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Review

Immunotherapy in colorectal cancer: What have we learned so far?

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ABSTRACT

After decades of progress based on chemotherapy and targeted agents, patients with metastatic colorectal cancer still have low long-term survival, with more than 500,000 deaths occurring worldwide every year. Recent results showing clinical evidence of efficacy using immunotherapy in other types of tumors, such as melanoma and lung cancer, have also made this a viable therapy for evaluation in colorectal cancer in clinical trials.

The development of cancer immunotherapies is progressing quickly, with a variety of technological approaches. This review summarizes the current status of clinical trials testing immunotherapy in colorectal cancer and discusses what has been learned based on previous results. Immunotherapy strategies, such as various models of vaccines, effector-cell therapy and checkpoint inhibitor antibodies, provide protection against progression for a limited subset of patients diagnosed with colorectal cancer.

A better understanding of particular immune cell types and pathways in each patient is still needed. These findings will enable the development of novel biomarkers to select the appropriate subset of patients to be treated with a particular immunotherapy, and the tendencies determined from recent results can guide clinical practice for oncologists in this new therapeutic area and in the design of the next round of clinical trials.

Contents

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1. Introduction

Despite very important therapeutic advances produced during the last decade, colorectal cancer (CRC) is the third most common cancer in men and the second in women in the world. There is still a real need for therapies that would reduce the risk of recurrence after surgery and chemotherapy treatment and prolong patient survival with metastatic disease.

Surgical resection of localized tumors improves patient's survival [1], but over half of them will develop metastasis [2]. CRC patients diagnosed in stage III and IV are treated with adjuvant chemotherapy such as 5FU, oxaliplatin, and anti-EGFR antibodies, but only a minority of them will benefit. Although using these drugs to treat CRC provides important treatment options for patients, their limitations including drug resistance, poor efficacy and severe side effects make necessary the development of new therapeutic options to avoid metastatic spread and eventually improve patient survival. In fact, chemotherapy is useful for the treatment of regionally metastatic CRC, but it shows low efficacy against distant metastasis [3]. The prognosis for patients with advanced disease remains unfavorable due to the frequency of recurrence, distant metastasis, and resistance to chemotherapy. Thus, novel therapeutic approaches are needed through understanding of the role of the immune system in the development and progression of CRC and by the use of immunotherapeutic approaches.

In addition to novel chemotherapy and radiation alternatives, harnessing the immune system by immunotherapy has been proposed as one of the most promising approaches in oncology. Therefore, immunotherapy may be effective for treating CRC patients and/or preventing relapse.

Immunotherapy refers to an active therapeutic approach designed to trigger the immune system to respond against tumor-associated antigens (TAAs) and attack tumoral cells. Although we are conscious of innate immune response, this review will discuss only “adoptive immunotherapy”.

The immune system can prevent the development and progression of cancer through immune surveillance. Immunosurveillance is the capacity of the immune system to promote an effective immune response against tumor cell-specific neoantigens that are not expressed by normal cells to eliminate cancerous cells before clinical expression of cancer [4].

Immunosurveillance may function as a component of a broader process, termed cancer immunoediting. Cancer immunoediting is a dynamic process consisting of three phases: elimination, equilibrium, and escape. Elimination represents the classical concept of immunosurveillance. In this phase, components of innate and adaptive immunity may eradicate the growing tumor and prevent carcinogenesis. However, if this process is not successful, the tumor cells that are not killed may enter the equilibrium phase, a subclinical phase in which continuous sculpting of tumor cells produces cells resistant to immune effector cells. This process leads to the immune selection of tumor cell variants with reduced immunogenicity. These variants may eventually evade the immune system by a variety of mechanisms to allow tumor progression and clinical expression in the escape phase [5,6].

