

Gemcitabine Plus Carboplatin in Patients with Advanced Hepatocellular Carcinoma (HCC): Results of a Phase II Study

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Abstract

Objectives: Assessment of Gemcitabine/Carboplatin combination in patients with advanced-stage HepatoCellular Carcinoma (HCC) in a Phase II trial for safety and efficacy.

Methods: Forty patients with previously untreated advanced-stage HCC were prospectively enrolled, and subjected to Gemcitabine/Carboplatin regimen which consisted of gemcitabine 1000 mg/m² on Day 1 and 8, and Carboplatin AUC6 on Day 1. The treatment was repeated every 3 weeks until disease progression or limiting toxicity.

Results: Forty patients were assessable for efficacy and toxicity. In all, 276 treatment cycles were administered. No toxic deaths occurred. Hematological grade 3-4 toxicity consisted of thrombocytopenia (27% of patients) and neutropenia (24%), including 2 febrile neutropenia and anemia (9%). Grade 3 Carboplatin-induced neurotoxicity was observed in 3 (9%) patients. ORR was 23% (95% CI, 0.10-0.29) with 9 partial responses and disease stabilization was observed in 46% (95% CI, 0.22-0.42) of patients, giving a disease control rate of 69%. Median progression-free and overall survival times were, respectively, 5 months (95% CI: 3-8 months) and 8 months (95% CI: 6-18 months).

Conclusion: The Gemcitabine/Carboplatin regimen seems to be effective and well tolerated and active in advanced HCC.

Keywords: Hepatocellular carcinoma; Chemotherapy; Gemcitabine; Carboplatin

Introduction

Hepatocellular carcinoma is the fifth most common cancer in men and eighth in women worldwide, resulting in at least 500,000 deaths per year. The burden of HepatoCellular Carcinoma (HCC) has been increasing in Egypt with a doubling in the incidence rate in the past 10 years. This has been attributed to several biological (e.g. hepatitis B and C virus infection) and environmental factors (e.g. aflatoxin). Other factors such as cigarette smoking, occupational exposure to chemicals such as pesticides, and endemic infections in the community, such as schistosomiasis, may have additional roles in the etiology or progression of the disease [1].

Over a decade, there was nearly a twofold increase of the proportion of HCC among CLD patients in Egypt with a significant decline of HBV and slight increase of HCV as risk factors. Alpha-fetoprotein played a limited role in diagnosis of HCC, compared to imaging techniques [2].

Diagnosis is usually made by history, physical examination, imaging (US, CT, MRI), and elevated serum AFP >400 ng/ml with 75% of hepatocellular carcinoma is multifocal at time of diagnosis. In most patients with HCC, we are dealing with two independent diseases, each determines the patient outcome. Treatment plan should consider the disease extent and hepatic functional reserve, and patient's performance status [3].

Liver resection is the first curative option with 3-yr survival of 54% in the non-cirrhotic liver after R0 resection. Transplantation comes next in patients fulfilling Milan criteria (single tumor ≤ 5 cm; 2 or 3 tumors, none >3 cm; with no vascular invasion), or the expanded UCSF criteria single tumor ≤ 6.5cm; 2 or 3 tumors, none >4.5 cm, total tumor diameter ≤ 8 cm; with no vascular invasion, with 3-yr survival of up to 88%. Ablative modalities such as TACE, RFA, and others are accepted alternatives either as palliation, or bridging before liver transplant. For HCC patients with extra hepatic extent or extensive disease not fit for surgery, systemic therapy is the only choice. Until recently there has been no standard medical therapy for advanced HCC. Sorafenib was

the first to show significant impact on survival and disease progression, and is widely accepted as a standard first-line systemic therapy [4].

Due to financial cost of sorafenib, and need to improve response and survival, the need to search for other non-hepatotoxic regimens of systemic therapy for HCC is investigated. Results obtained in phase II studies with different regimens using new cytotoxic drugs have not been very impressive. Thus, systemic chemotherapy cannot be considered as the standard of care for HCC patients. This situation could be related to a combination of poor efficacy and increased toxicity. Obviously the underlying liver cirrhosis increases the risk of severe adverse events as many chemotherapeutic drugs are metabolized or eliminated via the liver. Moreover severe complications are certainly more likely if a cytotoxicity-related side effect occurs on a cirrhotic liver. Certain causes of the underlying cirrhosis, e.g. hepatitis B virus infection, may be reactivated after chemotherapy-induced immunodepression, producing an additive toxic effect [5].

