A Phase II Clinical Trial with Cytotropic Heterogeneous Molecular Lipids (CHML®) for Patients with Hepatic Malignancies

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Abstract. *Hepatocellular carcinoma (HCC) and other forms of metastatic liver cancer (MLC) have poor outcomes due to the limited treatment options. Surgery, radiotherapy and chemotherapy have a limited success. Thus, there is an urgent need for novel therapies for patients with advanced HCC and MLC. The response and toxicity profile of a novel biological anticancer agent, cytotropic heterogeneous molecular lipids (CHML), in 135 Asian patients with hepatic malignancies treated at five different hospitals in China from April 1998 to August 2003 is described. This trial included 97 patients with HCC and 38 with MLC. The majority of these patients had received conventional therapies and many had failed to respond or relapsed. CHML was administered by intra-arterial (i.a.) infusion with or without simultaneous intravenous (i.v.) infusion for 25 days with a rest of 2-4 weeks between each cycle. Fifty three percent of patients received two cycles, and 47% received three cycles. The complete response (CR) rates were 23% for HCC and 29% for MLC with an overall CR of 24%. The overall partial response (PR) was 53%. The patients with earlier stages and limited tumor burden had a better response, but a few patients with advanced disease also achieved PR. The patients who achieved CR or PR had a significant increase in long-term survival for up to five years. The treatment with CHML resulted in minimal toxicity and the reported adverse reactions were not higher than grade II. CHML is an effective therapy for hepatic malignancies, showing responses and increases in survival in patients in whom other therapies have failed. CHML is well tolerated and is an excellent candidate for Phase III clinical trials.*

In spite of recent progress in early diagnosis and treatment, cancer is associated with significant disease-related mortality. Effective chemotherapeutic concentrations are often highly toxic, especially those for solid tumors of epithelial origin. Chemotherapeutic agents that are intended to destroy cancer cells are largely non-selective and also affect normal cells (1, 2). Recent advances have led to an improved understanding of the biological functions that control the proliferation of normal and malignant cells. Promising research is currently focusing on drugs that can selectively kill cancer cells with less toxicity to normal cells.

Hepatocellular carcinoma (HCC) is a major type of liver cancer and is the third leading cause of cancer-related death in the world (3). The overall 5-year survival rate of HCC is less than 5%. This lack of effective therapy for the majority of patients is due principally to the advanced stage at presentation and concomitant liver disease (4, 5). Surgery, radioablation and other local and regional therapies have been successful in improving survival only for patients with early stages of the disease (6-8). The liver is also a frequent

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site of metastatic disease from cancer in other organs. Metastatic liver cancer (MLC) frequently accompanies colorectal cancer and malignancies such as gastric, breast, and lung carcinomas. The therapies for these patients are also controversial and have limited success (9-11).

In this study the efficacy of a novel biological agent, CHML (cytotropic heterogeneous molecular lipids), in HCC and MLC was investigated. CHML is a new biological anticancer agent recently developed by Glory F&D Co. Ltd., U.S.A., which has the ability to selectively destroy cancer cells with potentially low side-effects (12, 13). All the components of CHML are isolated from natural products and prepared by lipid-activated methods. CHML consists of 80% unsaturated fatty acids, 15% saturated fatty acids, 4% liposoluble vitamins and 1% squalene, and its phospholipid composition facilitates penetration through the cellular plasma membrane. It is known that induction of tumor cell suicide through programmed cell death (apoptosis) has been widely used to study the mechanisms of tumor growth and to develop anticancer therapies (14-18). Similarly, CHML has been shown to bring about tumor cell apoptosis in several human cancer cell lines *in vitro*, as well as suppressing breast cancer growth in preclinical models based on xenografts in nude mice (12, 13). CHML has relatively high specificity for tumor cells with significantly lower toxicity to normal cells (12, 13).

Previous studies indicated that CHML was safe at clinically effective doses (based upon the *in vitro* and *in vivo* pharmacological studies) when tested in normal human participants in Phase I clinical trials (Xu *et al.*, a phase I trial with CHML, unpublished data). The present Phase II study was designed to evaluate the toxicity and efficacy of CHML in patients with clinically confirmed hepatic malignancies.

