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Increased survival of patients with end-stage hepatocellular carcinoma due to intake of ONCOXIN®, a dietary supplement

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Original Article

increased survival of patients with end-stage hepatocellular carcinoma due to intake of ONCOXIN®, a dietary supplement

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Abstract

BACKGROUND AND AIMS: Treatment and management of patients with end-stage hepatocellular carcinoma (HCC) represents a formidable challenge to contemporary branches of medical sciences. The study presented here was conducted to assess the utility of nutrient supplement, if any, for management of patients with end-stage HCC. **MATERIALS AND METHODS:** A total of 19 patients with end-stage HCC (Barcelona Clinic Liver Cancer [BCLC] staging D) were provided with ONCOXIN® for 3 months. Another 10 patients with end-stage HCC (BCLC stage D) with similar clinical conditions received conservative management, but they did not give consent for taking ONCOXIN® (non-ONCOXIN® group). All patients of both groups were followed on regular basis until their death. **STATISTICAL ANALYSIS:** The results were expressed as mean and standard deviation. Comparison between groups was performed using Student's *t*-test or the Mann-Whitney U test. For categorical data, Chi-square or Fisher exact test was applied. **RESULTS:** All patients of the control group (non-ONCOXIN® group) (10 of 10 patients) died within 2 months after study commencement. On the other hand, 10 of 19 patients receiving ONCOXIN® died within 2 months (less than 53% patients) after the start of taking ONCOXIN® ($P < 0.05$, compared with patients of non-ONCOXIN® group). Five more patients died within 5 months after the start of intake of ONCOXIN®. Four patients receiving ONCOXIN® survived for more than 6 months after study commencement. **CONCLUSIONS:** Although this is a preliminary report, it inspires considerable optimism about safety and efficacy of a food supplement for management of patients with end-stage HCC.

Key Words: Diet supplement, end-stage hepatocellular carcinoma, hepatocellular carcinoma, increased survival, ONCOXIN®

Introduction

Due to significant developments about epidemiology, etiological factors, mechanism of carcinogenesis and new therapeutic approaches, notable progresses have been made about surveillance, early detection and evidence-based therapeutic interventions of cancer patients around the world, especially in the developed, advanced and rich countries.[1,2] However, most of these preventive, surveillance and therapeutic measures are mostly non-available in most developing countries of Asia and Africa that are resource-constrained and traditionally endowed with comparatively poorly-developed health-care delivery system.[3,4]

Hepatocellular carcinoma (HCC) is one of the most common cancers in the world. HCC is also highly prevalent in most developing countries of Asia and Africa. High prevalence of HCC in these countries is attributable to increased prevalence of two hepatotropic viruses, hepatitis B virus (HBV) and hepatitis C virus (HCV).

Recent epidemiological studies have indicated that about 10 million people of Bangladesh, a developing country of Asia, are chronically infected with HBV and/or HCV.[5] Epidemiological estimations suggest that several thousand new HCC patients emerge each year in Bangladesh. However, most of these patients are diagnosed with advanced HCC because there is no effective surveillance and monitoring system for detection of HCC or pre-HCC liver cirrhosis at Bangladesh. Thus, most HCC patients of Bangladesh merely receive therapy for HCC either in the form of surgery or ablation or radiotherapy or chemotherapy or combination of these therapeutic approaches.

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We encountered several patients with HCC at their terminal stage. They were diagnosed late and abandoned by their physicians as there were no therapeutic options for these patients. We also found that interventional therapy or anti-cancer therapy was neither indicated for these patients nor were they able to take newly-developed costly medicine, like sorafineb.

To provide some alternative management strategy for these patients, we provided attention to food supplements. In fact, positive impacts of different food supplements have been reported in patients with HCC and liver cirrhosis. Matsui *et al.* have shown that intake of active hexose correlated compound, a functional food, improved prognosis of post-operative HCC patients.[6] Viusid, a nutritional supplement, increased survival of HCV-related decompensated cirrhosis.[7] Branched chain amino acid treatment has been shown to improve hepatic functional reserve in HCC patients.[8] Black tea has shown to have anti-cancer effect in rat.[9] The role of a snack enriched in branched-chain amino acid in HCC has been shown by Nishikawa *et al.*[10]

However, these studies were conducted either in patients with liver cirrhosis or early stage of HCC. In fact, there is a paucity of information about the role of food supplement in patients with advanced HCC or end-stage HCC. In this clinical trial, we assessed the safety and clinical efficacy of ONCOXIN®, a food supplement, in patients with end-stage HCC to develop insights about an alternate management strategy of these patients.

Materials and Methods

Patients

The study was conducted in 29 patients with end-stage HCC, who were told by their physicians that there was no therapy or management strategy for their diseases. Nineteen of these patients gave consent to receive ONCOXIN®, a diet supplement. The rest 10 patients refused to take ONCOXIN® and these 10 patients were managed with conservative management and they were

regarded as controls. The study was conducted at Farabi Hospital, Dhaka, Bangladesh between January 2012 and December 2012. All patients gave their consent to study after explaining the nature and purpose of the study. Furthermore, the study was approved by a departmental review board of the hospital. The study was conducted in accordance with the declaration of Helsinki.

