Interactions between Anti-Vegf Therapy and Antitumor Immunity as a Potential Therapeutic Strategy in Colorectal Cancer

David Buka[1,*], Josef Dvořák[2], Igor Richter[3], Pavel Škrobánek[2], Tomáš Buchler[2], Bohuslav Melichar[4]

ABSTRACT
There is a growing corpus of evidence indicating that anti-VEGF therapy may normalize the abnormal tumor vasculature with the potential to re-program the tumor immune microenvironment to a more immunosupportive profile. Tumor vessel normalization increases tumor perfusion, and, consequently, oxygen and nutrient supply, and thus can be assumed to improve the general response to anticancer immunotherapy. The increased antitumor immunity responses seen following anti-VEGF therapy may also be associated with the inhibition of the immunosuppressive action deployed by VEGF on effector T cells. Bearing in mind the recent advances of combination immunotherapy, combinations of anti-VEGF therapy with immune checkpoint inhibitors now appear to represent an attractive strategy. Key to the successful implementation of a combination strategy for treating cancer is understanding the interaction of these two therapeutic interventions, particularly in regards to appropriate reprogramming of the tumor immune microenvironment to improve antitumor immunity.

KEYWORDS
vascular endothelial growth factor inhibition; antitumor immunity; colorectal cancer

AUTHOR AFFILIATONS
[1] Department of Oncology and Radiotherapy, Charles University Medical School and Teaching Hospital, Hradec Králové, Czech Republic
[2] Department of Oncology, First Medical Faculty, Charles University and Thomayer Hospital, Prague, Czech Republic
[3] Department of Oncology, Regional Hospital, Liberec, Czech Republic
[4] Department of Oncology, Palacký University Medical School and Teaching Hospital, Olomouc, Czech Republic
* Corresponding author: Department of Oncology and Radiotherapy, Teaching Hospital, Hradec Králové, Sokolská 581, 500 05 Hradec Králové, Czech Republic; e-mail: davidbuka@seznam.cz

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INTRODUCTION

There is a growing corpus of evidence indicating that anti-VEGF therapy may normalize the tumor vasculature with the potential to switch the tumor immune microenvironment to a more immunosupportive profile (1).

The efficacy of anticancer immunotherapy using immune checkpoints blockade is compromised by hypoxia and poor T cell infiltration within the tumor resulting from poor perfusion in the disorganized tumor vessels. Abnormal tumor vessels also limit the adhesion and extravasation of leukocytes and impair leukocyte infiltration into the tumor tissue. Hypoxia increases the immunosuppressive nature of the stromal tumor microenvironment, by impairing T-cell effector functions including T-cell receptor signaling, proliferation, and cytokine production. Hyperoxia also increases the performance of cytotoxic T-cell, which may result in better clinical responses to the blockade of the immune checkpoints, e.g. programmed death receptor 1 (PD-1) (2). The hypoxic tumor is geneticall-ly unstable, giving rise to a new genotype with increased production of angiogenic factors. This transformation, known as the angiogenic switch, initiates the angiogenesis process.

The inhibitors of VEGF enhance the influx of immune cells into the tumor by restoring vessel integrity, increasing tumor perfusion and decreasing interstitial fluid pressure. The normalized tumor vasculature not only results in reduced tissue hypoxia and improved delivery of cytotoxic agents as well as oxygen (enhancing the effect of radiation therapy), but also augments anti-tumor immunity (3). In addition, deprivation of nutrients including glucose impedes T-cell proliferation and activation of CD8+ effector cells. Hence, tumor vessel normalization may be, consequently, expected to enhance the overall anticancer immunotherapy response (2).

The increased antitumor immune response seen with anti-VEGF therapy might be also related to the countering of the direct and indirect immunosuppressive activity of VEGF on effector T cells (Fig. 1). VEGF can inhibit the T cell function while increasing the recruitment of myeloid-derived suppressor cells (MDSC) and regulatory T cells (Tregs), and suppressing the differentiation and activation of dendritic cells (4). Hence, blocking VEGF signaling enhances effector T-cell function by increasing the activation and trafficking to the tumor due to both tumor vessel normalization and by inhibiting the VEGF-induced upregulation of inhibitory immune checkpoints (3, 5).

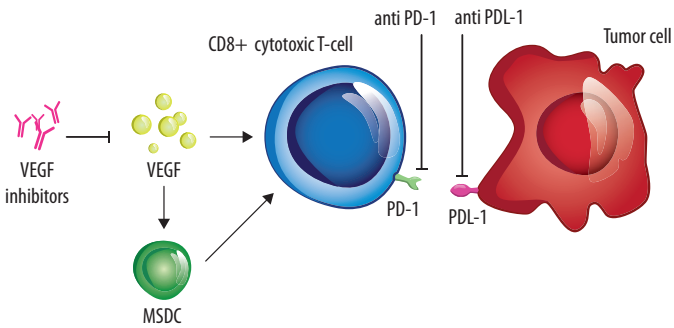

Fig. 1 Interactions between VEGF inhibitors and PD-1/PD-L1 inhibitors in colorectal cancer microenvironment. Abbreviations: PD-1 – programmed cell death protein 1; PD-L1 – programmed cell death protein ligand 1; MSDC – myeloid-derived suppressor cells; VEGF – vascular endothelial growth factor.