Materials and Methods

Patient information. To establish an objective evaluation of response, the trial was conducted simultaneously at five independent hospitals in China. The accrual, therapy and evaluation of response of 135 patients with HCC and MLC were performed between April of 1998 and August of 2003. All the patients were Asian with clinically and pathologically confirmed HCC or MLC, and 119 (88%) were male and 16 (12%) were female. The patient selection criteria were: clinically and pathologically confirmed malignancies of Stage II or higher (according to the UICC TNM classification (19) by histology of surgical specimens or biopsy and other imaging modalities); measurable tumor size by X-ray, computed tomography (CT), magnetic resonance imaging (MRI), or ultrasonography; no chemotherapy or radiation within four weeks of this trial; Karnofsky Performance Status (KPS) scale ≥60; estimated survival time ≥3 months; age of 21-75 years; adequate major organ functions (heart, lung, liver, kidney, stomach, colon and bone marrow) according to World Health Organization criteria. Standard Toxicity Guidelines of grade 0-IV were used (20). All patients signed a common informed consent approved by the Institutional Review Board of each participating hospital.

Therapeutic agent. CHML (US patent number 5, 260, 067; product lot numbers were 9709147, 9803077, 9907077, 20000707, 20010707 and 20020707) was manufactured by Glory F & D Co Ltd, USA according to Good Clinical Practice Standard (issued by the Food and Drug Administration: Guidance for Industry, E6 Good Clinical Practice, Consolidate guidance, 1996) (21, 22). The CHML was provided at 25 mg/ml and 50 mg/ml for CHML-6.0 (100 mg total) and CHML-6.1 (250 mg total), respectively.

Administration and dosage. Intra-arterial (*i.a.*) drip was the main method used to administer CHML. The decision to use a particular route of administration was based on the common routes used by the participating physicians for conventional chemotherapy. These were also selected with the objective of delivering a maximal dose of CHML to the tumor. An arterial catheter was inserted into a tumor artery using Digital Subtraction Angiography (DSA). CHML (a mixture of 100 mg of CHML-6.0, 250 mg of CHML-6.1 and 500 ml of GNS solution containing 5% glucose and 0.9% sodium chloride) was delivered by arterial infusion pump into the tumor artery for 8 hours/day, daily for 25 days during the first cycle, repeated at least once after 2-4 weeks of rest. A combination of *i.a.* drip and intravenous (*i.v.*) drip was also used in some patients who had stage IV tumors depending upon the evaluation of the patient's condition. For the *i.v.* drip, a mixture of 200 mg of CHML-6.0, 500 mg of CHML-6.1, and 400 ml of 5% GNS was administered for 8 hours/day for 25 consecutive days during the first cycle, which was repeated at least once after 2-4 weeks of rest.

Criteria for objective response. The criteria of response were adapted from the WHO recommendations (23). A complete response (CR) was defined as the disappearance of a detectable tumor lasting for more than four weeks after the completion of therapy. A partial response (PR) was defined as a 50% or greater reduction in tumor size measured at the two greatest perpendicular diameters or at least a 30% reduction in hepatomegaly without the appearance of new lesions, lasting for more than four weeks after the completion of therapy. No change (NC) was defined as no change or up to 25% progression in tumor size four weeks after the treatment. Any reduction and/or duration of response insufficient for classification as a PR was counted as NC. Progressive disease (PD) was defined as a greater than 25% increase in tumor measurements or the appearance of new lesions within four weeks from the beginning of treatment.

Toxicity criteria and examination. Assessment guidelines from the literature were applied (21, 24). All patients were examined daily to evaluate general health including weight, diet, sleep pattern, nausea, vomiting, diarrhea, and alopecia, with follow-up for three months, and a re-evaluation if abnormal symptoms occurred. White blood cell (WBC), platelet (PLT) and hemoglobin (Hgb) levels were evaluated the week prior to therapy, one week after completion of the first cycle and one week after completion of treatment. These tests were then continued weekly for three months. To assess liver function, glutamic oxaloacetic transaminase (SGOT), glutamic-pyruvic transaminase (SGPT), alkaline phosphatase (AKP) and total bilirubin in serum (TBIL) levels were evaluated at the same intervals as the blood tests. To assess kidney function, creatinine and proteinuria levels were evaluated at the same intervals as routine blood tests. Any

