Immune Checkpoint Inhibitors in MSI-H/dMMR Colorectal Cancer: A Mini-Review

Ali Sanjari Moghaddam^{1,2}, Roham Salman Roghani^{1,2} and David S Hsu^{1,2*}

¹Department of Medicine, Division of Medical Oncology, Duke University Medical Center, Durham, North Carolina, USA

²Duke Cancer Institute, Duke University, Durham, North Carolina, USA

***Corresponding author:** David S Hsu, 3008 Snyderman Building, 905 S. LaSalle St., Duke University, Medical Center, Durham, NC 27710, USA.

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Abstract

Microsatellite instability-high/mismatch repair deficient (MSI-H/dMMR) colorectal cancer accounts for 15% of all colorectal cancer cases and 5% of metastatic colorectal cancer. Although cancer immunotherapy has been effective in various cancer, its activity has been limited in colorectal cancer. However, cancer immunotherapy has been shown to be effective in MSI-H/dMMR colorectal cancer. Specifically, among immunotherapeutic modalities, immune checkpoint inhibitors have shown the most promising results in MSI-H/dMMR colorectal cancer and to date, the Food and Drug Administration (FDA) has approved three checkpoint inhibitors for the treatment of metastatic MSI-H/dMMR colorectal cancer. With the recent advances, checkpoints inhibitors can now be considered as the first line of therapy in advanced dMMR/MSI-H colorectal cancer, and in this review, we will examine the development and use of immune checkpoint inhibitors in the treatment of metastatic colorectal cancer.

Keywords: Colorectal cancer; Immunotherapy; Immune Checkpoint Inhibitor; Microsatellite instability; Mismatch repair deficiency

Abbreviations: MSI-H/dMMR: Microsatellite instability-high/mismatch repair; FDA: Food and Drug Administration; ORR: Objective response rate; PFS: Progression-free survival; OS: Overall survival

Introduction

Colorectal cancer with an estimated 147,950 new cases in 2020 is the fourth most common cancer in the United States and with about estimated 53,000 death in 2020 stands as the second most lethal cancer in the United States. Due to colorectal cancer screening, colorectal cancer-related mortality has been decreasing, but at the time of diagnosis, 22% of patients present with advanced metastatic disease with a 5-year survival of <10% [1]. Colorectal cancer can be classified as either microsatellite instability-high/mismatch repair deficient (MSI-H/dMMR) or microsatellite stable tumor (MSS). MSI-H/dMMR tumors account for approximately 15% of all colorectal cancer cases and 5% of metastatic cases [2]. The MSI-H/dMMR phenotype results from a deficiency in the mismatch repair pathway [3]. Approximately eighty percent

of MSI-H/dMMR colorectal cancer are sporadic and result from either somatic mutation or most commonly hypermethylation of promotor region of DNA mismatch repair gene such as MLH1. The remaining twenty percent results from a germline mutation in DNA mismatch repair genes such as MLH1, MSH2, MSH6, and PMS2 and constitutes the Lynch syndrome [4]. Recently, MSI-H/dMMR has been shown to be a predictor of response to immunotherapy [5]. It has been proposed that defective expression of mismatch repair gene and high microsatellite instability lead to high mutational burden and neoantigen presentation, and subsequent infiltration of tumor with immune cells [6]. The high level of neoantigen presentation and strong antitumor immune response make MSI-H/dMMR colorectal cancer a good candidate for immunotherapy, particularly immune checkpoint inhibitors. Currently, there are

three immune checkpoint inhibitors that have been FDA approved for the treatment of metastatic colorectal cancer, ipilimumab, pembrolizumab, and nivolumab. Ipilimumab, which targets CTLA4, is approved for the treatment of MSI-H/dMMR metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, in combination with nivolumab. Pembrolizumab, which targets PD-1, is approved for the treatment of MSI-H/dMMR metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan or who have no satisfactory alternative treatment options. Nivolumab, which targets PD-1, is approved for the treatment of MSI-H/dMMR metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, as a single agent or in combination with ipilimumab.

