al., which had patients with advanced HCC and treated with sorafenib alone – in line with the SHARP study – resulted in 54% of patients with stable disease [13], which is similar to our findings. Thus, in terms of tumor response, no improvement was observed with the combination of sorafenib and gemcitabine in the present study compared to the sorafenib treatment as seen in the Asia–Pacific (Cheng et al.) and the SHARP studies.

Serum AFP response has been related to the prediction of radiological response and survival as an independent prognostic factor [14] There was no relation between tumor response and baseline AFP level in this study.

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Most of the TEAEs related to sorafenib observed in this study (hand-foot skin reaction, diarrhea and anorexia) are similar to the adverse effects reported in earlier studies [12,13] The gemcitabine-related hematological toxicities observed in the present study are also seen in earlier reported studies. Earlier studies with gemcitabine in HCC, used as single agent [15] or in combination with cisplatin or doxorubicin, have shown similar toxicity [16] However, there were frequent dose adjustments, and delays during the treatment due to gemcitabine-related hematological toxicities for almost all the patients at least once in the 16-week treatment. In addition to this, corrective treatments like blood transfusion (two patients) and platelet transfusion (four patients) were needed during the treatment.

Eric Assenat et al. presented the GONEXT study from France in the 2013 meeting of the American Society of Clinical Oncology. Sorafenib plus gemcitabine and oxliplatin (twice weekly) was found to be feasible although subset analysis as to who benefitted most is awaited. Hematological toxicity was common but was not the limiting factor in this study. In our study, all patients had cirrhosis liver: 80% of those with Child–Pugh score A.

The limitation was that this was a non-randomized study, and only 60% of patients were evaluable.

Gemcitabine alone administered in the same dose but on day 1 and day 8 of a four-weekly cycle plus sorafenib was found to be hematologically more toxic.

CONCLUSION

There is no difference between the efficacy of sorafenib and gemcitabine combination therapy and sorafenib alone treatment. However, higher gemcitabine-related toxicity followed by frequent dose adjustments, delays, and corrective treatment including blood component therapy makes this combination therapy unsuitable for the treatment of advanced HCC.

REFERENCES

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005;55(2):74–108.

2. WHO World Health Organization, Cancer factsheet <http://www.who.int/mediacentre/factsheets/fs297/en/index.html> (Feb 2012).

3. Simonetti RG, Liberati A, Angiolini C, Pagliaro L. Treatment of hepatocellular carcinoma: a systematic review of randomized controlled trials. *Ann Oncol* 1997;8(2):117–36.

4. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359(4):378–90.

5. Chenivesse X, Franco D, Bréchot C. MDR1 (multidrug resistance) gene expression in human primary liver cancer and cirrhosis. J Hepatol 1993;18(2):168–72.

6. Zhu AX. Systemic therapy of advanced hepatocellular carcinoma: how hopeful should we be? Oncologist 2006;11(7):790–800.

7. Leung TW, Patt YZ, Lau WY, Ho SK, Yu SC, Chan AT, et al. Complete pathological remission is possible with systemic combination chemotherapy for inoperable hepatocellular carcinoma. Clin Cancer Res 1999;5(7):1676–81.

8. Nerenstone SR, Ihde DC, Friedman MA. Clinical trials in primary hepatocellular carcinoma: current status and future directions. Cancer Treat Rev 1988;15(1):1–31.

9. Abou-Alfa GK., Johnson P, Knox J, et al. Final results from a phase II (Ph II) randomized, double-blind study of sorafenib plus doxorubicin (S + D) versus placebo plus doxorubicin (P + D) in patients (pts) with advanced hepatocellular carcinoma(AHCC). Presented at the 2008 Gastrointestinal Cancers Symposium, Orlando, FL (January 25–27, 2008; abstract 128).

10. Field KM, Michael M. Part II: Liver function in oncology: towards safer chemotherapy use. *Lancet Oncol* 2008;9(12):1181–90.

11. Venook AP, Egorin MJ, Rosner GL, Hollis D, Mani S, Hawkins M, et al. Phase I and pharmacokinetic trial of gemcitabine in patients with hepatic or renal dysfunction: cancer and leukemia group B 9565. *J Clin Oncol* 2000;18(14):2780–7.

12. NCCN Guidelines (2010) practice guidelines in oncology hepatobiliary cancers. See <URL:http://www.nccn.org/professionals/physicians_gls/PDF/hepatobiliary> [Please include date of access].

13. Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients in the Asia–Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009;10(1):25–34.

14. Chan SL, Mo FK, Johnson PJ, Hui EP, Ma BB, Ho WM, et al. New utility of an old marker: serial alpha-fetoprotein measurement in predicting radiologic response and survival of patients with hepatocellular carcinoma undergoing systemic chemotherapy. *J Clin Oncol* 2009;27(3):446–52.

15. Guan Z, Wang Y, Maoleekoonpairoj S, Chen Z, Kim WS, Ratanatharathorn V, et al. Prospective randomised phase II study of gemcitabine at standard or fixed dose rate schedule in unresectable hepatocellular carcinoma. *Br J Cancer* 2003;89(10):1865–9.

16. Ulrich-Pur H, Kornek GV, Fiebiger W, Schüll B, Raderer M, Scheithauer W. Treatment of advanced hepatocellular carcinoma with biweekly high-dose gemcitabine. *Oncology* 2001;60(4):313–5.