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Editorial Open Access

Targeting the PD-1 Pathway in MSI-Stable Metastatic Colorectal Cancer

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Editorial

PD-1 Pathway Inhibition and MSI-H CRC

In patients with microsatellite instability-high (MSI-H) metastatic colorectal cancer (CRC), the inhibition of programmed death-1 (PD-1) pathway has achieved promising response [1]. PD-1 is an immune inhibitory receptor, expressed in many cells, including T cells. Its ligand, PD-L1, is expressed on surface of several cell types, especially tumor cells. When PD-L1 binds to PD-1, an inhibitory signal is transmitted into the T cell, which suppresses T-cell proliferation. MSI-H metastatic CRC gives rise to high percentage of mutations which is proportional to mutational load. High mutational load of MSI-H CRC correlates with increased PD-L1 expression which indicates a higher likelihood of response to PD-1 inhibitors, compared to microsatellite instability-stable (MSI-S) CRC [2-4]. Thus, MSI-H CRC could respond to single agent PD-1 pathway inhibition.

PD-1 Pathway Inhibition and MSI-S CRC

However, MSI-H only comprises of 15% of metastatic CRC. The majority of patients have MSI-S disease. Microsatellite instability is a genomic instability associated with defective DNA mismatch repair that occurs during the replication of DNA, and is characterized by the accelerated accumulation of nucleotide mutations in repetitive microsatellite sequences [5]. MSI-H indicates instability of >30% of loci in large panel of mononucleotide repeats or dinucleotide repeats. MSI-S is defined as having instability of <10% of loci [6]. MSI-S metastatic CRC patients have shown minimal response to PD-1 pathway inhibitors [7].

Rationale of PD-1 Pathway Inhibition in MSI-H CRC

In order to utilize immunotherapy in MSI-S CRC, we need to first understand the rationale that leads to efficacy of single agent PD-1 pathway inhibitors in MSI-H CRC. Several studies indicate that tumors with a high mutational load trigger high frequency of CD8+ T cell response and are therefore sensitive to PD-1 pathway inhibitors. Mutational load is a set of somatic, non-synonymous, exonic mutations of each gene. The high frequency of gene mutations among cancers increases the likelihood of neoantigens generation. Neoantigens are non-self antigens. The more neoantigens a tumor contains, the higher the possibility for the tumor to be recognized by the immune system [8]. This is a major reason why tumors with high mutational load such as melanoma and non-small cell lung cancer respond remarkably well to single agent PD-1 pathway inhibition [9].

On the other hand, mutational load is not the only factor that determines tumor response to PD-1 pathway blockade. Any tumors with low mutational load but high percentage of PD-L1 expression can also yield meaningful response to single agent PD-1 pathway inhibition [10]. For instance, urothelial cancers tend to have a low mutational load, yet the expression of PD-L1 can be as high as above 80% and PD-1 pathway inhibitor as a single agent improves overall survival (OS) in such patient population [11]. PD-L1 expression is demonstrated by immunohistochemical (IHC) staining. IHC data is assessed using the semi-quantitative immunoreactive score (IRS). This IRS score is calculated by multiplying the staining intensity (graded as follows: 0=no, 1=weak, 2=moderate, 3=strong staining) and the percentage of positively stained cells (0=less than 10% of stained cells, 1=11-50% of stained cells, 2=51-80% of stained cells, 3=more than 81% of stained cells) [11,12]. Such evidence indicates contribution of PD-L1 overexpression in response to PD-1 pathway inhibition [6].

In MSI-H tumors, high mutational load indicates a vigorous immune microenvironment that upregulates PD-L1 overexpression [13]. In addition to a high mutational load and PD-L1 overexpression, CD8+ cytotoxic T cells are frequently found in the microenvironment in MSI-H tumors.

