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Mini Review

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Immunotherapy in pMMR/MSS Pancreatic Cancer

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Abstract

Over the last two decades, there have been remarkable improvements in the management of patients with various solid tumors characterized by deficient mismatch repair or high microsatellite instability. This progress can be attributed to the emergence of immune checkpoint inhibitors. However, pancreatic cancer with proficient mismatch repair/microsatellite stable (pMMR/MSS) status has not derived this advantage. Unfortunately, it has yet to be demonstrated that immune checkpoint inhibitor therapy yields significant clinical advantages for patients with pMMR/MSS pancreatic cancer. In these patients, many studies have been conducted on the use of immune checkpoint inhibitors in combination with tyrosine kinase inhibitors and targeted therapies to ascertain their potential for amplifying antitumor efficacy within the tumor microenvironment, enhancing clinical and radiologic outcomes. We also examine the utilization of immune checkpoint inhibitors in pancreatic cancers with pMMR/MSS and assess the molecular obstacles that block the efficacy of immunotherapy. In this review, we analyze the use of immune checkpoint inhibitors in treating pMMR/MSS pancreatic cancer and the molecular barriers to effective immunotherapy. Additionally, we discuss strategies to enhance the responsiveness of pMMR/MSS pancreatic cancer to immunotherapy.

Keywords: Immunotherapy, Pancreatic cancer, PD-L1, MSS, Tumor microenvironment

Introduction

Pancreatic cancer is among the most lethal gastrointestinal malignancies, ranking as the third leading cause of cancer-associated mortality in Western countries.[1] Progress in the field has resulted in modest improvements in survival for patients with advanced pancreatic cancer in the past two decades, attributed to advances in therapeutic management. The utilization of different strategies, encompassing the incorporation of novel drugs in conjunction with gemcitabine-based chemotherapy and the identification of distinct genetic alterations through targeted therapeutic interventions, has yielded incremental advancements in the prognosis of patients with metastatic pancreatic cancer.[2] The mean overall survival (OS) for patients with metastatic pancreatic cancer remains approximately 8-11 months, indicating a substantial requirement for enhanced management, particularly in cases of proficient mismatch repair/microsatellite stable (pMMR/MSS) disease. A limited number of studies have indicated the decreased effectiveness of immune checkpoint inhibitors in pMMR/MSS pancreatic cancer,[3,4]a tumor type distinguished by its immunosuppressive tumor microenvironment and decreased immunological activity. Over the course of the previous decade, the utilization of immune checkpoint inhibitors has exerted a contemporary influence on the management of different types of solid tumors, leading to substantial alterations in their treatment strategies.[5] The utilization of checkpoint blockade has yielded notable advancements in the treatment of various cancers characterized by deficient mismatch repair/high microsatellite instability (dMMR/MSI-H), demonstrating long-lasting and profound therapeutic outcomes.[6] However, pancreatic cancer with pMMR/MSS manifests chromosomal instability, resulting in genomic structural aberrations, which are accompanied by a characteristically low tumor mutation burden and limited neo-antigen generation.[7] This theory offers a partial explanation for the limited activity of immune checkpoint inhibitors observed in pancreatic cancer patients. However, it is worth noting that numerous molecular factors may contribute to the development of immunotherapy resistance in MSS pancreatic cancer, including its dense stromal compartment and immunosuppressive microenvironment. This review delves into biological obstacles that can

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be overcome to boost the ability to combat tumors. Furthermore, we present an analysis of potential treatment options for patients with pMMR/MSS pancreatic cancer.

Methods

We searched PubMed (www.ncbi.nlm.nih.gov/pubmed) for full-text articles from 2017 to May 31, 2023, using the keywords “immunotherapy”, “colorectal”, “cancer”, “PD-L1”, and “MSS”. The full-text articles found were carefully examined. In addition, all abstracts presented at international conferences between January 2020 and October 2023 were examined.

