Updates on immunotherapy for colorectal cancer

Aparna Kalyan[1,2], Sheetal Kircher[2], Hiral Shah[1,2], Mary Mulcahy[2], Al Benson[2]

[1]Developmental Therapeutics Program, Division of Hematology and Oncology, Feinberg School of Medicine, Chicago, IL, USA; [2]Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL, USA

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Correspondence to: Aparna Kalyan, MBBS. Division of Hematology and Oncology, 676 N St.Clair, Suite 850, Chicago, IL 60611, USA.
Email: Aparna.kalyan@northwestern.edu.

Abstract: Despite significant advances in standard of care therapies, the 5-year survival rate for metastatic colorectal cancer (CRC) remains around 12%. Immunotherapy has not provided the stellar advances in colorectal cancer that has been seen in other malignancies. Immunotherapy appears to play a pivotal role in microsatellite unstable CRC tumors where the response rates are profound. These results have led to FDA approval of pembrolizumab for MSI-H CRC tumors. Additional research into several new immune agents including IDO inhibitors, vaccine therapy and combinatorial agents are being evaluated for CRC. This review will provide an overview of the approaches currently being investigated.

Keywords: Colorectal cancer (CRC); immunotherapy; microsatellite instability (MSI); vaccine therapy

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Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed malignancy worldwide and in the United States, CRC is the second leading cause of cancer related deaths (1). By 2030, the projected global burden of CRC is expected to reach more than 2.2 million new cases and 1.1 million deaths (2). Despite significant advances in standard of care therapies, the 5-year survival rate for patients diagnosed with metastatic CRC remains very poor at approximately 12% (1). In the recent years several great advances in our understanding of the intricate relationship between the immune system and cancer has led to significant developments in tumor immunotherapy. Malignancies such as melanoma, renal cell carcinoma and non-small cell lung cancer, have already seen promising clinical benefit from immunotherapy such as check point inhibitors leading to FDA approval for the immunomodulatory monoclonal antibodies (mAb) such as ipilimumab, nivolumab, pembrolizumab and atezolizumab (3-6). Despite the overall advances in immunotherapy, this therapeutic approach for patients with CRC is still under development and there are many immunotherapies currently undergoing clinical investigation. This review article will highlight updates in several immunotherapy approaches for CRC including cancer vaccines, oncolytic virus therapy, immune checkpoint inhibitors therapy and immune modulators such as IDO1-inhibitors and anti-OX40 agonist therapy.

Microsatellite instability (MSI) in CRC immunotherapy

The one area within CRC where immunotherapy appears to play a pivotal role is in microsatellite unstable tumors. CRC can be divided into subsets based on the tumor's molecular profile which provides important predictive and prognostic information (7). Microsatellites are short tandem DNA repeats and MSI defined as a change in the microsatellite region within the tumor cells compared to

normal cells. MSI results for either insertion or deletion of repeating units attributed to defects in the DNA mismatch repair (MMR) system (8). The MSI subgroup makes up approximately 15% of all CRCs and its prevalence is stage dependent; 15% of stage II–III CRC are MMR deficient (dMMR) and only 4–5% of stage IV CRC are dMMR (9,10). The inherited cases of MSI represent the molecular hallmark of hereditary non-polyposis colorectal cancer (HNPCC), also known as Lynch Syndrome (LS). The associated germ line mutations in LS are seen in one of the following MMR genes; MLH1, MSH2, HSH6, PMS2 (11). However, most cases of MMR deficiency (nearly two thirds of MSI CRC) are sporadic in nature and are associated with epigenetic modification that leads to the inactivation of the MLH1 gene (12). It is important to note that CRC patients with MSI high (MSI-H) tumors present with a distinct clinic-pathological pattern such as proximal colon location in younger patients, early stage and poorly differentiated tumors that exhibit an abundance of tumor infiltrating lymphocytes (TIL) (13). In recent years, it has also been established that MSI-H status convers a better overall prognosis compared to patients with microsatellite stable disease (MSS or pMMR) (14).

