The Role of Mismatch Repair Deficiency in the Treatment, Diagnosis, and Pathophysiology of Endometrial Cancer

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Abstract

Endometrial cancer impacts thousands of women worldwide and has many risk factors. Risk factors include obesity, diabetes, infertility, history of endometrial hyperplasia, menstruating before the age of twelve, having menopause later, or receiving estrogen replacement therapy. Mismatch repair deficiency is found in about 30% of endometrial cancers and worsens the prognosis as well as increases the recurrence rate of endometrial cancer. Currently, most common treatments for cancer are chemotherapy and surgery. To combat endometrial cancer with mismatch repair deficiency, immunotherapy has gained traction. Immunotherapy has considerably fewer side effects than the more invasive treatments currently being used. Specifically, drugs, like dostarlimab and pembrolizumab, are used to trigger the immune system to fight the cancer cells. This review article focuses on the effect mismatch repair deficiency has on the progression of endometrial cancer as well as the efficacy of immunotherapy drugs on mismatch repair deficient endometrial cancer.

Keywords

Mismatch repair deficiency, endometrial cancer, immunotherapy, dostarlimab, pembrolizumab

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Introduction

Endometrial cancer is a disease caused by the formation of malignant cells in the endometrial tissues. It is the most common type of cancer in the uterus. According to the American Cancer Society, over 66,000 cases of endometrial cancer will be diagnosed in 2023, with about 13,000 women dying from the disease. (1) Several factors increase the risk of developing endometrial cancer, including obesity, age, diet, type 2 diabetes, family history, and fluctuations in hormone levels. Endometrial cancer may cause abnormal vaginal bleeding, pelvic pain, spotting, and weight loss. The stage of this cancer is classified by the extent of the tumor, the spread to nearby lymph nodes, and the spread to distant sites.

Mismatch repair deficiency has been found in about 30% of endometrial cancers and can cause several DNA mutations in cells, leading to cancer and affecting its progression. (2) Mismatch repair deficiency is the loss of function in the mismatch repair pathway and causes mismatch mutations in the genome. Despite its prevalence, treatments for mismatch repair deficiency in endometrial cancer continue to remain obscure. Even with advancements in technology and immense research, mismatch repair deficiency in endometrial cancer continues to remain prevalent. While cancer is not hereditary, cancer-related genetic changes can be passed down from one's parents if present in their egg or sperm cells, increasing the risk for one to develop the cancer. Similarly, genetic changes that were inherited could cause mismatch repair deficient endometrial cancer. Mismatch repair deficiency is typically caused by mutations in the *PMS2, MLH1, MSH2, or MSH6* genes, which are involved in correcting any errors made when DNA is copied before cell division begins. Mutations in any of these genes can cause proteins to lose their function, eliminating mismatch repair activity. The errors, then, continue to accumulate and disrupt the activity of other cells involved in controlling cell growth and division, which leads to development of tumors.

Currently, to combat endometrial cancer, the most common treatment courses are surgery, radiation therapy, and chemotherapy. These current treatments are highly invasive and cause extensive side effects, including pain and fatigue. However, to combat endometrial cancers with mismatch repair deficiency, immunotherapy - a treatment that triggers the immune system to fight cancer cells- has gained traction in the last couple of decades. Immunotherapy has considerably fewer side effects, causing less pain and fatigue, than other treatments since they primarily target the immune system rather than all the cells in the body. In the treatment, drugs are provided to stimulate the natural defenses of the immune system, allowing it to target and attack cancer cells more efficiently. A common type of immunotherapy is checkpoint inhibitors, which are drugs that help the immune system identify and attack cancer cells, preventing the cancer cells from further replicating and accumulating. Another way the treatment could be done is by extracting immune cells from the tumor and cultivating them in a lab to insert intravenously in the human body and restore the immune system. Some drugs that are used for immunotherapy, or antibodies, include dostarlimab and pembrolizumab. Pembrolizumab, a drug that blocks PD-1 on T-cells, allows these white blood cells that are part of the immune system to fight against the cancer cells. As immunotherapy becomes more vital to treat cancers, this paper aims to address how mismatch repair deficient endometrial cancer reacts to immunotherapy treatments and affects the progression of the cancer.