Systemic chemotherapy likely lacks efficacy because of the frequently observed multidrug tumor resistance (P-glycoprotein overexpression, p53 gene mutations) [6,7].

Patients and Methods

Patients were eligible if they had:

- 1- Advanced stage HCC not amenable to curative treatment;

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- 2- HCC had to be pathologically documented, regardless of EGFR expression status, or to meet the following criteria: α -FetoProtein (AFP) level over 400 ng/ml, together with a hypervascular liver tumor and cirrhosis;
- 3- Measurable disease according to the RECIST system, with at least one lesion measuring at least 2 cm on Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) performed <20 days before accrual;
- 4- Documented progressive disease on 2 consecutive CT scans and/or MRI performed at a 2-month interval, or clinical progression according to RECIST;
- 5- Compensated Child-Pugh stage A or B cirrhosis, score <9;
- 6- No previous systemic chemotherapy or radiotherapy for HCC;
- 7- Age at least 18 years;
- 8- World Health Organization (WHO) performance status (PS) of 0 to 2;
- 9- The patients had to have adequate blood cell counts (neutrophils $>1.5 \times 10^9$ /L and platelets $>100 \times 10^9$ /L) and renal function (s.creatinine <1.4 mg/dl) within the 2 weeks before study entry.

Exclusion criteria included:

- 1- Known central nervous system metastases;
- 2- Human immunodeficiency virus (HIV) infection;
- 3- An interval shorter than 8 weeks since transarterial chemoembolization (if performed);
- 4- History of sensory peripheral neuropathy;
- 5- Alkaline phosphatase >5 times the upper normal limit (UNL), INR $<60\%$, serum albumin <3.0 g/L, and bilirubin ≥ 1.5 UNL.

Pretreatment investigations

This included a complete medical history and physical examination, AFP assay, electrocardiogram, hematologic and biochemical profiles, abdominal CT or MRI, and thoracic CT in case of suspected lung metastases. Body weight, PS, and clinical manifestations were recorded before the outset of therapy. The study was conducted in Ain Shams university hospitals through the period from June 2009 to March 2011.

Treatment protocol and dose modification

Chemotherapy consisted of gemcitabine at a dose of 1000 mg/m² as a fixed-dose-rate intravenous infusion of 10 mg/m²/minute on Day 1 and 8, followed by Carboplatin AUC 6 as a 2-hour infusion on Day 1. Treatment was repeated every 3 weeks. If grade 3/4 (non-neurosensory) toxicity occurred the subsequent cycle was postponed until recovery to grade <2; the gemcitabine dose was then reduced to 800 mg/m² and the Carboplatin dose to AUC 5. If grade 3 cumulative sensory peripheral neuropathy occurred, Carboplatin was discontinued and gemcitabine was administered alone as initially scheduled. Preventive calcium and magnesium infusions were used. Antiemetic prophylaxis was done routinely before infusion. Treatment was continued until disease progression, unacceptable toxicity, or patient refusal, or until chemotherapy had to be delayed for more than 3 weeks because of toxicity.

Response assessment

The primary endpoint for efficacy was the objective response rate

(ORR), defined as the sum of complete and partial responses based on the RECIST system. Tumor responses were assessed by means of helical CT every 2 months (after 4 cycles), or earlier in patients with suspected disease progression. Complete responses (CR) were defined as complete disappearance of all assessable disease. Partial responses (PR) were defined by a decrease of $>30\%$ in the sum of the largest dimensions of target lesions. Stable disease (SD) was defined as a decrease of $<30\%$ or an increase of $<20\%$ in measurable lesions. Progressive disease (PD) was defined as an increase of at least 20% in measurable lesions or the appearance of new malignant lesions. A second CT scan was performed 4 and 8 weeks after the first to confirm response. Secondary endpoints for efficacy included progression-free (PF) and overall survival (OS) times. AFP levels were measured every 2 months. Body weight, PS, and symptoms were recorded before each cycle.

Toxicity assessment

Toxicity was graded according to the National Cancer Institute's Common Toxicity Criteria (NCI-CTC; version 4.0, December 2010), based on clinical and biologic findings before each treatment cycle, then at the end of treatment and one month later. The patients were interviewed before each session, focusing on pain, nausea, vomiting, mucositis, diarrhea, asthenia, weight loss, and dermatologic and neurologic disorders. All patients who received at least one dose of study treatment were evaluated for toxicity.

