Acta Scientific MEDICAL SCIENCES (ISSN: 2582-0931)

Volume 6 Issue 6 June 2022

Research Article

Real Life Experience of Combining Atezolizumab (Immunotherapy) and Bevacizumab (Antiangiogenic Agent) in Patients with Unresectable Hepatocellular Carcinoma in Bangladesh

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Received: May 16, 2022

Published: May 19, 2022

Abstract

Introduction: In a global, phase 3, multi-center,open label clinical trial combination of atezolizumab and bevacizumab has yielded encouraging results, including better survival benefit and safety in patients with unresectable hepatocellular carcinoma.

Methods: We conducted a real-life observational study in small number of Bangladeshi patents with unresectable HCC on the background of decompensated liver cirrhosis.

Results: We had 6 patients in our study and the patients took the drugs in diverse number of cycles. One of the patients who took six cycles of the drugs have been surviving for about 15 months. Atezolizumab and bevacizumab combination proved to be safe during 48 hours of follow up, however, long-term follow up had not been possible for all patients due to their unavailability after administration.

Conclusion: Atezolizumab and bevacizumab combination seem to have encouraging outcome with approved dosage and administration, however, clinical study with larger cohort should be accomplished in Bangladesh to properly assess its possible usage in Bangladeshi patients.

Keywords: Hepatocellular Carcinoma; Combination Immunotherapy; Atezolizumab; Bevacizumab

Introduction

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related deaths in global perspective [1]. The main causes of HCC are hepatitis B virus (HBV) and hepatitis C virus (HCV). As Bangladesh harbor millions of chronic HBV-infected persons and most of these patients do not receive relevant treatment properly due to social, economic and other factors. Thus, the incidence and prevalence of HCC is also considerably high in Bangladesh. For early HCC, there are several curative options including surgical resection, radiofrequency ablation or liver transplantation [2]. Also, patients with early HCC get more time to select therapeutic endeavors. However unfortunately most patients in Bangladesh

as well as in other resource-constrained regions present with unresectable advanced HCC associated with poor prognosis [2]. Surgical resection is not a choice for treating these patients and liver transplantation is neither available nor feasible in Bangladesh. In this perspective there remains some conservative treatment for these patients.

Currently multikinase inhibitors namely, sorafenib and lenvatinib are used as first-line agents for management of unresectable HCC. Both the drugs offer modest survival benefit; however, they are associated with significant adverse events interfering with quality of life.

Recent advancement of scientific field has unmasked that immune checkpoint inhibitors such as programmed death ligand-1 (PD-L1) inhibitors yield promising clinical data in international clinical trials [3,4] with significant survival benefit [5,6]. In accordance with this, it has also been found that overexpression of vascular endothelial growth factor (VEGF) is responsible for HCC progression [7,8]. The role of VEGF is also immense in the progression of HCC. It has been suggested that overexpression of VEGF is supposed to be responsible for progression of HCC. Therefore, VEGF-mediated immunosuppression is considered to reduce the efficacy of anti-PD-1 and anti-programmed death ligand-1 (PD-L1) [9-12].

In this perspective, we postulated that a combination therapy targeting the activity of PD-L1 and VEGF may have therapeutic effects in advanced HCC patients. Considering individually, atezolizumab is a cancer immunotherapy that specifically targets PD-L1 and prevents interaction with PD-1 and B7-1 receptors which in turn reverses T-cell suppression [13]. Bevacizumab is a monoclonal antibody that inhibits tumor growth and angiogenesis by targeting VEGF [14]. A global, multicenter, open label, phase-3, randomized trial combining atezolizumab with bevacizumab in patients with untreated, unresectable HCC demonstrated antitumor activity without significant adverse event [15].

However, combination therapy of these two agents in advanced HCC has not been accomplished in Bangladesh and thus there is no information regarding adverse effects, efficacy, and adherence to therapy of advanced HCC patients.

The study presented here is a real-life study with atezolizumab with bevacizumab in a small number of Bangladeshi advanced HCC patients. The possible study unveils the scope and limitation of this type of therapy for end stage HCC patients in Bangladesh.

Methods

A total of six patients were enrolled in this preliminary study. The patients were between 48 to 72 years of age. All were male. The profiles of the patients are given in table 1. The underlying causes of HCC was hepatitis B virus infection in 3 patients and non-alcoholic steatohepatitis related liver cirrhosis in other 3 patients. Diagnosis of HCC was made by imaging, such as ultrasonography (USG) or triphasic computed tomography (CT) of hepato-biliary system and serum alpha fetoprotein (AFP). American Association for the Study of Liver Diseases (ASLDB) criteria was employed for diagnosis [16]. Three of the 6 patients had metastasis in organs other than liver and these were in portal vein, regional lymph node and right adrenal gland. (Table 1). All had locally advanced or unresectable HCC. Ascites were present in 4 patients. The extent of esophageal varices was in 4 patients and gastric varices in 2 patients and they received treatment of esophageal varices before entry into immune therapy. All of them were treatment naïve and presented with advanced HCC at the time of diagnosis.