There is increasing evidence suggesting that immune cells play an important role in regulating the development of tumors in CRC, including cells of innate and adoptive immunity, and supporting the concept of immunosurveillance and immunoediting. Among the innate immune system, the main cells involved are 1) natural killer (NK) cells, which play a major role in preventing recurrence and are a prognostic factor [7,8], 2) unconventional T lymphocytes, including Natural Killer T (NKT) cells that are associated with better prognosis in CRC [9] and Vgamma9Vdelta T cells, which have a strong cytotoxic activity against tumor cells in CRC [10], and 3) tumor infiltrating macrophages (TIM), which have been associated with better prognosis in CRC. The most important cells of adaptive immunity are involved in intratumoral memory CD8 T cells, and CD45RO memory T cell lymphocytes infiltrate, which has been shown to be a better prognostic factor than classic tumor node metastasis [11] [12].

TAAs are also involved in immunosurveillance. TAAs are molecules that are expressed by tumor cells and allow the immune system to recognize the tumor cells. In CRC, TAAs are normal self-antigens expressed at low levels in normal cells and in embryonic tissues and at high levels in tumor cells. The most important TAA in CRC is the carcinoembryonic antigen (CEA), which is normally expressed in fetal tissue and is overexpressed in CRC. In CRC patients, it has been shown that CEA may have immunosuppressive activity [13]. Therefore, TAAs seem to play an important role in immunosurveillance and are potential targets for immunotherapy in vaccination strategies.

Microsatellite instability (MSI) is linked to immunogenic TAAs, and it has been observed in both sporadic and Lynch syndrome-associated CRC. It has been shown that MSI CRC patients have high levels of tumor infiltrating lymphocytes (TILs) and better prognosis than patients without MSI [14–16].

MSI induces frameshift somatic mutations in target genes with repeated sequences leading to its inactivation and the creation of potentially immunogenic neoantigens. The major gene in MSI CRC patients is TGF®R2, which is mutated in 90% of cases [17]. It has been suggested that these neoantigens are correlated with better prognosis in MSI CRC patients by inducing a specific immune response against tumors.

The immune system can fail to control tumor growth through the development of efficient escape mechanisms by the tumor cells. Several escape mechanisms have been described in CRC. Downregulation of major histocompatibility complex class I (MHC-I) expression has been shown in more than 70% of CRC [18], which has been associated with poor prognosis [19]. Induction of regulatory T cells (Tregs) is an important escape mechanism in cancer by blocking antitumor immune responses via the secretion of immunosuppressive cytokines, such as IL-10 and TGF®, and via cell-cell contact mechanisms. In CRC patients have been found increased levels of Tregs in peripheral blood and a high density of infiltrating Tregs in tumor tissue, which have been associated with poor prognosis in CRC [20–22]. PDL-1, an immunoregulatory protein that inhibits T cell activation by binding to its receptor PD-1, is strongly expressed in CRC and is associated with poor outcome [23]. MSI CRC may also develop effective escape mechanisms, such as high levels of intratumoral Treg [24] or downregulation of HLA class I [22,25]. The development of these escape mechanisms represents the major obstacle for the development of effective immunotherapy in CRC.

The aim of this study was to investigate what is known about immunotherapy advances in CRC and the current progress of clinical trials being developed. Herein, we elucidate some particular characteristics that could differentiate CRC from other tumors in generating strategies for response to immunotherapy and consequently discuss feasible actions to follow in future clinical trials.

2. Immunotherapeutic approaches

Causes that decrease immunity in CRC patients include 1) specific changes that make tumoral cells express new antigens that are not properly recognized by the immune system or lack expression of those that could be naturally recognized, 2) specific chemotherapy treatment inducing immunogenic cell death, for example, oxaliplatin reducing dendritic cell (DC) reactivity [26,27] and 3) anti-VEGF agents inhibiting regulatory T cell (Treg) expansion [28].

Immunotherapy for CRC is directed to either increase anti-tumor immune response with vaccines or stimulating cytokines or avoid the suppression of immune response against tumoral cells by using checkpoint inhibitors with specific antibodies.

The goal of CRC vaccination is to elicit an anti-tumor immune response that will eliminate a tumor and provide ongoing surveillance to protect against its re-growth. In contrast, the aim of antibodies that