Statistical analysis

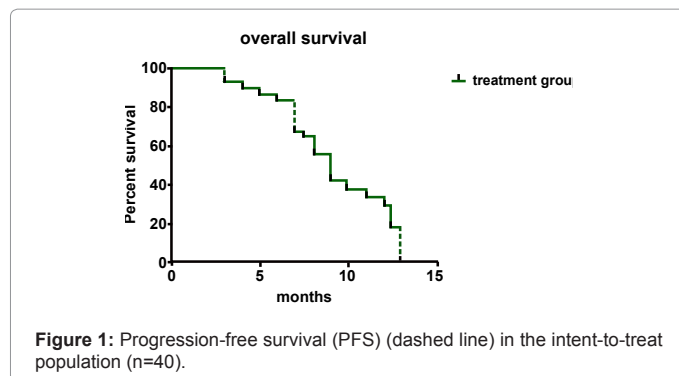
The primary endpoint was the ORR, as assessed by the ERRC, and its exact 95% confidence interval (95% CI). The 1-sample multiple testing procedure for phase 2 clinical trials was used to calculate the sample size [8]. On the basis of an anticipated ORR of 25% for Gemcitabine and Carboplatin, and the best rates obtained in recent trials (approximately 10%), a total of 39 patients were required with $\alpha=5\%$ and $\beta=20\%$. The secondary efficacy endpoints were the disease control rate (DCR: CR + PR + SD), changes in the AFP plasma level, and PFS and OS. The toxicity analysis was based on the worst grade in each patient during any chemotherapy cycle. All analyses were performed on an intention-to-treat (ITT) basis. The results were expressed as the mean \pm standard

| Characteristic | No. of patients (%) |
|----------------------------------------------|---------------------|
| No. of patients | 40 |
| Median age (range), y | 55 (44–69) |
| Male: female ratio | 37:3 |
| WHO performance status | |
| 0 | 1 (2.5%) |
| 1 | 30 (75%) |
| 2 | 9 (22.5%) |
| Child-Pugh stage | |
| A | 28 (70) |
| B | 12 (30) |
| Median AFP (range), ng/ml | 450 (3–99500) |
| AFP >400 ng/ml | 31 (77.5%) |
| Histologic diagnosis of HCC | 20 (50%) |
| Diagnosis of HCC based on Barcelona criteria | 20 (50%) |
| Previous treatment | |
| None | 15(37.5%) |
| Radiofrequency ablation | 10 (25%) |
| Curative surgery | 3 (7.5%) |
| TACE | 12 (30%) |
| Systemic chemotherapy | 0 |

Table 1: Patient Characteristics.

| Response rate | No. (%) |
|---------------------|----------|
| Partial response: | 9 (23%) |
| Stable disease: | 18 (46%) |
| Progressive disease | 13 (31%) |

Table 2: Response rate.



deviation, or range, as appropriate. Follow-up started at the first dose of study treatment. The censoring event for responses was the onset of disease progression. The censoring event for survival was the date of death or lost follow up. Survival curves were plotted with Graph Pad prism version 4.03 using the Kaplan-Meier method.

Patient characteristics

Between June 2009 and Mars 2011, 40 patients with unresectable or metastatic HCC were enrolled and treated at Ain Shams university hospitals, clinical oncology department. Patient characteristics are shown in table 1.

Efficacy

ORR was 23% (95% CI, 0.10-0.29), pattern of response is shown in table 2. The responses lasted from 3 to 12 months. Stable disease was observed in 46% (95% CI, 0.22-0.42) of patients, in assessable patients who had at least 1 post-baseline tumor assessment (n=40) the disease control rate was 69% (PR, 23% and SD, 46%). In the ITT population, the median PFS was 5 months (95% CI, 3-8 months) and the median OS was 8 months (95% CI, 6-18 months) (Figure 1). The 1-year survival rate was 35.4%. The AFP level fell by >50% during therapy in 12 (38%) of the 31 patients with elevated AFP levels at baseline (>400 ng/ml).

Treatment exposure

Overall, 276 cycles of treatment were administered to the 40 patients, with a mean of 5 cycles per patient (range, 1-8 cycles). The chemotherapy dosage was reduced in 10 patients (25%), because of hematologic toxicity (n=10) or Carboplatin-induced decreased GFR (n=5), after a mean of 12 weeks on full treatment. Treatment had been discontinued in 39 patients; because of surgery in one patient (n=1), disease progression (n=30), adverse events (n=4), patient refusal to continue (n=4) (Figure 2).

Subsequent treatments

Thirteen patients received subsequent treatments; ten patients received UFT, two patients had chemoembolization, and one patient received sorafenib.

