Immunotherapy regimens for metastatic colorectal carcinomas

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ABSTRACT

Metastatic colorectal cancer (mCRC) is a leading cause of cancer-related mortality with a 5-year overall survival rate of 13%. Despite recent advances in cancer immunotherapy, only the minority of CRC patients (<15%) with microsatellite instability can potentially benefit from immune checkpoint inhibitors, the only immunotherapy currently approved for mCRC. In that context, there is an unmet need to improve survival in mCRC. Our ever-increasing understanding of the immune system and its interactions with cancer has allowed development of multiple strategies to potentially improve outcomes in the majority of mCRC patients. Various approaches to manipulate patient immunity to recognize and kill colorectal cancer cells are being explored simultaneously, with combination therapies likely being the most effective. Ideally, therapies would target tumor-restricted antigens selectively found in tumors, but shielded from immune attack in normal tissues, to mount an effective cytotoxic T-cell response, while also overcoming cellular and molecular inhibitory pathways, self-tolerance, and T-cell exhaustion. Here, we provide a brief overview of the most promising immunotherapy candidates in mCRC and their strategies to produce a lasting immune response and clinical benefit in patients with mCRC.

Colorectal cancer (CRC) is the 2nd leading cause of cancer related death in the United States. At diagnosis, 20% of CRC patients have distant metastasis (mCRC) and half of all recurrences are in the form of metastatic disease. The overall survival in mCRC is 13% at 5 years. Excluding oligometastatic disease, the first-line treatment in mCRC consists of fluoropyrimidines and oxaliplatin or irinotecan chemotherapeutic agents. Adding targeted agents like cetuximab, bevacizumab, or panitumumab offers a modest increase in overall survival. The accelerated development of cancer immunotherapy over the last decade has revolutionized the current landscape for many cancer types. Here, we discuss some of the most promising developments in immune checkpoint inhibitor therapies and tumor vaccines for mCRC.

As with viral antigens, tumor-associated antigens (TAAs) are degraded into small peptides which are ultimately packaged in the groove of newly synthesized major histocompatibility complex (MHC) class I and II molecules and delivered as peptide-MHC complexes to the cell membrane of antigen presenting cells (APCs). T cell receptors (TCRs) on CD8+ and CD4+ T cells recognize these peptide-MHC complexes, and in the presence of the appropriate costimulatory signals from APCs, such as CD80, CD86, CD40, CD137, OX40L, and others, this in turn leads to activation of the T cells to proliferate, acquire effector functions such as cytokine production and cytolsis, and to produce long-lasting memory responses. In this context, development of cancer vaccines is often limited by the discovery of TAAs which are ubiquitously expressed by the cancer cells and absent from normal cells or immunologically compartmentalized to prevent damage to normal tissues from cytotoxic T cells (CTLs).

The efficacy of checkpoint inhibitors such as nivolumab and pembrolizumab has recently been established in microsatellite instability (MSI) CRC, likely reflecting the immunological benefit derived from abundance of mutation-associated neoantigens that serve as targets of effector T cells. This hypothesis is further supported by the poor efficacy of checkpoint inhibitors in microsatellite stable (MSS) CRC. Moreover, distinct cancer immune phenotypes are increasingly being recognized, with tumors characterized by an "immune desert," lacking CTLs due to an absence of T-cell priming, tolerance, and/or immunologic ignorance due to a paucity of neoantigens or presentation by APCs, as the most difficult to treat. Approximately 85% of CRC patients have MSS disease, and often produce an abundance of transforming growth factor (TGF)-β contributing to immunologic tolerance by activation of Foxp3+ regulatory T cells (Tregs) as well as activation of stromal elements in the tumor microenvironment that inhibit CTL penetration, such as myeloid-derived suppressor cells (MDSCs). Nevertheless, novel therapeutic combinations are being explored to increase the presentation of neoantigens in MSS CRC, such as dual immune checkpoint blockade with Durvalumab and Tremelimumab following targeted exposure to stereotactic body radiation therapy.

Among the earliest modern attempts to harness the power of the immune system to fight cancer cells was the development of autologous cancer cell vaccines. These are comprised of...
autologous whole tumor cell lysates combined with immune adjuvants such as bacillus Calmette-Guérin (BCG), bacterial cell wall products, or virus-infected and irradiated tumor cells that are administered back to the patient to elicit adaptive antitumor immunity to multiple TAAs. OncoVAX (Vaccinogen, Inc.) utilizes irradiated, non-tumorigenic autologous tumor cells with BCG and had success in early phase clinical trials with improvement in disease-free and overall survival. The pivotal Phase II trial of OncoVAX [NCT02448173] started in 2015 under an FDA Special Protocol Assessment classification and is expected to complete enrollment by July, 2020. This approach may result in effective antitumor immunity but the personalized nature of this vaccine generation may pose a significant hurdle to its widespread adoption. Unfortunately, a similar approach using Newcastle disease virus-infected autologous tumors did not improve overall and disease-free survival in a randomized study.

In addition to autologous tumor vaccines, immune responses can also be elicited with peptide, dendritic cell, DNA, or live attenuated viral vector-based immunotherapy. In the simplest form, tumor-associated peptides are isolated and administered to the patient with immunologic adjuvants. The peptide vaccine OCV-C02, containing epitopes derived from human papillomavirus CIN3+ cell wall products, or virus-infected and irradiated tumor cells are administered back to the patient to elicit adaptive antitumor immunity in preclinical models of CRC, alone or in combination with other vaccines.

Among viral vectors, adenovirus and poxviruses (vaccinia, fowlpox) are popular due to their potential for pathogenesis as well as insertional mutagenesis. The safety and efficacy of some viral vectors in clinical trials has not been consistent due to potential for pathogenesis and potential for insertional mutagenesis. Attenuated viral or bacterial vectors is likely the most robust way to induce tumor immunity in preclinical models of CRC, alone or in combination with other vaccines.

