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The latest treatment of colorectal cancer – a review paper

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Abstract

The review article discusses the latest therapeutic approaches in the treatment of colorectal cancer (CRC), with a particular focus on metastatic disease. Despite advancements in standard treatments such as surgery, chemotherapy, and targeted therapies, the prognosis for patients with metastatic CRC remains poor, with five-year survival rates still low. The article examines the potential of immunotherapy, including PD-1 inhibitors like dostarlimab, which have shown promising results in treating selected patient groups. Additionally, the role of the ketogenic diet and probiotics as supportive strategies in CRC treatment is discussed, highlighting their

potential to influence cancer metabolism and improve therapeutic outcomes. The article also addresses the development of nanotechnology-based therapies, such as PEGylated PLGA nanoparticles and sphingomyelin nanosystems, which may enhance drug delivery precision, thereby improving treatment efficacy and minimizing side effects. The conclusion emphasizes the need for further research into these innovative therapies and their integration with existing treatment protocols to improve survival and quality of life for CRC patients.
Keywords: colorectar cancer; immunotherapy; oncology; crc; latest treatment of colorectal cancer; nutrition in colorectal cancer

Introduction

Colorectal cancer ranks as the third most prevalent cancer globally, representing around 10% of all cancer cases, and it is the second most common cause of cancer-related deaths worldwide due to WHO (World Health Organisation)(1). In 2020, it was estimated that over 1.9 million new cases of colorectal cancer occurred globally, along with more than 930,000 deaths caused by the disease. According to the National Cancer Registry in Poland, colorectal cancer is the cancer of high incidence among both men and women, ranking 2-3 among incidence and deaths(2). For malignant tumors of the colon and rectosigmoid junction, the male population continues to experience a consistent rise in both incidence and mortality rates. In contrast, among women, although incidence has been increasing, the rise in mortality has been halted, with mortality rates remaining stable for over a decade(3). Despite considerable progress in standard treatment options, the 5-year survival rate for metastatic colorectal cancer (CRC) remains approximately 12%(4).

Colorectal cancer is frequently asymptomatic in its early stages. When symptoms do manifest, they commonly include: alterations in bowel habits, such as persistent diarrhea, constipation, or narrowing of the stool, hematochezia or melena, characterized by the presence of blood in the stool, either bright red or dark and tarry, persistent abdominal pain, cramping, or bloating, unintentional and unexplained weight loss, chronic fatigue and decreased energy levels despite sufficient rest, iron deficiency anemia resulting from chronic occult bleeding, which may lead to fatigue, weakness, and pallor(1).

Materials and Methods

This review article was conducted through a comprehensive and systematic analysis of the

existing literature related to colorectal cancer. The primary objective was to synthesize and critically evaluate the current knowledge, identify gaps in the research, and suggest potential areas for future investigation. The literature search was conducted across multiple electronic databases, including PubMed, Web of Science, Scopus, and Google Scholar. The search focused on identifying peer-reviewed articles, clinical trials, meta-analyses, and review papers published in the last 10 years. Keywords used in the search included "colorectal cancer," "latest treatments," "targeted therapy," "immunotherapy," "chemotherapy," and "surgical interventions," among others.

Current treatment recommendations

Currently, according to the diagnostic and therapeutic management guidelines, the recommended treatment for patients with colon cancer is based on the outcome of the cancer staging assessment. The assessment of disease progression is based on the TNM classification. For surgical treatment, segmental resection of the colon with adequate margins and removal of regional lymph nodes is the standard approach. In advanced specific cases, preoperative radiotherapy may be considered, especially when the tumour infiltrates adjacent anatomical structures. For systemic treatment, complementary chemotherapy is recommended in stage III, and in cases of metastatic disease the emphasis is on combination therapy with biologic drugs. In cases where metastases are surgical, metastasectomy is also possible. Follow-up after treatment is crucial for early detection of recurrence and includes regular imaging and CEA determination(3).