Table I. *Clinical characteristics of patients.*

Clinical Variable	n (%)
Gender	
Male	119 (88)
Female	16 (12)
Ethnic	
Asian	135 (100)
Age at diagnosis – yr	
25-30	3 (2)
31-40	13 (10)
41-50	32 (24)
51-60	54 (40)
61-70	30 (22)
>70	3 (2)
Pathological types	
HCC	97 (72)
Metastatic cancer to the liver	38 (28)
Performance Status prior to CHML treatment	
90	5 (4)
80	37 (27)
70	43 (32)
60	50 (37)
Prior Treatment	
Chemotherapy	73 (54)
Surgery	30 (22)
Radiotherapy	5 (4)
Any 1	51 (38)
Any 2	27 (20)
Any 3 or more	2 (1)
Response to CHML treatment	
CR	33 (24)
PR	71 (53)
NC	26 (19)
PD	5 (4)

CR, complete response; PR, partial response; NC, minor response or no change; PD, progressive disease. Performance Status, Karnofsky scale.

abnormal pulmonary symptoms were followed by evaluation of pulmonary function (BRMP) when reported, and repeated daily or bi-weekly for 3 months until the readings normalized. The cardiovascular system was checked by physical examination or ECG. Cardiac rhythm, cardiac function, cardiac ischemia and blood pressure were monitored daily if any of the readings were abnormal and then bi-weekly for three months after the readings normalized. Assessments were made of neurosensory, motor, cortical and cerebellar function, as well as mood, headache, constipation, hearing and vision. Evaluations were made daily if abnormal or bi-weekly for three months if normal.

Authorship contribution. Drs. XC Chen, B Yu and Z Xu were involved in the study design, patient management and data acquisition. Drs. JC Dong, YX Gu, L Chen, QZ Wu, NP Hou, JX Liu, JT Xu, RX Jin, GQ Jin, XD Yang, YW Cao, JJ Tan, B Zhu and JC Shen were involved in patient management and data acquisition. Drs. L Varticovski and XW Wang were involved in data analyses and manuscript preparation.

Table II. *Objective responses of patients with hepatic malignancies to CHML treatment.*

Cancer type	Total patients (%)	Response to CHML treatment[a]			
		CR	PR	NR	PD
HCC	97 (72%)	22 (23%)	52 (54%)	20 (21%)	3 (3%)
MLC	38 (28%)	11 (29%)	19 (50%)	6 (16%)	2 (5%)

[a]Objective responses were determined four weeks after the completion of the treatment cycles. CR, complete response; PR, partial response; NC, minor response or no change; PD, progressive disease.

Results and Discussion

Among the patients with hepatic malignancies, 77 (57%) had stage III disease, while 56 (41%) had stage IV cancer. Stage I patients were not included and only two stage II patients were included in this study. The majority of patients (59%; n=80) had refractory disease and had received prior treatments (Table I). Of these, one half had failed to respond to previous chemotherapy and 21% of them had received a prior combination of chemotherapy, radiation therapy and/or surgery. The majority of patients (n=97) had HCC and the remaining patients with MLC mostly had liver metastasis from colorectal cancer.

Overall, a total of 333 cycles of CHML were administered, 72 patients received two cycles and 63 patients received three cycles. The evaluation of patients with HCC four weeks after completing the therapy showed that 23% had CR and 54% had PR (Table II). About 20% of patients showed no response to CHML and less than 5% of patients had progressive disease. It was apparent that patients with HCC and MLC responded equally to CHML treatment (Table II). Figure 1 shows three examples of patients enrolled in the study who achieved a complete remission of hepatic tumors following CHML therapy.

When the overall response rates were stratified according to TNM staging, it became apparent that patients with advanced disease (Stage IV) responded less favorably to CHML, while complete responses were documented mostly in patients with Stages II and III (Figure 2). None of the Stage IV-B patients with primary HCC responded to CHML, while more than half of the patients with Stage III A and B had at least a PR within 6 months and the Stage II patient achieved a complete response (see Figure 1A). Similar results were obtained with MLC patients (Figure 2B).

