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A new chemoimmunotherapy regimen (OXAFI) for advanced hepatocellular carcinoma

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BACKGROUND: Chemotherapeutic treatment options for advanced unresectable and/or metastatic hepatocellular carcinoma (HCC) are limited. Currently available treatments are associated with low response rates and little evidence of improved survival, so we evaluated a new chemoimmunotherapy regimen.

METHODS: Seven patients with unresectable and/or metastatic HCC were treated with intravenous oxaliplatin (30mg/m^2) and doxorubicin (20mg/m^2) given on days 1, 8 and 15 in a 28-day cycle, a daily continuous infusion of fluorouracil (200mg/m^2) and subcutaneous interferon alfa-2b 5 MU administered thrice weekly (OXAFI). Treatment was administered to a maximum of six cycles. Data on the response to treatment, toxicity, surgical procedures and survival outcome was reviewed.

RESULTS: The best response was three partial responses, three stable disease responses and one progressive disease response. Two patients underwent interval hepatic resection, and histological analysis in one patient showed a complete pathological response. Another patient underwent a liver transplant after four cycles of treatment. These three patients were alive with no evidence of disease at 23, 21 and 18 months follow-up, respectively. At a median follow-up of 14 months (range 2-23 months), one patient died 2 months after diagnosis due to progressive disease, while all six other patients were alive. Neutropenia was the predominant toxicity, but there were no episodes of febrile neutropenia, hospital admissions or deaths. There were no cases of hepatitis B virus re-activation.

CONCLUSIONS: OXAFI shows activity in HCC and has manageable toxicity. Complete pathological remission is possible with this regimen.

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide. In Singapore, HCC has an age-standardized incidence rate of about 19 per 100 000 per year,[1] and is commonly associated with chronic hepatitis B virus (HBV) infection in the local population. Surgical resection is the only treatment that offers possible cure, but the majority of patients present with advanced, unresectable disease, and only 9% to 27% are suitable for resection.[2,3] Reasons for inoperability are commonly the presence of advanced cirrhosis, a large primary lesion, multifocal disease, invasion or thrombosis of major blood vessels, and poor liver function. These patients have a median survival of 4.1 months.[4]

Single agent systemic chemotherapy has been used to treat inoperable HCC with only modest efficacy. Various clinical trials have demonstrated response rates of 0% to 20% with single-agent chemotherapy in HCC. Among these agents, anthracyclines such as doxorubicin have been the most effective, yielding response rates of up to 20% and a median survival of 4 months.[5-8] Other agents that have shown some activity are fluorouracil,[9,10] cisplatin,[11] gemcitabine,[12] and oxaliplatin.[13-15] Interferons have been reported to have a modest degree of activity in HCC.[16] Interferons have immunomodulatory and antiproliferative effects on tumor cells,[17] and in one randomized study, interferons were reported to be superior to doxorubicin in terms of survival, tumor response, and toxicity in patients with HCC.[18] Various combinations of chemotherapy including doxorubicin, cisplatin, and fluorouracil, with or without interferon, have been studied.[19,20] Synergism between continuous

infusion fluorouracil and interferon has been noted and previous studies of continuous infusion fluorouracil and interferon have yielded complete responses to treatment.[21,22] Individual reports on combination chemotherapy[19,20] have yielded higher response rates than those found for single agents historically.[8,10] Several reports of gemcitabine combinations have been promising, in particular. A phase II study of gemcitabine and oxaliplatin yielded a response rate of 18% with a disease stabilization rate of 58%.[14] A phase II study of a regimen consisting of doxorubicin, cisplatin, fluorouracil, and interferon (referred to as PIAF) showed a response rate of 26% in 50 patients with unresectable HCC, and a 28% stable disease rate.[19] Nine of 13 patients with partial responses proceeded to have surgical resection, and 4 patients had a pathological complete response on surgical resection and median survival of 8.9 months. However, a subsequent phase III study of PIAF compared with single agent doxorubicin showed a non-significant higher response rate for PIAF (20.9% vs 10.5%) and no significant difference in overall survival.[23] PIAF had significantly more grade 3 and 4 toxicities (neutropenia and thrombocytopenia in 82% and 57%, respectively). Forty percent of patients had HBV reactivation and of these, 30% died from liver failure.