Discussion

Immunotherapy

A Phase II study on patients with advanced mismatch repair-deficient (dMMR) rectal cancer treated with the PD-1 inhibitor dostarlimab resulted in a 100% clinical and pathological response across all 12 participants, with no remaining tumors detected after six months. None of the patients required additional treatments like chemoradiotherapy or surgery, and there were no cases of disease progression or recurrence during the follow-up period. The treatment was well-tolerated, with no reports of severe side effects. These results suggest that dostarlimab could be a non-invasive alternative to conventional treatments, potentially avoiding the complications associated with surgery and chemoradiotherapy. However, more research is

needed to validate the long-term success of this treatment strategy(5). Another article from Journal of Clinical Oncology evaluates recent developments in the treatment of metastatic colorectal cancer (mCRC), focusing on the efficacy of combining targeted therapies with immunotherapy. It highlights the benefits of incorporating novel agents, such as small-molecule inhibitors and immune checkpoint inhibitors, into treatment regimens. The review emphasizes that combining these therapies with traditional chemotherapy has shown promise in improving clinical outcomes for patients with mCRC. According to this article Nivolumab in conjunction with low-dose ipilimumab proved to be highly effective and enduring in its clinical benefits and was well tolerated as an initial treatment for MSI-H/dMMR mCRC(Microsatellite Instability-High/Deficient Mismatch Repair Metastatic Colorectal Cancer)(6). Another article reviews the efficacy of various targeted therapies for metastatic colorectal cancer (mCRC). It presents evidence showing that combining anti-VEGF and anti-EGFR agents with traditional chemotherapy significantly improves patient outcomes. The results highlight that these targeted treatments can enhance response rates and prolong survival in mCRC(7).

Chemotherapy

The recommendations for adjuvant treatment of colorectal cancer differ based on the disease stage. For Stage I, adjuvant therapy is unnecessary due to the favorable prognosis, with observation being the preferred approach. In Stage II, the benefit of adjuvant chemotherapy is minimal for most patients, though it may be an option for those with high-risk characteristics; adding oxaliplatin does not significantly improve outcomes. For Stage III, adjuvant chemotherapy is recommended for all patients without contraindications and should ideally commence within 4–6 weeks post-surgery. A 6-month course of fluorouracil with leucovorin or capecitabine is effective, and incorporating oxaliplatin enhances survival, although its advantage may decrease in older individuals. Shorter, 3-month regimens may be suitable for patients with better prognosis. Irenotecan and anti-EGFR treatments are not advised, and using portable infusion pumps can reduce hospitalizations(3).

Nutrition

While the exact mechanisms behind CRC formation are not fully understood, chronic inflammation is known to play a role in the onset of malignancy(8). It is believed that around 20% of malignant tumors in the colon are preceded by chronic inflammation(9). In recent years, growing evidence has also indicated a link between intestinal microbial dysbiosis and the

development of CRC. The article "The Intestinal Microbiota and Colorectal Cancer"(10) examines the significant impact of gut microbiota on colorectal cancer (CRC). It explains how an imbalance in gut bacteria, known as dysbiosis, is strongly connected to CRC, with certain bacteria playing crucial roles in triggering and advancing the disease. The paper discusses mechanisms by which gut microbiota contribute to cancer(11), including chronic inflammation(12), DNA damage(13), and disruption of the intestinal barrier(14). The authors identify specific bacteria, such as Fusobacterium nucleatum and Escherichia coli, that are associated with CRC and describe how they promote tumor development through various pathways, including immune modulation and genotoxic effects. The study also highlights the potential of using gut microbiome composition as biomarkers for CRC diagnosis and prognosis. The article explores therapeutic strategies like dietary changes, probiotics, prebiotics, and fecal microbiota transplantation (FMT) to restore a healthy gut microbiome and potentially reduce CRC risk. In another meta-analysis utilizing the rank sum method, seven bacterial markers were identified as consistently enriched in CRC across four different cohorts(15). Notably, six of these bacteria, including P. asaccharolytica, F. nucleatum, B. fragilis, P. intermedia, P. micra, and A. finegoldii, have previously been associated with CRC, supporting the findings of this analysis. However certain bacteria, primarily probiotics like Lachnospiraceae species, Bifidobacterium animalis, and Streptococcus thermophilus, have been observed to be reduced in patients with CRC(16). The article "Nutritional Treatment of Patients with Colorectal Cancer"(17) highlights the importance of proper nutrition in managing colorectal cancer. Malnutrition is a frequent problem for these patients, which can worsen outcomes and reduce the effectiveness of treatment. Regular monitoring and tailored nutritional support are essential to improve therapy response and recovery. SPEN guidelines suggest at least 1 g of protein per kilogram of body weight daily, with higher intake for those at nutritional risk. Omega-3 supplements may help maintain appetite and muscle mass. During radiotherapy, a diet that avoids hard-to-digest foods can help reduce gastrointestinal side effects. The article also emphasizes the benefits of oral nutritional supplements in preventing muscle loss and improving chemotherapy tolerance. When patients can't meet their nutritional needs through regular food intake, enteral or parenteral nutrition becomes necessary(17). Also, various studies have indicated that using probiotics, prebiotics, or a combination of both (referred to as synbiotics to enhance synergistic effects) has demonstrated a protective effect in CRC mice models, such as DMH or AOM models(16,18). According to some research probiotic strains that focus on key proteins essential for apoptosis can help overcome CRC's resistance to