Kaplan-Meier survival analyses indicated that over 30% of patients with CHML treatment survived over three years (Figure 3A). These results were encouraging as most of the patients in this trial were expected to live less than one year after either failure of other conventional

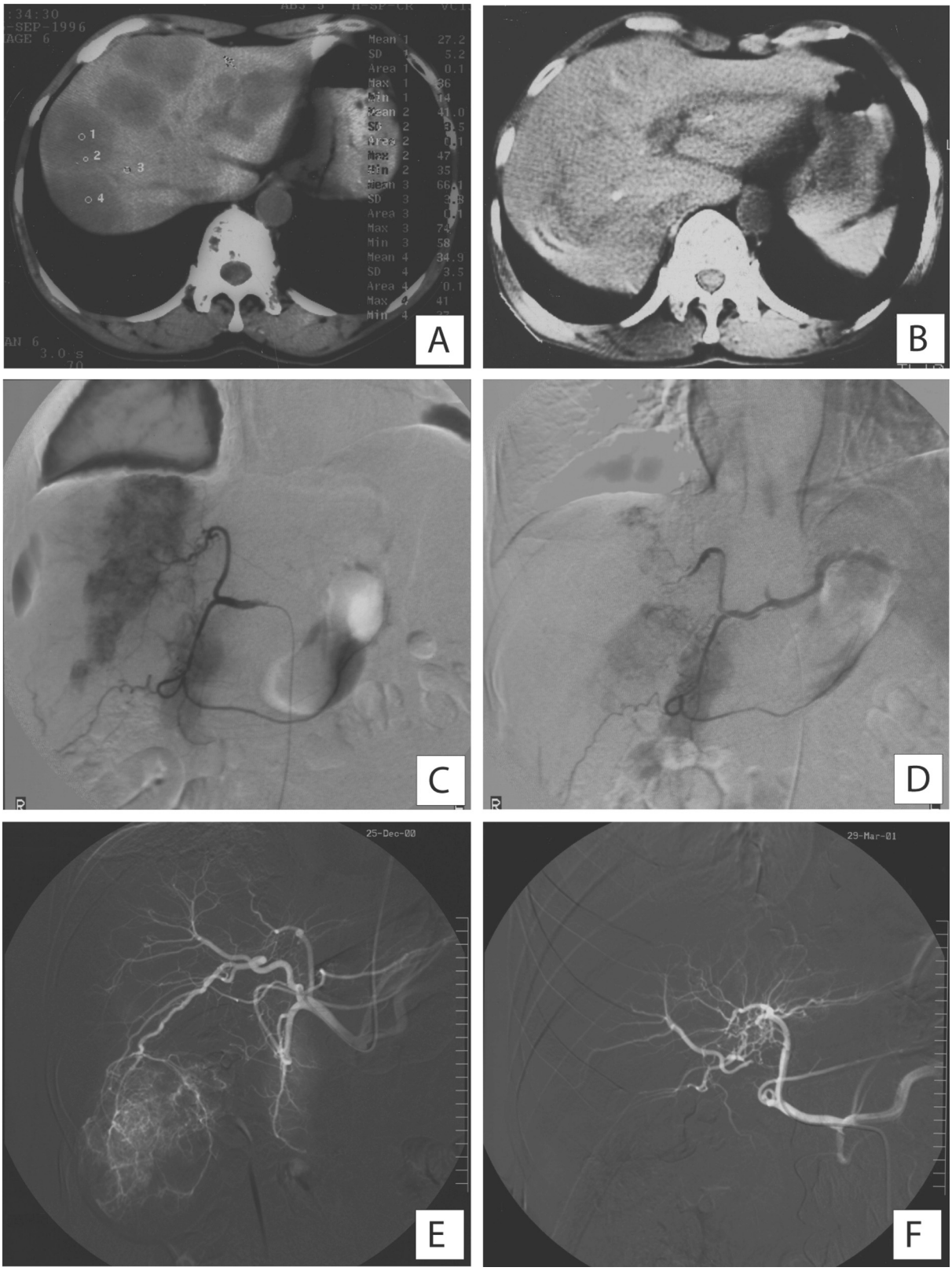

Figure 1.