Toxicity

Toxicity pattern is shown in table 3. Myelosuppression,

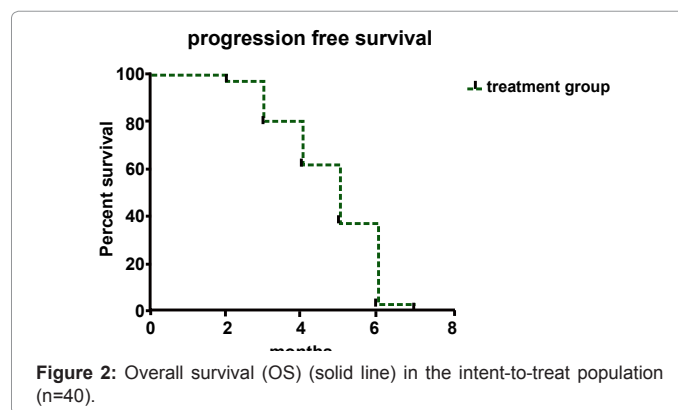
nephrotoxicity, and neurotoxicity were the most frequent adverse effects. No treatment-related deaths occurred.

Discussion

Gemcitabine and Carboplatin are active agents against HCC. A combination of both is tested in this phase II study for response, and toxicity as primary outcome, and for impact on survival and disease progression as secondary outcome. Overall response rate was 23% (95% CI: 8-34). Stable disease was obtained in 46%, with disease control rate of 69%. Median progression free and overall survival were respectively 5 months (95% CI: 3-8), and 8 month (95% CI: 6-18).

Regarding toxicity assessment, no toxicity related death occurred, however grade 3 and 4 were encountered as follows; neutropenia (40%), thrombocytopenia (17.5%), anemia (25%), alopecia (0%), diarrhea (0%), vomiting (2.5%), neurotoxicity (20%), nephrotoxicity (15%), hepatotoxicity (15%).

Tumour response rates of 15-25% were previously obtained with doxorubicin and cisplatin combinations with either capecitabine or UFT. However, this did not seem to affect significantly PFS and OS found to be less than 4 months and 8 months, respectively [9,10]. Response rate was similar to that in this study. Randomized phase III study comparing single agent doxorubicin versus PIAF regimen (cisplatin/ interferon a-2b/doxorubicin/fluorouracil) did not show any significant difference in OS between the two arms despite borderline statistical significance in favour of PIAF (6.8 and 8.7 months for doxorubicin and PIAF arms, respectively) [11]. Xelox regimen was assessed in phase II trial in 50 patients with HCC, best tumour response was partial response (PR) in 3 patients (7%), stable disease (SD) in 33 patients (81%), and disease progression in 5 patients (12%). Partial response duration in the three



| Toxicity (NCI-CTCAE), No. (%) | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Any |
|-------------------------------|------------|------------|------------|----------|------------|
| Neutropenia | 5 (12.5%) | 10 (25%) | 15 (37.5%) | 1 (2.5%) | 31 (77.5%) |
| Thrombocytopenia | 4 (10%) | 15 (37.5%) | 6 (15%) | 1 (2.5%) | 26 (65%) |
| Anemia | 13 (32.5%) | 15 (37.5%) | 10 (25%) | 0 | 38 (95%) |
| Alopecia | 6 (15%) | 1 (2.5%) | 0 | 0 | 7 (17.5%) |
| Diarrhea | 10 (25%) | 10 (25%) | 0 | 0 | 20 (50%) |
| Nausea/vomiting | 15 (37.5%) | 5 (12.5%) | 1(2.5%) | 0 | 21 (52.5%) |
| Neurotoxicity | 14 (35%) | 2 (5%) | 8 (20%) | 0 | 24 (60%) |
| Nephrotoxicity | 10 (25%) | 4 (10%) | 6 (15%) | 0 | 20 (50%) |
| Hepatotoxicity | 10(25%) | 5(12.5%) | 6(15%) | 0 | 21(52.5%) |

NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events
Table 3: Number of Patients With Treatment-related Toxicity in the Safety Population (n=40).

patients was 1.1, 5.0, and 7.3 months respectively, whereas duration of SD ranged from 2.2 to 20.5 months (median: 5.4 months). In the intention-to-treat group (N=50), the tumour control rate (PR and SD) was 72% (95% confidence interval (CI) 57-83%). The tumour control rate was 77% (95% CI: 61-88%) in the 43 patients with Child-Pugh A score cirrhosis, including the three patients with PR Progression-free survival rates at 6 and 12 months were 38% (95% CI: 26-52%) and 14% (95% CI: 7-26%), respectively. Main grade 3-4 drug-related toxicities included diarrhea (16%), elevation of aminotransferases and/or bilirubin (16%), thrombocytopenia (12%), and neurotoxicity (6%) [12]. Tumour control rate and toxicity were comparable to that in our study. In another phase II trial assessing 41 patients with HCC subjected to Gemcitabine and pegylated liposomal doxorubicin, the median TTP and OS were 5.8 and 22.5 months, respectively. Hematologic toxicity was the most common side effect, including neutropenia (17%) and anemia (7%) [13].