Patient (age of the patient)	Age (in yrs)	Cause of HCC	Ascites	Size of HCC/ Numbers of HCC nodules	Metastasis	Endoscopy	Intervention	Survival	Cause of Death
Patient 1	70	NASH	++	Multifocal	Portal vein	OV +GV	EVL + Glue inj.	<6 months	HE
Patient 2	55	HBV	-	Multifocal	-	OV	EVL	7 months	HRS
Patient 3	52	HBV	-	7.5 x 8 cm	-	-	-	Alive	-
Patient 4	60	NASH	+	6.8 x 9.3 cm	-	OV	EVL	<6 months	HRS

Patient 5	72	HBV	+	3, largest 11.1 x 10.3 cm	Regional lymph node	OV	EVL	Lost on FU	-
Patient 6	48	NASH	+	Multifocal	Right adrenal gland	GV	Glue inj.	Lost on FU	-

Table 1: Patient's profile and treatment outcome.

NASH: Non-alcoholic Steatohepatitis; HBV: Hepatitis B Virus; OV: Esophageal Varices; GV: Gastric Varices; EVL: Esophageal Variceal Ligation; HE: Hepatic Encephalopathy; HRS: Hepato-renal Syndrome.

After commencement of administration of drugs, the patients were hospitalized for 48 hours and all sorts of parameters related safety were observed. Later, the patients were discharged based on their condition and advised to attend hospital after 3 weeks for next cycle of therapy. All patients received atezolizumab (1200 mg) plus bevacizumab (15 mg per kg of body weight) intravenously and that was regarded as a single cycle. Treatment was planned for 6 cycles. Tumors were assessed by CT or USG imaging every 24 weeks. Safety of patients was ensured by monitoring vital signs and adverse events and laboratory tests. Primary end point of this study was the safety of the patients following administration of drugs. The final end point was related to survival of the patients.

Results

The therapy was tolerated by the patients and no serious adverse effects attributable to the therapy were observed during 48 hours of hospitalization. In some cases, the condition of the patients was monitored by telephonic discussion. Some patients completed six cycles, whereas, some didn't. Two patients with HCC died within treatment period. One patient died seven months after initiation of treatment. Interestingly, one patient is still alive and has been passing more or less uneventful life for 15 months after treatment commencement (Table 1).

The patients who is still surviving is infected with HBV and belongs to HBV-related HCC. The patents who survived 7 months after end of therapy was infected by HBV. These two patients did not exhibit features of distal metastasis. The ages of these two patients were within 50 years. On the other hand, the two patients who died before 6 months after therapy commencement had been suffering from NASH and one of them had metastasis at portal vein. The age of the patients were 60 years and 70 years respectively.

Discussion

Our real-life experience was similar to the experience in IMbrave150 (NCT03434379) trial which showed significantly better overall survival with atezolizumab plus bevacizumab in treatment naive patients with unresectable HCC [13]. IMbrave150 is the first phase III study to show superiority versus sorafenib in over a decade. In IMbrave150, 101 patients in total (20%) met those criteria of "high risk"- and this subgroup also derives a survival benefit compared to sorafenib. Similarly, our study included patients with "high-risk" criteria's like patients with metastasis in portal vein and other places were present in 3 out of 6 patients. In IMbrave150 study 15% patients discontinued treatment due to adverse events [13]. In our case, we also could not continue the treatment in all patients, however, this may be due to economic cause mostly and other factors. Upper gastrointestinal bleeding is a recognized adverse event with bevacizumab, but that was not our experience. Our patients underwent screening endoscopy of upper gastrointestinal tract prior to initiation of treatment and those who had significant oesopghageal and/or gastric varices underwent prophylactic endoscopic intervention, i.e. oesophageal band ligation and gastric variceal glue injection.

Before IMbrave150 (NCT03434379) clinical trial, previous studies with single immune checkpoint inhibitor failed to demonstrate survival benefit in HCC patients [7,8]. Survival was however better in HCC patients in IMbrave150 study and we also had similar observation with atezolizumab plus bevacizumab [13]. This indicate that bevacizumab may contribute to the treatment benefit when given in combination with atezolizumab. However, more studies will be required to validate these points.

It has been suggested that IMbrave150 trial yielded better survival as the trial was conducted in patients with Child-Pugh class-A liver cirrhosis, who had preserved liver function and decreased risk of variceal bleeding. The novelty of our study is that although we had only a hand full of patients, they all had Child-Pugh class-B or C liver cirrhosis. Our study can be considered as a pilot study, which suggests safety of atezolizumab and bevacizumab

in HCC patients with less preserved liver function. Also, variable factors starting from etiological agents to age with distal metastasis may have dominant role in the action of these drug combination.

The study lacks control group with treatment with another agent or single agent. In fact, this is a difficult task to be accomplished but should be attempted in a multicenter approach. Also, one of the weak point of the study is low concurrence with full treatment strategy in our case. Even then, one patient with unresectable HCC is still surviving and this induce considerable hope and optimism about the usage of this regimen.

Conclusion

In conclusion, our study reconfirms observations of the IMbrave 150 study in a small group of Bangladeshi patients, although with some limitations. This is important as our IMbrave 150 study did not include Bangladeshi patients. Also, our study signifies the need for evaluation of the efficacy of atezolizumab plus bevacizumab in HCC patients end stage liver cirrhosis with an emphasis on the etiology and other relevant factors.

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