therapies or following palliative treatment such as pain control. When the survival analyses were stratified either by patients' responses (Figure 3B) or by TNM staging (Figure 3C), those patients who had early stage tumors or responded favorably to CHML had a statistically significant increase in survival when compared to those with advanced stage or no response to CHML. In addition, patients treated with three cycles of CHML had a significantly longer survival when compared to patients treated with two cycles of CHML ($p<0.03$) (Figure 3D). In contrast, no difference in survival was observed when tumor type or prior treatment was stratified (Figure 3E, F). Since prior treatment did not contribute to overall survival, the observed increase in survival appeared to be a result of the CHML treatment.

It should be noted that the quality of life in CHML-treated patients as determined by Karnofsky Performance Status (KPS) showed a small but consistent improvement that was statistically significant ($p<0.001$). For example, the median performance status in the HCC patients was 71 prior to the CHML treatment and was 82 following the treatment (Table III). Similar results were observed in patients with MLC. A noticeable improvement was observed in the patients' physical strength. However, whether such an improvement was due to the CHML treatment or a placebo effect remains to be determined.

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Figure 1. *Radiological findings of patients with hepatic malignancies in response to CHML. Computed tomography (CT) scan taken before (A) or 6 months after (B) the CHML therapy in a 64-year-old male diagnosed with a poorly differentiated gastric adenocarcinoma metastastatic to the liver. Multiple tumors were found in both the left and right lobes of the liver prior to therapy so no other conventional therapy was offered. The patient had anorexia, fever, night sweat, weight loss and abdominal distension. Following 3 cycles of CHML, the patient had an improved appetite and disappearance of other symptoms, including a decrease in abdominal distention. Complete resolution of liver disease and no detectable liver abnormalities were observed 4 weeks after completion of the last CHML cycle. Digital subtraction angiography (DSA) using an arterial catheter canalized into a tumor artery before (C) or 4 weeks after (D) therapy in a 60-year-old male with a nodular HCC (7 cm in diameter) in the right lobe of the liver, which was confirmed by needle biopsy. The patient had anorexia and abdominal distension. DSA prior to therapy showed well demarcated hypervascular staining in the right lobe. Following 1 cycle of CHML, the patient's symptoms improved and no visible tumor could be detected by DSA 4 weeks later. DSA before (E) and 3 months after (F) the CHML therapy of a previously untreated 43-year-old male diagnosed with multinodular HCC (a 2.2 cm nodule in the right lobe and an 8.5 cm mass involving liver, colon and kidney). The patient had anorexia, fever, night sweat, weight loss and abdominal distension prior to treatment. After 2 cycles of CHML, the patient had no complaints and had a good appetite. The DSA image showed no sign of tumor 3 months after therapy (F). This patient remained cancer-free after 5 years' follow-up and enjoyed a normal healthy lifestyle.*