Immunotherapy in pMMR/MSS mCRC

The CRC with pMMR/MSS is characterized by chromosomal stability and is correlated with a lower tumor mutation burden and reduced neoantigen generation.[7–9] The adaptive immune system regulates tumor-specific immune activation by utilizing neoantigens associated with mutations. Tumor-infiltrating lymphocytes are abundant in MSI-H CRCs, as well as in immune-reactive tumors such as melanoma.[6,10] However, patients with pMMR/MSS mCRC exhibit infrequent tumor-infiltrating lymphocytes due to a lower occurrence of neoantigens associated with mutations and a tumor microenvironment that hinders the infiltration of lymphocytes. The tumor microenvironment in pMMR/MSS differs from that in dMMR/MSI-H, thereby impacting the response to immune checkpoint inhibitor therapy. The tumor microenvironment in pMMR/MSS CRC exhibits increased populations of tumor-associated macrophages,[11] which has been associated with a dismal prognosis in most scientific investigations, although contradictory studies suggest a potential beneficial impact on survival outcomes.[12,13] Although there is no consensus regarding their predictive value, multiple studies have shown that they have an adverse effect on the adaptive immune response, particularly in the context of “immune exclusion”.[14] Studies have shown that increased activation of β-catenin in melanoma cells results in a reduction of the cluster of differentiation 8 + (CD 8+) and CD103+ dendritic cell populations, leading to the block of T-cell recruitment to the tumor microenvironment. This phenomenon is referred to as T-cell exclusion.

Beta-catenin is responsible for the activation of the Wnt signaling pathway in CRC. The frequency of antigen-presenting cell (APC) protein mutations in MSS CRCs exceeds 70%.[15–18] Alterations in the APC gene have been observed in approximately 20% of patients with dMMR/MSI-H CRC, accounting for the disparate underlying mechanisms of oncogenesis in the “immune hot” and “immune cold” subgroups. Elevated expression of the wingless-type MMTV integration site family (Wnt/b-catenin) signaling pathway in CRC is correlated with diminished T-cell infiltration in the tumor microenvironment, thus elucidating the limited efficacy of immune checkpoint inhibitors in the context of CRC. According to a study documented in the Cancer Genome Atlas database,[19] the incidence of mutations in the β-catenin pathway was found to be three times higher in non-T-cell-inflamed cancers than in T-cell-inflamed cancers. Additionally, the amplification of Wnt/β-catenin signaling in CRC can be observed through the occurrence of other alterations, including RNF43, Axin 1/2 mutations, and R-spondin gene fusions.[20–22] While APC alterations are more infrequent than alterations in other systems, it is worth noting that the preceding modifications also contribute to the immune regulation driven by the Wnt pathway.19 The Wnt/β-catenin signaling pathway has the potential to impede the effectiveness of immunotherapy by facilitating immune exclusion. The progression of CRC is associated with transforming growth factor-β. (TGF-β).[23] The mesenchymal nature of TGF-β-driven CRC is identified through its genomic profile, specifically its categorization in the consensus molecular subgroup 4. Consequently, this classification triggers the activation of the epithelial mesenchymal transition.[24] The TGF-β signaling pathway assumes a pivotal role in governing immune regulation within the tumor microenvironment. Increased levels of TGF-β have been observed to result in a heightened presence of regulatory T cells (T-regs) within tumors, subsequently diminishing the efficacy of the antitumor immune response. Additionally, the data indicate that the TGF-β pathway diminishes the efficacy of natural killer cells, which possess the ability to identify and target cancerous cells.[25] The expression of CD41 and CD81 in T cells is reduced in liver metastases of CRC, suggesting significant activation of TGF-β.[26] Liver metastasis in CRC and other tumors may exhibit resistance to immunotherapy, potentially owing to elevated TGF-β signaling.[27]

Suppression of the TGF-β pathway through the use of a small-molecule inhibitor demonstrates a notable decrease in liver metastasis and immune evasion in preclinical models of CRC.[28,29] TGF-β impedes the effectiveness of therapies involving immune checkpoint inhibitors, thereby functioning as an obstacle to the immune response against tumors. Rat sarcoma (RAS) and B-Rapidly Accelerated Fibrosarcoma (BRAF) mutations are commonly observed in CRC, resulting in alterations within the mitogen-activated protein kinase (MAPK) pathway. The MAPK pathway has been linked to the initiation and progression of several types of malignant tumors, such as CRC, and is considered an oncogenic driver. Activation of the MAPK signaling pathway not only facilitates carcinogenesis but also plays a crucial role in orchestrating the heterogeneity of the tumor microenvironment. The presence of the BRAF V600E mutation results in reduced T-cell infiltration and hinders the process of neoantigen presentation in cancer cells.[30,31] The inhibition of

BRAF signaling results in a reduction in suppressor cells, an increase in the recruitment of lymphocytes, enhancement of neoantigen presentation, and improvement in the immune response. Mutations in the KRAS gene have the potential to impede the process of interferon-based antigen presentation and the subsequent recruitment of T cells, thereby impacting the evasion tactics employed by the immune system.[32–36] A study conducted on a mouse model revealed that the oncogenes BRAF and MYC played a role in facilitating immune evasion, which is dependent on Ras. Interestingly, when the activity of BRAF was restored, the immune response against the tumor was restored.[35] The RAS oncogene contributes to the stabilization of programmed cell death–1 (PD-1) RNA, leading to sustained PD-1 expression and the ability to evade the immune response.[37] Inhibition of the KRAS 12C mutation promotes the infiltration of T cells and exhibits synergistic effects when combined with immune checkpoint inhibitors.[38] There is a growing body of evidence indicating that the MAPK pathway might have implications for immune exclusion, functioning as an obstacle to achieving favorable outcomes through immunotherapy.