As mentioned above, dMMR CRC is associated with a robust immune response such as higher concentrations of TILs, specifically CD8+ and memory CD45RO+ TILs, both of which have been established as good prognostic indicators in CRC (14). Despite this high level of immunogenicity, dMMR CRC is not spontaneously eradicated by the immune system, indicating that there are a number of escape mechanisms employed by the tumor. In a recent study, Llosa *et al.* demonstrated that in MSI-H CRC tumors there is an upregulation of check point inhibitory molecules such as PD1, PDL1, CTLA4, lymphocyte activation gene 3 and IDO (15). This discovery supports the use of check point blockade inhibitor therapy in this specific subset of CRC patients in order to take advantage of the endogenous immune response.

For example, the first phase I clinical trial that evaluated the use of an anti-PD1 mAb in patients with advanced solid malignancies showed that only one patient with CRC had a complete durable response. This patient had dMMR disease (16). Following this, a phase II study by Le *et al.* was published which evaluated the use of Pembrolizumab in CRC patients who were both dMMR and pMMR (17). At the 20-week follow up, the study reached its primary endpoint as the objective response rate was 40% dMMR CRC patients. Additionally, the study demonstrated 90% disease control rate and 78% immune-related PFS in the dMMR CRC cohort as compared to the pMMR group in which no objective response rate was seen and the immune-related PFS was only 11%. Interestingly, only three out of 11 patients with LS associated CRC experienced an objective response compared to all six patients with sporadic dMMR had a response (17). The possible explanation for this observation could be that germline dMMR CRC carries a lower number of mutations on average compared to the sporadic cases. This study provided support for the anti-PD1 approach for treatment of dMMR CRC, however due to a small sample size, there remains a significant need for larger randomized trials.

At present, there are three ongoing clinical trials designed to better answer this question of anti-PD1 utility in dMMR CRC. The phase II (KEYNOTE-164) and phase III (KEYNOTE-177) clinical trials are evaluating pembrolizumab in this patient population. CHECKMATE-142 trial is evaluating nivolumab and nivolumab plus ipilimumab in recurrent or mCRC. Additionally, the anti-PD-L1 mAb durvalumab is currently being tested in dMMR CRC patients (NCT02227667). Atezolizumab, another anti-PD-L1 mAb is being evaluated in combination with standard chemotherapy in this cohort as well (NCT01633970).

Therapeutic vaccines

Cancer vaccination has been used in multiple tumor types to elicit an anti-tumor immune response that can eliminate a tumor and provide ongoing surveillance to protect against its re-growth. The types of vaccines used in CRC in the past decade include autologous, peptide, viral vector and dendritic cell (DC).

Autologous vaccines

Autologous vaccines use cells directly removed from the patient's own tumor and by definition, they encompass all relevant tumor-associated antigens (TAAs). Compared to single peptide based vaccines, autologous tumor cells can eliminate the chance of tumor escape by inducing adaptive immunity against several tumor antigens (18). However, whole tumor cell vaccines have shown limited clinical utility because the majority of the antigens are present in normal cells and the generated immune response is not specific to cancer cells (19). Several attempts have been made to improve the efficacy of autologous vaccines. One

example of such modification was demonstrated by a multi-institution, randomized phase III trial in which a patient-specific vaccine was created using autologous cancer cells in combination with BCG vaccine (20). Patients were randomized to two groups, surgical resection plus the vaccine versus resection alone. There was no statistically significant difference observed in disease free and overall survival at median follow up of over seven years (20). Longer follow-up analysis did reveal statistically significant improvements in all endpoints including recurrence-free interval, overall survival, and recurrence-free survival but only in stage II colon cancer patients (21).

Another approach to improve the immunogenicity of autologous vaccines in CRC utilizes autologous tumor cell vaccine modified by a non-lytic, low pathogenic strain of the Newcastle disease virus (NDV). A phase II trial in which 23 patients with mCRC received metastasis-derived tumor cells incubated with NDV showed a decrease in recurrence rate of 61% compared to 87% in a historical matched control group (22). Based on this data a phase III trial randomized patients with colon or rectal cancer and confirmed liver metastases to either NDV-infected autologous tumor cell vaccine group or control group (23). No differences in overall or metastasis-free survival were detected between the two groups. However, subgroup analysis showed a significant improvement in both overall and metastasis free survival and in colon cancer patients compared to rectal cancer patients in the intention-to-treat analysis. Due to the limited efficacy demonstrated in most clinical trials, autologous vaccines have not significantly altered clinical practice to date. Overall, there is some evidence to support the use of autologous vaccines in the setting of colon cancer but the evidence is less robust for rectal cancer. Additionally, CRC stage II disease seems to receive more benefit in comparison to stage III disease, however the exact reasons for this distinction remain to be elucidated.