The diagnosis of HCC was made from the presence of HCC nodules in abdominal ultrasonography. Confirmed diagnosis of HCC was performed by assessment of findings of fine needle aspiration cytology. The demographic data of the patients are shown in Table 1. The mean age of the patients of ONCOXIN® group was 49.8 years (range 28-80 years). There were 17 male and 2 female. Out of 19 patients, 14 were infected with HBV (evident by the presence of HBV deoxyribonucleic acid [DNA]), 4 expressing antibody to HCV and the rest one was expressing both HBV DNA and anti-HCV. None of the patients had any history of alcohol intake and other etiological factors of HCC were not detected in any patient. The mean levels of alpha-fetoprotein (AFP) were 6113 ± 12327 ng/dl (mean ± standard deviation). The levels of bilirubin were more than the upper limit of normal in all patients and 11 patients had bilirubin more than 5 mg/dl. HCC nodules spreading over whole liver were detected in five patients (diffuse type). Multiple HCC nodules (more than two discrete nodules) were seen in nine patients, whereas, large solitary HCC nodules of more than 5 cm × 7 cm were found in four patients. One patient had a comparatively smaller HCC nodule of 2.7 cm × 1.5 cm, but he also had hemorrhagic ascites [Table 1].

The age of the patients in the control group (non-ONCOXIN® group) was 50.2 ± 12.3 years (range 32-76 years). No statistical difference was seen regarding age between ONCOXIN® group and non-ONCOXIN® group [Table 1]. Six of them were infected with HBV, 3 with HCV and the rest one showed markers of both HBV and HCV. The levels of bilirubin were more than 5 mg/dl in 6 of 10 patients of the control group. As shown in Table 1, ascites was detected in almost similar ratio in both groups. Furthermore, the nature of HCC nodules were similar in ONCOXIN® and non-ONCOXIN® groups.

ONCOXIN® (Catalysis SL, Madrid, Spain) contains high doses of different amino acids and other food supplements and details of their composition have been shown in Table 2. ONCOXIN® was given orally at a dose of 25 ml, twice a day for 3 months. Furthermore, three capsules of ONCOXIN® were given to these patients on a daily basis for the same duration. No other treatment, either anti-cancer or anti-viral or other food supplement, was given to any patient. All patients both receiving ONCOXIN® and control group were checked on a regular basis. A close contact was maintained between the relatives of the patients and the principal investigator (Al-Mahtab M) of this clinical trial.

Statistical analysis

The results were expressed as mean and standard deviation. Comparison between groups was performed using Student's *t*-test or the Mann-Whitney U-test. For categorical data, Chi-square or Fisher exact test was applied.

Table 1: Clinical profiles of the patients

Parameters	ONCOXIN® group	Control group
Number of patients	19	10
Male:Female	17:2	8:2
Age (years)	49.8±12.9 (28-80)	50.2±12.3 (32-76)
AFP	6113±12327 (5-50000 ng/ml)	7062.1±14464.8 (3.9-35000 ng/ml)
Bilirubin>2 mg/dl	8	4
Bilirubin>5 mg/dl	11	6
Clinical		
Ascites	11	6
Diffuse HCC	5	2
Multiple HCC	9	6
Solitary	4	2
Hepatic encephalopathy	6	4

Data are shown as mean and standard deviation. The ranges have been shown in bracket. AFP=Alpha-fetoprotein; HCC=Hepatocellular carcinoma

Table 2: Composition of ONCOXIN®

100 ml of ONCOXIN contains	
Glycine	2000 mg
Glucosamine	2000 mg
Malic acid	1200 mg
Arginine	640 mg
Cystine	204 mg
Mono-ammonium glycyrhizinate	200 mg
Ascorbic acid	200 mg
Sodium methylparaben	120 mg
Zinc suphate	100 mg
Green tea extract	80 mg
Calcium patothenate	25 mg
Pyridoxine	12 mg
Manganese sulphate	4 mg
Cinnamon extract	3 mg
Folic acid	400 µg
Cyanocobalamin	2 µg

Results

In the control group (patients receiving no ONCOXIN®), all patients with end-stage HCC died within 2 months of commencement of the clinical trial. Five of 10 patients died within 1 month after study commencement and the rest five patients died within 2 months after start of the study. Thus, there was a zero survival of end-stage HCC patients in the control group, 2 months after study commencement. All patients in this group ran a rapidly downhill course and all of them showed progressive elevated AFP. The patients also complained of pain, fever and anorexia because of their progressive illness. Patients were given palliative treatment to get rid of these complaints. The patients who died after 1 month of study commencement (five patients), the cause of death were hepatic failure in four patients and multi organ failure in one patient. In the rest five patients who died within 2 months following study commencement, the cause

of death was hepatic failure in one patient, variceal bleeding followed by shock in one patient and multi-organ failure in three patients.