OXAFI consists of intravenous oxaliplatin (30 mg/m^2), doxorubicin (20mg/m^2), daily continuous infusion of fluorouracil (200mg/m^2) and subcutaneous interferon alfa-2b. This regimen has the potential advantages of reduced myelotoxicity due to relatively low weekly dosing of oxaliplatin and doxorubicin as well as continuous infusion of fluorouracil. OXAFI is only mildly emetogenic due to the weekly dosing regimen, and thus the use of steroids as anti-emetics is reduced and the frequency of HBV flare may be lowered. Steroids directly induce nuclear transcription leading to HBV viral replication.[24] The thrice weekly dosing of interferon may also further lower the risk of HBV flare as it is the method used to treat chronic hepatitis related to HBV.[25] Finally, the OXAFI regimen may have the advantage of the anti-angiogenic properties of metronomic chemotherapy by way of low dose thrice-weekly interferon, weekly administration of oxaliplatin, doxorubicin, and continuous infusion fluorouracil.[26] In this case series, we report our preliminary experience with OXAFI in patients with advanced HCC.

PATIENTS AND METHODS

Between December 2005 and March 2007, a total of 7 patients with unresectable and/or metastatic HCC were treated with OXAFI regimen at our center. The diagnosis of HCC was made either by histological examination of tumor tissue or by non-histological criteria (established hepatic cirrhosis due to hepatitis B/C, or ethanol; alpha-fetoprotein [AFP] level greater than 500ng/mL; focal lesion in the liver on imaging). The lesion was deemed unresectable either due to the presence of distant metastases, and/or by local tumor characteristics (large primary lesion, multifocal disease, vascular invasion) or poor liver function. Chemoimmunotherapy treatment consisted of intravenous oxaliplatin (30mg/m^2) and doxorubicin (20mg/m^2) given on days 1, 8 and 15 in a 28-day cycle, daily continuous infusion of fluorouracil (200mg/m^2) and subcutaneous interferon alfa-2b 5 MU administered thrice weekly (OXAFI) (Table 1). Before weekly doses of oxaliplatin and doxorubicin patients were pre-medicated with 5-HT$_3$ antagonists and dexamethasone in a non-carrier of hepatitis B or C, as anti-emetics. In a hepatitis B or C carrier, dexamethasone administration was omitted. All treatment was administered on an outpatient basis. A maximum of 6 cycles of treatment was administered.

Response evaluation

All patients underwent a baseline ultrasound/CT or MRI scan together with renal and hepatic function tests and a full blood count prior to commencing treatment. Patients were seen once every 28 days and tumor evaluation via CT or MRI imaging was performed every 2 cycles. AFP levels were repeated every cycle. Classification of response on imaging was in accordance with RECIST (Response Evaluation Criteria in Solid Tumors)[27] criteria. Complete response (CR) was defined as complete disappearance of all target lesions on radiological modalities and normalization of the AFP level for at least 4 weeks. Partial response (PR) was defined by at least a 30% decrease in the sum of the longest diameter (LD). Stable disease (SD) was defined by a <30% decrease, or not more than a 20% increase in the LD. The best response to OXAFI treatment was recorded.

Treatment was discontinued if there was disease progression, intercurrent illness preventing further administration of treatment, adverse events, hepatitis flare, any cardiac event, insufficient patient compliance, or by patient choice. If there was a response to chemotherapy, the patient was referred to the surgical team for consideration of interval curative hepatic resection. In the event of surgery, OXAFI was stopped at least 2 weeks prior and restarted 4 weeks after surgery at the earliest. The maximum number of chemotherapy cycles administered was six. If surgery could not be performed, a maximum total of 6 cycles of OXAFI were completed. Overall survival was measured from the time of initiation of OXAFI to time of death or last contact.

Table 1. OXAFI single-cycle schedule.

	Dose	Week 1	Week 2	Week 3	Week 4
IV oxaliplatin	30 mg/m^2	(D1)	(D8)	(D15)	-
IV doxorubicin	20 mg/m^2	(D1)	(D8)	(D15)	-
IV continuous infusion fluorouracil	200 mg/m^2/day	Continuous infusion daily for 28 days			
SC interferon α-2b	5 MU three times a week	M W F or T TH S	M W F or T TH S	M W F or T TH S	M W F or T TH S

D: Day; M/T/W/TH/F/S: Monday/Tuesday/Wednesday/Thursday/Friday/Saturday

Table 2. Clinical characteristics of the seven patients treated with OXAFI.

