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Editorial

Checkpoint inhibitors: a new therapeutic arm in mismatch repair deficient metastatic colorectal cancers

Abdel Hadi El Hajjar, Elie Barouky

Université Saint-Jospeh, Faculté de Médecine, Damascus Street, Beirut, Lebanon

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Corresponding Author
Abdel Hadi El Hajjar
Corniche El Mazraa,
Beirut, Lebanon,
961 03 289294
abedelhajjar@hotmail.com

The past few years have witnessed an outstanding improvement in cancer treatment. Immunotherapy plays a major role in the revolution of cancer management. The role of the immune system in the human body is to protect its host from aggression, particularly infections and tumors. However, neoplasms have found several methods to escape the body's immune mechanism. In fact, some tumors can upregulate the expression of immune checkpoint molecules such as CTLA-4 and PD-1. PD-1 is a checkpoint protein expressed on T cells that, when it binds to PD-L1 expressed on some tumor cells, shall lead to inhibition of the T cell function. (1) Thus, it protects tumor cells from immune system attack. Therefore, antibodies targeting PD-1 (pembrolizumab and nivolumab) and PD-L1 (atezolizumab, avelumab and durvalumab) have been developed as a potential treatment for cancer. They got approved for melanoma, non-small cell lung cancer, kidney cancer, bladder cancer, head and neck cancers, and Hodgkin lymphoma. Ipilimumab and tremelimumab are also a drugs that target another checkpoint inhibitor: CTLA-4 in order to boost the body's immune system against cancer cells. They have been approved for melanoma.(2)

Preliminary results from phase 1 and 2 checkpoint inhibitors trials are reporting response rates of 15% to 25% in GIT cancers with the exception of pancreatic and colorectal cancer (CRC).(3) CRC, the third most common cancer in the United States(4), is treated by surgical resection and adjuvant oxaliplatine based chemotherapy in locally advanced primary lesions. (5) In contrast, metastatic CRC is treated with palliative systemic chemotherapy, with a survival rate less than 20% in 5 years. Then, studies have been undergone to see the efficacy of checkpoint inhibitors previously mentioned in CCR.

However, studies focusing on PD-1 and CTLA-4 inhibitors were unable to certify efficiency against CRC. Initially, only one patient responded to nivolumab. He was later, concomitantly, certified to have an MMR- deficient CRC (6).

MMR (Mismatch Repair) is a DNA integrity maintenance system; its main

goal is to correct DNA errors that occur during replication such as insertion and deletion. Microsatellites are prone to errors when MMR is compromised. Studying then Microsatellite instability (MSI) is then an effective way to detect MMR deficiency. MMR deficiency is then associated with high number of mutation, thus predisposing to tumors.

In the case of colorectal cancer, MMR deficiency is found in Lynch Syndrome. However, 15% of sporadic colorectal cancer show also MSI or MMR-deficiency. (7)

Many theories have been established to understand the correlation between MMR- deficiency and response to checkpoint inhibitors in CRC. First, MMR- deficiency is associated with increasing number of mutations. As previously mentioned, MMR corrects DNA errors occurring during replication. Consequently, a deficient MMR system increases chances of errors and mutations. In fact, CRC with MMR-deficiency harbor much more mutations than other types of cancer. Those mutations are the origins of new expressed antigens on the surface of the cell. Those antigens are recognized by the immune-system as “non self-antigen” leading then to activation of the immune system against tumor cells: those tumors are immunogenic. (8)

In addition, MMR-deficiency is also associated with an upregulation of certain genes that might lead to activation of PD-1 pathway. (6) A study showed significant expression of PD-L1 receptors on endometrial tumors with MMR-deficiency in comparison to MMR-proficient tumors (9). Therefore, they are most likely to show better results with immunotherapy than non MMR -deficient CRC.

Studies concerning CTLA-4 inhibitors have not shown significant results in the management of CRC (phase 2 trial on 47 patients treated with tremelimumab showed inefficiency and significant advised effects) (10).

