RESEARCH ARTICLE

Aggressive Treatment of Performance Status 1 and 2 HCC Patients Significantly Improves Survival - an Egyptian Retrospective Cohort Study of 524 Cases

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Abstract

Background: In the Barcelona Clinic Liver Cancer (BCLC) system, only sorafenib is suggested for HCC patients having performance status (PS) 1 or 2 even if they have treatable lesions. In the current study, we aimed to explore the outcome of using aggressive treatment for HCC patients with PS 1 and 2. Materials and Methods: Five hundred and twenty four patients with HCC were enrolled in this study and divided into 2 groups: 404 PS 1 and 120 PS 2. Of the included 524 patients, 136 recceived non-aggressive supportive treatment and sorafenib, while 388 patients were offered aggressive treatment in the form of surgical resection, transplantation, percutaneous ablation, trans-arterial chemoembolization and/or chemoperfusion. All the patients were followed up for a period of 2 years to determine their survival. Results: Most HCC patients were CHILD A and B grades (89.4% versus 85.0%, for PS1 and PS2, respectively). Patients with PS1 were significantly younger. Out of the enrolled 524 patients, 388 were offered aggressive treatment, 253 (65.2%) having their lesions fully ablated, 94 (24.2%) undergoing partial ablation and 41 patients with no ablation (10.6%). The median survival of the patients with PS 1 who were offered aggressive treatment was 20 months versus 9 months only for those who were offered supportive treatment and sorafenib (p<0.001). Regarding HCC patients with PS 2, the median survivals were similarly 19.7 months versus 8.7 months only (p<0.001). Conclusions: Aggressive treatment of HCC patients with PS 1 and 2 significantly improves their survival. Revising the BCLC guidelines regarding such patients is recommended.

Keywords: HCC - performance status - aggressive treatment - outcome - prognosis

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Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world and the third most common cause of cancer-related death worldwide, with a rising incidence in developing and well as developed countries to the extent that more than half a million individuals per year are diagnosed with HCC (Mittal and El-Serag 2013). Egypt has the highest prevalence of hepatitis C virus (HCV) worldwide (Strickland et al., 2002). This results in large numbers of HCV-related HCC (Omran et al., 2015). It had been reported that the annual proportion of HCC in Egypt showed an increasing trend (Shaker et al., 2013). It had been reported that more than 60 % of HCCs in clinical practice were diagnosed at late stages, thus not offered curative treatment. For the majority of symptomatic patients, curative treatments may not be suitable because of insufficient hepatic reserve, or overwhelming tumor burden. Moreover, the Barcelona Clinic Liver Cancer (BCLC) system suggested treatment of HCC patients having PS 1 or 2 with sorafenib being categorized as advanced stage (stage C) (Kim et al., 2012; Gomaa, 2014). However, patients with PS 1 or 2 categorized as BCLC class C could have treatable lesions.

In the current study, we aimed to explore the outcome of using aggressive treatment for HCC patients with PS 1 and 2

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Materials and Methods

Five hundred and twenty four patients with HCC attending the HCC multi-disciplinary clinic, Cairo University were included in this study. HCC was diagnosed by at least 2 imaging methods including ultrasound, magnetic resonance imaging, and contrast-enhanced triphasic dynamic computed tomography. Alternatively, the diagnosis was confirmed by 1 positive imaging modality and serum a-fetoprotein (AFP) level>400 ng/mL or histopathological confirmation. (Bruix and Sherman , 2011)

HCC patients were divided into 2 groups; 404 with PS 1 and 120 with PS 2. PS was determined according to the Eastern Cooperative Oncology Group (Hsu et al., 2013). [11] The baseline features, including age, gender, severity of chronic liver disease, presence of diabetes and ascites, liver biochemical profile as well as the number and size of HCC lesions were analyzed in the 2 groups.