Peptide vaccines

The rationale behind the use of peptide vaccine is based on the identification and synthesis of 8–11 amino acids long peptides that are antigenic epitopes derived from tumor associated antigens (TAA) or tumor specific antigens (TSA). Peptide vaccines are able to elicit specific T cells against TSA and can be co-administered with adjuvants in order to enhance the tumor specific immune response (24). In CRC, commonly targeted TAA by peptide vaccines include carcinoembryonic antigen (CEA) (25), epidermal growth factor receptor (EGFR) (26), mucin 1 (27), squamous cell carcinoma antigen recognized by T cells 3 (SART3) (28) and Survivin-2B (29). The important advantages of peptides vaccines include their safety profile, low cost of production and storage and the ability to induce a very specific anti-tumor immune response. However, there are several disadvantages that limit the effectiveness of peptide vaccines including weak immunogenicity, effect restricted to cell with specific HLA haplotype and the ability of tumor cells to evade the tumor-specific immune response (30). As a result of these limitations, most clinical trials have failed to show any survival benefit when using single peptide vaccine therapy.

The development of peptide vaccines directed against multiple epitopes with longer amino acid sequences have attempted to address these limitations. Inoda *et al.* provided evidence that three peptides vaccination mixture was safe and effective in six HLA-A24-positive patients with CRC (31). A phase II trial involving 96 patients with metastatic CRC showed that a "peptide cocktail" comprised of five HLA*2402-resticted peptides can be administered safely when given concurrently with chemotherapy (32). However, the trial failed to show any benefit in terms of response rate, progression free survival and overall survival. Okuno *et al.* reported a positive study in which a 7-peptide cocktail vaccine was administered with oral chemotherapy in patients with mCRC and resulted in improved overall survival compared with the control group (33). Additional clinical trials testing multi-antigen peptide vaccines plus an adjuvant are currently underway (34).

DC vaccines

DCs are an integral part of the antitumor immune response. As potent antigen presenting cells (APCs), DCs can present multiple TAA by MHC class I and II molecules (35). They also play a pivotal role in the programming and regulating the antitumor response by providing the appropriate co-stimulatory signals and directing the production of cytokines. DC based vaccine development for cancer treatment has been ongoing for decades (36). Recent approaches involve harvesting DCs from the patients, loading them *ex vivo* with TAAs, tumor cell lysates, apoptotic tumor cells, tumor RNA or whole tumor cells have been utilized. Once activated, the DC vaccine is re-infused into the patient with the goal of eliciting a tumor specific immune response (36).

Historically, CEA has been tested in clinical trials involving DC vaccines because it is a TAA found on most CRC cases. Multiple early phase trials have provided evidence that CEA DC vaccines are safe and effective in generating a CEA specific tumor response (37-39). However, there have not been any follow up phase III trials to date supporting the efficacy or survival benefit of these vaccines in CRC patients. Recently, a phase II trial randomized mCRC patients to receive an autologous tumor lysate DC vaccine plus best supportive care or best supportive care alone (40). This study demonstrated that there was evidence that the DC vaccine able to generate a tumor specific immune response, the study was terminated early due to futility as there were no benefits seen in terms of PFS (2.7 *vs.* 2.3 months, P=0.628) and OS (6.2 *vs.* 4.7 months, P=0.41) compared to best supportive care alone. Other TAAs have also been utilized in DC vaccines as demonstrated by a recent phase I trial evaluating the safety and immunogenicity of Wilms' tumor (WT1) class I/II peptides based DC vaccine for patients with advanced CRC (41). This trial confirmed DC vaccine efficacy based on WT1 expression in tissue using immunohistochemistry and identification of WT1-specific cytotoxic T cells using the Enzyme-Linked Immunosorbent Spot (ELISPOT) assays (Mabtech, Nacka Strand, Sweden) (42). Interestingly, the DC vaccine immunity persisted for two years associated with a prolongation in survival. This was however a very small trial adding to argument for larger randomized trials to support clinical benefit for DC vaccines.

