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Review Article

Homegrown Solutions for Advanced Hepatocellular Carcinoma in Bangladesh

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Abstract

Hepatocellular carcinoma (HCC) is primary malignancy of the liver and is one of the most common malignancies in the world. This is more so in the Asia-Pacific region. A significant challenge for HCC management in our part of the globe remains the complex reality that most HCC patients in our country and our region present very late with advanced disease, when we have very little to offer to them. As such, in addition to standard therapeutic approaches, innovative strategies are warranted to address the challenges of managing patients with advanced HCC. Over the past several years, our group has explored various methods, ranging from food supplements and traditional medicine to combination therapy, for the management of end-stage HCC. The purpose of this article is to review the works carried out by our group so far involving advanced HCC patients with or without metastasis, of variable etiology and severity of underline liver disease, without any second malignancy to summarize the knowledge and experience that we have so far gathered and outline our way forward.

We recruited total 67 patients in two studies by our group using green tea extract in advanced HCC. In our study exploring arabinoxylan rice bran in end-stage HCC, we included 52 patients while 60 HCC patients were included in our recently completed clinical trial with Indian gooseberry advanced HCC. We studied combination of nivolumab and lenvatinib for the treatment of advanced HCC in 48 patients and 4 patients with end-stage HCC were included in another study where they received a combination of atezolizumab and bevacizumab. In another large study, our group treated 177 HCC patients with a combination trans-arterial chemoembolization and sorafenib. Advanced HCC is incurable; however, there remains an opportunity to extend survival and improve quality of life. Our next goal is to develop novel therapies for the management of patients with HCC, particularly to improve their quality of life.

Keywords: Advanced HCC; Food Supplement; Combination Therapy; Autologous Anti-Tumor Immune-Therapy; Bangladesh

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies across the globe. It is particularly prevalent in the Asia-Pacific due to the high prevalence of hepatitis B (HBV) and C viruses (HCV) and fatty liver (MAFLD). In the global perspective, HCC stands 5th among all cancers in men and 8th in women and is ranked 3rd among all cancer-related deaths [1-3]. However, unfortunately, most HCC Bangladeshi patients are diagnosed with advanced HCC with a diameter of more than 5 cm [4]. This is due to a lack of effective surveillance and monitoring for HCC in the country [5]. In the context of Bangladesh's socio-economic status, the management of HCC largely remains a personal choice, contingent on the patient's financial status and the physician's expertise.

Therefore, in Bangladesh, most HCC patients are eligible for little or no treatment at diagnosis. As a result, the need to adopt an alternative approach for managing patients diagnosed with advanced HCC in Bangladesh remains a challenge, like elsewhere in the region. Here, we review different strategies adopted by our group in our quest to offer meaningful treatment to our HCC patients - a quest for a home-grown solution in a real-life situation.

Exploring the utility of food supplements for managing advanced HCC

Bangladesh has a long tradition of the practical use of food supplements in the management of many pathological conditions. Numerous studies have demonstrated the beneficial effects of food supplements in HCC. Studies with the hexose-correlated compound glycyrrhizin, branched-chain amino acids, and black tea have shown beneficial effects in advanced HCC [6-10].

Our group conducted two studies with green tea extract in advanced HCC [11,12]. Both studies yielded satisfactory results, with 47% and 26.7% of patients with end-stage HCC surviving beyond 60 days as according to published literature median survival of these patients are 3-5 months [13] and improvements in appetite and Eastern Cooperative Oncology Group (ECOG) performance status. It has been postulated that green tea extract, when combined with other adjuvants, exhibits anticancer and anti-inflammatory effects. It induces apoptosis in cancer cells and inhibits proliferation, differentiation, angiogenesis, invasion, and metastasis. The extract also stimulates anti-inflammatory cytokines and inhibits pro-inflammatory cytokines [12].

In a third study, we evaluated the role of arabinoxylan from rice bran, which has anti-oxidant and chemoprotective effects, in end-stage HCC [5]. Although no significant survival benefit was observed in advanced HCC with rice bran, patients who received rice bran showed a substantial improvement in ECOG performance status.