Methods

To obtain the studies used in this review, PubMed and Google Scholar were used. Study types included in this review when utilizing PubMed are “Free Full Texts,” “Clinical Trial,” “Meta-Analysis,” and “Randomized Controlled Trial.” Search terms used include “endometrial cancer mismatch repair” and “mismatch repair deficiency in cancers.” In Google Scholar, the inclusion criteria was “Any Type” to receive all the possible studies conducted on mismatch repair deficiency. The search terms used for Google Scholar included “mismatch repair deficiency endometrial cancer” or “DNA mismatch repair endometrial carcinomas.” Study abstracts were screened for relevance to mismatch repair deficiency in endometrial cancer. Out of 1,618 studies in PubMed, 1,578 studies were filtered out.

Results

Relationship Between Mismatch Repair Deficiency, Mutations, and Progression of Endometrial Cancer

A study conducted by Elena Fountzilas and her colleagues focused on the prognostic implications of mismatch repair deficiency in patients with non-metastatic colorectal and endometrial cancer (5). The Hellenic Cooperative Oncology Group identifies patients with non-metastatic colorectal and non-metastatic endometrial cancer who would be able to help provide analysis tissue blocks. The tissue that was collected from the patients were the formalin-fixed paraffin-embedded tissue. The expression of the mismatch repair proteins- *MLH1, PMS2M MSH2, AND MSH6*- were analyzed, and the intensity and percentage of each protein were recorded through immunohistochemistry. The expression of the mismatch repair protein was positive if more than one percent of the positive nuclei with an intensity ranging from mild to strong were counted. If the stromal cell and lymphocytic infiltrates (internal controls) were positive and the tumor cells were completely negative or were less than one percent, then the mismatch protein expression was considered negative. The expression was noninformative if both the tumor cells and internal controls were negative. Out of the 475 patients diagnosed with low-risk endometrioid endometrial cancer, 131 were mismatch repair-deficient and 344 were mismatch repair-proficient. Those that were mismatch repair-deficient had worse progression-free survival and higher recurrence rates than those who were mismatch repair-proficient.
Another study examines the relationship between POLE mutations, checkpoint mutations, and mismatch repair-deficient cancers (6). POLE mutations cause Polymerase Proofreading-Associated Polyposis (PPAP) syndrome, increasing the risk of developing polyps. Sequencing was performed for POLE on 202 endometrial cancers and immunohistochemistry. The study observed how POLE mutations and mismatch repair-deficient mutations were associated with clinicopathological features, checkpoint proteins, and density of tumor-infiltrating lymphocytes (TILs). The tumor-infiltrating lymphocytes identify and eliminate cancer cells. The POLE mutations and mismatch repair deficiency caused elevated levels of tumor-infiltrating lymphocytes. Also, a lower level of checkpoint proteins and higher levels of TILs resulted with a better prognosis for those with endometrial cancers.

A study conducted by D. Scott McMeekin and his colleagues examined the clinicopathological significance of mismatch repair defects in endometrioid endometrial cancer (7). To conduct the study, pathologists from the Gynecologic Oncology Group reviewed the clinical reports and tumor slides of 1,043 subjects with endometrioid endometrial cancer. The pathologists analyzed the patients' microsatellite instability, MLH1 methylation, and mismatch repair protein expression. The tumors of the patients were also assigned to the following categories: normal, epigenetic defect, probable mutation, or low microsatellite instability. After assessing the relationships, patients diagnosed with a higher stage of endometrioid endometrial cancer had more epigenetic defects. Additionally, the progression free survival was worse for patients whose tumors had epigenetic endometrial cancer than for those with normal mismatch repair.

