Neoadjuvant Immunotherapy in Stage III Colon Cancer with Deficient Mismatch Repair: A Step Towards Mainstream Adoption? Single-center Experience

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Abstract

Colon cancer remains a major cause of cancer-related mortality worldwide, with Locally Advanced Colon Cancer (LACC) accounting for a substantial proportion of newly diagnosed cases. Among these, tumors characterized by Deficient Mismatch Repair (DMMR) or High Microsatellite Instability (MSI-H) represent a distinct molecular subset, comprising approximately 10–15% of cases. While early-stage DMMR colon cancer is associated with a favorable prognosis, its resistance to conventional neoadjuvant chemotherapy has posed challenges in treatment optimization..

The emergence of immune checkpoint inhibitors has revolutionized the management of DMMR metastatic colorectal cancer, prompting investigations into their potential in earlier disease stages. Recent trials, including NICHE and NICHE-2, have demonstrated remarkable efficacy of neoadjuvant immunotherapy in DMMR colon cancer, reporting high Pathological Complete Response (PCR) rates. Despite these promising findings, the broader clinical adoption of neoadjuvant immunotherapy for resectable LACC remains under evaluation, with questions regarding optimal treatment regimens, timing, and patient selection.

In this study, we present real-world data from our single-center experience using a combination of nivolumab and ipilimumab as neoadjuvant therapy in patients with DMMR stage III colon cancer.

Our findings contribute to the growing body of evidence supporting the efficacy of neoadjuvant immunotherapy in this subset, highlighting its potential to redefine treatment paradigms. Further research is warranted to refine strategies and establish immunotherapy as a standard approach in resectable DMMR colon cancer.

Keywords: Colon cancer • dMMR • MSI-H • Neoadjuvant immunotherapy • Immune checkpoint inhibitors • Nivolumab • Ipilimumab • Pathological response

Introduction

Colorectal Cancer (CRC) remains a leading cause of cancer-related mortality worldwide, responsible for approximately 935,000 deaths in 2020. This includes 576,858 deaths from colon cancer and 339,022 from rectal cancer, accounting for 10% of all cancer-related deaths globally. Locally Advanced Colorectal Cancer (LACRC), defined as tumors invading adjacent tissues or involving regional lymph nodes, constitutes about 36% of initial diagnoses, while 22% of cases present with distant metastases. According to the National Cancer Institute (USA), the 5-year Overall Survival (OS) rates are 64% for colon cancer and 67% for rectal cancer [1].

High Microsatellite Instability (MSI-H) or Deficient Mismatch Repair (DMMR) colon cancer represents a distinct subtype of CRC identified by biomarker status. It is observed in approximately 10% to 15% of cases. These cancers often involve right-sided tumors and are more frequently associated with poorly differentiated and/or mucinous adenocarcinomas [2]..

Materials and Methods

The Mismatch Repair (MMR) system, which includes specific enzymes governed by four critical genes Mut L Homolog 1 (MLH1), Postmeiotic Segregation Increased 2 (PMS2), Muts Homolog 2 (MSH2), and Muts Homolog 6 (MSH6)-is vital for maintaining genomic stability [3]. Disruption of MMR function, known as Deficient Mismatch Repair (DMMR), results in malfunctioning or absent repair proteins. This leads to Microsatellite Instability (MSI), primarily characterized by insertion/deletion mutations in microsatellite regions during DNA replication [4]. Microsatellite Instability (MSI) refers to variations in microsatellite sequence length or base composition due to insertion or deletion mutations, typically arising from DMMR. Tumors are classified based on their MSI Status as Stable (MSS), Low Instability (MSI-L), or high instability (MSI-H). MSI-H is commonly observed in various solid tumors, including endometrial, colorectal, and gastric cancers [5]. The etiology of DMMR may be attributed to germline mutations in MMR genes, as in Lynch syndrome or to sporadic mutations often associated with CpG island methylation, resulting in a CPG island Methylation Phenotype (CIMP). Sporadic cases frequently exhibit a BRAF-activating mutation (V600E), which aids in distinguishing Lynch syndrome from sporadic cases [6].

Evidence suggests that the Microsatellite (MS) status of CRC may change during disease progression. Individuals with advanced-stage cancers are less likely to exhibit high Microsatellite Instability (MSI-H) [7]. While patients diagnosed with early-stage MSI-H/DMMR CRC generally have favorable prognoses, this status is recognized as a negative prognostic indicator among those with metastatic CRC (mCRC) [8].