Pembrolizumab

Pembrolizumab was the first immune checkpoint inhibitor to receive FDA approval for the treatment of metastatic MSI-H/dMMR colorectal cancer in 2017 [7]. Le and colleagues in a phase II clinical trial assessed the effectiveness of pembrolizumab for the treatment of progressive metastatic carcinoma with or without mismatch-repair deficiency. Overall, the study showed that immune-related objective response rate (ORR) and immune-related progression-free survival (PFS) rate for MSI/dMMR tumors were 40% and 78%, and 0% and 11% for MSS tumor, respectively. PFS and overall survival (OS) were 2.2 and 5 months for MSS colorectal cancer but have not been reached for MSI colorectal cancer [8]. KEYNOTE-164 (NCT02460198), was a phase II clinical trial of patients with MSI-H/dMMR advanced colorectal cancer with progressive disease after treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. There were two cohorts in the study with one cohort (A) receiving two lines of the standard of care therapy and the other (B) receiving only one line of therapy. This study showed an ORR of 33% in both cohorts with median PFS and OS of 2.3 and 31.4 months for cohort A and in cohort B, median PFS was 4.1 months but OS has not been reached [9]. KEYNOTE-177 (NCT02563002) was a phase III randomized trial on patients evaluating KEYTRUDA monotherapy versus standard of care chemotherapy for the first-line treatment of patients with MSI-H/dMMR advanced colorectal cancer and was recently presented at the plenary session at the ASCO Annual Meeting (2020). In this study, PFS and OR were found to be 16.5 months and 43.8% for pembrolizumab, and 8.2 months and 33.1% for chemotherapy. Results of KEYNOTE-177 demonstrated a significant clinical superiority of immune checkpoint inhibitor, pembrolizumab over chemotherapy for patients with MSI-H/dMMR colorectal cancer [10].

Nivolumab and Ipilimumab

Nivolumab was first shown to have activity in MSI-H/dMMR colorectal cancer in a phase I trial of refractory solid tumors

where one patient with MSI-H/dMMR colorectal cancer had a complete response of 21 months [11]. This led to CheckMate142, a multicenter phase 2 trial (NCT02060188), where Overman and colleagues studied the effect of nivolumab on dMMR/MSI-H recurrent or metastatic colorectal cancer on patients with no response or intolerance to fluoropyrimidine and oxaliplatin or irinotecan. After 12 months of follow up, 31% of patients showed an objective response and 69% of patients had stable disease for at least 12 weeks [12]. The results of this study led to FDA approval of nivolumab for the treatment of dMMR/MSI-H advanced colorectal cancer in 2017. Overman and colleagues then extended the CheckMate142 study to assess the efficacy of the combination of two checkpoint inhibitors in advanced dMMR/MSI-H colorectal cancer. Following initial treatment with four doses of nivolumab plus ipilimumab, patients were continued to be given nivolumab every 2 weeks. The results showed an ORR of 55% and more than 12 weeks of stable disease in 80% of patients after 13.4 months of follow up. Twelve-month PFS and OS were 71% and 85%, respectively. It was concluded that a combination of nivolumab and ipilimumab potentially improves the patient's outcome compared to nivolumab as a monotherapy [13]. As a result of this study, the FDA approved nivolumab/Ipilimumab for the treatment of metastatic dMMR/MSI-H colorectal cancer in 2018.

Conclusion

Currently, immune checkpoint inhibitors have been demonstrated to have clinical benefit in the treatment of dMMR/MSI-H colorectal cancer. Furthermore, the era of immunotherapy is moving forward in colorectal cancer and many clinical trials investigating the role of new immune checkpoint inhibitors such as atezolizumab (NCT02997228) and Durvalumab (NCT02227667) in dMMR/MSI-H colorectal cancer is underway. Currently, three immune checkpoint inhibitors including pembrolizumab, nivolumab, and ipilimumab are approved for the treatment of advanced dMMR/MSI-H colorectal cancer for the patients who have progressed on at least one line of therapy. However, with newly published results of KEYNOTE-177, checkpoints inhibitors can now also be potentially considered as the first line of therapy in advanced dMMR/MSI-H colorectal cancer.

Acknowledgement

None.

Conflict of Interest

No conflicts of interest.

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