Patient	1	2	3	4	5	6	7
Age	57	54	54	34	62	50	50
Gender	Female	Male	Male	Male	Male	Male	Male
AJCC stage	III T3N0M0	III T3N0M0	II T2N0M0	IV T3N0M0	III T3N0M0	III T3N0M0	III T3N0M0
Largest diameter of primary lesion (cm)	5.0	16.4	4.6	13.0	9.6	13.3	15.0
Vascular involvement	+	–	–	–	–	+	–
Child-Pugh score	A	A	B	A	A	B	A
Hepatitis B status	+	+	–	+	–	+	+
ECOG	0	0	0	1	1	1	0
No. of cycles received	6	4	3	5	2	1	3
Best response base on CT RECIST criteria	PR	SD	SD	PR	SD	PD	PR
AFP at diagnosis (μg/L)	6244	3.6	13	7617	5.5	96 190	48 556
AFP after 2 cycles (μg/L)	148	4.4	7.1	3682	6.9	-	3953
AFP after 4 cycles (μg/L)	3.5	4.6	-	-	-	-	-
Pursuant treatment	Surgery-pathological CR	Liver transplant	Surgery with clear margins	Targeted therapy	TACE	-	Phase I clinical trial alive
Status	Alive	Alive	Alive	Alive	Alive	Dead	Alive
Survival (months)	23	18	21	13	14	2	8

AJCC: American Joint Commission on Cancer; ECOG: Eastern Cooperative Oncology Group Performance Score; AFP: Alpha-fetoprotein; RECIST: Response Evaluation Criteria in Solid Tumors; PR: partial response; SD: stable disease; PD: progressive disease

RESULTS

The median age of the patients was 54 years (Table 2). Five patients had American Joint Commission on Cancer[28] (AJCC) stage IIIA (T3N0M0) disease, 1 had stage II (T2N0M0) disease and 1 had stage IV (T3N0M1) disease with lung metastases at presentation. Five patients with stage II and III disease were unresectable due to large primary lesions and/or the presence of portal vein thrombosis, and one patient was unresectable due to the presence of Child's B liver cirrhosis. Five patients were positive for hepatitis B infection and of these, one (patient 4) was taking lamivudine

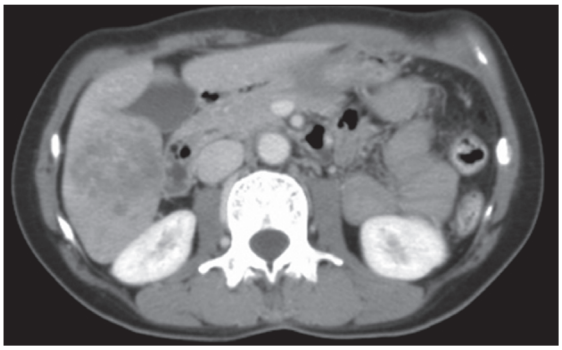

Figure 1A. CT scan showing pre-treatment liver lesion of 5.0×4.5 cm.

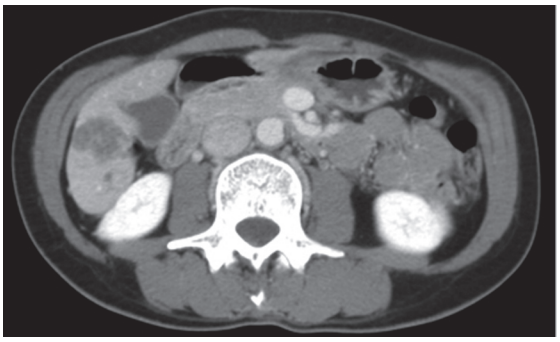

Figure 1B. CT scan showing interval reduction in size to 2.9×3.6 cm after two cycles of OXAFI.

therapy. One patient had a history of alcoholic liver cirrhosis. Five patients had a Child-Pugh score of A and 2 were Child-Pugh score B. All patients had an Eastern Co-operative Oncology Group (ECOG) performance status of 0-2. Four patients had elevated AFP at the time of initial diagnosis. All patients were chemonaive except for patient 4, who had previously been treated with transarterial chemoembolization.