Overcome resistance

Multiple attempts are required to overcome resistance and achieve a significant response to immune checkpoint inhibitors. Single-agent immune checkpoint inhibitors exhibit limited clinical efficacy. Pembrolizumab did not exhibit clinical efficacy or an overall response rate in patients with pMMR/MSS CRC.[39] The investigation of efficacy in treating solid tumors with nivolumab included a cohort of patients diagnosed with CRC, from which a single individual exhibited a complete response (1/14; 7.2%).[40] There was a lack of objective response in the dose expansion cohort of this study, which consisted of 19 patients diagnosed with pMMR/MSS.[41] The combination of nivolumab and ipilimumab was evaluated in the CheckMate-142 trial, a phase II trial conducted in patients, including mCRC dMMR/MSI-H and pMMR/MSS. Patients with pMMR/MSS CRC exhibited unfavorable outcomes, as evidenced by the median progression-free survival (PFS) 1.4 months, without efficacy signal of the combination of CTLA-4 and PD-1 blockade.[42] The Cancer Trial Group CO.26 study investigated the combined activity of durvalumab with tremelimumab.[43] Participants enrolled in this phase II trial were assigned to receive either best supportive care (BSC) or the durvalumab/tremelimumab combination. The experimental arm exhibited a median PFS of 1.8 months, whereas the control arm had a median PFS of 1.9 months. The investigator discovered that although there was a slight increase in OS (6.6 vs 4.1 months p = 0.07), there were no differences in PFS when compared to best supportive care (BSC). These findings support the hypothesis that concurrent blockade of PD-1 and cytotoxic T-lymphocyte associated protein 4 (CTLA-4) fails to induce a substantial immune response in mCRC pMMR/MSS patients. A new study is evaluating the effectiveness of combining an anti-lymphocyte-activating gene-3 (LAG-3), a relatlimab, with nivolumab in mCRC pMMR/MSS patients, as documented in the clinical trial NCT03642067. Efforts must be made to develop drugs that improve the recruitment of immune cells in the tumor microenvironment.

Targeted therapy and immunotherapy in pMMR/MSS mCRC

The combination of targeted therapy and immunotherapy holds the potential to improve the response in pMMR/MSS mCRC patients. Enhancing immune infiltration in CRC constitutes a crucial factor in enhancing the immune response. The combination of tyrosine kinase inhibitors and immune checkpoint inhibitors has been the subject of research based on data indicating that tyrosine kinase inhibitors, primarily angiogenesis inhibitors, can suppress tumor-associated macrophages (TAMs) and enhance T-cell infiltration.[44,45] The REGONIVO study, a clinical trial, assessed the efficacy of combining regorafenib and nivolumab in Asian patients with advanced CRC who had previously undergone unsuccessful systemic chemotherapy.[46] Participants enrolled in this phase Ib clinical trial were administered a combination of regorafenib (dosage of 80 mg, in the expansion cohort) in conjunction with nivolumab (intravenous dosage of 3 mg/kg, administered every two weeks). A total of twenty-five patients with pMMR/MMS were enrolled, with only one patient with MSI-H, refractory disease, and at least two lines of chemotherapy. The investigators reported an objective response rate (ORR) of 33% among patients with pMMR/MSS disease. The median progression-free survival was observed to be 7.9 months, while the median OS was not reached. The one-year PFS rate of 41.8% implies prolonged disease control. A post hoc analysis revealed that, in patients presenting liver metastasis, 8.3% exhibited an objective response, whereas patients with lung metastasis demonstrated a response rate of 63.6%.46 Subsequently, a trial was conducted in the United States to evaluate the efficacy of the identical combination in patients with pMMR/MSS mCRC.[47] The upper limit of regorafenib was identified as 80 mg, whereas patients also received 240 mg of nivolumab every 2 weeks. It was found that fifty-two patients included in this study, the ORR was 8%, and the median PFS was 4.3 months. The primary endpoint was not reached, in contrast to the results observed in the Asian REGONIVO trial. In a clinical investigation involving the combined usage of regorafenib and nivolumab in chemoresistant MSS CRC, it was observed that patients with lung metastasis exhibited a moderate level of response. However, no response was detected in patients with liver metas

tasis. The ORR was found to be 21%.[48]