Members of the HCC multidisciplinary clinic which included hepatologists, surgeons, radiologists and oncologists discussed the suggested treatment modality with the patients and all the patients supplied informed consent before participating in this study according to the 1975 Helsinki Declaration. Surgical resection, transplantation, percutaneous ablation (percutaneous ethanol injection, microwave ablation (MWA) and radiofrequency ablation (RFA), trans-arterial chemoembolization (TACE), chemoperfusion and combined treatment which usually involved TACE and percutaneous ablative techniques were classified as aggressive treatment modalities . Sorafenib and supportive care were considered as nonaggressive anticancer treatment modalities. Aggressive treatment modalities were offered to 311 HCC patients with PS 1and 77 HCC patients with PS 2. While non aggressive treatment was offered to 93 HCC patients with PS 1and 43 HCC patients with PS 2. All the patients were then followed up for a period of 2 years to determine their survival.

Statistical analysis

Numerical data are reported as means±standard deviation (S.D) or median and range while categorical data are represented as counts and percentages. The Mann-Whitney U test and the Chi-square test are used when appropriate. Statistical significance is considered if the probability of occurrence by chance is 5% or less ($p<0.05$).

Survival analysis using the Kaplan-Meier method is performed from the date of primary diagnosis to the date of last follow up or death.

Results

Patients with PS1 were significantly younger. Most HCC patients with PS 1& 2 were CHILD A and B grades (89.4% of patients with PS 1versus 85% of patients with PS 2). (Table 1)

Patients with PS 1 had significantly elevated ALT and significantly lower INR than those with PS 2. Two hundred twenty two patients with PS1 had a single lesion, 57 patients had 2 lesions and 125 had multiple lesions. Regarding those with PS 2, seventy had a single lesion, 15 had 2 lesions and 35 had multiple lesions. (Table 2)

Regarding the size of the HCC lesions, 137patients with PS 1 had lesions<3 cms , 138 patients had lesions ranging in size between 3-5 cms and 129 patients had

Table 1. Baseline Characteristics of HCC Patients with Performance Status 1 and 2

Parameter	PS 1	PS 2	P value
Age (years)			
Mean + SD	57.1 + 7.2	58.7 + 7.8	0.034
Family history of HCC			
No/yes	377/27 (93.3%/ 6.7%)	113/7 (94.2%/5.8%)	0.84
Diabetes mellitus			
No/yes	318/86 (93.5%/6.5%)	96/24 (80%/20%)	0.76
CHILD Score			
A/B/C	214/147/43 (53%/36.4%/10.6%)	47/55/18 (39.2%/45.8%/15%)	0.02

Table 2. Laboratory and Ultra-sonographic Findings for HCC Patients with Performance Status 1 and 2

Parameter	P S 1	P S 2	P Value
AST IU/L (median and range)	63.5 (8-824)	65.0 (6-1155)	0.91
ALT IU/L (median and range)	49.0 (3.4-630)	40.0 (4-395)	0.01
Albumin gm/dl (mean + SD)	3.2 + 0.62	3.15 + 0.68	0.4
Creatinine mg/dl (median and range)	1.00 (0.2 -2)	0.90 (0.2 -2.5)	0.13
INR (mean + SD)	1.2 + 0.23	1.35+ 0.27	0.005
AFP ng/mL (median and range)	35.1 (1.1 -200000)	47.0 (1 – 53675)	0.57
Ascites No/yes	305/99 (75.5%/24.5%)	73/47 (60.8%/ 39.2%)	0.002
No. of F.L 1/2/multiple	222/57/125 (55%/14%/31%)	70/15/35 (58.3%/12.5%/29.2)	0.795
Size of tumor			
< 3cm	137 (33.9%)	40 (33.3%)	0.456
>3-5cm	138(34.2%)	35(29.2%)	
>5 cms	129(31.9%)	45(37.5%)	

Table 3. 1st and 2nd Year Overall Probability of Survival for HCC Patients with PS1 and PS2