The FOxTROT (Fluorouracil, Oxaliplatin, and Targeted Receptor Pre-Operative Therapy) trial has highlighted the potential of neoadjuvant therapy in CRC, particularly among patients achieving a pathological Complete Response (pCR) [9]. However, the efficacy of neoadjuvant chemotherapy appears closely tied to MMR status, with DMMR tumors showing pCR rates of only 7%. Although these responses may not always translate into improved survival outcomes in LACRC, they underscore the need for tailored approaches.

Currently, treatment approaches for DMMR tumors mirror those for Mismatch Repair–Proficient (PMMR) tumors. However, significant progress has been achieved since the introduction of immunotherapies for MSI-H or DMMR MCRC in 2015. Immune checkpoint inhibitors have shown exceptional efficacy in this subset, reshaping treatment paradigms.

The NICHE study (Neoadjuvant Immune Checkpoint Inhibition and Novel IO Combinations in Early-Stage Colon Cancer) [10] and its follow-up, NICHE-2 [11], evaluated neoadjuvant immunotherapy in DMMR colon cancer patients using a single dose of the CTLA-4 inhibitor ipilimumab and two doses of the PD-1 inhibitor nivolumab. This approach yielded highly promising results, with a pathological Complete Remission (pCR) rate of 67% and a pathological response rate of 98%, further reinforcing the therapeutic potential of immunotherapy in this context.

Emerging clinical trials, both completed and ongoing, continue to explore the role of neoadjuvant immunotherapy in locally advanced CRC. Preliminary findings indicate substantial tumor regression, particularly in patients with DMMR tumors. However, questions remain regarding optimal timing, regimens, and patient selection criteria, underscoring the need for further investigation.

In this context, we present real-world data from our center's experience treating locally advanced, resectable colon cancer with DMMR using a combination of nivolumab and ipilimumab. Our findings aim to contribute to the growing evidence supporting the efficacy of neoadjuvant immunotherapy in resectable DMMR colon cancer, potentially paving the way for broader clinical adoption.

Results

Between December 2022 and July 2024, six patients with dMMR colon carcinoma, classified as clinical stage cT2-cT4 and cN0-cN+, were treated with neoadjuvant immunotherapy (Table 1).

Table 1. Demographic and disease characteristics.

Patients (n=6)	
Median age (range) – yr	68 (49- 88)
Sex	
Female-no. (%)	3 (50)
Tumor stage-no. (%)	
cT3	3 (50)
cT4	1 (16)
cT2	2 (33)
Nodal status-no. (%)	
cN0	0
cN+	6 (100)
Primary tumor location-no. (%)	
Right n (%)	4 (67)
Transverse n (%)	0
Left n (%)	2 (33)
dMMR (IHC)-no. (%)	6 (100)
Lynch syndrome-no. (%)	1 (16)

The treatment regimen followed the protocol of the NICHE-2 trial, consisting of ipilimumab (1 mg/kg) and nivolumab (3 mg/kg), with a second dose of nivolumab administered two weeks later. Surgery was performed in all patients during the sixth week after initiating immunotherapy.

The therapy was well-tolerated, with no>G1 Immune-Related Adverse Events (IRAE) reported in any of the patients and no ongoing IRAE at the patients last follow up visit.

A pathological response was observed in five out of six patients (83%) (Table 2), including three who achieved complete pathological remission (50%). One of these patients had a Lynch syndrome. Two additional patients demonstrated a major pathological response, while one patient showed no pathological regression.

Table 2. Pathological response.

Patient	CT stage	Pathological stage	Dworak TRG	Residual tumor rate
1	cT3 cN2 M0	ypT0 ypN0 (0/36), L0 V0 Pn0	4: CR	0% residual viable tumor
2	cT3 cN1 M0 (left)	ypT0 ypN0 (0/42), L0 V0 Pn0	4: CR	0% residual viable tumor
3	cT3 cN1 M0 (left)	ypT3 ypN0 (0/35), L0 V0 Pn0	2: PR	40% residual viable tumor
4	cT4 cN1 M0	ypT4a ypN0 (0/26), L0 V0 Pn0	3: NCR	≤ 10% residual viable tumor
5	cT2-3 cN1 M0	ypT0 ypN0 (0/18), L0 V0 Pn0	4: CR	0% residual viable tumor
6	cT3-4 cN2 M0	ypT4a ypN1b (2/32), L1 V0 Pn0	1: MR	>75% residual viable tumor

Note: TRG: Tumor Regression Grade; CR: Complete Response; PR: Partial Response; NCR: Near Complete Response; MR: Minimal Response.