Pembrolizumab and regorafenib were studied in combination in a phase I/II clinical trial involving patients with pMMR/MSS CRC with disease progression following two or three rounds of systemic chemotherapy.[49] The study involved a cohort of seventy-three patients, among whom no objective responses were observed. The median PFS was 2 months, while the median OS was 10.9 months. The prevalence of liver metastasis was 78%, exceeding the rate observed in the REGONIVO study (52%), which was characterized by a higher occurrence of lung metastasis (64%). A phase II trial combining regorafenib with avelumab did not obtain any objective response. Among those with the best response, stable disease was observed in 23 patients, which accounted for 53.5% of the total.[50]

The median PFS recorded a value of 3.6 months. Adverse prognostic implications were observed in cases with high tumor-associated macrophage counts, while improved outcomes were associated with increased CD81+ T-cell infiltration.50 The clinical utility of combination approaches involving tyrosine kinase inhibitors and immune checkpoint inhibitors is restricted in unselected patients with MSS CRC, despite ongoing investigations utilizing lenvatinib and cabozantinib.[51,52] LEAP-017 is an ongoing phase II study evaluating lenvatinib and pembrolizumab therapy in patients with pMMR/MSS CRC.

It remains unclear whether the signals observed in patients with lung metastasis are attributable to disease biology or an immune response.

The presence of the BRAF V600E mutation in patients with CRC is associated with an aggressive tumor profile, accelerated disease advancement, and unfavorable clinical outcomes. The BEACON trial revealed the transformative impact on medical practice through the combined administration of encorafenib and cetuximab.[51–53] Ongoing investigations are currently focused on the synergistic utilization of encorafenib, cetuximab, and nivolumab, aiming to exploit the immunomodulatory properties associated with BRAF inhibition. This approach is deemed essential for countering the immune evasion mechanisms associated with the BRAF V600E mutation. A recent clinical trial examined the efficacy of this approach in a cohort of 26 patients diagnosed with treatment-resistant BRAF V600E-mutant MSS CRC. The preliminary results of the examination employing nivolumab, encorafenib, and cetuximab demonstrated a 45% rate of objectively observed positive responses and a median duration of 7.3 months without progression.[54] The outcomes observed in this study were substantially better than those of the historical control provided by the BEACON study, which reported an ORR of 20% and a median PFS of 4.2 months with the doublet regimen. The efficacy of the combination of encorafenib, cetuximab, and nivolumab will be evaluated inthe SWOG-2107 clinical trial to confirm its effectiveness. There was no enhancement in OS when utilizing the combination of atezolizumab and cobimetinib in mCRC pMMR/MSS patients.[55] The efficacy of EGFR blockade in combination with immune checkpoint inhibitor therapy has been examined in patients with RAS/RAF wild-type disease. A study was conducted on patients with mCRC harboring wild-type RAS/RAF to evaluate the efficacy of combination therapy involving panitumumab, nivolumab, and ipilimumab.[56] The triplet regimen exhibited an ORR of 35% and a median PFS of 5.7 months, surpassing the efficacy of panitumumab monotherapy.[57] By directing therapeutic focus toward EGFR signaling, particularly the MAPK pathway, a synergistic effect can be achieved in combination with immune checkpoint inhibitors.

Chemotherapy and immunotherapy in pMMR/MSS mCRC

The combination of chemotherapy and immunotherapy to increase the response in pMMR/MSS mCRC involves the combination of cytotoxic agents and immune checkpoint inhibitors, with the specific aim of eliminating cancerous cells and inducing the release of neoantigens to stimulate T-cell activation. This strategy has demonstrated efficacy across diverse types of solid malignancies, including but not limited to lung carcinoma, gastric cancer, and most recently, cholangiocarcinoma.[58] The AtezoTRIBE study conducted an analysis to assess the effects of incorporating atezolizumab into the combination therapy of FOLFOXIRI with bevacizumab in patients with mCRC regardless of MMR status. The preliminary results of the study showed that the primary outcome of PFS was successfully achieved in the entire patient cohort. Nevertheless, the advantage observed in individuals with MSS CRC was only moderately increased, as evidenced by a rise in PFS from 11.4 months to 12.9 months (hazard ratio [HR], 0.78; 80% confidence interval [CI], 0.62–0.97; p = 0.071). No notable difference in the ORR was observed between the two groups (59% compared to 64% response rate, p value = 0.412), highlighting the restricted effectiveness of chemoimmunotherapy in individuals diagnosed with MSS CRC. The efficacy and safety of capecitabine and bevacizumab with or without atezolizumab were examined in the BACCI trial, which compared the outcomes of triple therapy versus doublet therapy in patients with mCRC MMR/MSS or dMMR/MSI-H.[59,60]