Viral vector vaccines

The rationale behind the use of viral antigen vaccines is to utilize the pathogenicity of the virus to generate a robust, tumor-specific and substantial immune response. The advantages of recombinant viral vectors are that they can be engineered to express any number of antigens of interest while providing innate pro-inflammatory signals that increase the TAA-specific immune response (43). These vaccines have shown greater efficacy in generating a tumor response compared to peptide vaccines as they include viruses with high transfection efficiency such as recombinant lentiviruses, poxviruses, adenoviruses and retroviruses. Some of the major arguments against the use of viral vector vaccines are the cost, potential for pathogenesis and potential for insertional mutagenesis.

Significant trials to date include a phase I study in which sequential vaccinations with fowlpox-CEA(6D)-TRICOM alone and sequentially with vaccinia-CEA(6D)-TRICOM, with and without GM-CSF were evaluated in patients with CEA-expressing carcinomas (44). The results indicated that this vaccine construct was safe and had limited efficacy in select patients with stable disease in 40% and response duration of at least 4 months. A similar phase II clinical trial examined the efficacy of chemotherapy (IFL/FOLFIRI) in combination with a vaccine based on a non-replicating canarypox virus (ALVAC) expressing CEA and B7-1 (ALVACCEA/B7-1) (45). Fifty percent of the patients showed anti-CEA-specific T cell responses and 40% of the patients shoed objective clinical response, however no overall differences were observed between the two treatment groups. More recently, 5T4 protein which is an oncofetal antigen and a transmembrane glycoprotein that is highly expressed in colon cancer but not in normal tissue, has become a successful target using the attenuated vaccinia virus known as TroVax (46). In small clinical trials TroVax has shown to be active in mCRC because it can lead to antibody formation against the 5T4 antigen and the virus as well (46).

Oncolytic virus therapy

The concept of Oncolytic virus therapy in which a virus is used as an active anti-cancer agent has been in existence for some time. One of the earliest published examples involved 22 patients with Hodgkin's disease that were treated with hepatitis virus in 1949 (47). The term "oncolytic virus" refers to a genetically engineered or naturally occurring virus that selectively replicates in and destroys cancer cells without harming normal tissue. This has been recently recognized as a promising new anti-cancer therapy approach due to significant developments in genetic engineering techniques and increase in understanding of the functions and structures of viral genes. This renewed interest in oncolytic virus therapy has led to the development of multiple pre-clinical models and a large number of clinical trials in the recent years (48). Most notably, the recently completed OPTiM trial showed clinical utility of talimogene laherparepvec (T-VEC), a granulocyte macrophage colony-stimulating factor (GM-CSF)-expressing variant of herpes simplex virus 1 (HSV-1) (49). This randomized phase III trial showed superior clinical activity, improvement in overall survival and tolerable toxicity profile for T-VEC as compared to subcutaneous granulocyte-macrophage colony-stimulating factor (GM-CSF) for the treatment of unresected stage IIIB/IV melanoma (49). The results of the

OPTiM trial resulted in the approval of T-VEC (IMLYGIC) for treatment of melanoma in the USA by October 2015 and were subsequently approved in Europe in January 2016 and most recently in Australia in May 2016 (50).

For CRC, there are currently no FDA approved oncolytic therapies available. However, there are several strategies currently under development especially in the setting of metastatic disease to the liver. In the pre-clinical setting, Kooby *et al.* demonstrated that G207 (a multi-mutated herpes simplex virus type-1) was effective in infecting and killing cells from five different human CRC cell lines (51). More recently, Warner *et al.* described the proof of principle that colon adenocarcinoma stem-like tumor-initiating cells (TIC) are sensitive to HSV-1-based oncolytic virus NV1066 (52). In this study, HCT8 human colon cancer cells were cultured to generate TICs and within 3 days of exposure to NV1066, over 80% cell kill was achieved in both cell types. In vivo efficacy was demonstrated by treatment of TIC-induced tumors with NV1066 which yielded tumor regression or decrease in tumor growth.