programmed cell death. They can enhance the production of anti-inflammatory cytokines, which are crucial in preventing cancer development, and can also eliminate cancer cells by activating immune responses mediated by T cells(19). An interesting take on the subject may be another paper that focuses on curcumin's potential as a treatment for colorectal cancer, emphasizing its anti-cancer effects such as improving gut microbiome balance, strengthening intestinal barriers, and reducing inflammation. It also discusses curcumin's role in inducing autophagy, targeting cancer stem cells, and enhancing the effectiveness of traditional chemotherapy. Despite these benefits, the article notes challenges with curcumin's bioavailability and suggests that better formulations are needed. Overall, curcumin appears to be a promising natural option for CRC prevention and treatment(20). An alternative approach to the topic is the article tha examines the potential role of the ketogenic diet (KD) in colorectal cancer (CRC) treatment, emphasizing its ability to restrict glucose to cancer cells while supplying ketone bodies as an energy source for healthy cells, thereby hindering tumor growth. It outlines various ways KD can impact cancer metabolism, such as reducing inflammation and modulating gene expression linked to cancer progression. Although KD shows potential in enhancing quality of life and mitigating cancer treatment side effects, challenges like adherence to the diet and potential weight loss are noted(21).

Genetics

The article "Metastatic Colorectal Cancer: Mechanisms and Emerging Therapeutics" discusses key factors contributing to CRC metastasis, including genetic mutations, the role of cancer stem cells, epithelial-mesenchymal transition (EMT), and the tumor microenvironment (TME). Specific genetic alterations, such as mutations in the TP53 gene, are emphasized as significant in CRC progression and therapy resistance. Additionally, the identification of metastasis-initiating cells and their markers, such as Lgr5 and L1CAM, is critical for understanding and preventing cancer spread(22). Another study(23) analyzed p53 expression in colorectal cancer and its impact on prognosis and treatment. It found that patients with complete p53 loss had poorer outcomes, while those with wild-type p53 might benefit more from systemic chemotherapy. The study observed no significant link between p53 expression and stem-like immunophenotypes, though wild-type p53 was associated with larger tumors. The findings suggest that p53 immunohistochemistry could be useful for guiding treatment decisions in CRC, particularly in settings without access to gene sequencing. In treating metastatic CRC, monoclonal antibodies that target signaling pathways associated with p53 mutants have the

potential to enhance standard chemotherapy regimens. Biological agents like Bevacizumab (anti-VEGF, targeting vascular endothelial growth factor) or Cetuximab and Panitumumab (anti-EGFR, targeting epidermal growth factor receptor) are utilized alongside standard treatments, with EGFR antibodies specifically used in combination with standard regimens in cases of wt-RAS mCRC(24). The article "Personalised neoantigen-based therapy in colorectal cancer"(25) thoroughly examines personalized neoantigen-based therapies for colorectal cancer (CRC), focusing on the potential of neoantigens—unique peptides formed from somatic mutations—as therapeutic targets. These neoantigens can effectively stimulate strong immune responses while minimizing side effects. The review covers various strategies for neoantigen-based treatments, including vaccines, T-cell therapies, and antibody-based approaches, and underscores their potential in improving CRC treatment outcomes. Additionally, it highlights the benefits of combining these therapies with other treatments like immune checkpoint inhibitors, chemotherapy, and radiotherapy to boost their effectiveness. The article concludes by identifying personalized neoantigen-based therapy as a promising area in CRC treatment, with further research required to enhance and optimize these approaches for clinical application.