Carcinoembryonic antigen (CEA), a common CRC tumor marker, has been used with a DC-based vaccine approach to elicit antitumor immune responses, however, in a Phase II trial of the vaccine, the PFS and OS were not superior to best supportive care in mCRC. On the other hand, DNA-based vaccines can be delivered to APCs as naked DNA plasmids, often combined with immunologic adjuvants such as IL-12, IL-15, and/or GM-CSF. Upon delivery to mammalian cells, DNA plasmids induce expression of specific antigens that are designed to activate the immune system directly by delivery into DCs or indirectly into parenchymal cells leading to antigen expression and subsequent uptake by APCs. CEA, nuclear oncoprotein MYB, heat shock protein 105, guanylyl cyclase C (GUCY2C), and human telomerase reverse transcriptase (hTERT) -based DNA vaccines have successfully induced antitumor immunity in preclinical models of CRC, alone or in combination with other vaccines.

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response.38 A Phase II study evaluated safety, tolerability, CEA-specific immunity, and objective clinical responses following administration of a non-replicating canarypox virus expressing CEA and B7.1 (ALVAC-CEA/B7.1) administered concurrently or sequentially with systemic chemotherapy (IFL/FOLIRI) and/or tetanus toxoid (TT) in 118 patients with mCRC. Gastrointestinal and hematologic serious adverse events (SAEs) were seen in 30 and 24 patients, respectively. The majority of patients across all groups developed a CEA-specific T-cell response which was not attenuated by chemotherapy. The total objective response was observed in 44.7% of subjects in the chemotherapy + ALVAC group (n = 38), 31.3% of subjects in the ALVAC + TT + chemotherapy group (n = 32), and 44.1% of subjects in the ALVAC + chemotherapy group (n = 34).39 Overall, the study demonstrated the feasibility of combination chemoimmunotherapy and provides rationale to develop combinations intended to achieve clinical remission in mCRC.39 Another study is currently evaluating a combination of adenovirus-CEA vaccine with avelumab (a checkpoint inhibitor) with or without chemotherapy in previously untreated mCRC (NCT03050814).40

Beyond CEA, mucin (MUC1), epithelial cell adhesion molecule (EpCAM), the oncofetal antigen 5T4, and guanyl cyclase C (GUCY2C) have also been in clinical development. MUC1 is normally expressed on the lining of human colon and is expressed in a modified form on advanced polyps and CRC. MUC1 with poly-ICLC adjuvant was tested in a Phase I/II setting in patients with a history of adenomatous polyps and found to be highly immunogenic in 43.6% of patients, whereas a high frequency of pre-vaccination MDSCs were found to be associated with immune non-responders.41 EpCAM is highly expressed in many epithelial cancers including CRC.42 EpCAM protein produced in a baculovirus expression system and conjugated to alum, was administered to 7 CRC patients with GM-CSF, inducing a Th1-biased humoral and cellular immune response.43 Future studies are needed to demonstrate objective clinical responses in patients. 5T4 is a trophoblast glycoprotein with high-level expression in human adenocarcinomas, including CRC where it is found in more than 90% of tumors.44 A poxvirus-based 5T4 vaccine (TroVax) was recently tested in mCRC patients with stable disease at completion of standard chemotherapy.45 Of the 52 patients in the study, 9 were randomized to surveillance alone, 9 to cyclophosphamide alone, 19 to TroVax only, and 18 to a combination of TroVax and cyclophosphamide. TroVax was safe, well tolerated, and resulted in significantly improved PFS (5.6 vs 2.4 months) and OS (20 vs 10.3 months). Interestingly, the combination of TroVax and cyclophosphamide was not superior to TroVax alone. These data look promising but a larger sample size is required to demonstrate efficacy of TroVax without the need for cyclophosphamide.

GUCY2C, a cyclic GMP (cGMP) synthesizing protein is universally expressed in apical brush border membranes of intestinal cells and GUCY2C protein is found in nearly all primary and metastatic CRCs, with uniform expression by tumor cells, regardless of location or grade.46–48 An adenosine vector (Ad5)-based vaccine expressing GUCY2C conjugated to the Pan DR epitope PADRE (Ad5-GUCY2C-PADRE) was evaluated in humans in an open-label, single-dose feasibility study in early-stage colorectal cancer patients [NCT01972737].49,50 The vaccine was safe and immunogenic, producing GUCY2C-specific CD8+ CTL responses in 40% of patients. A larger Phase II study is planned to begin in 2018 to explore the vaccine’s efficacy for GUCY2C-expressing gastrointestinal malignancies.

Interest in cancer immunotherapy development began in 1893 with William Coley,51 but little progress was made over the following century. Now, our understanding of the molecular and cellular mechanisms and complexities of the immune system has advanced significantly and the prospects of successful cancer immunotherapy development grow brighter with the pace of scientific discovery. The effectiveness of checkpoint inhibition in MSI tumors, including CRC, provides evidence that characterizing molecular and immunological subtypes may be important in determining patients most capable of inducing effective tumor immunity or selecting the immunotherapeutic approach most favorable for a given patient. Unfortunately, more than 95% of mCRC patients have MSS disease and cannot be treated with current immunotherapy options.52 A growing body of evidence suggests that effective antitumor immunity in mCRC may be achieved using experimental cancer vaccines in combination regimens that promote depletion of Tregs and MDSCs, and block checkpoints, that prevent the induction or intratumoral activity of T-cell responses.

Disclosure of potential conflicts of interest

A.E.S. has patents with royalties licensed to Targeted Diagnostics & Therapeutics, Inc. Sponsors had no role in the writing of this manuscript or in the decision to publish it.

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