OXAFI chemoimmunotherapy

Patients 1, 2, 3, 5, 6 and 7 were started on OXAFI at the doses and as per the schedule described for a maximum of 6 cycles. In patient 4, oral capecitabine (500mg/m^2) twice daily was substituted for intravenous fluorouracil infusion due to logistical reasons. Patient 3 was also switched from intravenous fluorouracil to oral capecitabine (500mg/m^2) from cycle 2 onwards due to patient request. The total number of cycles of OXAFI administered was 24, and the average number of chemotherapy cycles given was 3.4; only patient 1 completed all six cycles of treatment. Reasons for discontinuation of therapy were stable disease (patient 2, 3, 5, 7) and progressive disease (patient 4, 6).

The best response recorded based on CT RECIST criteria was three partial, three stable disease and one progressive disease responses (Table 2), giving an initial response rate of approximately 43%. Patients 1, 4 and 7 had a partial response on the CT scan and AFP levels after two cycles of chemotherapy (Figure 1) and patients 2, 3 and 5 had stable disease. Patient 1 underwent hepatic resection after two cycles of OXAFI and histological analysis of the resection specimen showed pathological complete response (Figure 2). Patient 4 completed five cycles of chemotherapy, with an initial partial response after two cycles of treatment; however, a later CT scan showed progressive disease and chemotherapy was discontinued. Patient 7 also showed an initial partial response after two cycles, but subsequent stabilization of disease after three cycles of chemotherapy.

Surgical procedures

Three patients underwent hepatic resection. Patient 1 had a partial response after 2 cycles of treatment with resolution of portal vein thrombosis on CT, and proceeded to have interval hepatic resection after three cycles of OXAFI. Histological analysis showed a pathological complete response and the patient proceeded to complete three further cycles of chemotherapy. Patient 2 had stable disease after 4 cycles of treatment and proceeded to have a cadaveric liver transplant. Patient 3 had stable disease after three cycles of OXAFI and underwent interval liver resection with clear margins obtained.

Survival and disease outcome

At a median follow-up of 14 months (range, 2-23 months), 1 patient (patient 6) had died 2 months after diagnosis due to progressive disease, while all six other patients were still alive. Patients 1, 2 and 3 underwent hepatic resection and were alive with no evidence of disease recurrence at follow-ups of 23, 18 and 21 months, respectively. Patients 4, 5, and 7 were receiving other treatments at the time of writing.

Toxicity of chemotherapy

The only grade 3/4 toxicity seen was neutropenia, which was experienced by four patients, but there were no episodes of febrile neutropenia. The most common non-hematological toxicity encountered during treatment was grade 2 mucositis in three patients and grade 1-2 fatigue in four patients (Table 3). There were no treatment-related deaths or hospital admissions. Treatment delays and dosage reductions were required in five patients due to neutropenia. There were no cases of hepatitis B re-activation in our population.

DISCUSSION

Treatment options in advanced HCC are limited. Although surgery offers the only hope of cure for HCC, only a small proportion of patients are resectable at the time of diagnosis. For the remaining patients with inoperable and metastatic disease, the prognosis is dismal. For disease that is confined to the liver, local treatment options such as intra-arterial infusion of combination chemotherapy, chemoembolization, radiofrequency ablation, and percutaneous ethanol injection offer some palliation, but these modalities are unsuitable for patients with extra-hepatic disease, a large primary lesion or multi-focal disease, a blocked portal venous system or established liver cirrhosis. Patients who are unable to undergo local therapies are treated with various combinations of chemotherapies, albeit with limited success and little survival benefit. More recently, targeted agents such as sorafenib, a multikinase inhibitor with anti-angiogenic, pro-apoptotic and Raf kinase inhibitory activity have been shown to have a 44% improvement in overall survival benefit compared with placebo in advanced HCC and with a median survival of 10.7 months (treatment group) versus 7.9 months in the placebo group.[29]

Response to chemotherapy and survival in HCC, in addition to tumor characteristics, is influenced by underlying hepatic function, the presence of hepatitis B infection, and by the toxicity of the chemotherapy regimen. In this study, we studied a new regimen, OXAFI, which consisted of weekly oxaliplatin, doxorubicin, continuous infusion fluorouracil and thrice weekly interferon in patients with advanced HCC. OXAFI had the potential advantages of reduced myelotoxicity, reduced emetogenicity and hence reduced use of steroids, and a reduction in the risk of HBV flare due to the reduced use of steroids as well as concurrent use of interferon, and it may have anti-angiogenic properties.