VASCULAR ENDOTHELIAL GROWTH FACTOR

Vascular endothelial growth factor (VEGF) has two fundamental roles, first, in developing and maintaining blood vessels, and, second in regulating vascular endothelial cell permeability (6). Immunohistochemical studies have shown that VEGF is not expressed in normal colorectal mucosa, but significantly expressed in adenocarcinomas. VEGF expression is an early event in the transformation sequence from adenoma to adenocarcinoma. Neovascularization, underpinned by increased expression of VEGF is required for both tumor nutrition and hematogenous spread (7). In colorectal adenocarcinoma high VEGF expression has been demonstrated to correlate with poor prognosis and higher incidence of liver metastases.

VEGF inhibition is used successfully in the treatment of metastatic colorectal adenocarcinoma with bevacizumab, aflibercept and regorafenib and of advanced gastric adenocarcinoma with ramucirumab. In addition, radiosensitivity may be increased by the anti-angiogenic effect of bevacizumab. Bevacizumab has been incorporated into phase I–II studies of preoperative chemoradiotherapy for rectal cancer but the toxicity pattern and surgical complications observed in some studies prevented its routine use. The abscence of a predictive biomarker for the therapeutic response to VEGF inhibitors means the selection of patients with a higher chance of response is currently impossible (8).

IMMUNOSCORE

Tumor infiltrating lymphocytes (TIL) are frequently found in colorectal tumors, indicating that these tumors are capable of triggering an immune response (9). The final effectors of antitumor adaptive immune response are predominantly cytotoxic T lymphocytes recognizing nonself antigens, leading ultimately to tumor cell killing. Several studies have reported that high abundance of CD8+ cytotoxic TIL is associated with a positive clinical outcome across various different primary tumors, including non-small cell lung cancer, colorectal carcinoma, esophageal cancer, breast cancer as well as urothelial cancers and melanoma (10).

All types of immune cell may be encountered in the tumor. Analysis of the location, density and functional orientation of different immune cell populations is refered to as the immune contexture (11). Thorough intra-tumor analysis demonstrates, that these immune infiltrates are not distributed randomly. The combination of two markers (CD3+ TIL and CD8+ TIL) in two regions (center of the tumor and its invasive margin) has been validated for standard clinical practice in colorectal cancer. The Immunoscore is a prognostic tool, which seems superior to the tumor-node-metastasis (TNM) classification in colorectal cancer (12).

A study of three independent cohorts of 415, 119 and 69 patients with stage I–III. colorectal cancer found a significantly lower recurrence rate and longer overall survival in patients with a high density of CD3+, CD8+, CD45RO+ TIL and granzyme B. The type, density, and location of immune cells in colorectal cancer was superior to and independent of those of the UICC-TNM classification (13).

A study in 411 patients with stage I and II colorectal cancer showed a favorable prognostic value of high-density CD8 + and CD45RO + TIL (14).

IMMUNE CHECKPOINT INHIBITORS IN THE TREATMENT OF METASTATIC COLORECTAL CANCER PATIENTS

Abundant infiltration by CD8+ TIL is characteristic for colorectal cancers with microsatellite instability that represent approximately 15% of sporadic colorectal cancer cases. Microsatellite instability is caused by deficiency of DNA mismatch repair (MMR) and associated with 10–50 times higher mutational load compared to colorectal tumors without MMR defects. There is evidence that cancers with high gene mutational load respond better to immune checkpoint inhibitor therapy (15). Tumour microsatellite instability testing is strongly asociated with response to immune checkpoint inhibitors when treating metastatic colorectal cancer patients. Patients with high microsatellite instability respond to PD-1 inhibitors (e.g. pembrolizumab or nivolumab) and PD-L1 inhibitors (e.g. atezolizumab) (16) alone or in combination with CTLA4 inhibitors (e.g. nivolumab with ipilimumab) (17, 18). The number of clinical trials that assess the efficacy of the checkpoint inhibitors in the treatment of colorectal cancer with or without combination with radiotherapy is increasing (Table 1) (19).

Tab. 1 Clinical trials currently underway (20 June 2019) evaluating the efficacy of the checkpoint inhibitors in the treatment of colorectal cancer with or without combination with radiotherapy, according to http://clinicaltrials.gov (19).

Checkpoint inhibitor	Target	Number of clinical studies
Pembrolizumab	PD-1	70
Pembrolizumab + RT	PD-1	5
Nivolumab	PD-1	67
Nivolumab + RT	PD-1	8
Durvalumab	PD-L1	28
Durvalumab + RT	PD-L1	7
Atezolizumab	PD-L1	26
Atezolizumab + RT	PD-L1	4
Avelumab	PD-L1	17
Avelumab + RT	PD-L1	4
Combinations with ipilimumab	CTLA4	24
Combinations with ipilimumab + RT	CTLA4	3

COMBINATION OF ANTI-VEGF THERAPY WITH IMMUNE CHECKPOINT INHIBITORS

The rationale of combining the VEGF blockade with the blockade of immune checkpoints has been reviewed above. This combined blockade represents an emerging strategy and probably a new standard of clinical management of renal cell carcinoma (20). Given the activity of both anti-VEGF agents and immune checkpoint inhibitors in colorectal carcinoma, this combination therapy represents an attractive approach that is being investigated also in patients with metastatic colorectal carcinoma.

CONCLUSION

Bearing in mind the recent successes for immunotherapies, combinations of anti-VEGF therapy with immune checkpoint inhibitors now appears an attractive strategy. Key to the successful implementation of a combination strategy for treating cancer is understanding the interaction between these two therapeutic interventions, particularly in regards to appropriate reprogramming of the tumor immune microenvironment to improve antitumor immunity (2, 21).

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