In this phase II clinical trial, patients were administered either a three-drug combination regimen incorporating atezolizumab or a two-drug combination regimen incorporating a placebo. The study successfully met the primary endpoint of median PFS, indicating marginal enhancement (4.4 vs. 3.6 months, HR = 0.75; 95% CI = 0.52–1.09; p = 0.07). The median PFS for patients with pMMR/MSS disease increased

modestly, with a duration of 5.3 vs 3.3 months (HR, 0.66; 95% CI, 0.44–0.99). The administration of the triplet regimen did not yield a significant advantage in terms of the median PFS among patients diagnosed with MSS mCRC (sensitivity analysis for median PFS: HR, 0.82; 95% CI, 0.56–1.20).60 The efficacy of the FOLFOX, bevacizumab, and nivolumab combination was evaluated in the CheckMate-9X8 trial, which included treatment-naive patients diagnosed with mCRC, regardless of their RAS/RAF and microsatellite instability status.61 The primary endpoint was the median PFS, which was the same (12.9 months) in the experimental arm and the control arm. After 12 months, a discernible divergence became apparent in the curves, leading to an increased rate of PFS at 18 months (28% in comparison to 9%). Currently, there is no established biomarker capable of identifying patients who are responsive to immunotherapy. The cohort treated with nivolumab exhibited a significantly elevated ORR of 60%, compared to the 46% response rate in the control group. The combination of immune checkpoint inhibitors with chemotherapy has limited efficacy and has not yet been used to modify established treatment methods. Additional investigations are required to understand the mechanisms by which immune evasion occurs within the tumor microenvironment of CRC.

Conclusions

Treatments for MSS CRC using immunotherapy, especially immune checkpoint inhibitors, are limited. However, the progress achieved in studies combining targeted TkIs and chemotherapy has paved the way for encouraging results. These treatments can help achieve clinical goals and shift cold tumors to hot responsive tumors. A deeper understanding of the foundation of diverse resistance mechanisms is needed to generate new possibilities with diverse routes to advance immunotherapy in CRC patients.

The SWOG-2107 trial will provide insights into the clinical importance of the potential synergistic effects of dual BRAF inhibition and immune checkpoint-positive inhibitors, opening therapeutic options and alternative opportunities in MAPK-targeted approaches.

Strategies targeting the Wnt and TGF-β pathways are currently under investigation. The aberrant activation of the Wnt signaling pathway in CRCs has a significant impact on establishing a protected environment to exclude the immune system from cancer cells with diminished neoantigen expression.

It may be crucial to know which CRC subsets benefit from each of these approaches. Therefore, molecular definitions, including consensus molecular subtypes, may aid in achieving this goal. Certain MSS CRCs showing mutations in POLE and POLD1 may be responsive to immunotherapy.

The combined power of all these drugs must be used to optimize the response in patients with mCRC pMMR/MSS.

Abbreviations

BRAF:
B-Rapidly Accelerated Fibrosarcoma
CD 103+:
cluster of differentiation 103+
CD 8+:
cluster of differentiation 8 +
CRC:
colorectal cancer
dMMR/MSI-H:
deficient mismatch repair or high microsatellite instability
ERKs:
Extracellular signal-regulated kinases
LAG-3:
Lymphocyte-activation gene-3
MAPK:
mitogen-activated protein kinase
MAPKs:
Mitogen-activated protein kinases
OS:
overall survival
pMMR/MSS:
proficient mismatch repair /microsatellite stable colorectal cancer
TAMs:
Tumor-associated macrophages
TGF-bβ:
transforming growth factor - b -β
Wnt/b-catenin:
wingless-type MMTV integration site family

Declarations

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Conflict of interest

The authors declare that they have no conflict of interest.

Authors' contributions

Conceptualised the contents for manuscript and written the manuscript: AC, CMP; reviewed the paper and approved the final version of ther article: SC, CMP, DP, VG. All the authors mentioned here made significant contributions in preparation of this manuscript and have approved the manuscript.

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