Overall survival							
Factor				Survival (%)			
	Treatment	Total number	Number of Events	1 year	2 years	Median (months)	P-value
Performance status	1	404	198	62.3	36	15.6	
	2	120	68	59.2	31.9	14.2	0.13
Performance status							
1	Non aggressive treatment	93	61	32.7	9.6	9	
	Aggressive treatment	311	137	71.4	43.4	20	<0.001
2	Non aggressive treatment	43	29	31.1	14.6	8.7	
	Aggressive treatment	77	39	73.5	40.5	19.7	0.001

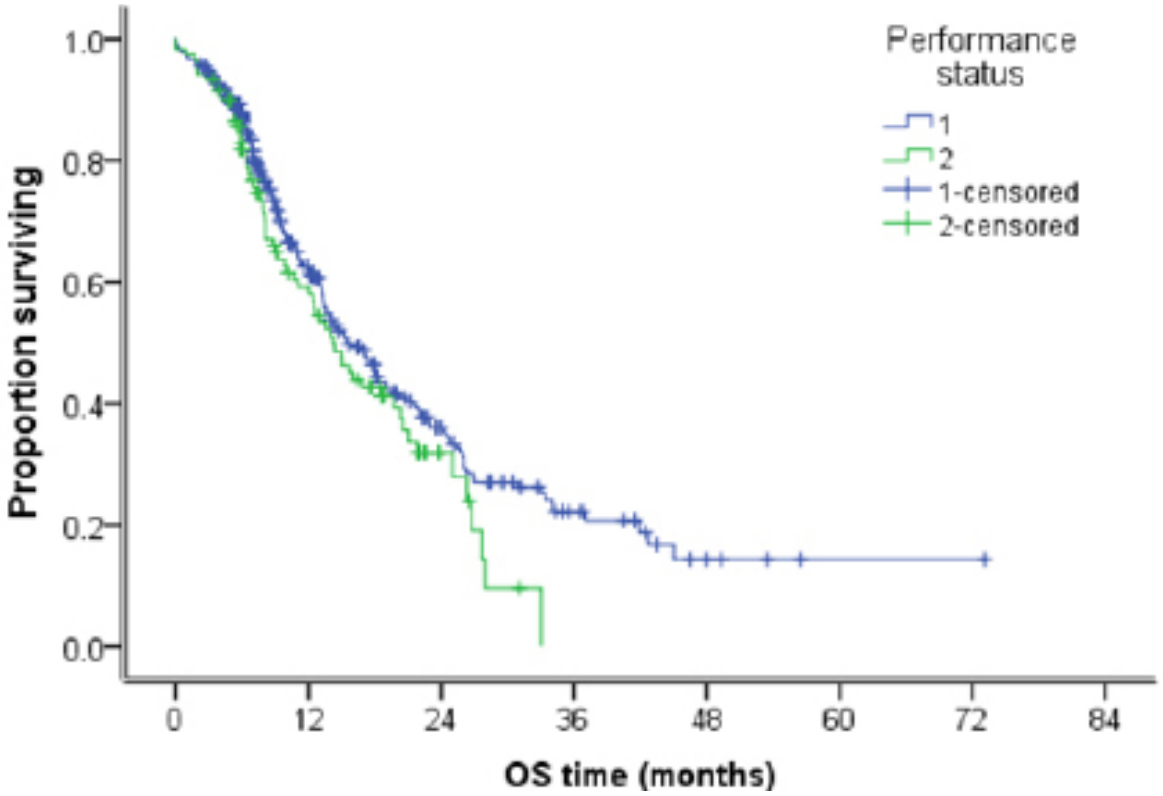

Figure 1. Overall Survival for HCC Patients with PS 1 and 2

lesions > 5 cms while 40 patients with PS 2 had lesions<3 cms , 45 patients had lesions ranging in size between 3-5 cms and 35 patients had lesions > 5 cms.(Table 2)

Out of the recruited 524 patients, 136 patients were given non aggressive treatment t. Out of those given aggressive treatment (388 patients), 253 patients (65.2%) had their lesions fully ablated, 94 patients (24.2%) have partial ablation and41 patients had their lesions not ablated (10.6%)

The median survival of the patients with PS 1who were offered aggressive treatment was 20 months versus 9 months only for those who were offered palliative therapy (p: <0.001). Regarding HCC patients with PS 2, the median survival of the patients who were offered treatment was 19.7 months versus 8.7 months only for the patients who were offered palliative therapy (p: <0.001). (Table 3, Figure 1).

