Vaccines in Gastrointestinal Malignancies

Subjects: Immunology

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Gastrointestinal (GI) malignancies are some of the most common malignancies and include colorectal, gastric, esophageal, hepatocellular, and pancreatic carcinomas. Overall five-year survival rates for many of these malignancies are low, with many patients presenting with advanced disease. Thus, it is important to continue to investigate and create novel therapeutic interventions to treat these malignancies.

Keywords: gastrointestinal cancer ; vaccines

1. Introduction

Gastrointestinal (GI) malignancies are some of the most common malignancies and include colorectal, gastric, esophageal, hepatocellular, and pancreatic carcinomas. Overall five-year survival rates for many of these malignancies are low, with many patients presenting with advanced disease. Thus, it is important to continue to investigate and create novel therapeutic interventions to treat these malignancies. Recently, with the advances in immunotherapy in GI malignancies, the development of cancer vaccines has become an important area of interest.

2. Role of Vaccines in Cancer

Therapeutic cancer vaccines are a form of immunotherapy that aims to utilize a patient's own immune system to treat their cancer. In contrast to prophylactic vaccines (such as influenza or pneumococcal vaccines), which are given to healthy patients, therapeutic cancer vaccines are administered to patients who have already been diagnosed with cancer [1]. There are many studies focusing on therapeutic cancer vaccines given their high potential for immunotherapy-based advancement in cancer treatment; however, relatively few cancer vaccines have had clinical success. With further development of this field and the ability to identify additional targets, some researchers have projected that therapeutic cancer vaccines will play a larger role in cancer treatment, serving as a supplement or even alternative to traditional treatment modalities including surgical resection, chemotherapy, and radiation [2].

3. Vaccines in Gastrointestinal Malignancies

Overall, vaccine-based therapies have had little success in treating GI malignancies. Earlier studies in the 1970s investigated targeting cancer antigens associated with certain mutations and tumor suppressor genes such as RAS and TP53 with the thought that vaccine targets could develop immunogenicity [3].

Some studies did find a benefit in MAGE-direct vaccination; however, overall clinical benefit has not been demonstrated [4]. For example, a phase I clinical trial combined the ring finger protein 43 (RNF43) with other peptides and showed an 83% disease stability; however, there was no reduction in tumor burden [5]. A phase I trial by Sato et al. showed that about half of the patients had an increase in functional CTL activity after the use of personalized peptide vaccines. However, other studies have shown that even with high immune response, this did not correlate with meaningful clinical benefit [6].

In gastric cancer, TAAs have been targeted by vaccines with limited efficacy. In a phase I trial of 14 patients with advanced refractory gastric cancer, there was safety in administration but without clinical efficacy [7]. Another trial of 28 patients with advanced, refractory gastric cancer showed that the combination of dendritic cell vaccine with chemotherapy was safe but did not demonstrate a signal for clinical benefit; furthermore, almost half of the patients experienced disease progression [8]. One phase I/Ib, open-label, single-arm trial to assess the safety of OTSGC-A24 cancer vaccine in advanced gastric cancer showed in 24 patients that an OTSGC-A24 combined peptide cancer vaccine was well tolerated and had a significant response in cytotoxic T lymphocyte (CTL) induction.

The initial rationale for these clinical trials was that the TAAs seen are overexpressed in HCC and are immunogenic in patients. Some phase I trials in peptide vaccines, dendritic cell vaccines, and oncolytic viruses that target certain TAAs have been shown to be tolerated by patients and have some immune response [9]. , the use of a dendritic cell vaccine was investigated in combination with sorafenib and showed a significant increase in specific CD8+ T cells in a majority of patients [10]. A phase II study using GPC3 peptide vaccines as adjuvant maintenance therapy in 35 patients with HCC showed efficacy in delaying HCC recurrence at the 1-year, however, not at the 2-year mark [11].

There have been various studies in pancreatic cancer looking at the effectiveness of cancer vaccines. Thus, this study showed the utility of combined chemotherapy and vaccines to promote increased levels of cancer-specific T cells in immunogenic cancers such as pancreatic cancer. For example, vaccines that target TAAs have been used for therapeutic interventions, specifically towards CA 19-9, which is a TAA that is highly expressed on pancreatic cancer cells. There has been data suggesting that using DC vaccines in pancreatic cancer could help inhibit pancreatic cancer metastases through the use of intraperitoneal injection of DC vaccines [12].

4. Vaccines in Prevention (HBV and HPV)

Vaccinations against cancer-causing infections are important to cancer prevention for specific malignancies. Data estimate that 10% of yearly cancers worldwide are caused by viral infections [13]. Vaccinations against hepatitis B virus (HBV) and certain genotypes of human papillomavirus (HPV) currently exist and show efficacy in the prevention of cancers.

HBV vaccines have been available for many years, and certain countries with high rates of endemic HBV infection have been shown to have associated high rates of HCC. In these countries, implementing universal infant HBV vaccination policies has helped reduce HBV infection, which led to a reduction in HCC incidence and mortality [14]. The impact of preventive vaccination programs in combating cancer was exemplified in the HBV immunization program started in Taiwan in 1982. This program initially targeted infants of HBV-infected mothers, then broadened to all infants, and eventually developed into a universal vaccination program leading to significant reductions in the incidence of HCC [15].

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