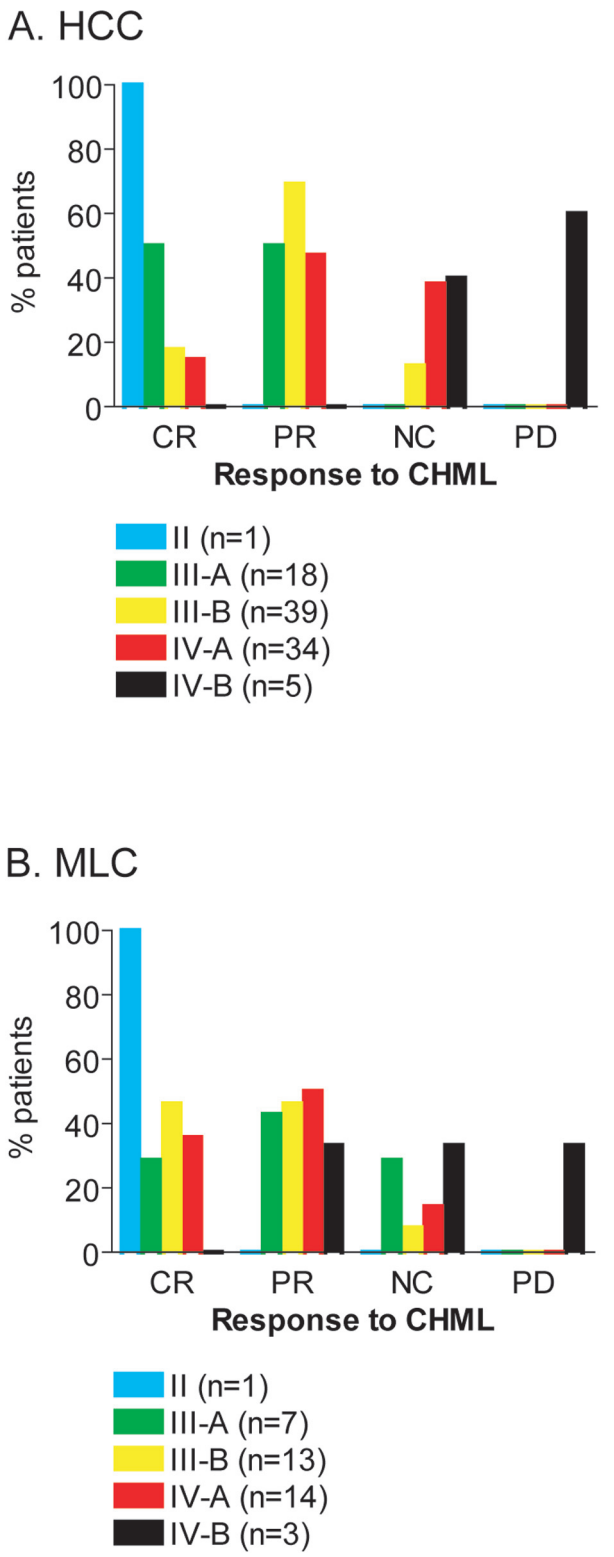

Figure 2. *Objective responses of patients with hepatic malignancies to treatment with CHML. The overall responses of 97 HCC patients (A) and 38 MLC patients (B) to CHML are stratified according to TNM staging (19).*