In patients of ONCOXIN® group, 8 of 19 patients with end-stage HCC died within 1 month of study commencement. The cause of death of these patients was hepatic failure (five patients), multi organ failure (two patients) and variceal bleeding (one patient). Two more patients (a total of 10 of 19 [53%]) patients receiving ONCOXIN® died within 2 months after the start of clinical trial (variceal bleeding: One patient and hepatic failure: One patient). Thus, 2 months after study commencement, 9 of 19 patients (47%) of the ONCOXIN® group survived. Taken together, there was a significantly increased rate of survival of and-stage HCC patients was recorded in patients of ONCOXIN® group (9 of 19 patients; 47%) compared with patients of non-ONCOXIN group (0 of 10; 0%) ($P < 0.0001$).

Out of total 19 patients with end-stage HCC receiving ONCOXIN®, 12, 13, 13, and 15 patients died 3, 4, 5, and 6 months after the start of intake ONCOXIN®, respectively (cause of death; multi-organ failure: Four and hepatic failure: One). Four patients with end-stage HCC receiving ONCOXIN® survived for more than 6 months.

There was no adverse effect due to intake of ONCOXIN® in any patient. However, most of the patients taking ONCOXIN® reported a feeling of well-being. Improvement of appetite was recorded in six patients (32%) and three patients of ONCOXIN® group reported that they were feeling well after intake of ONCOXIN®.

Discussion

Management of end-stage HCC is a major challenge in clinics around the world. This is specially an extremely difficult task in developing and resource-constrained countries. These patients are managed in the hospital with advanced life support system in developed and advanced countries. However, these patients are mainly sent to their home in developing countries because the health-care delivery system is neither able to provide adequate care nor these terminally-ill patients are hospitalized due to an inherent limitation about constrains of hospital beds in these countries. Even if they are hospitalized, they are not provided with any kind of management regimen.

The study presented here has shown that ONCOXIN®, a food supplement, appears to increase survival of some, but not all, patients with end-stage HCC. All patients receiving no ONCOXIN® died within 2 months after their entry in this study. Cabibbo *et al*. have reported that the median survival of end-stage HCC patients with Barcelona Clinic Liver Cancer stage D is about 1.8 months.[11] Thus, death of all patients of non-ONCOXIN® group indirectly support what that has been reported about survival of end-stage HCC patients.[4,11]

On the contrary, patients receiving ONCOXIN® showed a better survival as 9 of 19 patients (47%) with end-stage HCC survived for more than 2 months and 4 of 19 patients with end-stage HCC survived for more than 6 months. Taken together, it seems ONCOXIN® has a positive impact on the survival of end-stage HCC patients in our cohort, however, the exact mechanisms of action of ONCOXIN® remains to be addressed. Furthermore, the positive impact of ONCOXIN® on survival of end-stage HCC remains to be confirmed in large cohort study in the future. It is to be mentioned that ONCOXIN® was provided at home without hospitalization. This is particularly important in the context of health-care delivery system of developing countries because end-stage cancer patients are not usually hospitalized due to limited facility of hospital beds and ill-developed health-care delivery system of those countries.

The mechanism underlying increased survival of HCC patients receiving ONCOXIN® is not clear and this study was not planned to evaluate these mechanisms. However, others have shown that food and nutrients bear significant therapeutic efficacy in experimental models of HCC.[12,13] However, the utility of nutrients in end-stage HCC or advanced cancer have not been properly evaluated, especially in developing countries that cannot provide even minimum management for patients with end-stage cancers due to major constrain of their health-care delivery system. It is true that there are some options to treat advanced HCC in developed and rich countries;[14] however, duplication of that in developing countries would take more time and efforts. This study provides a rationale to assess the utility of food supplement in advanced HCC and other advanced cancers when other options of treatment become extremely limited.

The study is endowed with some limitations. Although we had one control group receiving no food supplements, there was an absence of control group that received some alterative food supplements comparable with ONCOXIN®. That would allow to assess the real impact of ONCOXIN® in end-stage HCC. Furthermore, the numbers of patients were low and that did not allow us to draw a clear conclusion from this study. In addition, it appeared that the quality-of-life of patients of ONCOXIN® group improved, but we could only assess appetite, overall feeling and incidence of fever of these patients. More elaborative study with different points of quality-of-life should be explored in future.

Taken together, this open-label clinical trial showed that terminally ill and end-stage HCC patients may be managed by food supplements. Based on the data of this pilot study, a randomized-controlled trial is warranted to assess if there is any real therapeutic effect of ONCOXIN®. Also, ONCOXIN® may be used with other food supplements that have shown therapeutic efficacy in early HCC patients.[6-10] It would also be tempting to assess the utility of ONCOXIN® in other cancers, especially in other advanced cancers.

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