HCC patients given the ECF/ECC regimen obtained objective response rate 22%, with a disease control rate (objective response plus stable disease) of 52%. The median time to progression was 6 months. In addition, despite the fact that most tumors were huge, the reduction in tumor size was sufficient to allow surgical resection in 2 patients having only one huge tumor. Toxicity was mild and most side effects were manageable; one patient died suddenly between two courses. These two regimens (ECF and ECC) are very similar in terms of response and toxicity since capecitabine is the oral form of 5FU [5]. Response rate is close to that obtained from gemcitabine/Carboplatin in this study.

In conclusion, Gemcitabine and Carboplatin is a safe and effective combination in management of advanced hepatocellular carcinoma not candidate for surgical resection or other interventional measures with fair control rate and accepted toxicity profile.

References

1. Anwar WA, Khaled HM, Amra HA, El-Nezami H, Loffredo CA (2008) Changing pattern of hepatocellular carcinoma (HCC) and its risk factors in Egypt: Possibilities for prevention. *Mutat Res* 659: 176-184.

2. el-Zayadi AR, Badran HM, Barakat EM, Attia Mel-D, Shawky S, et al. (2005) Hepatocellular carcinoma in Egypt: a single center study over a decade. *World J Gastroenterol* 11: 5193-5198.
3. Jelic S, Sotiropoulos GC; ESMO Guidelines Working Group (2010) Hepatocellular carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 21: v59-v64.
4. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, et al. (2007) Randomized phase III trial of sorafenib vs placebo in patients with advanced hepatocellular carcinoma. *J Proc Am Soc Clin Oncol* 25: 1384-1390.
5. Edeline J, Raoul JL, Vauleon E, Guillygomac'h A, Boudjema K, et al. (2009) Systemic chemotherapy for hepatocellular carcinoma in non-cirrhotic liver: A retrospective study. *World J Gastroenterol* 15: 713-716.
6. Chan KT, Lung ML (2004) Mutant p53 expression enhances drug resistance in a hepatocellular carcinoma cell line. *Cancer Chemother Pharmacol* 53: 519-526.
7. Endo T, Yoshikawa M, Ebara M, Kato K, Sunaga M, et al. (2004) Immunohistochemical metallothionein expression in hepatocellular carcinoma: relation to tumor progression and chemoresistance to platinum agents. *J Gastroenterol* 39: 1196-1201.
8. Fleming TR (1982) One-sample multiple testing procedure for phase II clinical trials. *Biometrics* 38: 143-151.
9. Kim SJ, Seo HY, Choi JG, Sul HR, Sung HJ, et al. (2006) Phase II study with a combination of epirubicin, cisplatin, UFT, and leucovorin in advanced hepatocellular carcinoma. *Cancer Chemother Pharmacol* 57: 436-442.
10. Yeo W, Mok TS, Zee B, Leung TW, Lai PB, et al. (2005) A randomized phase III study of doxorubicin versus cisplatin/interferon alpha-2b/doxorubicin/fluorouracil (PIAF) combination chemotherapy for unresectable hepatocellular carcinoma. *J Natl Cancer Inst* 97: 1532-1538.
11. Park SH, Lee Y, Han SH, Kwon SY, Kwon OS, et al. (2006) Systemic chemotherapy with doxorubicin, cisplatin and capecitabine for metastatic hepatocellular carcinoma. *BMC Cancer* 6: 3.
12. Boige V, Raoul JL, Pignon JP, Bouché O, Blanc JF, et al. (2007) Multicentre phase II trial of capecitabine plus oxaliplatin (XELOX) in patients with advanced hepatocellular carcinoma: FFCD 03-03 trial. *Br J Cancer* 97: 862-867.
13. Lombardi G, Zustovich F, Farinati F, Cillo U, Vitale A, et al. (2011) Pegylated liposomal doxorubicin and gemcitabine in patients with advanced hepatocellular carcinoma: results of a phase 2 study. *Cancer* 117: 125-133.