The Effects of Antibodies on Patients with dMMR Endometrial Cancer

In a non-randomized phase 1 clinical trial, a study performed by Oaknin and their colleagues (3), investigated how dostarlimab - an antibody that binds to the PD-1 receptor- affected patients with deficient mismatch repair (dMMR). As mentioned previously, the PD-1 receptor prevents the interaction with PD-L1 and PD-L2, stopping the anti-tumor immune response. However, dostarlimab functions to block the PD-1 receptor, effectively activating the anti-tumor response. The patients included in this trial were those who were eighteen and older, were histologically and cytologically diagnosed with recurrent or advanced endometrial cancer and had dMMR tumors. These patients had minimal treatment- 2 lines at most- to accurately analyze the effect of dostarlimab. They were included in the trial to understand how dostarlimab would affect anyone who was diagnosed with advanced/recurrent endometrial cancer with dMMR. For the treatment, patients were given 500 milligram infusions of dostarlimab every three weeks for twelve weeks. Then, they were given 1000 milligram infusions once every six weeks, which helped determine the antitumor activity of dostarlimab by calculating how many patients had a confirmed complete response or partial response to the dostarimab and by the duration of the response, which was the time from the partial or complete response to the first sign of disease progression or death. Out of 71 of the patients, 9 patients had a confirmed complete response while 21 patients had a confirmed partial response to dostarlimab.
Another study led by O'Malley and their colleagues determined the safety of pembrolizumab in patients with advanced MSI-H (microsatellite instability-high) /dMMR endometrial cancer (4). MSI-H/dMMr indicated high levels of mutations in DNA of cancer cells and increased risk of cancer. MSI-H tumors have immune checkpoint receptor death and unregulated ligand PD-1 receptors. In this nonrandomized phase 2 study, patients with endometrial cancer were placed in either cohort D, which had patients with advanced endometrial cancer regardless of their MSI status, or cohort k, which had patients with any MSI-H/dMMR advanced tumor with the only exception for colorectal cancer. The patients were grouped in this particular order to determine and compare the effects of pembrolizumab on populations who were diagnosed with advanced endometrial cancer and populations who were diagnosed with MSI-H/dMMR endometrial cancer. To be eligible, patients had to be eighteen or older and documented metastatic or unresectable disease. The patients were given 200 milligrams of pembrolizumab intravenously 35 times every three weeks. To determine patient-reported outcomes, health related quality of life questionnaires was provided to patients. Overall, the pembrolizumab either maintained or improved health-related quality of life. Patients with a confirmed objective response had even

greater improvements with patients indicating better health-related quality of life from the questionnaires.

Discussion

Mismatch repair deficient tumors have worse effects on patients- for instance, 77.5% of MMRd cases displayed protein loss (6)- with endometrial cancer than on patients without tumors, causing them to have a worse prognosis (5, 7). It also leads to higher recurrence rates for those with low endometrial cancer. These detrimental effects of mismatch repair deficient proteins were in accordance with a study by E Stelloo and their colleagues (9). The effects of POLE mutations caused by increased amounts of PD-1 and TILS, however, can be compensated by immune checkpoints, unlike in mismatch repair deficiency. As a result, more effective treatments to treat MMRd endometrial cancer are crucial.

The studies on dostarlimab and pembrolizumab show the tremendous effects that the antibodies have on patients with dMMR. Due to its promising results, the antibodies are gaining traction in the medical field as several oncologists have agreed to add either of these antibodies to chemotherapy in order to treat patients with advanced or recurrent endometrial cancer who have dMMR tumors. Another study on the drugs also observes promising results on patients with dMMR tumors with minimal side effects. (8) However, while these antibodies are effective treatments, further research is needed to improve the objective responses of these antibodies. Future clinical trials need to focus on expanding the effectiveness of the antibodies on more patients with dMMR endometrial cancer, which would contribute to more personalized treatments for patients.

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