The Potential Use of Cowpea Mosaic Virus as an Adjuvant After Cryoablation of Hepatocellular Carcinoma

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer in the world [2] and accounts for around 90% of cases of liver cancer [1]. In 2023, HCC accounted for 2.1% of all new cancer cases and 4.8% of all cancer deaths in the United States, with a 5-year survival rate of only 21.6% [3]. Therapeutic measures for HCC have been a topic of study for many years. Several systemic therapies are approved after completing phase III trials [1]. Curative measures for small HCC include resection and transplant [2]. Further studies may explore other immunotherapies, such as tyrosine kinase inhibitors [1], as well as locoregional therapy [2]. Cryoablation and the use of cowpea mosaic virus (CPMV) is one such potential therapy for HCC. The function of CPMV in this therapeutic model is to prevent relapse of the cancer following resection by inactivating tumor tissue and presenting its antigens to the patient's immune system in order to stimulate antitumor immunity systemically [5]. In this study, we review these methods in other cancer types and its potential role as a therapeutic agent for HCC.

Methods & Results

Our literature review included the search terms "cowpea mosaic virus" and "hepatocellular carcinoma" in PubMed. Articles that were included in the study contained material on topics that pertained to the efficacy of cowpea mosaic virus on various cancer types, epidemiology of hepatocellular carcinoma (HCC), as well as current and future therapies for HCC.

The studies specifically relating to CPMV have several methodologies. One article used a murine ovarian cancer model and delivered CPMV co-delivered with irradiated ovarian cancer cells [5]. Another study delivered weekly medical therapy either with CPMV or without CPMV as a control to dogs with inflammatory mammary cancer [6]. In a different article, mice with bilateral HCCs were treated with saline as a control, cryoablation only, CPMV only, or cryoablation plus CPMV [8].

The results showed significant improvement in several parameters with the CPMV groups in the studies compared to their respective controls. In the murine ovarian cancer study described above, the mice given a vaccine with CPMV with irradiated tumor cells had a 75% survival rate after the initial tumor challenge and 100% of these mice survived the subsequent rechallenges [5]. CPMV was compared with monophosphoryl lipid A (MPLA), which is an FDA-approved vaccine adjuvant. CPMV as an adjuvant with irradiated cells outperformed MPLA as an adjuvant and improved length of mouse survival significantly ($p = 0.03$) [5]. In the canine inflammatory mammary cancer study, the group treated with eCPMV (empty cowpea mosaic virus) in addition to medical therapy had tumor shrinkage and a decrease of Treg/CD8 ratio [6]. The group treated with eCPMV plus medical therapy had a significant ($p = 0.033$) overall survival compared to the group treated with only medical therapy [6].

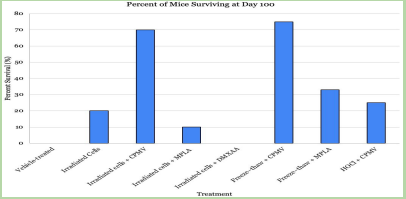
A study described that the inhalation of nanoparticles from CPMV activated neutrophils to generate an antitumor response, and it helped reduce existing lung metastatic melanoma [7]. Inhaled CPMV also helped with antitumor immunity in other tumor models, such as ovarian, colon, and breast cancers, as well as treatment efficacy in these cancers [7]. In the study of mice with bilateral HCCs, both cryoablation and CPMV-only groups had showed improved treatment of the tumor compared to control after two weeks, and a combination treatment of cryoablation and CPMV was significantly the most effective at reducing tumor growth compared to control ($p < 0.0001$) [8]. Cryotherapy plus CPMV inhibited the growth of treated and untreated tumors, caused transient immunosuppression followed by immunostimulation, and caused an increase in CD4 and CD8 cell counts in the center of tumors without causing increased toxicity or weight loss compared to the other treatment groups [8].

Conclusions

Cowpea mosaic virus (CPMV) shows promise as a possible therapeutic agent for HCC, specifically to help reduce recurrence of cancer after remission in addition to reducing existing tumor size and activating an immune response. CPMV was tested in several different cancer types in the studies described, including ovarian, inflammatory mammary, lung metastatic melanoma, and hepatocellular carcinomas. In HCC, CPMV with cryoablation was tested compared to control, cryoablation only, and CPMV only. This study showed that the only treatment group that slowed growth of untreated tumors was CPMV plus cryoablation. This shows the effectiveness of CPMV plus cryoablation in the treatment of HCC.

The immune response induced by CPMV is crucial to the goal of reducing recurrence of HCC. CPMV plus cryoablation resulted in an increase in tumor-infiltrating lymphocytes, which are associated with an antitumor response. Cryoablation and CPMV also resulted in lower CXCL1 levels, which is a chemokine associated with angiogenesis and pro-oncotic properties [8]. The safety profile of CPMV has also been promising in the studies described. CPMV nanoparticles are stable and nontoxic [7]. In addition, eCPMV (empty cowpea mosaic virus) was found not to have negative effects on hepatic, renal, and digestive functions in the canine study [6]. There was no significant difference in treatment toxicity between the groups studies in the HCC mice model [8].

Future research may focus on human models of carcinoma, such as common cancer cell lines. In addition, the combination of CPMV, cryoablation, and irradiated cancer cells may be tested as the latter two variables were tested separately with CPMV. Another consideration is the possibility of adding a PD-1 inhibitor to the cryoablation plus CPMV treatment proposal, as the treatment was shown to increase PD-1 expression on CD4 and CD8 lymphocytes [8].



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