Discussion

ALiver cirrhosis, tumor burden and PS have been recognized as strong predictors of HCC treatment outcome (Hsu et al., 2013, Lee et al., 2013a; Lee et al., 2013b). The BCLC system proposed the treatment algorithm

for HCC according to the patient's PS, severity of liver cirrhosis, and tumor burden, regardless of other important features as liver functions (Bruix and Sherman,2011; EASL-EORTC, 2012). So, patients with PS1-2, defined as symptomatic but completely ambulatory or with less than 50 % of their time in bed during the day, are classified as BCLC class C (advanced HCC). According to BCLC, they should not be offered aggressive anti-HCC treatments, due to a lower chance of cure and a higher risk of complications. Hence, sorofanib had been recommended (Llovet et al 1999; Bruix and Sherman, 2011). However, according to BCLC system, patients with PS 1-2 have treatable lesions or preserved liver function.

In the current study, most HCC patients with PS 1& 2 were CHILD A and B grades (89.4% of patients with PS 1versus 85% of patients with PS 2) and suffered treatable lesions. So, aggressive treatment strategies including aggressive anti-HCC treatments were offered to

311 patients with PS 1 and 77 patients with PS 2 against the recommendations of the BCLC that classified HCC patients with PS 1 & 2 as BCLC class C (advanced HCC).

Our findings showed that patients with PS 1 & 2 benefited of receiving aggressive anti-HCC treatments as evidenced by having complete ablation of their lesions (253 patients) and partial ablation of their lesions (94 patients). Moreover, they had a significantly higher overall survival than those offered Sorafenib and supportive treatment ($p<0.001$). It is important to note that the overall probability of survival in patients with PS 1was 62.3 % at one year and 36.0% at two years while it was 59.2% at one year and 31.9% at two years.

Other studies suggested that surgical resection could be considered safe and associated with improved outcome for advanced HCC (Ruzzenente et al., 2009). Ablation therapy and TACE could also improve survival for selected HCC patients with CTP class C cirrhosis (Kudo et al., 2013). Sorafenib improved the survival in patients with advanced HCC by approximately 3 months (Llovet et al., 2008). So, more patients could benefit from customized treatment strategies according to their state of illness (Tokushige et al., 2010; Cabibbo et al., 2011; Liu et al. 2014).

Similarly, Hsu et al. (2015) found that HCC patients with PS 1 and PS 2 who were offered aggressive therapy in the form of transplantation, resection, percutaneous ablation, and TACE had significantly better survival. Yau et al., 2014 found that the 5-year probability of survival was, 48.6% on using radical treatment modalities for BCLC class C patients versus 0.0% on using systemic treatment.

Surgeons stated that they treated approximately half of the BCLC class B and C HCC patients surgically. They suggested that the recommendations of BCLC regarding surgical resection for HCC is very limited causing them not to follow the BCLC recommendations in real life practice (Nuzzo et al., 2013). Others suggested that experts should revise which HCC patient belong to which BCLC stage in order to propose better classification of HCC patients (Yang et al., 2015) and to include theraputic modalities not currently mentioned in the BCLC staging system such as Yttrium (90) radioembolization, cryotherapy, microwave ablation therapy, radiotherapy, laser therapy and immunotherapy (Poon et al., 2002; Poon et al., 2009; Greten et al., 2015).

In conclusion; Aggressive treatment of HCC patients with PS 1 and 2 significantly improved their survival. From our study, we can suggest modification of the current recommendations of the BCLC system for patients with PS 1 and PS 2 so that they can benefit of having curative or palliative anti HCC treatments thus alleviating their symptoms.

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