Recently, we have completed a clinical trial with Indian gooseberry (i.e., amlaki) in patients with advanced HCC [14]. It led to improvements in patients' performance status and demonstrated survival benefits, although neither was statistically significant. Indian gooseberry occupies an essential position in both Ayurveda and Unani medicine. It is rich in polyphenols and hydrolysable tannin-derived compounds, which prevent carcinogen-induced mutagenesis and lipid peroxidation. It also exerts pro-apoptotic and anti-proliferative effects on cancer cells and acts as a free radical scavenger, protecting DNA from reactive oxygen species

(ROS) [14].

Exploring the 'Combo' approach

Bangladesh has a strong base of generic medicine. Locally produced generics not only meet over 95% of the country's demand but are also exported to more than 130 countries across the globe. Therefore, our other approach was to focus on our generic medicines and advanced treatment modalities for HCC. One such study involved the combination of nivolumab and lenvatinib for the treatment of advanced HCC [15]. We enrolled advanced HCC patients in this study; partial response, defined as reduction of tumor size by 30% to 50% from baseline, was achieved in 35%, shrinkage or disappearance of tumor i.e. objective response rate (ORR) in 40% and disease control rate (DCR) in 78%. Therefore, there may be potential for the combination of nivolumab and lenvatinib. Nivolumab is an immune checkpoint inhibitor that restores the immune response to cancer cells. Lenvatinib, by contrast, is a multikinase inhibitor that reduces angiogenesis and suppresses tumor growth [16].

In our other small study involving an immune checkpoint inhibitor, we recruited patients with end-stage HCC who received a combination of atezolizumab and bevacizumab [17]. 50% of patients in our study survived beyond 6 months. Atezolizumab is an immune checkpoint inhibitor that specifically targets the PDL-1 receptor on T cells. Bevacizumab, by contrast, is a vascular endothelial growth factor (VEGF) inhibitor. Overexpression of VEGF facilitates HCC progression, a process that bevacizumab opposes.

Our group introduced trans-arterial chemoembolization (TACE) for HCC in Bangladesh, and we conducted a study that included HCC patients, who were treated with a 'combination' TACE and sorafenib, a multi-kinase inhibitor indicated for systemic treatment of advanced HCC [18]. 90-day survival was recorded at 57% in this study.

Autologous Anti-tumor immune-therapy - The way forward

Different immune checkpoint inhibitors act by binding to specific receptors on T cells, namely programmed death ligand-1 (PD-L1) and/or programmed death ligand-2 (PD-L2), with significant survival benefit [19,20]. Cancer cells bind to these receptors, leading to T-cell suppression and thereby interfering with their elimination by the immune system. However, when immune checkpoint receptors bind to their ligands, cancer cells can no longer bind to them, rendering T cells ineffective. Immune checkpoint inhibitors thus nullify this unique survival skill of cancer cells [21].

The concept of 'autologous anti-tumor immune-therapy', although different from immune checkpoint inhibitors, is based on the same principle, i.e., increasing the availability of T-cells to ensure cancer control by the host immune system. It has been hypothesized that the human body typically has an adequate number of T cells to counter malignancies; therefore, if T cells can be stimulated, we can expect a promising outcome in cancer management with this innovative approach [22].

Dendritic cells (DCs) are antigen-presenting cells (APCs). They are central in regulating immune response [23-25]. DCs have several key roles for inducing antigen-specific immune responses, including antigen recognition, capture and internalization, intracellular antigen processing, surface expression of antigenic epitopes and lymphocyte activation by presenting antigenic epitopes to lymphocytes [26-29].

It has been hypothesized that inadequate immune response leads to chronic hepatitis, which is characterized by repeated hepatocyte necrosis and regeneration, which in turn is likely to be the 'trigger' for HCC development [30]. On the one hand, there are reports of DC dysfunction in malignancies [31], while on the other hand, protection from cancer by immunization with DCs, as well as cancer regression following DC-based immunotherapy, have also been reported [32,33]. Moreover, experiments have shown that antigen-pulsed DCs elicit antigen-specific immune responses that are not observed with free antigens or vaccines [34-36]. It was observed that HBsAg-pulsed DCs induced higher levels of anti-HBs in HBV transgenic mice, a murine model of chronic HBV infection [37].