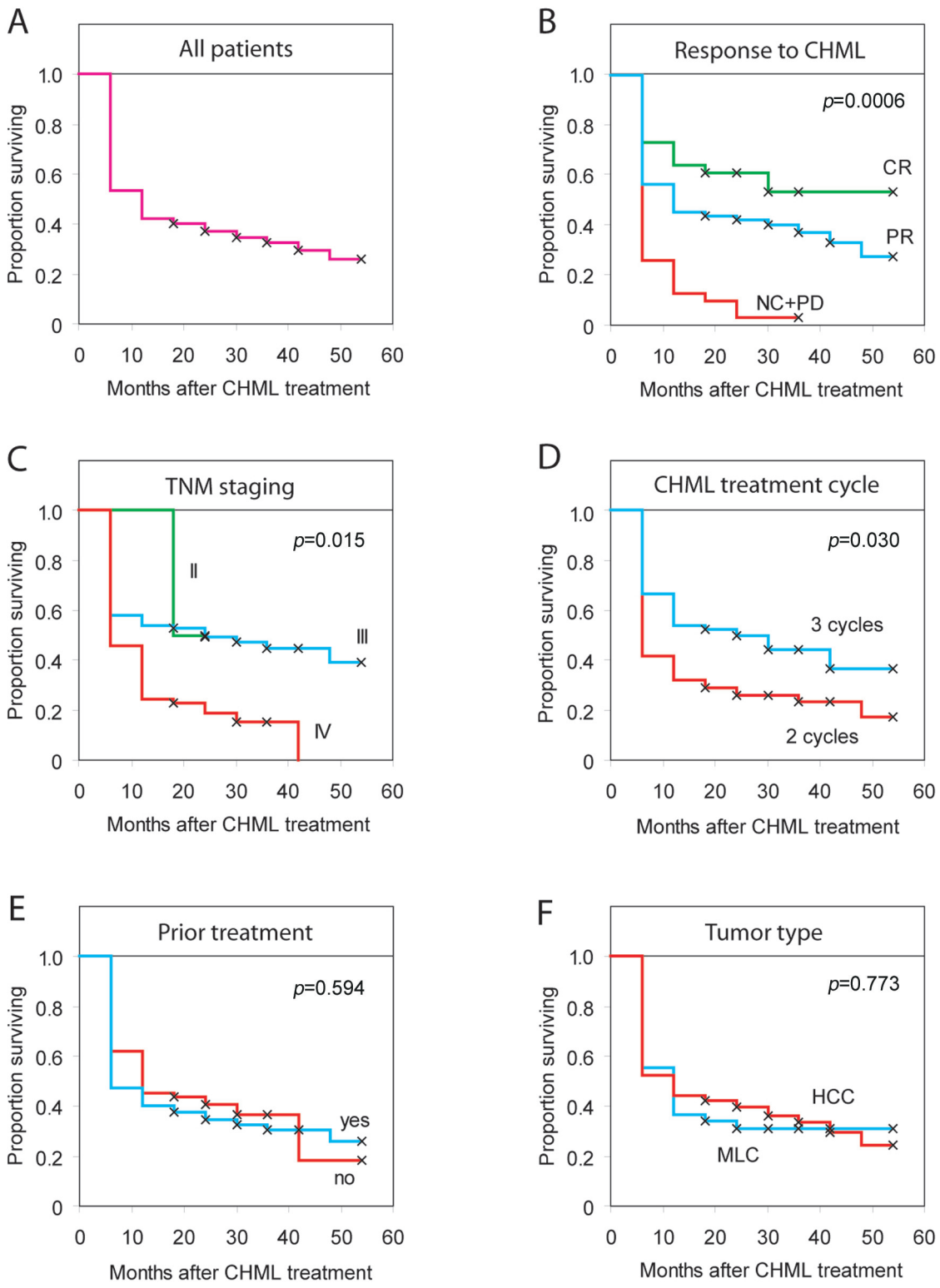

Figure 3. *Prognosis of patients with hepatic malignancies in response to CHML therapy as analyzed by Kaplan-Meier survival. P-values were generated by the two-sided Cox-Mantel log-rank test. (A) Cumulative survival of all 135 patients with hepatic malignancies treated with CHML. (B) Cumulative survival based on patients' responses to CHML. CR: complete response; PR: partial response; NC+PD, no response or progressive disease, cases combined. (C) Cumulative survival based on TNM staging. (D) Cumulative survival based on the number of CHML treatment cycles. (E) Cumulative survival based on prior treatments before the trial. (F) Cumulative survival based on tumor types.*

Table III. *Summary of the Performance Status of cancer patients prior to and 6 months after CHML treatment.*

		Karnofsky Performance Status						
		Before			After			
Cancer type	N	Mean	SD	range	Mean	SD	range	*P* value*
HCC	97	71	9	60-90	82	11	50-100	<0.001
MLC	38	67	9	60-80	82	11	60-100	<0.001

*paired Student's *t*-test.

At the doses used in the study, the patients had only minimal side-effects. Seven patients experienced Grade I nausea and 11 patients had a Grade I elevation of liver function parameters (ALT or SGPT). The degree and the number of patients with side-effects were not significantly different between the two types of cancer. In view of the minimal side-effects, it is possible that higher doses or a combination of local and systemic therapies may be more effective for some patients, especially those that present at an advanced stage. These issues will need to be addressed in further clinical trials.

The results indicate that CHML is effective against several aggressive types of human carcinomas that are ineligible for or refractory to conventional treatments. Our results also suggest that CHML is specifically active when the tumors are confined locally regardless of detectable vascular invasion, as it occurs in HCC and carries worse prognosis (25, 26). The results of this trial indicate that CHML appears to be equally effective in controlling both HCC and MLC. Whether a combination of systemic and regional therapy can improve the response observed in this trial needs to be established. We could not determine whether a specific tumor type metastatic to the liver is more sensitive to CHML because of the small number of patients with MLC. Thus, clinical trials using this novel anti-cancer biotherapy in other human malignancies and Phase III clinical trials for hepatic malignancies are warranted.

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Conflict of interest. Zheng Xu is the president and director of Glory F&D Co. Ltd. Other authors declare that they have no competing financial interests.

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