Two patients in this case series received oral capecitabine instead of infusional fluorouracil due to logistical reasons. Capecitabine has shown equivalence with fluorouracil/leucovorin in adjuvant as well as metastatic colon cancer,[30-32] and is effective as an alternative to infusional fluorouracil in the treatment of advanced esophagogastric cancer.[33] The combination of capecitabine and oxaliplatin was shown to be non-inferior to FOLFOX in metastatic colon cancer.[34] Capecitabine has also demonstrated efficacy in combination with oxaliplatin for treatment of advanced HCC in the FFCD 03-03 trial with a disease control rate of 72%.[35]

OXAFI resulted in three initial partial responses, three stable disease reponsees and one progressive disease response with survival ranging from 2 to 23 months. Eight of nine patients were alive at a median follow-up of 14 months. Two patients with initially unresectable disease underwent successful surgical resection, one of which had a complete pathological response on histological examination.

The toxicity of OXAFI was manageable and was mainly limited to neutropenia in no more than half of the patients, but there were no episodes of febrile neutropenia and no treatment-related deaths. No pa-

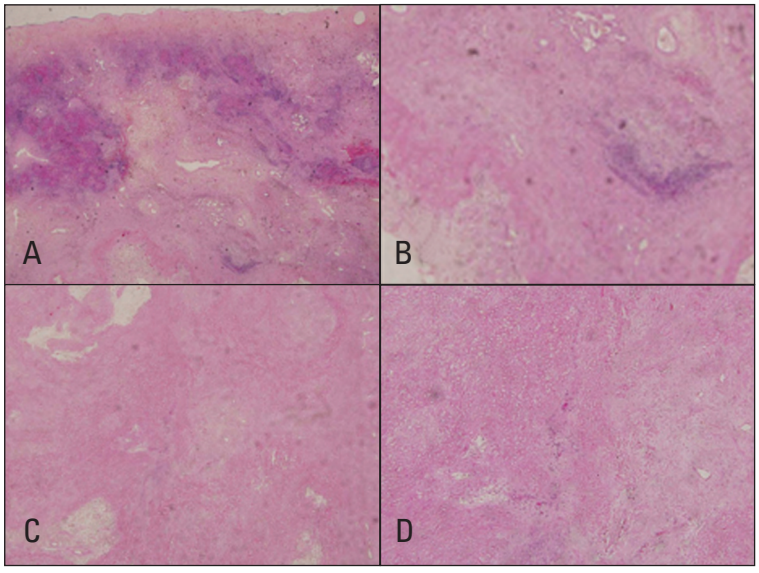

Figure 2. Sections of the resection specimen (from patient 1) demonstrating changes compatible with post-chemotherapy effect on hepatocellular carcinoma. No residual tumor is seen (hematoxylin-eosin, A: ×20, B: ×40; C: ×100; D: ×200).

Table 3. Treatment-related toxicity.

Toxicity (NCI-CTC)	No. of patients			
	Grade 1	Grade 2	Grade 3	Grade 4
Neutropenia	1	1	3	1
Thrombocytopenia	0	1	0	0
Anemia	0	2	0	0
Alopecia	3	4	-	-
Diarrhea	2	0	0	0
Nausea/vomiting	2	0	0	0
Stomatitis	0	3	0	0
Hand-foot syndrome	2	0	0	0
Neurotoxicity	0	1	0	0
Fatigue	3	1	0	0

NCI-CTC: National Cancer Institute - Common Toxicity Criteria

tient stopped treatment due to toxicity, but rather due to lack of response/stabilization of disease. In addition there were no episodes of hepatitis B re-activation during the treatment course, which may be due to minimization of steroid usage, as well as use of interferon in OXAFI.

In our study, only patients with elevated AFP levels at diagnosis showed responses; conversely, none of the patients with stable disease had elevated AFP levels at diagnosis. Interestingly, in the phase II study evaluating the PIAF regimen, all responders to PIAF chemotherapy were noted to have elevated pre-treatment AFP levels.[19] Our study demonstrates that the OXAFI regimen shows activity in advanced HCC with manageable toxicities. Of note, two patients with initially inoperable disease were rendered operable, and complete pathological remission was observed in one patient. Based on these initial results our institution is currently evaluating the role of OXAFI as neoadjuvant chemotherapy to improve the operability rate in unresectable non-metastatic HCC in a phase II single-arm trial.

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