Other methods

One study has attempted to use nanotechnology to treat colorectal cancer. Biodegradable nanoparticles loaded with 5-fluorouracil (5FU) were developed and optimized for improved drug encapsulation and controlled release. In vivo testing in a murine tumor model showed that these nanoparticles significantly reduced tumor size with minimal toxicity compared to the free drug. The study concluded that PEGylated PLGA nanoparticles enhance the anti-tumor efficacy of 5FU while reducing side effects. Another article focuses on creating sphingomyelin nanosystems loaded with uroguanylin and etoposide as a treatment for metastatic colorectal cancer. The researchers developed an amphiphilic derivative of uroguanylin and integrated it into the nanosystems, which target the Guanylyl Cyclase C receptor found in metastatic colorectal cancer cells. Their study showed that these nanosystems efficiently delivered the drug combination to cancer cells, leading to enhanced therapeutic effects in both lab and animal models. The findings suggest that this targeted therapy could be a promising strategy for treating metastatic colorectal cancer.(26)

Conclusions

In conclusion, despite significant progress in the treatment of colorectal cancer (CRC),

particularly in early stages, the prognosis for metastatic CRC continues to be poor, with a 5-year survival rate remaining disappointingly low. Standard treatments, including surgical resection, chemotherapy, and targeted therapies, have improved outcomes for many patients, yet they often fall short in cases of advanced disease. The integration of emerging therapies, such as immunotherapy, holds considerable promise. For instance, PD-1 inhibitors like dostarlimab have shown remarkable efficacy in specific patient groups, achieving complete clinical and pathological responses in advanced mismatch repair-deficient (dMMR) CRC, and potentially offering a non-invasive alternative to traditional treatments. However, these findings are still in the early stages, and further research is necessary to confirm their long-term benefits.

In addition to immunotherapy, dietary interventions like the ketogenic diet (KD) and the incorporation of probiotics have shown potential as complementary strategies. The KD, by limiting glucose availability to cancer cells while providing ketone bodies as an alternative energy source, may hinder tumor growth and improve patients' quality of life. Probiotics, on the other hand, could help overcome CRC's resistance to apoptosis and modulate the gut microbiome, which plays a crucial role in cancer progression and patient outcomes. These approaches highlight the importance of addressing cancer metabolism and the tumor microenvironment in the fight against CRC.

Furthermore, advancements in nanotechnology present exciting opportunities for more effective and targeted treatments. Studies involving PEGylated PLGA nanoparticles loaded with chemotherapeutic agents like 5-fluorouracil (5FU) have demonstrated enhanced drug delivery and reduced toxicity, leading to better tumor control in preclinical models. Similarly, sphingomyelin nanosystems loaded with a combination of uroguanylin and etoposide have shown potential in effectively targeting metastatic CRC cells, offering a promising new avenue for treatment. These nanotechnology-based strategies aim to increase the precision of drug delivery, thereby maximizing therapeutic efficacy while minimizing adverse effects.

Overall, while significant strides have been made in the management of CRC, particularly through the development of novel therapies and supportive dietary strategies, much work remains to be done. Continued research into these emerging treatments and their integration with existing protocols is essential to improve outcomes for patients with CRC, especially those with metastatic disease. The future of CRC treatment likely lies in a multifaceted approach that combines traditional methods with innovative therapies, personalized medicine, and lifestyle modifications to enhance survival and quality of life for all patients.

Disclosure

Author's contribution

Conceptualization: Anna Wojtkiewicz; Methodology: Mateusz Górka; Software: Zuzanna Kudas; Check: Magda Piekarska; Formal analysis:Anna Wojtkiewicz; Investigation: Anna Wojtkiewicz, Resources: Anna Wojtkiewicz; Data curation: Anna Wojtkiewicz; Writing - rough preparation: Anna Wojtkiewicz and Magda Piekarska; Writing - review and editing: Anna Wojtkiewicz; Visualization: Krzysztof Szerej, Project administration: Weronika Stec;

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