Of the limited clinical data available, a multicenter phase I/II study evaluated repeated doses of a genetically engineered oncolytic herpes simplex virus (NV1020) in patients with liver-dominant metastatic CRC (53). Patients were treated with four fixed doses of NV1020 via hepatic artery infusion, followed by conventional chemotherapy. Patients experienced minimal toxicities and the median time to progression was 6.4 months (95% confidence interval: 2, 8.9); median overall survival was 11.8 months (95% confidence interval: 8.3, 20.7), and one-year survival was 47.2%. Another phase 1b trial of Pexa-Vec (pexastimogene devacirepvec; JX-594), an oncolytic vaccinia virus used in patients with treatment-refractory CRC resulted in radiographically stable disease in 67% of the patients (54). Pexa-Vec was well tolerated, resulted in limited grade 1 or 2 adverse events but since no dose limiting toxicities occurred. However, the trial was unable to formally define the maximum tolerated dose of Pexa-Vec.

IDO1 inhibitors

Indoleamine 2, 3-dioxygenase 1 (IDO1), and IDO2 are a part or a family of enzymes that catalyze the first and rate-limiting step in the conversion of the essential amino acid *L*-tryptophan (Trp) into *L*-kynurenine (Kyn) (55). Depletion of Trp and accumulation of Kyn has been shown to cause T cell growth arrest in the G1 phase in addition to induction of highly immunosuppressive regulatory T-cells (Treg) (56). In CRC patients, IDO expression has been shown to be associated with lesser CD3+ infiltrating T cells and worse prognosis (57). There are currently no IDO1 inhibitors approved by the FDA and there are no clinical trials dedicated only to CRC only. Indoximod (D-1-methyl-tryptophan) was one of the first inhibitors of the IDO pathway and in pre-clinical studies indoximod use was shown to decrease the number of Tregs and reverse IDO-medicated immune suppression (58,59). There are multiple clinical trials underway evaluating the use of either indoximod (NLG8189), second generation IDO1 inhibitor Epacadostat (INCB024360) and IDO1-targeting vaccines either as monotherapies or in combination with multiple other modalities for potential synergistic value. Preliminary data from a few recently completed early phase studies have demonstrated that these IDO1 inhibitors are safe, well tolerated by patients and have clinical benefit in a subset of patients (60). The very first phase I clinical trial evaluated the safety of indoximod in combination with docetaxel in patients with metastatic solid malignancies (61). With 27 patients enrolled, this combination showed a tolerable safety profile as the most common reported side effects were fatigue, anemia, hyperglycemia, infection and nausea. The dose of 1,200 mg indoximod twice daily in combination with docetaxel 75 mg/m^2 every 3 weeks was recommended and a phase II clinical trial is already underway in patients with metastatic breast cancer. A recent phase I clinical trial enrolled 48 patients with refractory solid malignancies and demonstrated that single agent indoximod was well tolerated with major toxicities being grade 1 fatigue and grade 2 hypophysitis (62). In terms of combination immunotherapy trials, the safety and efficacy of the IDO1-targeting peptide vaccine NCT01219348 in combination with Toll-like receptor 7 (TLR7) agonist imiquimod was evaluated in a phase I trial for patients with metastatic non-small cell lung cancer (63). This vaccine combination was well tolerated without any reported severe side effects. Other promising combinatorial approaches include IDO1 inhibition with pembrolizumab have shown high level of activity in patients with melanoma with tolerable toxicity profile in the ongoing ECHO-202/KEYNOTE-037 trial (NCT02752074). No combination data is currently available for CRC patients, however a promising clinical trial evaluating the effects of epigenetic modulation with azacitidine in combination with pembrolizumab and Epacadostat is currently underway in patients with lung cancer and MSS colorectal cancer (NCT02959437).