Strategies to Enhance Activity of PD-1 Pathway Inhibition in MSI-S CRC

On the contrary, MSI-S tumors have less mutational load than MSI-H tumors, and possesses less numbers of tumor infiltrating CD8+ cytotoxic T cells, which could contribute to poor response to PD-1 pathway inhibition [14,15]. Such observation was demonstrated in other animal tumor models with intrinsically low mutational load such as pancreatic cancer. A study examining pancreatic cancer specimens from patients demonstrated the shortest OS in the group with low CD8+ T cell infiltration and high PD-L1 expression. When murine pancreatic cancer cell lines were subcutaneously injected into mice, a pancreatic mouse model was created to mimic low CD8+ T cell infiltration and high PD-L1 expression [16]. Vaccination of such mouse model using live MC 57-SIY peptide synthesized by f-moc chemistry increased CD8+ T cell infiltration, and the addition of PD-L1 blockade to vaccination enhanced the effector function of tumor-infiltrating T cells [16]. Providing CD8+ T cell infiltration into tumor with low mutational load was essential to elicit a synergistic immune response with immunotherapies, which was demonstrated in a phase IIA study of 2nd line metastatic pancreatic cancer patients. All patients were initially treated with the combination of cyclophosphamide (CY) and GVAX. Cyclophosphamide was used to deplete immunosuppressive regulatory T cells, and GVAX is a whole cell vaccine expressing human granulocyte macrophage-colony stimulating factor (GM-CSF) that stimulates the body's immune responses against tumor cells. Listeria monocytogenes vaccine (CRS-207) induces robust CD8+ T-cell immunity by targeting dendritic cells. Patients were

randomized to receive CY/GVAX followed by CRS-207 or CY/GVAX. All patients achieved increased number of CD8+ T cells. Only the group treated with CY/GVAX and CRS-207 improved OS compared to CY/GVAX alone [17].

In a study of 389 CRC patient specimens, where 55% were stage III and IV, more CD8+ T lymphocytes were found in the MSI-H group compared to the MSI-S group [18]. High tumor-infiltrating CD8+ T cell lymphocytes were associated with a favorable outcome in MSI-H CRC patients. Tumors with low levels of CD8+ T lymphocytes had poor prognosis, regardless of PD-L1 expression [19].

One effective strategy to enhance the activity of immunotherapy in MSI-S CRC patients directs at tumor infiltrating lymphocytes. In immunocompetent tumor-bearing mice model, treatment with mitogen/extracellular signal regulated kinase inhibitor (MEKi) led to a decrease in phosphorylated extracellular signal-regulated kinase (ERK). Such effect in turn resulted in the expansion of T cell clones and accumulation of tumor-infiltrating CD8+ T cell effectors that target the tumor, including expression of T-bet and Eomes that control CD 8+ T cell differentiation [20]. Therefore, MEKi provides a higher number of CD8+ T cells and maintains CD8+ T cell activity to optimize PD-1 pathway inhibition in MSI-S CRC [20].

A recent phase Ib trial in patients with MSI-S CRC utilized the above strategy to explore the activity of combination therapy using MEKi and PD-L1 inhibitor [21]. In this study, 4 of 23 patients (17%) achieved partial response (PR), and 5 of 23 patients (22%) had stable disease (SD) which lasted up to 15 months. Part of the rationale for such combination to work depends on the increase in CD 8+ T cell quantity and quality in MSI-S CRC. However, it also reveals an opportunity to explore another approach for 61% of the patients (14 of 23) who showed no response to this therapeutic strategy.

Beyond MEKi and PD-1 Pathway Inhibition in MSI-S CRC

Are there alternative pathways that MSI-S tumors can exploit to bypass the effects of MEKi and PD-1 pathway inhibitors? Current understanding regarding resistance to MEKi includes restoration of ERK and cross talk between MEK and phosphoinositide-3-OH kinase (PI3K) [22]. Human genome study of CRC showed that nearly 40% of colorectal tumors habor alterations in PI3K pathway genes. Most of these encode protein kinases could serve as targets for therapeutic intervention [23]. Phosphatase and tensin homolog (PTEN) is an important tumor suppressor gene which primarily negatively regulates PI3K-pathway. Downregulation of PTEN expression correlated with increased PD-L1 expression in a study of CRC patient specimens [24]. This study suggested a correlation between PTEN loss and poor prognosis in CRC. It hints that restoration of PTEN function could enhance the activity of PD-1 inhibition.

MEKi in combination with PI3K inhibitor demonstrated synergy in tumor inhibition and induction of apoptosis in MEKi-resistant human colorectal cancer cells. Dual blockade of MEK and PI3K pathways could overcome resistance to MEK inhibition [25]. Triple therapy that includes MEKi, PD-1 pathway inhibition and PI3K inhibitor could be explored in MSI-S patients.

Conclusion

Immunotherapy in MSI-S CRC is promising using combination therapy strategies to allow increase in quantity or activity of tumor infiltrating T cells. In addition, a strategy to increase mutational load represented by neoantigens can also be a potential combination approach for MSI-S CRC.

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