Discussion

The evaluation of MSI and MMR status has become essential for determining which patients may respond favorably to immunotherapy in CRC and other solid tumors. The KEYNOTE-177 [12] and Check Mate 8HW [13] trials showed notably longer progression free survival among patients with MSI-H/dMMR status treated with first-line Immune Checkpoint Inhibitors (ICIs) compared to those receiving standard chemotherapy.

The NICHE study was groundbreaking in introducing neoadjuvant ICI therapy for early-stage dMMR/MSI-H colon cancer, including stage I (10%), stage II (10%), and stage III (80%) disease. The study assessed the combination of nivolumab, an anti-PD-1 antibody, and ipilimumab, an anti-CTLA-4 antibody, in individuals with resectable colon cancer. Amazingly, every patient with dMMR/MSI-H colon cancer (32 out of 32) experienced a pathological response, with 97% (31 out of 32) showing a significant pathological response (<10% viable tumor) and 69% (22 out of 32) achieving complete pathological remission after a median follow-up of 25 months [10]. Expanding on these findings, the NICHE-2 study included a larger group of 107 nonmetastatic dMMR/MSI-H colon cancer patients. The results were similarly impressive, with 95% achieving a major pathological response and 68% achieving complete pathological response. After a median follow-up of 26 months, no disease recurrences were observed, underscoring the efficacy of neoadjuvant immunotherapy in this patient population [11].

Although MSI/MMR status serves as a crucial biomarker for predicting immunotherapy outcomes, it is present in just 5-9% of Metastatic CRC cases (MCRCS). Moreover, some patients with MSS/PMMR CRC have also responded to ICI treatment, highlighting the need for more precise and reliable predictors of immunotherapy response.

Tumor Mutational Burden (TMB) has been identified as a promising predictor, with elevated TMB (>10 Mut/MB) linked to greater immunogenicity and enhanced effectiveness of ICIs. Similarly, mutations in DNA Polymerase Epsilon (POLE) and Polymerase Delta 1 (POLD1), which disrupt DNA replication accuracy and lead to high mutation rates, have potential as biomarkers for ICI efficacy. Despite most POLE-mutated CRCs being MSS or MSI-L, they display immune characteristics similar to MSI-H tumors, such as increased CD8+ T-cell infiltration and higher expression of immune checkpoint molecules [12,13]. A previous study demonstrated that tumors with higher densities of infiltrating lymphocytes, particularly CD8-positive T cells, were associated with better responses to ICIs.

However, challenges remain in ICI treatment. The optimal treatment duration and need for combination therapy remain debated. Evidence from rectal cancer suggests that anti-PD-1 monotherapy may suffice for locally advanced cases, but this is less certain for colon cancer, where no study has shown 100% complete response rates. Treatment schedules have varied widely, ranging from six weeks (nivolumab/ipilimumab,two cycles) to six months (dostarlimab, eight treatments) and up to a year (pembrolizumab). Longer follow-up, including disease-free survival data, will be crucial to assess the efficacy of these differing regimens [14].

While neoadjuvant immunotherapy for locally advanced dMMR/MSI-H CRC has delivered encouraging results, controlled trials comparing it to adjuvant ICI therapy are lacking. The ATOMIC trial is currently exploring the additive role of immune checkpoint therapy combined with chemotherapy in the adjuvant setting for MSI-H stage III colon cancer. Whether chemotherapy is necessary for these patients remains an unanswered question. More studies are needed to compare neoadjuvant and adjuvant immunotherapy approaches to better define the role of neoadjuvant treatment in locally advanced colon cancer [15].

Another concern is Immune-Related Adverse Events (IRAES) during neoadjuvant ICI treatment in CRC, which could delay surgery, increase morbidity risk, or even lead to mortality.

In the NICHE trial, 5% of patients did not exhibit pathological regression, underscoring the need for reliable predictive biomarkers to identify non-responders before initiating treatment.

Conclusion

In summary, ICIs have demonstrated significant efficacy for patients with dMMR/MSI-H CRC across all stages. Recent studies highlight their potential for use in neoadjuvant settings, offering promising therapeutic outcomes for this patient population. However, additional research is essential to optimize treatment duration, determine the most effective monotherapy or combination strategies, and investigate the mechanisms behind resistance in non-responders. Moreover, it is crucial to explore the feasibility of organ preservation in patients who achieve pathological complete remission through ICI therapy.

Author's Contribution

Dr. Zuniga, Dr. Boehm, and Dr. Ortega Sanchez contributed equally to this work.

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