The efficacy of immature DCs in inducing anti-tumor immunity has been evaluated in a mouse model of colon cancer, established by subcutaneous injection of CMT-93 in the flank of C57BL/6 mice. CMT-93 is a murine colon cancer cell. The tumors were necrotized by injecting 100% ethanol (10 ml) into the tumors after they attained a minimum diameter of 10 mm. Bone marrow-derived immature DC from syngenic mice was injected into these necrotized tumors 48 hours after the ethanol injection. CD86-expressing

mature DC were detected in the tumors after injection of immature DC plus ethanol. However, such DCs were almost absent in tumors of non-treated mice. Injected DCs were detected in the spleen after 48 hours. These spleen DCs had significantly higher stimulatory capacity than those from untreated mice. There was a reduction in tumor size at 3 weeks of follow-up. These mice also survived longer than untreated mice [38].

Later another study assessed safety of directly injecting DCs into human HCC tumors. DCs were cultured from peripheral blood mononuclear cells (PBMCs) with granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-4 (IL-4) for 7 days prior to administration. 100,000 DCs were directly injected into tumor of 4 patients diagnosed with HCC. It was done under ultrasound guidance. Forty-eight hours before the DC injection, the tumors were destroyed by injecting 100% ethanol into the tumors, also under ultrasonographic guidance. DC injection was well tolerated, with no immediate or delayed adverse events observed in any patient. One patient also experienced a reduction in tumor size after intra-lesional DC injection [39].

These observations suggest that direct injection of ethanol plus DC therapy in tumors may represent a new therapeutic approach for 'autologous anti-tumor immune-therapy' for HCC. However, the stimulatory effect of DCs from HCC patients is significantly lower compared to those from liver cirrhosis patients and healthy individuals. This may be because DCs from HCC patients produce higher levels of nitric oxide (NO) and tumor necrosis factor-α (TNF-α) than those from patients with liver cirrhosis and healthy individuals [30]. DCs from HCC patients also exhibit reduced HLA-DR expression and lower IL-12 production.

In different types of human cancers, DC dysfunction, immature DC phenotype, reduced IL-12 production, increased IL-10 level and reduced surface antigen levels (e.g., CD86 and CD83) have also been reported [40-42]. A study further reported immature phenotype of most DCs from HCC [30].

Although encouraging results were obtained with immature DCs in murine malignant tumors, this poses a challenge for 'autologous anti-tumor immune-therapy' because the anti-tumor effect of DCs depends on DC maturity, with mature DCs having better anti-tumor efficacy and vice *versa* [40]. *In vivo*, DCs mature after capturing an antigen. They then produce cytokines and induce antigen-specific lymphocyte production [23,24]. *In vitro*, DCs cultured from PBMCs with GM-CSF and IL-4 exhibit an immature phenotype, with lower levels of CD83 and CD86 [30].

To enhance the efficacy of DC-based 'autologous anti-tumor immune-therapy', various approaches have been adopted. These include pulsing DCs with antigens, peptides, or tumor lysates, or fusing DCs with carcinoma cells [29,31,43,44]. DCs are first isolated from PBMC and then 'pulsed' before reinjection into hosts [29,33,43-45]. These pulsed DCs exert an antitumor effect either by infiltrating tumors or by activating lymphocytes and inducing cytokine production [30]. DCs-pulsed with autologous antigen, tumor extracts, tumor antigen, or tumor RNA, DC-fused with cancer cells, DC-based vaccination and IL-12-based immune-therapy to activate DC *in situ* have all been used for treatment of cancers [29,32,43,44,46,47].

An unresolved query about the efficacy of ICI in cancer management

Various publications have demonstrated the beneficial effects of ICI and kinase inhibitors in patients with advanced HCC, as discussed in this review. However, these drugs failed to show effective therapeutic potentials in many cancer patients, especially those with solid cancers [48,49]. The mechanism underlying this remains to be ascertained, but a major constraint remains within the concepts and overall theories of cancer management. The role of ICI is supported by evidence that it targets immune checkpoints and enables immune cells to attack cancer. The primary variability lies in the immune system's specificity in cancer patients. Cancer antigen-specific immunity may be low or ineffective in cancer patients, making ICI therapy ineffective. This can be partially addressed by administering antigen-specific immunocytes in cancer, with or without ICI. A simple approach may be to collect mutant cancer antigens from patients and pulse them with various types of immune cells. This can be administered to patients with or without ICI.

Conclusion

HCC remains a global management challenge, more so in a resource-constrained setting like Bangladesh, where the majority of HCC patients are diagnosed with an untreatable disease. We have been evaluating different approaches to develop a suitable solution to this problem. Management strategies for cancer are diverse, and additional approaches should be considered in light of multiple

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