Anti-OX40 agonists

OX40 (CD 134) is a member of the tumor necrosis factor (TNF) family of receptors that acts as a T-cell costimulatory molecule by way of the transcription factor NF-κB pathway. This 47–51 kD glycoprotein is expressed on the surface of activated T-cells and consists of an extracellular region, a transmembrane domain and cytoplasmic tail. It has one known ligand, OX40L that is present on the surface of activated APCs and activated endothelial cells, epithelial cells, and B and T cells. Within the subsets of T cells, OX40 upregulation can be seen preferentially on CD4+ T cells and less so on CD8+ T cells after T cell receptor engagement and during antigen specific priming (64). Activated CD4+ cells that receive a signal through the costimulatory OX-40 show enhanced proliferation, cytokine production, and increased survival of antigen-specific memory T cells (65). In several preclinical models, treatment with OX40 agonists, including both anti-OX40 mAb and OX40L-Fc fusion proteins, resulted in tumor regression and one specific study showed that anti-OX40 administration was able to restore the cytotoxic activity of a CD8+ T cell by overcoming tolerance to self-antigen (66,67).

Ox40 is also known to be strongly expressed on Treg cells and OX40 engagement leads to direct regulation of Tregs, however the direction of its impact has not been fully understood. There are studies that support that anti-OX40 exposure promotes Treg cell response and others suggest that anti-OX40 mAbs block the suppressive functions of Tregs (68). The general understanding is that OX40 agonist can regulate Tregs in either direction depending on the existing environment, influenced by a number of other factors such as cytokines.

With reference to CRC, there have been several animal studies using CT 26 colon cancer model that showed that monotherapy with OX40 agonist resulted delayed tumor progression and significant survival benefit (69-71). A study by Petty *et al.* showed that high expression of OX40 on TILs are present in half of the primary colon cancer samples and this correlated with a better overall survival, however this was not independent of the tumor stage (72). There have also been a number of early phase clinical trials over the past decade using five different molecules to target OX40, however no trials recruiting only CRC patients have been completed as most current trials are multi-histology trials for patients with advanced malignancies. There is currently one ongoing clinical trial specifically for patients with metastatic CRC using single agent anti-OX40 antibody MEDI6469 (NCT02559024).

In patients with advanced malignancies, the early phase clinical trial data has demonstrated promising results. In one phase I clinical trial, patients treated with one course of anti-OX40 mouse mAb showed regression of at least one metastatic lesion in 12 out of 30 patients (73). This treatment was associated with an acceptable toxicity profile as the most common adverse effect was temporary lymphopenia. The study was able to further demonstrate that this treatment increased T and B cell responses which in turn lead to expansion of CD4+ and CD8+ T cells without inducing the proliferation of Treg cells.

The current direction of OX40 based therapy involves combinatorial approaches incorporating check point inhibitors due to the lack of durable responses from anti-OX40 mAb monotherapy clinical trials. The combination of CTLA-4 blockade with OX40 agonist has been proven effective in a number of clinical trials and the rationale behind this approach is that these individual molecules exert their respective effects by distinct pathways which may be complimentary as the end result is the amplification of the cytotoxic T-cell response (74-76). There are a few clinical trials currently underway testing this approach and important questions that remain to be answered are regarding the rout and sequence of administration of the two medications. The same level of interest has been observed in the combinatorial approach using OX40 agonist therapy with PD-1 blockade (77). This particular combination may prove to be especially synergistic because OX40 co-stimulation has been shown to enhance INF-γ production by T-cells and in a number of animal models, cancer cells have demonstrated PDL-1 expression upregulation in response to INF-γ exposure, thus exhibiting unique complimentary properties (78).

There are other ongoing clinical trials examining the benefits of OX40 agonist therapy in combination with other therapies such as chemotherapy, radiation therapy and targeted therapies. The major concern in all of these combination trials remains the possibility for increased toxicities, especially the immune-related adverse events when combining multiple immune-modulating therapies. Preliminary results from clinical trial that combined OX40 agonist with other immunotherapies suggest that dose modification along with early recognition and management of immune-related adverse effects can be an effective strategy for patients receiving this type of therapy.

Conclusions

While significant strides have been made in the treatment of cancer overall, there has been minimal change in the current standard in the era of immunotherapy. It is very promising that immune modulatory agents have shown excellent response rates in MSI-H CRC tumors. With oncolytic vaccines, dual check-point inhibitors being investigated, perhaps it is more the selection of patients that is important in garnering a durable and effective combination treatment strategy with immunotherapy.

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Footnote

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