A phase 2 study conducted on 41 patients in 2015 treated with pembrolizumab, an anti-PD1 agent, was revolutionary and innovative in term of CRC immunotherapy approach. It demonstrated a significant objective response rate (ORR) of 40 % in MMR-deficient patients. Instead, it shows 0% response rate in MMR-proficient patients. Therefore, MMR status or MSI-high CRC emerge as crucial elements to predict efficiency of checkpoint blockage therapy in colorectal cancer. (11)

A most recent study (CheckMate 142) of 74 patients with MMR deficient metastatic colorectal cancer treated with nivolumab, an anti-PD1 agent, (3mg/kg every 2 weeks). 23 (31%) had an objective respond and 51 (68%) had disease control for 12 weeks or longer. Consequently, nivolumab was considered as a new treatment option in MMR- deficient CRC. (12)

The FDA approved in May 2017 the pembrolizumab in unresectable or metastatic MSI-H or MMR-deficiency refractory solid tumors with no other treatment option or in patients with MSI-H or MMR-deficiency CRC who become resistant to fluoropyrimidine, oxaliplatin and irinotecan.(8) The approval was based on data from 149 patients with MSI-H or dMMR cancers enrolled across 5 single-arm clinical trials. Ninety patients had colorectal cancer (CRC) and the remaining 59 patients had 1 of 14 other tumor types. The FDA also approved the nivolumab in august 2017 for the treatment of patients 12 years and older with mismatch repair deficient (dMMR) and microsatellite instability high (MSI-H) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

With the promising future of immunotherapy in treatment of CRC, many studies targeting other checkpoint inhibitors are in progress. A phase 3 study (NCT02788279) investigates overall survival of patients with metastatic colorectal adenocarcinoma receiving 3 different regimen of treatment: cobimetinib plus atezolizumab (PD-L1 inhibitor) and atezolizumab monotherapy vs. regorafenib, a standard of care therapy in this setting. Study population includes patients with histologically confirmed stage 4 colorectal adenocarcinoma who experienced disease progression or was intolerant to at least two systemic chemotherapy regimens for metastatic colorectal cancer that must have included fluroropyrimidines, irinotecan, and oxaliplatin. Another phase 2 study (NCT02870920) aims to compare overall survival with Durvalumab and tremelimumab and best supportive care vs. best supportive care alone in patients with advanced colorectal adenocarcinoma. Inclusion criteria includes a RAS-wild type unresectable CRC who received a prior thymidylate synthase inhibitor. In addition, a phase 2 study (NCT02227667) is conducted to evaluate the efficiency of MEDI4736 (synthetic antibody targeting PD-L1) in advanced colorectal cancer. CRC in this study is chosen to MMR-deficient, or with increased Tumor-Infiltrating Lymphocytes in an archived tumor specimen or fresh biopsy.

Checkpoint inhibition therapy might also be valid in CRC expressing POLE mutation, a more rare condition. POLE is a gene that encodes for the DNA polymerase epsilon catalytic subunit while POLD1 encodes for catalytic subunit of the DNA polymerase delta. A mutation affecting one of those genes affect the fidelity of DNA replication, exposing then to an even higher number of mutations than with MMR-deficiency (hypermutated tumors). (13) Cancers with POLE mutation is associated with increased expression of PD-1 and PD-L1 establishing those tumors as strong candidate for checkpoint inhibitors. (14) A case report concerning an 81 year old man with metastatic POLE mutated CRC has shown positive response to pembrolizumab. Therefore, POLE associated hypermutated phenotype may be a good predictor for favorable checkpoint inhibitor response. (15)

After being considered as immune-resistant tumors, checkpoint inhibitors seem to be promising agents in the management of MMR-deficient metastatic CRC cancers. More prospective trials are necessary to evaluate the role of these agents in earlier lines of the treatment and their combination to chemotherapy or targeted therapies.

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